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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.
GMN is indexed in MEDLINE, SCOPUS, VINITI Russian Academy of Sciences, is available on-line at www.geomednews.ge

In 2009, GMN's SJR - 0.038; SNIP- 0.030

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, рецензии, научные сообщения, новости медицины и здравоохранения.
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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. 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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8. 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.

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

10. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: შესავალი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

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

ХИРУРГИЧЕСКАЯ ТАКТИКА ПРИ ОСТРЫХ ТОЛСТОКИШЕЧНЫХ КРОВОТЕЧЕНИЯХ

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Острые толстокишечные кровотечения (ОТК), частота которых по данным авторов [2,3,9] составляет 11-12% от всех кровотечений желудочно-кишечного тракта (ЖКТ), остаются одной из серьезных проблем ургентной абдоминальной хирургии.

Хотя случаи профузных кровотечений из толстой кишки встречаются гораздо реже, чем из верхних отделов ЖКТ, летальность при данном осложнении достигает 15-20% [8]. Ряд авторов [5,7] связывают столь высокую летальность с поздней обращаемостью больных, которая, в свою очередь, обусловлена тем, что практически все больные вначале заболевания расценивают кровотечение как геморроидальное и занимаются самолечением, а иногда и врачи на догоспитальном этапе лечат геморрой.

Усилия многих ученых и исследовательских коллективов [1,4,6,10] сказались на некотором улучшении результатов лечения больных с ОТК, однако они не удовлетворяют запросам клинической практики, что диктует необходимость разработки рационального алгоритма лечения больных с ОТК.

Целью настоящего исследования явилось определение хирургической тактики при острых толстокишечных кровотечениях и разработка мероприятий, направленных на повышение эффективности обследования и улучшение результатов лечения больных с острым толстокишечным кровотечением.

Материал и методы. Основой настоящего исследования явился анализ результатов комплексного клинического обследования 134 больных с ОТК, находившихся на лечении в Медицинском центре “Сурб Григор Лусаворич” города Ереван за последние 12 лет. Больные были условно подразделены на две группы. В I (контрольную) группу вошли 58 (43,3%) больных с ОТК, находившихся на лечении в период с 1998 по 2003 гг. II (основную) группу составили больные, находившиеся под нашим наблюдением с 2003 г. по настоящее время - 76 (56,7%) больных, при лечении которых была применена разработанная нами хирургическая тактика. Среди обследованных мужчин было 81 (60,4%), женщин - 53 (39,6%). Возраст больных колебался в пределах от 15 до 88 лет.

При анализе этиологических факторов ТК выявлено, что в обеих группах самой частой причиной кровотечений является рак ободочной и прямой кишок - 28,3%. Вторая по частоте причина - дивертикулез толстой кишки - 14,9%. Затем в убывающей последовательности эрозивно-геморрагическое и эрозивно-язвенное поражения (в основном инфекционно-паразитарной этиологии) - 13,5%, полипы прямой и ободочной кишок - 11,9%, геморроидальное кровотечение - 11,2%. К последним мы относили только те случаи, при которых имелось не симптоматическое, а обильное кровотечение, приводящее к постгеморрагической анемии. Заслуживает внимания, что ОТК выявлено также у 3,7% больных с хронической почечной недостаточностью (ХПН), находившихся на гемодиализе, что известно в литературе под названием “уремический колит” и является довольно редкой формой кишечного кровотечения. Больные с неспецифическим язвенным колитом (НЯК), осложненным массивным кишечным кровотечением, составили в данном исследовании 1,5%. Болезнь Крона толстой кишки редко осложнялась кровотечением, лишь в одном (0,7%) наблюдении основной группы. Ишемический колит и гемангиоматоз толстой кишки с кровотечением установлен у 3,7% и 0,7% обследованных, соответственно.

В структуре сопутствующих заболеваний у больных с ОТК наиболее часто встречались хронические сердечно-сосудистые заболевания: атеро-

склероз аорты и коронарных сосудов – 54 (40,3%) случая, гипертоническая болезнь – 48 (35,8%) случаев, различные нарушения ритма сердечной деятельности - у 23 (17,2%) больных; сахарный диабет - у 27 (20,1%), ХПН - 5 (3,7%).

При диагностике основного заболевания у больных с ОТК проводилась оценка общего состояния, определялись локализация и интенсивность кровотечения, а также клинико-биохимические отклонения с применением комплекса клинико-лабораторных исследований, инструментальных, рентген- и эндоскопических методов на основании разработанного нами диагностического алгоритма.

Результаты и их обсуждение. Первостепенное значение в диагностике ОТК имеет эндоскопическое исследование – колоноскопия, имеющая целью исследовать толстую кишку - до слепой, а при необходимости - и терминальный отдел подвздошной кишки. При колоноскопии решались следующие задачи: 1) локализация источника кровотечения; 2) характеристика источника кровотечения; 3) определение статуса кровотечения (продолжающееся или состоявшееся); 4) эндоскопический гемостаз.

Колоноскопию производили в срочном или экстренном порядке, в зависимости от степени тяжести больных и интенсивности кровотечения. Основной проблемой при выполнении экстренных колоноскопий является невозможность полноценной подготовки толстой кишки к эндоскопическому исследованию.

Для очистки толстой кишки во время эндоскопии без подготовки нами разработан и применен на практике метод активного промывания просвета кишки через специальный зонд, который вводится вместе с колоноскопом (патент на изобретение №1527А2, зарегистрировано 01.12.2004 г.). Проведенный анализ показал, что информативность предложенного нами способа экстренной колоноскопии при ОТК составляет: чувствительность - 94,6%, специфичность - 100%, точность - 95,4%, а информативность традиционной экстренной колоноскопии при ОТК в контрольной группе составляет: чувствительность - 76,2%, специфичность - 100%, точность - 77,5%. Сравнительный анализ показал, что предлагаемый нами способ экстренной колоноскопии способствует повышению показателей информативности эндоскопического исследования: чувствительности - на 18,2%, точности - на 17,5%.

Современные эндоскопические методы позволяют не только диагностировать причину кровотечения, но и проводить ряд лечебных мероприятий, позволяющих уменьшить частоту рецидивов кровотечений, добиться окончательного или временного гемостаза (как этап подготовки к хирургической операции), чем и обусловлена их значительная роль в выборе тактики лечения больных с ОТК (таблица).

Таблица. Характеристика эндоскопических вмешательств при ОТК

Операции \ Группы больных	I группа (контр.)		II группа (основная)		Всего	
	абс.	%	абс.	%	абс.	%
Полипэктомия через колоноскоп	6	35,3	10	32,2	16	33,3
Орошение гемостатиками	7	41,2	14	45,2	21	43,7
Электрокоагуляция	4	23,5	7	22,6	11	23

Эндоскопический гемостаз мы обычно производили всем больным с продолжающимся толстокишечным кровотечением, а при состоявшихся кровотечениях ограничивались интубацией кишечника для контроля рецидива. Среди имеющихся современных методов эндоскопического гемостаза нами применялись электрокоагуляция и орошение гемостатиками, среди местных гемостатиков в клинической практике хорошо себя зарекомендовал препарат капрофер, который мы широко применяли для орошения в разведении с водой 1/3-1/5. Орошение с использованием капрофера применено 21 больному, кровотечение было остановлено у 19 больных.

Организация лечебного процесса у больных с ОТК предполагает решение 2 основных задач: лечение последствий острой кровопотери и воздействие на патогенетические механизмы основного заболевания, осложнившегося кровотечением, с целью его

прекращения (консервативный, эндоскопический, хирургический гемостаз). Проведенное нами исследование показало, что данные задачи у одного и того же больного следует решать комплексно, параллельно, дифференцированно, с учетом особенностей конкретной патологической ситуации.

Все больные с ОТК госпитализировались изначально в отделение реанимации, где им и проводилось консервативное лечение по разработанной нами схеме, основанной на традиционной. При поступлении, с учетом клинико-лабораторных данных и эндоскопической оценки характера кровотечения, определялась тяжесть состояния больных, и составлялась программа консервативных мероприятий, предусматривающая сочетанное решение ряда взаимосвязанных задач: 1) восполнение объема циркулирующей крови; (А - стабилизация гемодинамики; Б - восстановление микроциркуляции); 2) медикаментозная остановка кровотечения (гемостатическая терапия); 3) ликвидация анемии и ее последствий; 4) коррекция обменных нарушений.

Консервативная терапия является ключевым фактором в комплексном лечении больных с ОТК. Среди 134 больных консервативный гемостаз, как монотерапия, проведен 35 (26,1%) больным. Консервативному гемостазу хорошо поддавались в основном кровотечения воспалительной этиологии, во время которых эндоскопический гемостаз нами применен лишь в 2 (5,6%) случаях из 35.

Консервативные мероприятия (плазмозамещающая и гемостатическая терапия) позволили достичь положительного эффекта более чем у 25% больных с ОТК, без применения эндоскопических методов и хирургического вмешательства.

Проведенные нами исследования показали, что вопросы окончательной остановки толстокишечных кровотечений не всегда удается решить лишь с применением методов консервативного и эндоскопического гемостаза. В определенном проценте случаев стойкое прекращение кровотечения из толстой кишки достигалось применением хирургических вмешательств. Согласно полученным нами данным, 48,3% больным контрольной и 42,1% основной группы проведены оперативные вмешательства.

Необходимо отметить, что подавляющему большинству больных оперативные вмешательства были выполнены после временного консервативного и эндоскопического гемостаза в зависимости от причин ОТК.

Оперативные вмешательства в экстренном порядке на высоте кровотечения произведены 9 (32,1%) больным I группы и 5 (15,6%) больным II группы. Выполнены следующие операции: правосторонняя гемиколэктомия – 3, резекция сигмовидной кишки – 2, сигмостомия – 3, трансанальная тумоэктомия – 4, левосторонняя гемиколэктомия – 1, колэктомия – 1.

Снижение числа экстренных операций в основной группе, на наш взгляд, обусловлено повышением эффективности проводимых нами комплексных мероприятий, как в плане диагностики, так и применения эндоскопических методов. Экстренные оперативные вмешательства при ТК выполнялись в случаях: 1) неэффективности проводимого консервативного и эндоскопического гемостаза; 2) повторного рецидива кровотечения в течение одних суток; 3) наличия источника кровотечения в тонкой кишке.

На наш взгляд, именно указанные показания являются абсолютными для проведения экстренных оперативных вмешательств.

Отсроченные (плановые) оперативные вмешательства проводились, в первую очередь, больным с опухолями толстой кишки различной локализации, приведшими к развитию постгеморрагической анемии, а также при тотальном или частичном поражении толстого кишечника патологическим процессом с высокой вероятностью рецидива кровотечения.

При этом, критериями подготовленности таких больных к плановому оперативному вмешательству считали восстановление показателей красной крови (на фоне гемотрансфузии), а также коррекцию сопутствующих заболеваний различных органов и систем. В качестве пограничных данных, позволяющих оперировать больных с наилучшими результатами в послеоперационном периоде, нами выделены уровень гемоглобина периферической крови не ниже 100 г/л. Данный показатель является наиболее приемлемым с учетом величин

интраоперационной кровопотери. При этом оперативные вмешательства преследовали целью не только остановку ТК, но и радикальное лечение основного заболевания, осложнившегося кровотечением. Особенно к этому стремились в случае больных опухолями различной локализации, даже при наличии у них метастазов.

Необходимо отметить, что в обеих исследуемых группах как плановые, так и экстренные оперативные вмешательства носили радикальный характер и заключались в удалении (резекции) части, либо всей пораженной толстой кишки. На долю паллиативных вмешательств пришлось всего лишь 11,7% произведенных вмешательств – в случае иноперабильного рака, либо наличия противопоказаний со стороны других органов и систем. Уменьшение количества экстренных операций в основной группе способствовало увеличению количества радикальных, одномоментных операций, поскольку предоставлялась возможность полноценной подготовки толстого кишечника к операции. Так, если в I группе из 14 резекций толстой кишки различных объемов 6 (42,9%) закончились временным наложением различных стом, то во II группе из 21 резекции временным наложением стомы завершились только 4 (19,0%) операции.

В послеоперационном периоде у 10 (35,7%) оперированных больных I группы и у 3 (9,4%) II группы отмечались следующие послеоперационные осложнения: несостоятельность анастомоза – 3 случая, стриктура анастомоза - 1, внутреннее кровотечение - 1, пневмония - 3, мерцательная аритмия - 2, тромбоз глубоких вен нижних конечностей – 3.

Летальность в I группе составила 9 (15,5%), а во II – 3 (3,9%). Причиной смерти были тромбоэмболия легочной артерии - 5 случаев, инфаркт миокарда – 4, синдром диссеминированного внутрисосудистого свертывания - 3.

Таким образом, разработанная нами тактика ведения больных с ОТК позволила повысить эффективность обследования больных и улучшить результаты их лечения: увеличить число одномоментных радикальных операций на 23,9%, уменьшить послеоперационные осложнения на 26,3% и снизить летальность на 11,6%.

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SUMMARY

SURGICAL TACTICS AT ACUTE COLONIC BLEEDINGS

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The analysis of complex clinical examination of 134 patients with acute colonic bleeding treated at Medical Centre «St. Grigor Lusavorich» in Yerevan during last 12 years is presented. It was found that causes of acute colonic bleeding are very diverse. The main ones are:

cancer, colorectal cancer (28,4%), diverticulosis of the colon (14,9%), hemorrhagic erosive and erosive-ulcerative lesions of the colon (13,5%), colon polyps (11,9%). Technique of emergency colonoscopy with intubation of the colon is proposed and an increase in 18,2% sensitivity and 17,5% accuracy was observed. In cases of conservative hemostasis without application of endoscopic methods and a surgical intervention positive results were obtained in 26,5% cases of acute colic bleedings. Application of modern methods of endoscopic haemostasis reduced the number of emergency operations in 1,7 times; the recurrence rate of bleeding in 2,6 times. The differentiated surgical treatment of patients with acute colonic bleeding increases the number of simultaneous radical surgery on the colon by 23,9%, reduces postoperative complications by 26,3%, lethality - by 11,6%.

Key words: acute colonic bleeding, emergency colonoscopy.

РЕЗЮМЕ

ХИРУРГИЧЕСКАЯ ТАКТИКА ПРИ ОСТРЫХ ТОЛСТОКИШЕЧНЫХ КРОВОТЕЧЕНИЯХ

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Представлен анализ комплексного клинического обследования 134 больных с острыми толстокишечными кровотечениями, находившихся на лечении в Медицинском центре “Сурб Григор Лусаворич” города Ереван за последние 12 лет. Причины острых толстокишечных кровотечений отличаются большим разнообразием-более 15 нозологий. Основными из них являются: рак прямой и ободочной кишки (28,4%), дивертикулез толстой кишки (14,9%), эрозивно-геморрагическое и эрозивно-язвенное поражения толстой кишки (13,5%), полипы толстой кишки (11,9%). Разработанный нами способ проведения экстренной колоноскопии с интубацией толстой кишки способствует повышению показателей информативности эндоскопического исследования: чувствительности на 18,2% и точности на 17,5%. Консервативный гемостаз без применения эндоскопических методов и хирургического вмешательства дает возможность достичь положительного результата у 26,5% больных с острыми толстокишечными кровотечениями. Применение современных методов эндоскопического гемостаза позволяет снизить число экстренных операций в 1,7 раза, уменьшить частоту рецидивов кровотечения в 2,6 раза. Применение дифференцированной хирургической тактики ведения у больных с острыми толстокишечными кровотечениями способствует увеличению числа одномоментных радикальных операций на толстой кишке на 23.9%, снижению числа послеоперационных осложнений на 26,3%, летальности - на 11,6%.

რეზიუმე

ქირურგიული ტაქტიკა მსხვილი ნაწლავიდან სისხლდენების დროს

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წარმოდგენილია მსხვილი ნაწლავიდან მწვავე სისხლდენით 134 ავადმყოფის კომპლექსური კლინიკური გამოკვლევის ანალიზის შედეგები. გამოკვლევა ჩატარდა უკანასკნელი 12 წლის განმავლობაში ერევნის სამედიცინო ცენტრში “სურფ გრიქორ ლუსავორიჩ”. მსხვილი ნაწლავიდან სისხლდენის მიზეზი მრავალგვაროვანია და 15-ზე მეტი სხვადასხვა პათოლოგიით შეიძლება იყოს განპირობებული, რომელთა შორის უმეტესად გვხდება სწორი და კოლინჯი ნაწლავების კიბო (23,4%), შედარებით ნაკლები სიხშირით აღინიშნება მსხვილი ნაწლავის დივერტიკულოზი (14,9%), სწორი ნაწლავის ეროზიულ-ჰემორაგიული და ეროზიულ-წყლულოვანი დაზიანებები (13,5%). მსხვილი ნაწლავის პოლიპები (11,9%).

ავტორთა მიერ შემუშავებულია სასწრაფო კოლონოსკოპიის მეთოდი მსხვილი ნაწლავის ინტუბაციის გზით,რაც 18,2%-ით ზრდის ენდოსკოპიური გამოკვლევის მგრძნობელობის ინფორმაციას, ხოლო სიზუსტეს კი – 17,5%-ით. კონსერვატიული ჰემოსტაზი ენდოსკოპიური მეთოდების გამოყენებისა და ქირურგიული ჩარევის გარეშე უზრუნველყოფს დადებითი შედეგების მიღწევას სწორი ნაწლავიდან მწვავე სისხლდენით

26,5% ავადმყოფთა მკურნალობისას. თანამედ-როვე ენდოსკოპიური ჰემოსტაზის მეთოდების გამოყენების შედეგად მიღწეულ იქნა სასწრაფო ოპერაციების მაჩვენებლის შემცირება 1,7 ჯერ, ხოლო სისხლდენების რეციდივების სიხშირის – 2,6 ჯერ. მსხვილი ნაწლავიდან მწვავე სისხლდენისას,ავტორთა დასკვნით, დიფერინცირებული ქირურგიული ტაქტიკა ხელს უწყობს ერთმომენტიანი რადიკალური ოპერაციების ზრდას მსხვილ ნაწლავზე 23,9%-ით, პოსტოპერატიული გართულებების შემცირებას – 26,3%-ით, ხოლო ლეტალობის მაჩვენებლის შემცირებას – 11,6%-ით.

STRATEGIC ASPECTS OF STOMACH CANCER SURGERY

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According to the data from WHO, over 750 000 new cases of stomach cancer are annually registered in the world [9]. The present problem still has a leading place in the structure of oncological morbidity and mortality [5]. The multicentric growth, the early lymphogenic metastasis, the possibility of the emergence of the jumping metastases, the low sensitivity towards the conservative types of the treatment of stomach cancer causes indication for extensive and extensively-combined operations, diminishing the appearance of local-regional recurrence [11,15].

The majority of researchers show reliable improvement of late fates among the patients with stomach cancer after extensive operations [2,3,7]. Convincing works, carried out over the past decade led to the fact that at the 4th International Gastric Cancer Congress the total gastrectomy with lymph node dissection at D2 level was recognized as a standard procedure in the surgical treatment of stomach cancer (4th International Gastric Cancer Congress, New York, 2001).

The establishment of the degree of the radicalism of the surgical treatment of stomach cancer depends on the groups of lymphatic nodes, put forward by the Japanese Gastric Cancer Assosiation and subject to dissection. In this way the radicalism of the performed operation, indicated with the symbols p0, p1, p2 and p3 is determined by the level of dissection of the groups of lymphatic nodes with the cellular tissue surrounding them N1, N2 and N3 accordingly. At the same time, the degree of radicalism p0 implies the incomplete removal of lymphatic nodes N1.

The modern principles of operative treatment of stomach cancer is concluded in the provision of the safety of surgical intervention, oncological adequacy and the choice of the most functionally justified method of reconstruction. The choice of the operative access, providing visualization of the conducted manipulations, adequate methods of mobilization and the formation of reliable esophageal-intestinal anastomosis provide the safety of the surgical treatment of stomach cancer. The correct sequence of mobilization provide oncological adequacy of the performed operation. The choice of the rational method of reconstruction improves level of patients' quality of life.

Another important position of the treatment of stomach cancer is the provision of the patients' quality of life. Principally, no method of reconstruction after total gastrectomy excludes the problem of the postoperational disease [1,6,10,14]. The frequency and degree of the manifestation of the post-operation pathology predetermines the necessity to compensate for the absence of abdomen with jejunal "reservoir" [4,8,12,13]. The sparsity of the randomized researches, the absence of objective parameters of assessments of various methods complicates the choice of the optimal method of reconstruction.

The aim of the research is to study both immediate and long-term results of treatment in patients with gastric cancer after extended and expanded-combined gastrectomy; assessment of quality of life of patients, depending on the methods of reconstruction.

Material and methods. 90 extensive and extensively-combined operations regarding stomach cancer have been performed in the National Centre of Oncology during January 2003 to December 2008. Patients with distal metastases and dissemination have not been undergone the above mentioned operations. There have been performed palliative operations to this category of patients by life-saving indication. These patients have not been included in the present research. In the control group have been included 82 patients who has been undergone gastrectomy with lymph node dissection D1 during 1998 to 2002. The patients' age ranged from 35 to 77. In 62 cases lymph node dissection corresponded to D2 volume, and in 28 – D3. The volume of dissection corresponding to the degree of radicalism p2 is considered authentically radical at the absence of metastases in N2 lymphatic nodes.

In case of cancer of the distal parts of stomach, the removal of the 1 to 15 and 110 groups of lymphatic nodes relates to the standard operational intervention corresponding to p2 degree of radicalism, but in case of cancer of the proximal part of stomach, the indicated volume of the surgical treatment corresponds to p3 radicalism.

The removal of the 16 group of lymph nodes in case of cancer of the distal part of stomach corresponds to radicalism p3. In 26 cases operation bore a combined character, including resection of adjacent organs. Besides the removal of stomach 1 organ among 15 patients has been additionally resected. 6 of them had distal resection of pancreas, 3 of them had resection of transverse colon, 5 – atypical resection of pancreas and 1 – atypical hepatic resection. 5 patients had additional resection of 2 organs. Among them 3 had resections of pancreas and transverse colon, 1 – resection of transverse colon and atypical resection of II and III segments of liver, and the fourth – distal resection of pancreas and bisegmentectomy (II and III) of liver. 4 patients underwent resection of 3 organs: pancreas, transverse colon and small intestine. 2 patients along with gastrectomy underwent multivisceral resection of 4 organs: liver, pancreas, small and large intestine.

23 patients were given operations with a plastic component at the reconstructive stage, i.e. by overlaying 2 "reservoirs". The essence of the given method is overlaying the first reservoir in Roux-loop after oesophagojejunoanastomosis, and the second one – 40 sm away from the first one.

Methodology of extensive gastrectomies. Mobilization is conducted uniquely in an acute method with the observation of the principle "from vessel to organ" with provision of abdominal and mediastinal lymph node dissection.

The expansion of paracardial lymphatic nodes causes the excision of diaphragmatic ring with the removal of 110 group of lymphatic nodes. The ligation of the right gastric artery is made in the place of origin from the common hepatic artery, and then the cellular tissue is replaced to lesser curvature. Only in this case the complete removal of suprapyloric lymphatic nodes is achieved. The lymphatic nodes from the distal parts of stomach, located in the area of the common hepatic artery are removed together with the leaf of peritoneum and the cellular tissue of the hepatoduodenal ligament. At the same time, the visual landmark is the common and proper hepatic arteries, portal vein and head of pancreas. The complete removal of lymphatic nodes, relating to the area of the left gastric artery, is achieved during its ligation at the place of the origin from the celiac trunk. The transaction of gastropancreatic ligament with the mobilization of the lymphatic nodes and the surrounding fat cellular tissue, in which they are located, of the celiac trunk allows performing paraaortic lymph node dissection. The spleen and distal parts of pancreas are mobilized for the purpose of control and visualize the vessels of blood flow of pancreas and removal of the lymphatic nodes from the splenic porta, along the splenic artery and the root of mesentery.

To remove the lymphatic nodes from the hepatoduodenal ligament, retropancreaticoduodenal lymphatic nodes and lymphocollectors along the mesenteric artery and the abdominal part of aorta it is necessary to conduct mobilization of the descending part of duodenum and head of pancreas, continuing it to the hepatic curvature and further to the right paracolic gutter, ending it at the level of the middle of the ascending colon according to Kocher. The paraaortic lymphatic nodes are removed from the aortocaval space and the front-right semicircle of aorta; the dissection of the retropancreaticoduodenal lymphatic nodes and hepatoduodenal ligament is performed.

The removal of the greater omentum and the elements of the omental bursa, especially at the invasion and outlet of the malignant tumor on the serous membrane of the stomach enables the removal of the tumor cells and lymphatic vessels with metastatic spread dissemi-

nated in the present zone. The removal of the upper leaf of the transverse colon and the posterior leaf of the parietal peritoneum creates conditions for the complete removal of the sub-pyloric lymphatic nodes and the lymphatic nodes of the middle colic artery. At the correct transaction of the gastrocolic ligament and hitting the layer, the present manipulation goes without blood. The ligation of the right gastroepiploic artery and vein at their origin provides the guaranteed removal of the present groups of lymphatic nodes.

Results and their discussions. The post-operational complications were observed in 19 (22.11%) cases. The post-operational hypostatic pneumonia was established among 6 patients after the operation. In 5 cases post-operational pancreatitis was stated. Left-sided subdiaphragmatic abscess was established among 3 patients, who were given drainage under ultra sound research.

5 patients passed away in the early post-operational period. One of them died of respiratory failure, one – of sepsis, one - of mesenteric vessels thrombosis, two – as a result of the inconsistency of esophageal-intestinal anastomosis. In total, mortality constituted 5.56% (Table 1).

Table 1. Distribution of patients depending on the volume of operation and post-operational course

Post-operational period	Lymph node dissection D2 (62)		Lymph node dissection D3 (28)	
	D2 (52)	D2 comb. (10)	D3 (12)	D3 comb. (16)
Post-operational complications	3 (5,36%)	5 (8,93%)	4 (16%)	6 (24%)
Re-operation	2 (3,57%)	-	1 (4%)	1 (4%)
Post-operational lethality	2 (3,57%)	1 (1,78%)	-	2 (8%)

The data of the table 1 indicate that performing extensive and extensively-combined operations isn't followed by statistically authentic increase in rate of post-operational complications and mortality compared to standard gastrectomy ($p>0,05$).

The early emergence of the post-operational disease, expressed by reflux-oesophagitis, has been established among 17 (25,37%) patients after the standard reconstruction. 2 (7,69%) of the patients after gastrectomy, at whose reconstructive stage inter-intestinal reservoirs were overlaid, were noticed to have post-operational pathology. The difference between the obtained data is statistically authentic ($p<0,01$).

Most of the patients applied to the hospital at the later stage of the stomach cancer, chiefly during the complication of the main disease, as seen in the table 2. I stage was established among 11 (12,2%) patients with stomach cancer, II - 21 (23,3%), III – 44 (48,9%), IV – 14 (15,6%) (Table 2).

Table 2. Distribution of the indicator T and N according to the result of the morphological research of the ablated specimen

	N0	N1	N2	N3
T1-2	11	6	2	-
T3	15	12	8	1
T4	4	18	12	1

Analysis of the obtained results showed that the annual disease free survival made up 94,11%, 3-year – 58,82%. The general 3- and 5-year over all survival rate constituted 70,59% and 37.65% correspondingly. In control group annual disease free survival constituted 73,2%, 3-year – 32,9%. 3- and 5-year over all survival constituted 47,6% and 13,4% correspondingly. The difference between the obtained data is statistically authentic in the range $p<0,01$.

The conducted research revealed that the implementation of the lymph node dissection is the main factor improving the distant results of the surgical treatment of the patients with stomach cancer. The obtained preliminary results show the advantage of overlaying reservoirs at the reconstructive stage of gastrectomy, statistically authentically showing decrease in the frequency of the early manifestations of the post-operational reflux-pathology. Conducting extensive gastrectomy with detailed morphological research of the ablated specimen gives the possibility to precisely establish the stage of the disease. The present

fact allows making individual prognosis for each patient. The conditionally radical operations, being palliative by character, but in fact cyto-reductive can create favorable conditions for carrying out adjuvant chemical therapy.

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SUMMARY

STRATEGIC ASPECTS OF STOMACH CANCER SURGERY

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The aim of the research is to study both immediate and long-term results of treatment in patients with gastric cancer after extended and expanded-combined gastrectomy; assessment of quality of life of patients, depending on the methods of reconstruction.

90 extensive and extensively-combined gastrectomies have been performed. 23 patients have been given operations with overlaying reservoirs at the reconstructive stage.

The post-operational complications were observed among 18 (20%) patients in the main group, mortality was constituted 5 (5,6%). In the control group the above mentioned rates was constituted 14 (17,1%) and 3 (3,37%) correspondingly. The difference between the obtained data is statistically non-authentic ($p>0,05$).

Reflux-oesophagitis was detected among 17 (25,37%) patients after standard reconstructions and 2 (7,69%) – after overlaying the reservoirs ($p<0,01$).

In the main group an annual disease free period constituted 94,11%, 3-year – 58,82%, in the control group – 73,2% and 32,9%, respectively. 3- and 5-year survival rate in the main group constituted 70,59% and 37,65%, in the control group – 47,6% and 13,4% correspondingly ($p<0,01$).

Extensive and extensively-combined gastrectomies improve distant results of the treatment among the patients with stomach cancer and aren't followed by increase in rate of post-operational complications and

mortality. Overlaying the reservoirs decrease the rate and intensity of reflux pathology.

Key words: gastric cancer, expanded-combined gastrectomy, extended lymph-node dissection.

РЕЗЮМЕ

СТРАТЕГИЧЕСКИЕ АСПЕКТЫ ХИРУРГИИ РАКА ЖЕЛУДКА

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Цель исследования - изучение непосредственных и отдаленных результатов лечения больных раком желудка после расширенных и расширенно-комбинированных гастрэктомий с оценкой качества жизни больных в зависимости от методов реконструкции.

Проведено 90 расширенных и расширенно-комбинированных гастрэктомий. 23 больным выполнены операции с наложением «резервуаров» на реконструктивном этапе.

В основной группе у 18 (20,0%) больных отмечены послеоперационные осложнения, летальность составила 5,6% (5 больных). В контрольной группе данные показатели составили, соответственно, 14 (17,1%) и 3 (3,37%). Разность между полученными результатами оказалась статистически недостоверной (p>0,05).

Проявления рефлюкс-эзофагита выявлены у 17 (25,37%) больных - после стандартных реконструкций и у 2 (7,69%) - при наложении «резервуаров»; разность между данными статистически достоверна (p<0,01).

В основной группе годовой безрецидивный период составил 94,11%, 3-летний – 58,82%. Общая 3-х и 5-летняя выживаемость составили соответственно 70,59% и 37,65%. В контрольной же группе годовой безрецедивный период составил 73,2%, а 3-летний 32,9%. 3-х и 5-летняя выживаемость составила, соответственно, 47,6% и 13,4%. Разность между данными статистически достоверна (p<0,01).

Проведенными исследованиями установлено, что расширенные и расширенно-комбинированные гастрэктомии улучшают отдаленные результаты лечения больных раком желудка, не сопровождаются увеличением частоты послеоперационных осложнений и летальности. Наложение «резервуаров» уменьшают частоту и степень выраженности рефлюкс-патологии.

რეზიუმე

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კვლევის მიზანს წარმოადგენდა კუჭის კიბოთი დასნეულებულთა შორის ქირურგიული მკურნალობის შედეგების შესწავლა გაფართოვებული და გაფართოვებულ-კომბინირებული გასტრექტომიის ჩატარების შემდგომ და ავადმყოფთა ცხოვრების წესის შეფასება გამოყენებული რეკონსტრუქციის მეთოდისდა მიხედვით.

ჩატარდა 90 გაფართოვებული და გაფართოვებულ-კომბინირებული გასტრექტომია, მათ შორის 23 შემთხვევაში ოპერაციის რეკონსტრუქციულ ეტაპზე „რეზერვუარის“ შექმნით.

ძირითადი ჯგუფის 18 (20,0%) ავადმყოფს განუვითარდა ოპერაციისშემდგომი გართულება, ხოლო ლეტალობამ 5,6% (5 ავადმყოფი) შეადგინა. საკონტროლო ჯგუფში ანალოგიური მაჩვენებლები, შესაბამისად, 17,1% (14 ავადმყოფი) და 3,4% (3 ავადმყოფი) ტოლი აღმოჩნდა; სხვაობა მიღებულ მონაცემთა შორის სტატისტიკურად არასარწმუნოა (p>0,05).

რეფლუქს-ეზოფაგიტის მოვლენები გამოუვლინდა 17 (25,37%) ავადმყოფს სტანდარტული რეკონსტრუქციის ჩატარების შემდგომ,ხოლო „რეზერვუარის“ შექმნისას – მხოლოდ ორს (7,69%); სხვაობა სტატისტიკურად სარწმუნოა (p<0,01).

ძირითად ჯგუფში ერთწლიანი ურეციდივო პე-

რიოდი აღენიშნა ავადმყოფთა 94,11%-ს, ხოლო სამწლიანი – 58,82%-ს. ზოგადი 3- და 5-წლიანმა სიცოცხლის ხანგრძლივობამ შეადგინა,შესაბამისად,70,59% და 37,65%. საკონტროლო ჯგუფის პირთა შორის კი ერთწლიანი ურეციდივო პერიოდი აღენიშნა 73,2%, ხოლო სამწლიანი – 32,9%-ს; 3-და 5-წლიანი სიცოცხლის ხანგრძლივობის მაჩვენებელი, შესაბამისად, 47,6% და 13,4%-ის ტოლი იყო (სხვაობა აღნიშნულ მაჩვენებელთა შორის სტატისტიკურად სარწმუნოა: $p<0,01$).

ჩატარებული კვლევის შედეგებით დადგინდა, რომ კუჭის კიბოთი დასნეულებულ პირთა გაფართოვებული და გაფართოვებულ-კომბინირებული გასტრექტომიის შემდგომ აღინიშნება მკურნალობის შორეული შედეგების გაუმჯობესება: არა აქვს ადგილი ოპერაციის შემდგომი სიხშირისა და ლეტალობის მაჩვენებლების ზრდას, „რეზერვუარის“ შექმნით კი აღინიშნება რეფლუქს-პათოლოგიის სახშირისა და გამოხატვის ხარისხის შემცირება.

ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ НЕКОТОРЫХ ПОКАЗАТЕЛЕЙ ИММУННОГО БАЛАНСА ПРИ ПРЕЭКЛАМПСИИ

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Актуальной проблемой акушерской патологии является преэклампсия в виде полиорганного патологическового синдрома, который проявляется во второй половине беременности и манифестируется триадой основных симптомов: отёк, протеинурия и гипертензия, в тяжелых случаях судорогами или коматозным состоянием [7,6]. Несмотря на успехи, достигнутые в области изучения патогенеза и этиологии преэклампсии, по сей день не существует единной теории причин и механизмов развития этого синдрома, что особенно важно для его своевременной диагностики и превенции. Считается, что развитие преэклампсии в организме беременной в основном обусловлено нейрогенными, гормональными, генетичекскими и иммунологическими факторами [1,5]. Преэклампсия рассматривается, как недостаточность адаптационных механизмов организма.

Как известно во время физиологической беременности на фетоплацентарной границе превалируют антивоспалительные Th-2 цитокины [2,4], тогда как количество цитотоксических Т клеток уменьшается. В то же время на переферии распределение Т-клеток остается неизменным [8,11]. Во время преэклампсии возрастает содержание цитокинов типа Th-1 и уменьшается содержание цитокинов типа Th2 [9]. Многочисленные исследования показывают, что баланс цитокинов играет особое значение в регуляции течения беременности [12-13]. Однако диагностическое и прогностическое значение нарушений иммунного баланса при преэклампсии до сих пор не установлены[14,10].

Целью исследования явилось определение прогностической значимости про- и антивосполительных цитокинов при преэклампсии беременных.

Материал и методы. Проведено одномоментное, открыто-контролируемое клиническое исследование. В основную группу вошли 30 беременных с преэклампсией. Критериями включения пациенток в основную группу были: 1) репродуктивный возраст; 2) верифицированный диагноз преэклампсии с учетом критериев современной классификации; 3) информированное согласие пациента на участие в исследовании.

Критериями исключения являлись: острые и хронические генитальные и экстрогенитальные заболевания (эссенциальная гипертензия, пороки сердца, сахарный диабет, ожирение третьей степени, иммунодефицит, системные заболевания, хронические инфекционные заболевания, вегетодистония, генетические патологии). Контрольную группу составили 20 женщин репродуктивного возраста с физиологическим течением беременности.

Обе группы беременных были гомогенны по возрасту, социальному положению, местожительству и паритету.

В крови беременных исследовалось количество провоспалительных (IL-2, TNF-α) и антивоспалительных (IL-10) цитокинов иммуноферментным методом ELISA с использованием диагностических наборов Human Diagnosticum.

При установлении достоверности изменений показателей, сопоставляли содержание про- и антивоспалительных цитокинов в крови женщин с физиологическим и осложненным преэклампсией течением беременности.

На основании сравнения полученных данных основной и контрольной групп определялась чувствительность, специфичность, прогностическая ценность положительных и отрицательных результатов [15].

Результаты исследования обрабатывались статистически программой SPSS (v. 19.0)

Результаты и их обсуждение. Анализ полученных данных (таблица 1) выявил, что при осложненной преэклампсией беременности 20 недель спустя после гестации в крови женщин наблюдалось увеличение содержания TNF-α и снижение содержания IL-10, а содержание IL-2 оставалось при этом в пределах нормы. Отношение концентрации про- и антивопалительных цитокинов в крови женщин с физиологическим и осложненным преэклампсией течением беременности: $\left(\frac{[TNF\alpha]\,[TNF\alpha]}{[IL-10][IL-10]}\right)_{физ} = 0{,}16$, $\left(\frac{[IL-10][IL-10]}{[IL-2]\,[IL-2]}\right)_{физ} = 2{,}0$; $\left(\frac{[TNF\alpha]\,[TNF\alpha]}{[IL-10][IL-10]}\right)_{преэкл} = 0{,}34$, $\left(\frac{[IL-10][IL-10]}{[IL-2]\,[IL-2]}\right)_{преэкл} = 1{,}6$. Следовательно, при осложненной преэклампсией беременности баланс цитокинов отклоняется в пользу провоспалительных.

Таблица 1. Содержание про- и антивоспалительных цитокинов в крови женщин с физиологическим и осложненным преэклампсией течением беременности

Группы женщин		Статистическая величина	IL-2	TNF-α	IL-10
Контроль (физиологическая беременность)		M±m	12,30±0,30	4,05±0,19	25,10±0,36
Преэклампсия		M±m p<	14,17±0,26 0,05	7,40±0,30 0,05	20,14±0,48 0,05
20-28 триместр	Физиологическая беременность	M±m p<	12,00±0,42 0,05	4,00±0,25 0,05	25,20±0,55 0,05
	Преэклампсия	M±m p<	14,53±0,39 0,05	8,40±0,30 0,05	18,80±0,44 0,05
28-40 триместр	Физиологическая беременность	M±m p<	12,60±0,45 0,05	4,10±0,31 0,05	25,10±0,36 0,05
	Преэклампсия	M±m p<	13,80±0,33 0,05	6,40±0,37 0,05	21,33±0,71 0,05

С целью установления динамики дисбаланса иммунологических параметров при преэклампсии пациентки были разделены на две подгруппы - 20-28 недель и 28-40 недель гестации (рис.). Отношение концентрации про- и антивопалительных цитокинов в крови женщин с физиологическим течением беременности не отличалось у пациенток обоих групп ($\left(\frac{[TNF\alpha]\,[TNF\alpha]}{[IL-10][IL-10]}\right)_{физ} \approx 0.16$, $\left(\frac{[IL-10]}{[IL-2]}\right)_{физ} \approx 2{,}0$ в обоих группах). У пациенток с осложненной преэклампсией беременностью $\left(\frac{[TNF\alpha]\,[TNF\alpha]}{[IL-10][IL-10]}\right)_{преэкл} = 0{,}45$, $\left(\frac{[IL-10][IL-10]}{[IL-2]\,[IL-2]}\right)_{преэкл} = 1{,}3$

при сроке 20-28 недель и $\left(\frac{[TNF\alpha]\,[TNF\alpha]}{[IL-10][IL-10]}\right)_{преэкл} = 0{,}3$, $\left(\frac{[IL-10]\,[IL-10]}{[IL-2]\,[IL-2]}\right)_{преэкл} = 1{,}5$ при сроке 28-40 недель гестации. Из приведенных данных следует, что отношение содержания интерлейкинов $\left(\frac{[IL-10][IL-10]}{[IL-2]\,[IL-2]}\right)$ у беременных, как с физиологическим, так и патологическим течением беременности меняется незначительно; на сроках 20-28 недель гистации наблюдается резкое увеличение содержания макрофагального TNF-α, что, в свою очередь, вызывает подавление пролиферации Th2 клеток, способствует снижению экспресии IL-10 и активации клеточного иммунитета, являясь решающим моментом в отклонении иммунного баланса в сторону провоспалительного.

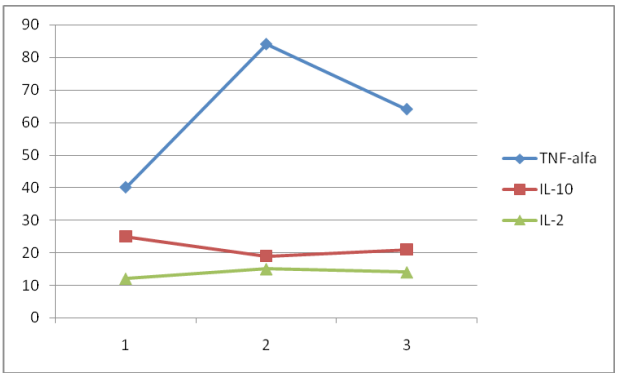

Рис. Динамика изменения содержания цитокинов в крови беременных с преэклампсией (1 - контроль, 2 - 20-28 недель; 3 - 28-40 недель)

Результаты приведенных исследований показывают, что при преэклампсии пик активации провоспалительных реакций приходится на срок гестации - 20-28 недель; при этом, ярко выражено увеличение содержания TNF-α. Полученные данные позволяют предположить о возможной прогностической роли TNF-α в патогенезе преэклампсии.

При определении специфичности, чувствительности и прогностической ценности [15] установлено, что наибольшей специфичностью обладает провоспалительный цитокин TNF-α (93%), затем антивоспалительный IL-10 (90%) и провоспалительный IL-2 (86%). Аналогичная последовательность наблюдается при определении чувствительности параметра: наибольшая чувствительность выявлена у провоспалительного цитокина TNF-α (65%), затем у антивоспалительного - IL-10 (50%), и наконец, у провоспалительного цитокина IL-2 (40%).

Что касается прогностической ценности положительных результатов, то она наиболее высокая у антивоспалительного цитокина IL-10 – (72%), и одинаковая у провоспалительного IL-2 и провоспалительного TNF-α (по 68%).

Прогностическая ценность отрицательных результатов теста самая высокая у провоспалительного цитокина IL-2 (33%), затем у антивоспалительного - IL-10 (23%) и наименьшая у провоспалительного цитокина TNF-α (22%).

Таким образом, следует заключить, что:
- при преэклампсии пик сдвига иммуного баланса в сторону провоспалительных цитокинов приходится на срок гестации 20-28 недель (конец второго триместра);
- IL-2 является относительно стабильным параметром клеточного иммунитета при преэлампсии;
- увеличение уровня TNF-α на сроке гестации 20-28 недель можно считать прогностическим маркером развития преэклампсии.

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SUMMARY

PREDICTIVE VALUE OF SOME PARAMETERS OF IMMUNE BALANCE IN PREECLAMPSIA

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The goal of our research was to reveal correlation between pro- and anti-inflammatory cytokines in preeclamptic women. The research was conducted on pregnant women with physiologic pregnancy and with preeclampsia. Parameters of immune system - pro-inflammatory cytokines (IL-2; TNF-α) and anti-inflammatory cytokine (IL-10) were measured in venous blood by ELISA. The increase of TNF-α and decrease of IL-10 in blood of pregnant women with pre-eclampsia after 20 weeks of gestation were observed; the content of IL-2 was in norm. The highest activation of inflammatory reactions was at the 20-28 weeks of gestation. It was found that women with preeclampsia had high levels of TNF- α in their blood. The increase of TNF- α has a prognostic significance.

Key word: preeclampsia, cytokines, cytotoxity of tumor nectosis factor-α (TNF-α).

РЕЗЮМЕ

ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ НЕКОТОРЫХ ПОКАЗАТЕЛЕЙ ИММУННОГО БАЛАНСА ПРИ ПРЕЭКЛАМПСИИ

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Преэклампсия – специфический для беременности синдром, который клинически проявляется после 20 недель гестации повышенным артериальным давлением, протеинурией, и оттеками.

Целью исследования явилось определение прогностической значимости про- и антивосполительных цитокинов при преэклампсии беременных.

Наблюдались женщины с физиологическим течением и осложненной преэклампсией беременностью. Параметры иммуной системы беременных – провоспалительные (IL-2, TNF-α) и антивоспалительные (IL-10) цитокины, исследовались в венозной крови беременных иммуноферментным методом ELISA.

Полученные в результате исследования данные показали, что при осложненной преэклампсией беременности после 20-й недели гестации в крови женщин наблюдается увеличение содержания TNF-α и снижение содержания IL-10, содержание IL-2 оставалось при этом в предклах нормы. При преэклампсии пик активации провоспалительных

реакций приходится на срок гестации - 20-28 недель; при этом, ярко выражено увеличение содержания TNF-α, что указывает на прогностическое значение данного показателя.

რეზიუმე

პრეეკლამპსიის დროს ზოგიერთი იმუნური მაჩვენებლის ბალანსის დარღვევა და მისი პროგნოზული მნიშვნელობა

მ. თორთლაძე, ნ. კინტრაია, თ. სანიკიძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი,მეანობა-გინეკოლოგიის დეპარტამენტი; ბიოფიზიკის დეპარტამენტი, თბილისი, საქართველო

კვლევის მიზანს წარმოადგენდა პრეეკლამპსიის პათოგენეზში პრო- და ანტიანთებითი ციტოკინების ბალანსის დადგენა. გამოკვლევა უტარდებოდა ფიზიოლოგიური ორსულობითა და პრეეკლამპსიით გართულებულ ორსულებს. ორსულთა პროანთებითი (IL-2, TNF-α) და ანტიანთებითი (IL-10) ციტოკინები გამოკვლეულ იქნა ორსულთა სისხლში იმუნოფერმენტული მეთოდით ELISA. გამოკვლევებმა აჩვენა, რომ პრეეკლამპსიით გართულებული ორსულობის დროს ქალების სისხლში აღინიშნება TNF-α-ის შემცველობის მომატება და IL-10-ს შემცველობის შემცირება, ხოლო IL-2 ნორმის ფარგლებში რჩებოდა. პრეეკლამპსიის დროს პროანთებითი რეაქციის აქტივაციის პიკი მოდის გესტაციის 20-28-ე კვირის ვადაზე, ამავე დროს მნიშვნელოვნად არის გამოხატული TNF-α-ს შემცველობის მომატება.

ამრიგად, შეიძლება დავასკვნათ:
- პრეემკლამპსიის დროს იმუნური ბალანსის პიკის გადახრა პროანთებითი ციტოკინების მხარეს, ხდება გესტაციის 20-28-ე კვირის (მეორე ტრიმესტრის ბოლოს) ვადაზე;
- პრეეკლამპსიის დროს IL-2 წარმოადგენს უჯრედული იმუნიტეტის შედარებით სტაბილურ პარამეტრს;
- 20-28 კვირეებზე TNF-α-ს დონის მომატება შეიძლება მიჩნეულ იქნას პრეეკლამპსიის პროგნოზულ მარკერად.

ACOUSTIC NEUROMA DIAGNOSIS

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Acoustic neuroma, AN, denotes a benign tumor of the 8th cranial nerve. Vestibular schwannoma is a more accurate designation for, as far as the inherent pathological process primarily involves vestibular/balance rather than cochlear/hearing branch of the 8th nerve while arises just from schwann layer cells but not from intrinsic neural units [6,8]. About 95% of ANs represent a local entity and are correspondingly a unilateral affair. Remainders are regional manifestation of the global neurofibromatosis and appear in the main bilaterally.

AN grows as a rule slowly and is expanded within the restricted location space selectively. Initial AN complains include gradual hearing loss and ringing in the ear. Dizziness, swaying, disequilibrium, other vestibular symptoms are also common adjuncts of. True vertigo occurs rare [6,8]. When AN starts to compress the brainstem, balance impairments become particularly disturbing [7]. With a further tumor growth due to the power on trigeminal and facial nerves a face numbness and mimic muscle weakness can arise additionally. Some AN patients suffer from ear- and/or headache. With an increase in AN size, the complications can also comprise nausea, vomiting, respiratory dysfunctions. Coma can happen even.

AN ablation at earlier otological rather than later neurological stage of the tumor development can restrict or reduce both pre- and postoperative complications. Moreover, due to the in time surgical approach, the damaged part but not the whole 8th nerve can be ablated, preserving correspondingly the actual hearing status on the tumor side. Early verification of ANs and consequent surgical intervention are therefore particularly important for beneficial outcome of operations.

In the present paper the characteristic AN case is described. Applying a set of audio-vestibular tests, AN has been verified just at the starting step. Individual data are generalized and efficiencies of utilized diagnostic tools for early AN detection are debated.

Material and methods. *General notes.* K.M., 38 years of age, female, complained of right-sided progressive hearing loss and tinnitus as well as vertigo/spinning. Other oto- and neurological symptoms were absent and any earlier respective disorder had been disclaimed also. The patient appeared non-smoker while refused incidences of high-intensity sound exposures and intakes of ototoxic drugs. Visual inspection did not reveal any outward disorder. The patient was subjected at first to pure tone audiometry, PTA, while afterwards to electronystagmography, ENG, and recordings of auditory brainstem responses, ABRs. Considering the ENG and ABR data, the contrasting magnetic resonance imaging, MRI, had been implicated finally.

PTA examination. The tonal audiometer of the ITERA model (Madsen) had been utilized for the hearing assessment. Both air- and bone-conduction thresholds were measured within the range of leading auditory frequencies, 0.125-8 kHz.

Vestibular testing. The balance function was searched applying the Otoscreen ENG device. Three principal test-trials were accomplished by computer estimation of ENGs: (1) Oculomotor tests that included evaluations of saccadic, smooth pursuit, and optokinetic tracks; (2) Positional and positioning examinations; (3) Caloric inspection. During the latter probe, the head of the patient under the lying position was situated at the angle of 30º relative to the prone plane. It provided vertical orientation of the inner-ear horizontal semicircular canals. Warm and cold waters were flushed consecutively into the left and right outer ear canals. Utilized temperatures, 44ºC and 30ºC, by about 7º exceeded and lagged behind, respectively, the mean normal body temperature. Thermal flooding served for irritation of inner-ear labyrinths and initiation thus of vertigo and nystagmus.

ABR study. During ABR recordings the subject sat in reclining armchair located in a sound-attenuated and electrically-shielded room. ABRs were registered in response to clicks of 70-dB nHL intensity presented monaurally at a rate of 11/s. For ABR derivation the active electrode was fixed on the vertex while the reference and grounded electrodes on the earlobes of stimulated and non-stimulated ears, respectively. The derived activity was amplified within the bandwidth of 50-2000 Hz and was averaged then by the specialized computer system (Eclipse). The bin width was 25 μs, analysis time 15 ms, acquisition number 2000. ABRs were registered under successive stimulation of left and right ears. Intervals between peaks of Waves I, III, and V, i.e. interpeak intervals, IPIs, I-III, III-V, and I-V had been measured in both left and right ABRs while interaural differences of IPIs I-III, III-V, and I-V were determined afterwards. The obtained data were referred to 99% tolerance limits, TLs, of the respective ABR indices calculated in a group of normally hearing healthy subjects. Proceeding from the classical standpoint (cf. [3,4]), individual ABR values, exceeding 99% TLs in the reference group, were judged as a sign of retrocochlear pathology.

MRI scan. The T1se-T2tse-Flair MRI System was utilized for the head scanning. The procedure was fulfilled under intravenous application of contrasting material Gadolinium. To visualize and to get detailed information on AN, regular MRI scans covered both horizontal and vertical planes.

Results and their discussion. By the PTA, the patient had been investigated twice (Fig. 1). At the first, hearing thresholds on the left ear at most frequencies equaled 5 dB nHL. From the total number of nine constituents of a 0.125-8-kHz frequency range, the thresholds exceeded this level and reached 10 dB nHL at 4- and 6-kHz frequencies only. Generally, thus, the hearing in the left ear was definitely normal. On the right ear a distinct sensorineural hearing loss, SNHL, had been evidenced. The thresholds in this ear approximated the normal limits, 10-15 dB nHL, at lower frequencies only, 0.125, 0.25, 0.5, and 1 kHz. At higher frequencies, 2, 3, 4, 6, and 8 kHz, they were augmented, the rise being amounted to 45, 55, 55, 70, and 45 dB, respectively.

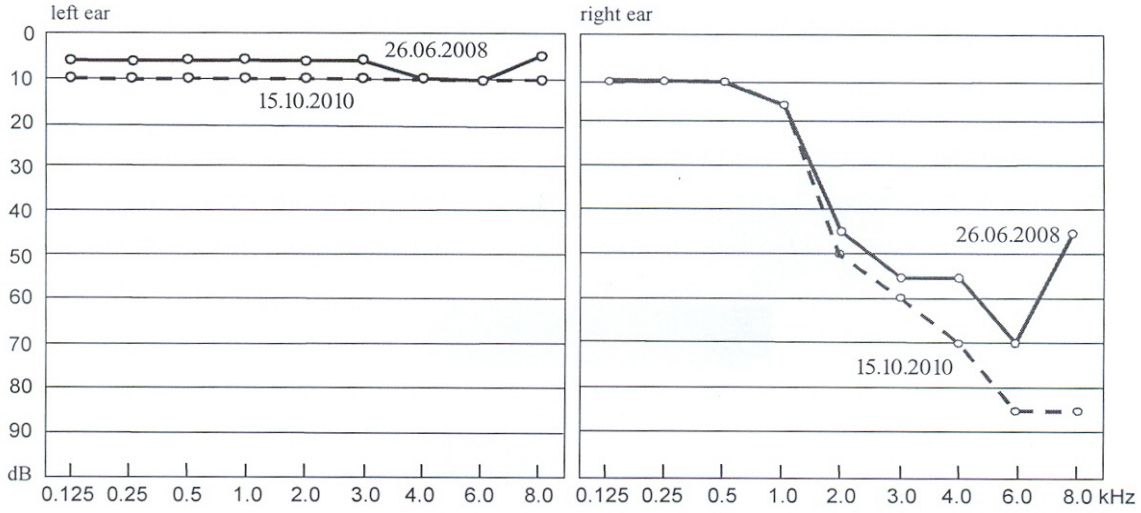

Fig. 1. Hearing thresholds (dB nHL) of K.M. in left normal and right AN ears at different sound frequencies (kHz) at two consecutive investigation days (26.06.2008 and 15.10.2010)

At the second PTA inspection, carried out two years and four months later of the first one, auditory thresholds in the left ear remained within the normal limits, although were worsened by 5 dB, i.e. extended up to 10 dB nHL at most frequencies tested, 0.125, 0.25, 0.5, 1, 2, and 8 kHz (Fig. 1). The thresholds remained the same, 10 dB nHL, at two frequencies only, 4 and 6 kHz. On the right ear, previous SNHL indices demonstrated further growths. The thresholds at the involved frequencies, 2, 3, 4, 6, and 8 kHz, now equaled 50, 60, 70, 85, and 85 dB, respectively (Fig. 1). At the second vs. first PTA probe they were additionally shifted thus within the whole impaired frequency range while the differences regularly accelerated upward, the gaps between two examinations being 5, 5, 15, 15, and 40 dB at 2-, 3-, 4-, 6-, and 8-kHz frequencies, respectively.

The data of the most applied ENG trials were within the normal boarders. No spontaneous, gaze, or positional nystagmus has been observed while horizontal saccadic movements similarly demonstrated standard patterns, latencies, and velocities. No feature of central vestibular dysfunction has been also noted under eye-tracking and optokinetic tests. Correspondingly, the Dix-Hallpike maneuver as well as the side-rolling probe did not reveal any signs of canalo- or cupulolithiasis either with left or right ear. Obvious abnormalities occurred under bithermal caloric irrigations only (Fig. 2). Calculating the slow component velocity, a noticeable interaural difference was documented in magnitudes of caloric reactions registered. The vestibular weakness was in particular evident under caloric influence on right AN vs. left normal ear, the deviation between amounting to 55% on the mean.

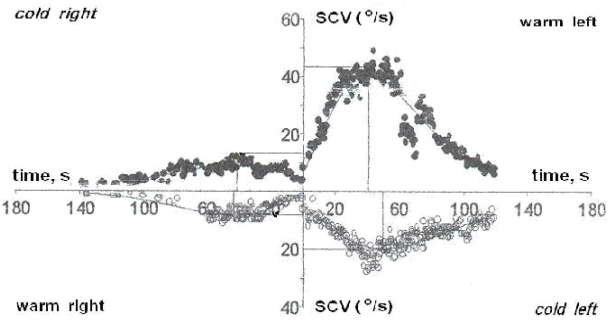

Fig. 2. ENGs recorded in K.M. under irrigation of right AN and left normal ears (left and right halves of the drawing, respectively) with warm and cold waters (44°C and 30°C, respectively). Time (seconds, s) after the onset of irrigation and slow component velocity (SCV°/s) of nystagmic eye reactions are presented on horizontal and vertical axes, respectively

Under stimulation of the intact left ear, ABR IPIs I-III, III-V, and I-V equaled 2100, 1730, and 3830 μs, respectively (Fig. 3). All three IPIs appeared normal as far as fell within the borders of 99% TLs calculated in a group of normally hearing healthy subjects (Table).

Under stimulation of the affected right ear, on the opposite, IPIs possessed greater values. From those, only IPI I-III, 2330 μs, still remained within 99% TL of the norm, 2549 μs, while IPIs III-V and I-V amounted to 2670 and 5000 μs, respectively, and significantly surpassed 99% TLs in a healthy group, 2308 and 4668 μs, respectively. Due to IPI lengthening of ABRs registered under stimulation of the right

ear selectively, interaural IPI differences demonstrated enlargements. Right/left gaps of IPIs I-III, III-V, and I-V equaled 230, 940, and 1170 μs, respectively, while IPI I-III coincided with and IPIs III-V and I-V apparently exceeded 99% TLs of those in healthy subjects, 230, 220, and 220 μs, respectively (Table).

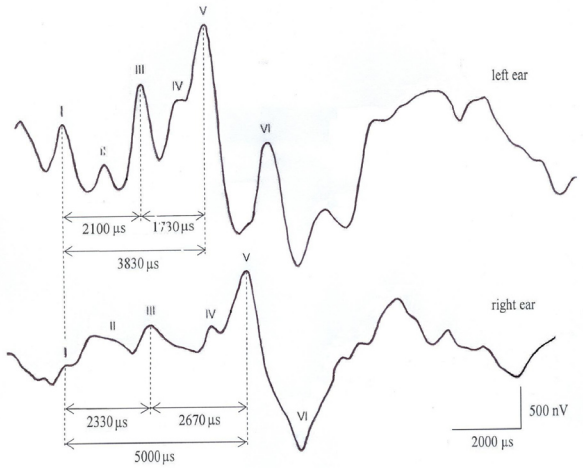

Fig. 3. ABRs recorded in K.M. under stimulation of left normal and right AN ears (upper and lower traces, respectively). The peaks of Wave I of both ABRs are adjusted to each other to promote interaural IPI matching

Table. IPIs I-III, III-V and I-V of ABRs registered in K.M. under stimulation of left normal and right AN ears and interaural (right/left) difference of IPIs I-III, III-V and I-V (in μs). Below individual K.M. data, 99% TLs of the respective measures in a group of healthly subjects are presented

	I-III	**III-IV**	**I-V**
Left normal ear	2100	1730	3830
Right AN ear	2330	*2670*	*5000*
99% TL	2549	2308	4668
Interaural (right/left) difference	230	*940*	*1170*
99% TL	230	220	220

Individual IPIs and interaural differences of IPIs in K.M., exceeding 99% TLs in the control group. Are presentede in italics

In contrasting MRI scan, the left half of the head appeared normal while a distinct 8-11-mm AN mass of a rectangular oblong configuration was evident within the right temporal bone (Fig. 4). The AN seemed to protrude into the cerebellopontine angle through the inner auditory meatus, although without invasion either in cerebellum or brainstem. Considering the noted characteristics, the detected AN had been classified as of the second grade.

Asymmetrical SNHL that being evident in the described case is a conventional AN feature. The asymmetry is generally defined as an interaural threshold difference exceeding 15 dB at a single frequency or 10 dB at two and more neighbor frequencies within 0.25-8.0-kHz range [12]. Three principal mechanisms appear to exist responsible for hearing disorders in ANs: 8th nerve destruction by tumor pressure or invasion, labyrinth ischemia due to blood supply deficits, and biochemical degradation of receptors and/or neural units [13]. The hearing disturbance in AN cases starts usually from high frequencies and invades gradually middle and then low frequencies also. The reason for initially and preferentended for high frequencies, are disseminated superficially, just around the nerve trunk, while those from the middle and apical turns, tuned to middle and low frequencies, respectively, are consolidated centrally, within the core segment of the conductive bulk. As far as the AN is originated from the schwann layer cells (cf. Introduction), the tumor exerts immediate pressure effects on neighbor fibers located on the periphery, around the nerve bundle while destined for perception just of high frequencies. Central fibers, responsible for the receipt of middle- and low-frequencies, are subjected to the later and weaker tumor effects just under the further AN growth. In the rare AN occasions, due to local blood circulation disturbances in middle and/

or apical cochlear turns, hearing loss can primarily invade middle and/or low frequencies, respectively. PTA curves in these cases possess correspondingly a mid-shaped or an ascending/upgrade but not a descending/downfall character, the latter being typical for most ANs.

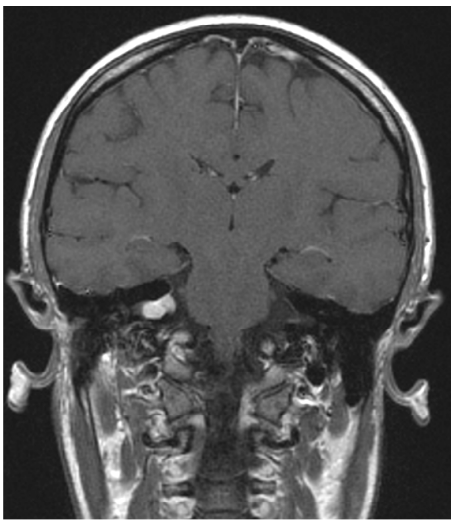

Fig. 4. Coronal MRI brain scan of K.M. Within the right temporal bone (on the left of the scan) AN is visible as a rectangular prolonged whiteness

Because of predominantly unilateral being of ANs (cf. Introduction), the resultant SNHL primarily involves the tumor side. In later stages, hearing dysfunction can occur on the non-AN side too. Contralateral problems are evidently caused by the brainstem shift due to AN growth and subsequent pressure rise within the ventricles (cf. [3,4]). Slight but regular elevation of hearing thresholds on the non-AN ear happened at later vs. earlier PTA testing in the described case (Fig. 1). It can be attributed just to the brainstem shift and the successive pressure effects.

In large majority of AN cases, obvious hearing impairment on an AN side is escorted thus either by normal hearing or slight/moderate hypofunction contralaterally. SNHLs are therefore mostly of a unilateral/asymmetrical type. From the general population of subjects with such SNHLs about 5% have been estimated to suffer just from ANs [1]. Asymmetry at 4-kHz frequency component appears the particular AN feature [14]. Taking into account the knowledge above, in authors' institution all patients with unilateral/asymmetrical SNHLs are insistently asked for AN diagnostic procedures. Agreements were got and ABR technique was utilized in all cases while in many later instances ENG recordings were also employed for the double checking of hearing disproportion causes.

Conventional PTA has to apply thus initially when starting AN detecting service. If revealing unilateral/asymmetrical SNHL, other tests, particularly ENG and ABR, have to utilize. It should be noted nevertheless that the normal PTA does not necessarily decline AN existence, particularly at initial tumor stages. Under tinnitus and/or vertigo complaints, even normal PTA data should not dissuade therefore the investigator from an employment of appropriate diagnostic tools, e.g. of ENG and ABR, for a strict AN examining.

Apart from hearing disturbances, AN patients frequently suffer from vertigo/spinning and disequilibrium/nausea/vomiting, the typical adjuncts of vestibular pathologies. Despite AN origin preferentially from vestibular branch of the 8th nerve (cf. Introduction), vertigo is differentiated in about 20% of tumor cases only. It mostly supplements ANs of restricted sizes. Posture unsteadiness occurs more often, in about 70% of ANs, particularly of greater dimensions. By the accurate ENG examining, horizontal nystagmus can be detected at initial AN stages already. Vertical nystagmus, on the other hand, is manly coupled with ANs of later stages exerting compressive influences on the brainstem. Greater ANs, in general, create global ENG confusions: failures in suppression of gaze fixation, slowing of optokinetic nystagmus, saccadic pursuits, spontaneous nystagmus, etc.

The bithermal caloric probe seems to be the most efficient ENG test for AN diagnosis [9]. Vestibular caloric reactions are reduced significantly on an AN side while in about 60% of cases are eliminated totally [2]. Under caloric irrigations, horizontal vestibular canals are activated selectively. These canals are innervated by the superior vestibular nerve. Lessened caloric reactions follow therefore the compression just of this vestibular limb. When ANs invade not superior but inferior vestibular or cochlear nerve, caloric irritations can fail to give an abnormal reaction. Generally, thus, a normal caloric response does not necessarily rule out the AN existence.

The method of registration of averaged ABRs is an approved mean for AN detection [3,4,10,15]. Due

to high costs of MRI, the cheaper ABR technique should be advocated as an initial effective approach for AN screening. ABR results are considered to be indicative of retrocochlear disorders when IPIs and/or interaural differences of IPIs of registered waveforms exceed the boarders calculated under appropriate methodical conditions in healthy individuals. An absolute Wave V peak-latency shift and/or interaural Wave V peak-latency gap exceeding normal limits are also considered as characteristic AN features [15]. Own experience (cf. [3]) indicates however that both absolute as well as interaural Wave V peak-latency indices are valid far not in all AN cases.

Calculation of amplitude ratio between Waves I and V has been introduced also in AN diagnosis [3-5]. Under proper arrangement of band-pass filters of ABR registration system, the amplitude of Wave I lags behind that of Wave V. In AN patients due to the selective diminution just of the later retrocochlear rather than the earlier intracochlear ABR constituents, I/V amplitude ratio rises up. High variability of ABR magnitudes is however a serious obstacle for a reliable I/V ratio measuring. To negotiate the interference, cross-summation of proper separate averaged ABRs has been instructed to perform in respective diagnostic trials [3]. Conventionally, estimated ABR averages represent 1000, 2000 individual responses. The cross-summated waveforms, instead, can mirror 4000, 6000, 8000, 16000 averages. Cross-summation positively balances therefore the ABR variability and promotes the reaching of genuine magnitude as well as temporal response indices.

In dubious ABR recordings, application of slower stimulation rates, e.g. of 5/s, instead of faster standards, e.g. of 10/s, is also considered as a helpful maneuver for improvement of response designs and proper parameter estimations thus [5]. Because of brainstem distresses due to tumor actions, in many extended AN cases ABR recovery function is retarded and response restoration time is lengthened consequently. By that reason, under conventional stimulation rate ABR recordings can be doubtful. Application of slower rates is a constructive approach in such occasions. Under slower rates, ABR recovery cycle is completed and higher response magnitudes and better signal-to-noise ratios are reached thus. In the described case ABR designations met no serous problems. That was a reason for utilization of the fast repetition rate, 11/s, and of the limited averaging number, 2000. In some other cases of own experience, however, the required ABR quality was hard to attain. The problems demanded therefore utilization of slower stimulation rates and of greater averaging numbers (cf. [4]). Generally, difficulties in obtaining reliable ABR waveforms at routine stimulation rates and averaging numbers under slight/moderate SNHLs or under even normal PTA are suspicious for brainstem involvements, e.g. for advanced ANs, influencing just the brainstem, and, especially, for intrinsic neurological disorders, e.g. for multiple sclerosis [4,5].

ABR sensitivity in AN diagnosis has been denoted to reach 90% [11]. Efficacy of the method is judged thus as being impressive but not absolute. Long-term own practice proves however that under proper ABR recordings and reliable component designations and parameter estimations the validity of the test in detecting of retrocochlear processes matches the absolute identification score, 100%. The positive evidence of ANs by ENG/ABR should be confirmed and detailed by MRI, carried out under application of contrasting material, e.g. of Gadolinium as in the described case.

Generally, neither diagnostic tool, except MRI, possesses both maximal sensitivity and perfect specificity in AN diagnosis. Only contrasting MRI is capable to verify AN regularly while to offer simultaneously proper information regarding the tumor location and dimensions. If thus by three relalow-cost diagnostic procedures, PTA, ENG, and ABR, the retrocochlear pathology is screened positively, more expensive MRI technique should be applied for detailing of the pathology and elaboration of the strategy of surgical intervention. Under negative ENG and ABR outcomes, on the other hand, MRI performance seems generally as a hardly urgent task.

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SUMMARY

ACOUSTIC NEUROMA DIAGNOSIS

Kharkheli[1] E., Shurigina[1] L., Davitashvili[1] O., Tushishvili[1] M., Chibalashvili[1] N., Korteweg[2] M., Kevanishvili[1] Z.

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Pure tone audiometry, PTA, has been regarded as an initial step when starting acoustic neuroma, AN, diagnostic service. If observing unilateral/asymmetrical sensorineural hearing loss, electronystagmography, ENG, and registration of auditory brainstem responses, ABRs, are instructed to perform. The measures of the methods are listed appearing particularly effective for AN detecting. Efficacy of ENG and ABR approaches in verification of ANs of even initial stages has been stated to reach the absolute identification score, 100%. In tinnitus and/or vertigo complaints, ENG and ABR examinations are recommended to utilize under normal PTA even. The positive evidence of ANs via ENG and ABR has to validate by contrasting magnetic resonance imaging, MRI, while MRI data are advised to utilize for assessment of concrete strategy of surgical intervention. Under negative ENG and ABR outcomes, on the other hand, MRI is considered as a hardly urgent procedure.

Key words: acoustic neuroma; diagnostic tools; pure tone audiometry; asymmetrical sensorineural hearing loss; electronystagmography; auditory brainstem response; magnetic resonance imaging.

РЕЗЮМЕ

ДИАГНОСТИКА АКУСТИЧЕСКИХ НЕВРОМ

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Тональная аудиометрия считается стартовой процедурой при начале мер по детекции

акустических невром (АН). При выявлении асимметрической сенсоневральной тугоухости рекомендуется провести компьютерную электронистагмографию (ЭНГ) и исследование по компьютерным записям слуховых стволомозговых ответов (ССО). Эффективность оперативных и относительно недорогих ЭНГ и ССО методов считается абсолютной даже при АН начальных стадий. При ушных шумах и/или головокружении, к ЭНГ и ССО исследованиям рекомендуется прибегнуть даже при нормальных аудиометрических данных. При позитивных результатах ЭНГ и ССО, по контрастной магнитной резонансной томографии (МРТ), оценивается патологический процесс и конкретизируется хирургическая стратегия. При негативных результатах ЭНГ и ССО проведение МРТ считается необязательным.

რეზიუმე

აკუსტიკური ნევრომის დიაგნოსტიკა

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აკუსტიკური ნევრომის საწყის სადიაგნოსტიკო ტესტად ტონალური აუდიომეტრია სახელდება. ასიმეტრიული სენსონევრალური სმენაჩლუნგობის გამოვლინებისას რეკომენდებულია ელექტრონისტაგმოგრაფიის (ენგ) და ტვინის ღეროს სმენის პასუხის (ტღსპ) კომპიუტერული რეგისტრაციის მეთოდების გამოყენება. შედარებით იაფი და ოპერატიული ენგ-ის და ტღსპ-ის რეგისტრაციის მეთოდების მგძნობელობა საწყისი სტადიის ნევრომების შემთხვევებშიც კი აბსოლუტურად მიიჩნევა. ყურში ხმაურისას და/ან თავბრუხვევისას ორივე ტესტის გამოყენება ნორმალური აუდიომეტრიული სურათის პირობებშიც ცხადდება მიზანშეწონილად. ენგ-ის და ტღსპ-ის მეთოდებით ნევრომის ვერიფიცირებისას კონტრასტული მაგნიტური რეზონანსული ტომოგრაფიით პათოლოგია და ქირურგიული ჩარევის კონკრეტული სტრატეგია განისაზღვრება. ენგ-ის და ტღსპ-ის უარყოფითი მონაცემების შემთხვევაში, პირიქით,ტომოგრაფიის ჩატარება აუცილებლად არ ითვლება.

PECULIARITIES OF THE ANATOMO-MORPHOLOGICAL PARAMETERS OF TEETH AND ROOT CANALS IN PERMANENT DENTITION IN GEORGIAN POPULATION

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The elaboration of the novel methods of endodontic treatment and effective application of them in practice is one of the topical issues of present-day dentistry[1,3]. Endodont [2] mainly stays beyond the dentist's sight. Even the radiography on inner structure of the tooth gives the picture of only organic structure. For this very reason, much effort and energy have been invested in research into the normal anatomy of teeth [4].

In the daily practice of endodontics we can single out various factors causing unsuccessful treatment: among them in the first place is insufficient knowledge of complex anatomy of the tooth cavity. The exact knowledge of the anatomy of tooth cavity is first of all associated with the perception of pulp chamber. It is different configurations of the cavities that provide the uniqueness of each tooth.

Numerous researches in the course of years have created the awareness of the complexity of the structure (form) of the system. The first detailed systematic description of root canal anatomy found in the literature is by Carabelli (1844). The data of inner anatomical description of the tooth studied by Carabelli which have been obtained in different planes of longitudinal and transverse sections are used even today in contemporary literature [3]. The complicated system of tooth canals is represented mainly by magistral canals and accessory lateral canals, deltas, apical ramifications. The magistral canal, as a rule, is located in the centre of the root and accessory (lateral) canals are located at various levels of the root length. There are numerous transverse anastomoses between the canals [4,5,11].

That canal is considered magistral which starts from the bottom of pulp cavity, is directed along the whole length of the canal and is opened at apical foramen [6]. Of special attention are the researches conducted by Meyer in the years between 1955 and 1970 [4]. It is by his researches that the complicated structure of the root canals was established and he was the first who introduced the term "system', and the first data "of the root canal system" on different configuration appeared.

Endodont [2,4] consists of *cavum dentis* in which pulpa dentis is located. It is divided into crown and canal parts. The crown part is located in crown cavity (*cavum coronare*) – canal pulp in *canalis radicis dentis*. The *cavum dentis* is a spacious cavity and in tooth crown part in main cases repeats the crown form of the tooth. Along with the age the pulp cavity is reducing, against the background of caries process, abrasion or restoration treatment takes different form [4]. The canals around the root tip are ended with apical foramen (foramen *apicis dentis*). An ideal endodontic cavity can be described as a round, equally narrowed space from coronal cavity up to the narrow apical foramen [1,2,3].

Tooth canal in transversal section is of rather complex structure; it can have different shapes such as oval circle, fissured or eight curve. The tooth roots are frequently narrowed mezio-distally and in vestibular-oral direction "narrowed" canals are found in single cases [4,5].

According to numerous studies an ideal mechanical processing of tooth canals is practically impossible. This view is justified by the fact that the canals represent the system of complex, branched, and connected with each other spaces. The tooth groups differ from each other by shape, size and length. Various researches laid the foundations to anatomo-morphological peculiarities of tooth roots, their systematization, and nomenclature indices. The "norms" of the tooth anatomical picture, form, the root length have determined in the course of years. Multiple statistical data laid the foundations to the establishment of the average index of the tooth root length, "norm", morphological difference, deviation from the norm.

For this purpose the researchers conducted racial studies. In 1902 GV Black emphasized the importance of the acquirement of knowledge of the details of specific forms of human teeth. Since Blacks time extensive research has been carried out in the field of dental anatomy. As early as in 1925 Hess indicated that of 513 molar models of the upper jaw 54% was 4 -canal. This supposition has been disputable for many years and did not correspond to the criteria of that time "norm". However, the fourth canal cannot be excluded and ignored. This fact might become the reason of the failure in endodontic treatment. In 1992 Ferrazz investigated anatomical peculiarities of the tooth and changes by race line. Based on the same methods Matzer (1993) studied and published the data of Gvatemala population. Mandibular canines were examined and in 4.1% of the total number was marked as deviation from the "norm", i.e. two rooted canines.

The researches conducted by Kim E., Fallahrastegar A. et. al in 1995-2001 deserve special consideration. The investigation was based on morphological study of tooth, namely the establishment of root lengths in populations with Asian and Caucasian background [11].

The purpose of the study was to establish whether there was or not the difference between the average indices of canal length on the basis of racial features, namely between Asian and Caucasian population. General methodology of study was employed. A total

of 515 patients, the Asians who undergone endodontic treatment at Yonsei University Hospital, Korea from 1995 including 2001 and a total of 324 patients of Caucasian background who undergone endodontic treatment on the base of Pennsylvania University (US). Clinical-endodontic procedures in both clinics were carried out in agreement using the similar method. The results were summarized and by the obtained data the lengths of tooth root in Asians and Caucasians fluctuated within 0.5-2.5 mm (1.2 mm in average). The root lengths of Asian patients were less (in some mm) than those of the Caucasians. The well-expressed difference was revealed in the lengths of the tooth root, in first molar of the upper jaw, low second molars and in the second premolars of the upper jaw [11].

In 2004 the investigation was carried out in Turkey on a national scale [9]. Morphological peculiarities of permanent teeth were researched. With this respect interesting researches were conducted in Arabic, Indian, Korean populations. In recent years we often see the investigations conducted in various countries which manifest endodontic parameters in the existed populations [9-11].

Statistical indices do not represent universal criteria because anthropometric data of the roots and canals are subjected to variations according to nationality and geographical zones. But the data obtained through each research - endodontic parameters, knowledge of morphological or anatomical peculiarities are important to carry the endodontic treatment successfully [1].

The object of our research is to establish the anatomo-morphological peculiarities of roots and canals of tooth groups within Georgian population and to elaborate reliable statistical indices on the basis of the obtained anthropological and clinical data. The obtained data will help to increase the efficiency of endodontic treatment and to avoid further after-effect of filling.

The study conducted by us is based on both laboratory (*ex vitro*) and clinical (*in vitro*) methods of investigation and hence, the use of clinical and experimental material. Laboratory study has been mainly carried out on the extracted teeth caused by different reasons. (The grouping of the teeth does not occur on the basis of gender and age-related data). The research material is collected from Tbilisi city and other regions of Georgia: Kvemo Kartli, Shida Kartli, Imereti, Samegrelo, Achara, Svaneti, Racha, etc.

Extracted teeth are irrigated at place by our indication with running cold water and placed in 95% alcohol. After transportation the cleaning of the teeth occurs by means of curette from solid and soft masses and is placed in 5% sodium hypochlorite solution for 24 hours and then irrigated in running water. From the studied group were excluded the teeth marked with immature apices, resorbed apexes, those with pathological rubbing, with large scale defect of the crown, wisdom (the eights) teeth. Currently topological measurements have been performed on 271 investigated extracted teeth and the registration of the data is taking place.

The measurement of the root length is taken using special Digital Pakimetter (Vorel, Poland) (fig. 1). The measurement is taken between reference points of the tooth – from the highest point of the crown (incisal edge or occlusal surface) to the apex.

Fig. 1. Digital Pakimetter(Vorel, Poland)

The obtained data are registered as index of TL-tooth length. To study morphological parameters of root canal system of the studied material (teeth) is performed – intracoronal preparation. After finding the canal entrances, the endodontic file #10 is placed into the root canal until the tip of the file is just visible at the apical foramen. After this, the file is withdrawn by 0.5 mm (or by deduction we diminish 0.5 mm), the stopper is fixed on cutting edges and the obtained data are measured with endodontic ruler. The 0.5-1 mm is those safety zones where the narrowest section of the canal physiological apex or the section of cement-dentin junction is located. The obtained data were registered

as working length (WL). By comparison of these two indices (WL and TL) we obtain the difference which fluctuates within 0.3-1.2 mm in the teeth of different groups.

Clinical investigation has been carried out on the base of Dental Clinic, Training and Research Center "Unident". For those patients who need endodontic treatment a special medical map has been created with criteria which represent the object of our research, namely, patient's age, sex, tooth formula, diagnosis the number of roots and canals, working length of the canal, the ultimate point of obturation (physiological or anatomical apex), type of configuration, etc. The determination of working length of the canal was performed by radiographic method (visiograph X-genus, Italy) (fig. 2) and electrometric method (Apex-locator,C-Root v. Coxo.China) (fig. 3). For today there has been described about 452 endodontic parameters of the treated teeth.

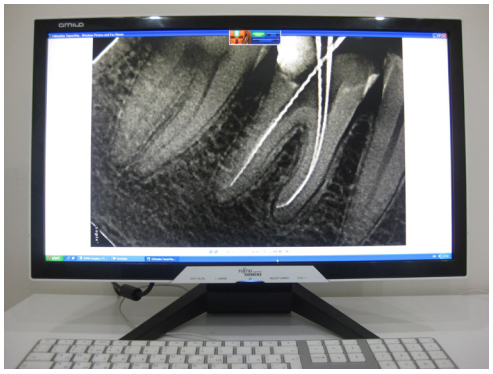

Fig. 2. Visiograph X-genus, Italy

Fig. 3. Apex-locator,C-Root v. Coxo, China

Radiographic method described by Ingle is one of the most common and reliable methods used in determination the working length. However, the accuracy is difficult to achieve using this technique because the apical constriction cannot be identified [2,3]. Determining the length by this method, we encounter an obstacle of laterally situated foramina, when radiographic and anatomical apices do not coincide with each other (fig. 4) [5].

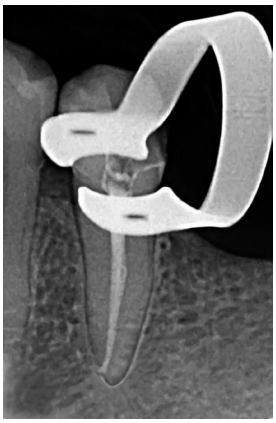

Fig. 4. Laterally situated foramina

For the accuracy of the data the research was performed using the apex locator (Fig.3). This method of the determination of root canals length is considered most reliable, easy and rapid [2,7,8]. However, its accuracy depends on electrical condition of the canal. The apex locator is used in already formed teeth. In case of the immature apices (young tooth), root resorption and the existence of calcification the application of this method is restricted (for the purpose of avoiding the inaccuracy).The comparison of this method with that of radiographic solves lots of problems and the obtained data are rather reliable and accurate[2,3,7].

When it concerns the indices of endodontic length, we should differentiate from each other the following notions: "tooth length" and "working length of the canal". The "tooth length" is the distance determined from coronal point up to the anatomical apex. And "working length" of the canal is called the distance from any orientation point of the tooth crown (incisal edge or occlusial surface) up to the physiological apex. Due to the fact that an exact determination of physiological and anatomical apices location radiographically (visiographically) is difficult, the tooth length is measured *(in vivo)* as a distance from the highest point of the crown (incisal edge or occlusal surface), up to radiographic apex [4,5].

There are differentiated various methods and means of determination of working length. Among them one of the recognized, attested significant method

is "mathematical" with average calculations, data given in the form of tables the so-called "tabular procedure" offered by the researches and is known average lengths of teeth in various groups. Currently we use the tables and length indices offered by different authors. The difference between the data given in these tables varies within 3-5 mm on average.

The results of the investigation of 723 teeth are reported in table.

Table. Morphology of the root canal system and access guidelines, tooth by tooth considerations: external anatomy-crown/root ;Number of roots/canals ;Lateral/accessory canals

Group of Teeth	Maxilary		Mandibular	
	Average length	Morphology	Average length	Morphology
central incisor	23,0	1 root 1 canal 100%	20,5	one root – 1canal 73% 2canals/1 foramen- 27%
lateral incisor	21,5	1 root 1 canal 100%	21	one root – 1canal -69% 2canals/1 foramen- 31%
canine	26	1root 1canal 100%	24	one root – 1canal 78% 2canals/1 foramen 21% two roots – 2 canals -1%
first premolar	20,5	one root -39% two root - 59% three root- 2%	21,5	one root - 1canal 75% 2canals - 24% two roots – 2 canals -1%
second premolar	21,5	one root -48% two root -24% three root - 27%	22	one root – 1 canal 96% 2 canals -4%
first molar	21,5	three root /three canals- 64% three root /four canals - 30%	21,5	two roots /3 canals-54% two roots /4 canals - 33% two roots / 2 canals - 3%
second molar	20	three root /three canals 74% three root /four canals -24%	19,5	two roots /3 canals -77% two roots /4 canals - 19% two roots / 2 canals – 4%

There is no doubt that endodontic treatment of full value can be attained by means of qualitative medico-instrumental processing of tooth canals and reliable obturation. The above mentioned is impossible without knowledge of tooth root length and anatomo-morpholoogical peculiarities. Recent research has improved the knowledge and understanding of the morphology of the roots of all teeth, and root canal anatomy in Georgian population.

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SUMMARY

PECULIARITIES OF THE ANATOMO-MORPHOLOGICAL PARAMETERS OF TEETH AND ROOT CANALS IN PERMANENT DENTITION IN GEORGIAN POPULATION

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One of the main reasons that cause the failure of endodontic treatment is the lack of knowledge of complex anatomy of the tooth cavity. Numerous studies over the years have established a complex structure of the tooth root system, a particular configuration of which determines the uniqueness of each tooth.Numerous researches have laid the foundation for anatomical and morphological peculiarities of root system of the tooth, their classification and nomenclature indices. The anatomical picture of the tooth, its shape, root length - the "norms" have been established in the course of years. Statistical indices do not represent universal criteria due to the fact that anthropometric data are subjected to variations in accordance with national and geographic zones.

The aim of our study is to establish anatomo-morphological peculiarities of the groups of teeth, roots and canals in Georgian population and to develop statistically reliable indicators on the basis of anthropological and clinical data. The obtained data will help to improve the effective endodontic treatment and avoid complications after obturation.

Key words: Georgian population, anatomo-morphological parameters of teeth and root canals.

РЕЗЮМЕ

АНАТОМО-МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ПАРАМЕТРОВ ЗУБОВ И КОРНЕВЫХ КАНАЛОВ В ПОСТОЯННОМ ПРИКУСЕ СРЕДИ НАСЕЛЕНИЯ ГРУЗИИ

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Одним из важнейших факторов неудачного лечения в эндотонтической практике является недостаточное знание комплексной анатомии полости зуба. Многочисленные исследования на протяжении многих лет установили сложное строение корневой системы зубов, особенная конфигурация которых обуславливает уникальность каждого зуба.

Многочисленные исследования заложили основу анатомо-морфологическим особенностям корневой системы зубов, их систематизации и номенклатурным показателям. На протяжении многих лет устанавливалась анатомическая картина зубов, формы, длина корней, т.н. «нормы», устанавливались среднестатистические показатели. Статистические показатели не являются универсальными критериями, так как антропометрические показатели корней и каналов зубов подвержены вариациям в зависимости от национальных и географических зон.

Целью нашего исследования явилось установ-

ление анатомо-морфологических особенностей групп зубов, корней и каналов зубов среди населения Грузии и на основе антропологических и клинических данных выработать статистически достоверные показатели. Установленные показатели позволяют увеличить эффективность эндодонтического лечения и избежать развитие осложнений после пломбирования.

რეზიუმე

მუდმივ თანკბილვაში კბილის და ფესვის არხთა ანატომო-მორფოლოგიური პარამეტრების თავისებურებანი საქართველოს მოსახლეობაში

ნ. ჭიპაშვილი[1], ე. ბეშკენაძე[2]

[1]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, ოდონტოლოგიის დეპარტემენტი; [2]სტომატოლოგიის კლინიკა და სასწავლო-კვლევითი ცენტრი "უნიდენტი"

ენდოდონტიურ პრაქტიკაში წარუმატებელი მკურნალობის ერთერთი მნიშვნელოვანი ფაქტორს, კბილის ღრუს კომპლექსური ანატომიის არასათანადო ცოდნა წარმოადგენს. მრავლობითმა კვლევებმა წლების განმავლობაში დაამტკიცა კბილის არხთა სისტემის რთული აღნაგობა, რომელთა განსხავებული კონფიგურაციები განაპირობებს თითოეული კბილის უნიკალობას.

მრავალი კვლევა საფუძვლად დაედო კბილის ფესვების ანატომიურ და მორფოლოგიურ თავისებურებების, მათ სისტემატიზაციასა და ნომენკლატურული მაჩვენებლების დადგენას. წლების განმავლობაში დგინდებოდა კბილის ანატომიური სურათის, ფორმის, ფესვის სიგრძის - "ნორმები" და საშუალო სტატისტიკური მაჩვენებლები. სტატისტიკური მაჩვენებლები არ წარმოადგენენ უნივერსალურ კრიტერიუმებს,რადგან ფესვების და არხების ანტროპომეტრიული მონაცემები ეროვნების და გეოგრაფიული ზონების მიხედვით განიცდიამნ ვარიაციებს.

ჩვენი კვლევის შედეგად მიღებული წინასწარი მონაცემები საშუალებას გვაძლევს საქართველოს მოსახლეობაში კბილთა ჯგუფების, ფესვების და არხების ანატომიურ- მორფოლოგიური თავისებურებები და მოპო-ვებული ანტროპოლოგიური და კლინიკური მონაცემების საფუძველზე შემუშავდეს სარწმუნო სტატისტიკური მაჩვენებლები, რაც უზრუნველჰყოფს ენდოდონტიური მკურნალობის ეფექტურობის გაზრდას და დაბუნის შემდგომი გართულებების თავიდან აცილებას.

НОВЫЕ ВОЗМОЖНОСТИ ЭЛИМИНАЦИИ ВИРУСА ПАПИЛЛОМЫ ЧЕЛОВЕКА ИЗ ОРГАНИЗМА

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Проблема папилломавирусной инфекции (ПВИ) приобрела особую значимость в связи с высокой контагиозностью, широкой распространенностью и онкогенным потенциалом возбудителя инфекции - вируса папилломы человека (ВПЧ) [1,5]. Характерной особенностью данной патологии является поражение больных в молодом возрасте: максимальная заболеваемость ПВИ регистрируется в возрасте от 15 до 30 лет. Описано более 100 серотипов ВПЧ, из них около 30 пора-

жают аногенитальную область. Выделяют типы ВПЧ низкого онкогенного риска [6,11], которые обычно ассоциированы с доброкачественными экзофитными аногенитальными бородавками, тогда как ВПЧ высокого онкогенного риска обнаруживаются в 95-100% случаев рака шейки матки [2,6,8]. Большое количество методов лечения ПВИ (деструктивные, цитотоксические, иммунологические, комбинированные) в целом способствуют решению проблемы генитальной ПВИ, однако частота рецидивов после проведенной терапии остается высокой (30-70%), что диктует необходимость всестороннего изучения патогенеза и поиска новых эффективных методов профилактики и терапии данного заболевания [4,7]. В настоящее время установлено, что резистентность генитальной ПВИ к лечению во многом обусловлена иммунными нарушениями, на фоне которых ВПЧ переходит в персистентное состояние, длительное существование которого инициирует развитие вторичного иммунодефицита благодаря реализации своего иммуносупрессивного свойства. В основе ПВИ-индуцированной иммуносупрессии лежат особенности строения ВПЧ. Белки Е 6, Е 7 ВПЧ подавляют индукцию гена интерлейкина (ИЛ-18), играющего важную роль в формировании иммунного ответа с участием лимфоцитов CD 8, а также ингибируют экспрессию генов главного комплекса гистосовместимости; белок Е5 вызывает закисление среды в эндосомах, препятствуя процессу и эффективной презентации антигена дендритными клетками, а также связывается с ИЛ-18, блокируя индукцию γ-интерферона. Эти феномены рассматриваются как механизмы ускользания ВПЧ от влияния иммунной системы «хозяина» в условиях развивающейся инфекции. При таком многообразии механизма развития ПВИ успех лечения зависит от выбора «универсального» метода, действие которого объединяет этиотропный, патогенетический и симптоматический подходы, не вызывая при этом нежелательных побочных эффектов [9-11]. Именно всем этим требованиям отвечает препарат на основе продуктов растительного происхождения – индинол «Миракс Фарма» (Россия) [3].

Целью исследования явилось определение терапевтической эффективности препарата индинол в лечении больных рецидивирующей папилломавирусной инфекции гениталий как в форме монотерапии, так и в комплексе с локальным использованием инфракрасных лучей.

Материал и методы. Под наблюдением находились 70 пациентов в возрасте 23±1,2 года с клинической формой ПВИ гениталий, вызванной ВПЧ типов 6/11. После установления окончательного диагноза всем пациентам проводили лечение по общепринятым подходам: деструкция кондилом методом электрокоагуляции в комбинации с иммунотропной терапией, в том числе с использованием индукторов интерферона. Применение интерфероновых препаратов в течение одного месяца и более предусматривало использование неовира или циклоферона. В результате динамического наблюдения было установлено, что в 50% случаев (у 20 женщин и 15 мужчин) проведенная в течение 4-5 месяцев терапия не имела успеха: у пациентов возникали рецидивы заболевания. В дальнейшем эти пациенты были подразделены на 3 подгруппы, в зависимости от вновь назначенного лечения: пациентов I группы продолжали лечить по общепринятым схемам; во II группе больным дополнительно назначался индинол по 2 капсулы (200 мг) 2 раза в день в течение 90 дней, пациентам III группы одновременно с индинолом проводили локальное облучение инфракрасными лучами. Изучение иммунного статуса больных предусматривало определение содержания лимфоцитов CD 16 и показателей иммунорегуляторного индекса CD4/CD 8. В качестве искусственного источника инфракрасных лучей нами использован рефлектор Минина с обычной лампочкой 40-75 вт. Процедуры отпускались на кушетке в положении лежа или сидя - в зависимости от локализации патологического процесса. Рефлектор устанавливался на расстоянии 5-10 см, продолжительность процедуры 10-20 минут, ежедневно 1 раз в день.

У мужчин папилломы наиболее часто располагались на головке полового члена, венечной борозде и внутреннем листке крайней плоти, реже - вокруг наружного отверстия уретры, лишь в одном случае - в перианальной области. У женщин патологический процесс часто локализовался в области больших и малых половых губ и перианальной области, реже - во влагалище, на шейке матки и у наружного отверстия уретры. Сначала появлялись сгруппированные сосочковидные узелки диаметром до 3-5 мм, мягкой консистенции, телесного или бледно – розового цвета. По-

ражения увеличивались в размерах, превращаясь в дольчатые сосочковидные разрастания, чаще на узкой ножке (в случаях, если ранеее не подвергались криотерапии)

Результаты исследования статистически обрабатывались с применением критерия Пирсона.

Результаты и обсуждение. Как показали результаты исследования, включение индинола в общепринятую схему лечения оказало существенно положительное влияние на процесс выздоровления больных с резистентными формами остроконечных кондилом гениталий. Эффект препарата заключался в статистически значимом (в 3 раза) снижении частоты рецидивов заболевания при клинически выраженных формах заболевания. В течение первых 3 мес. от начала приема индинола рецидивы инфекции прекратились и в дальнейшие сроки наблюдения не отмечались у 75% больных с клинической формой заболевания (при 45% в группе сравнения), у остальных 25% в течение последующих 3 мес. регистрировалось по 1-2 рецидива (при 4-7 рецидивах у больных в группе сравнения). Рецидивы в группе больных, неполучавших индинол, возникали еще до окончания периода наблюдения – в течение одного года (таблица 1). Противорецидивный эффект индинола объясняется его ВПЧ-элиминирующим свойством. В настоящее время определены и продолжают изучаться механизмы действия индинола, которыми во многом объясняется клиническая эффективность препарата.

Таблица 1. Показатели эффективности комплексного лечения больных остроконечными кондиломами аногенитальной области

Период	**Число рецидивов**		
	I группа (n=11)	**II группа (n=12)**	**III группа (n=12)**
спустя 6 месяцев	12/67*	4/78*	3/56*
спустя один год	5/87*	-	-

** - статистически значимые различия (p<0,05)*

Индол-3-карбинол блокирует синтез белка Е7 ВПЧ, останавливает пролиферацию ВИЧ-инфицированных эпителиальных клеток, индуцирует их апоптоз, препятствуя фосфорилированию цитоплазматических белков-участников каскадной передачи, активируемой эпидермальным фактором роста, а также блокирует действие факторов роста и цитокинов, стимулирующих пролиферацию тканей. Динамика показателей активности иммунного статуса свидетельствует о более ранней и полной нормализации под влиянием комплексной терапии с применением индинола и инфракрасных лучей в сравнении с соответствующими значениями у пациентов в группе сравнения. При этом, наиболее значимые изменения претерпевали содержание лимфоцитов CD16 и показатели иммунорегуляторного индекса CD4/CD8, которые у пациентов, принимавших индинол, статистически значимо не отличались от нормы уже спустя 3 месяца от начала лечения (таблица 2).

Таблица 2. Изменения иммунного статуса больных остроконечными кондиломами аногенитальной области при комплексном лечении индинолом (M±m)

Параметры / **Группы**	**до лечения**		**спустя 6 месяцев от начала лечения**	
	CD16	CD4/CD8	**CD16**	CD4/CD8
доноры	0,28±0,02	1,62±0,09	-	-
I группа (n=11)	0,15±0,02*	0,75±0,11*	0,19±0,02*	1,1±0,10*
II группа (n=12)	0,14±0,02*	0,77±0,11*	0,26±0,02*	1,6±0,10*
III группа (n=12)	0,13±0,04*	0,76±0,10	0,25±0,02*	1,59±0,11*

** - статистически значимые различия (p<0,05, t-тест) по сравнению с соответствующими значениями показателей у доноров*

В группе больных, получавших наряду с индинолом сеансы светотерапии, вышеуказанные показатели иммунного статуса существенно не отличались от показателей во II группе больных. Таким образом, в комплексном лечении больных рецидивирующими клинически выраженными формами ПВИ гениталий, ассоциированными с ВПЧ типов 6/11, целесообразно использование индинола, проявляющего выраженные вирус-элиминирующий и противорецидивный эффек-

ты. Исходя из вышеизложенного, применение в клинической практике индинола - препарата с широким спектром противовирусного и противоопухолевого действия, является перспективным и необходимым для решения проблемы распространения и последствий вирусных урогенитальных инфекций, в частности, ПВИ генитальной локализации.

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SUMMARY

NEW POSSIBILITIES FOR ELIMINATION OF HUMAN PAPILLOMAVIRUS FROM THE ORGANISM

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TThe variety of mechanisms of human papillomavirus (HPV) infection suggests that the success of treatment depends on the choice of a universal method, which combines the actions of etiotropic, pathogenetic and symptomatic approaches, without causing unwanted side effect.

All these requirements are met by a drug based on the products of plant origin – Indinol.

The observed patients with resistant forms of genital warts were divided into 3 groups: first group received the treatment according to the standard, conventional scheme; patients of the second group in addition to the standard scheme 2 times a day (for 90 days) received 2 capsules of Indinol (200 mg) and the patients of third group simultaneously with Indinol undergo infrared irradiation.

The results of the observation have shown that the addition of Indinol to the standard treatment had a significant positive effect on the healing process of patients with resistant forms of genital warts. The effects of the Indinol in combination with infrared therapy revealed a statistically significant reduction (3 times) the frequency of relapses in cases of clinically sever forms of disease.

Thus, during combined treatment of patients with recurrent, clinically severe forms of genital HPV, it is advisable to use the Indinol, which evidently has the

well pronounced virus-eliminative and anti-recurrent actions.

Key words: human papillomavirus, Indinol, HPV elimination.

РЕЗЮМЕ

НОВЫЕ ВОЗМОЖНОСТИ ЭЛИМИНАЦИИ ВИРУСА ПАПИЛЛОМЫ ЧЕЛОВЕКА ИЗ ОРГАНИЗМА

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При многообразии механизма развития папилломавирусной инфекции успех лечения зависит от выбора универсального метода, действие которого объединяет этиотропный, патогенетический и симптоматический подходы, не вызывая при этом нежелательных побочных эффектов. Всем этим требованиям отвечает препарат на основе продуктов растительного происхождения – индинол «Миракс Фарма» (Россия). Наблюдаемые больные с резистентными формами остроконечных кондилом гениталий были подразделены на 3 группы: I группа получала лечение по общепринятым схемам, во II группе больным дополнительно назначался индинол по 2 капсулы (200 мг) 2 раза в день в течение 90 дней, пациентам III группы одновременно с индинолом проводили локальное облучение инфракрасными лучами. Как показали результаты исследования, включение в общепринятую схему лечения индинола оказало существенно положительное влияние на процесс выздоровления больных с резистентными формами остроконечных кондилом гениталий. Эффект препарата в сочетании с сеансами светотерапии заключался в статистически значимом (в 3 раза) снижении частоты рецидивов при клинически выраженных формах заболевания. Таким образом, в комплексном лечении больных рецидивирующими клинически выраженными формами ПВИ гениталий целесообразно использование индинола, проявляющего выраженные вирус-элиминирующий и противорецидивный эффекты.

რეზიუმე

ადამიანის პაპილომავირუსის ორგანიზმიდან ელიმინაციის ახალი შესაძლებლობები

ნ. ცისკარიშვილი, ლ. ნადარეიშვილი, ც. ცისკარიშვილი

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, დერმატოვენეროლოგიის დეპარტამენტი; ი. ჟორდანიას სახ. ადამიანის რეპროდუქციის სამეცნიერო-კვლევითი ინსტიტუტი, თბილისი, საქართველო

პაპილომავირუსული ინფექციის განვითარების მექანიზმის მრავალფეროვნებიდან გამომდინარე, მკურნალობის ეფექტურობას ისეთი უნივერსალური მეთოდის არჩევანი განსაზღვრავს, რომლის მოქმედება მოიცავს ეტიოტროპულ, პათოგენეზურ და სიმპტომურ მიდგომას, და, ამავე დროს არ იწვევს არასასურველ თანამოვლენებს. ზემოჩამოთვლილ ყველა მოთხოვნას პასუხობს მცენარეული წარმოშობის პრეპარატი – ინდინოლი. საზარდულის მახვილწვეტიანი კონდილომების რეზისტენტული ფორმებით დასნებოვნებული პაციენტები დავყავით სამ ჯგუფად: I ჯგუფი მკურნალობდა საყოველთაოდ მიღებული სქემის მიხედვით, მეორე ჯგუფში პაციენტებს დამატებით ენიშნებოდათ ინდინოლი: ორ-ორი კაფსულა 2-ჯერ დღეში 90 დღის განმავლობაში, მესამე ჯგუფის პაციენტებს კი ინდინოლთან ერთად ადგილობრივად უტარდებოდათ დასხივება ინფრაწითელი სხივებით. დადგინდა, რომ სა-ყოველთაოდ მიღებულ სამკურნალო სქემაში ინდინოლის ჩართვამ საზარდულის მახვილწვეტიანი კონდილომების რეზისტენტული ფორმებით დასნებოვნებული პაციენტების ჯანმრთელობა არსებითად გააუმჯობესა. პრეპარატის ეფექტურობა, ფოტოთერაპიის სეანსების შერწყმასთან, გამოიხატებოდა და-ავადების კლინიკურად გამოხატული ფორმების დროს რეციდივების სიხშირის სტატისტიკურად სარწმუნო შემცირებაში. აქედან გამომდინარე, საზარდულის პაპილომავირისული ინფექციის კლინიკურად გამოხატული მორეციდივე ფორმების კომლექსურ მკურნალობაში ვირუსმაელიმინირებელი და ანტირეციდივული მოქმედების მქონე პრეპარატ ინდინოლის გამოყენება მიზანშეწონილად მიგვაჩნია.

CHANGES IN COGNITIVE EVOKED POTENTIALS DURING NON PHARMACOLOGICAL TREATMENT IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER

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Attention deficit/hyperactivity disorder (ADHD) is one of the most widely spread condition of school aged children affecting 5% of children of this age [50]. Diagnosis of ADHD increased and the rate had risen to 3.4% and it continues to rise [38]. The core clinical signs of ADHD are inattention, restlessness and impulsivity. It is known that there are a numerous neurometric tools widely used for assessment of children with ADHD. According to various authors direct measures of attention are of two types [34]:

1. Recording the alpha rhythm on the EEG and event-related potentials (ERP);
2. Tests of reaction time, continuous performance tests, paired associated learning, and tests of memorization.

The last one is clinically proved and used in routine practice but as for the first one its validity is still ambiguous and has limited application in clinical practice especially of long latency event-related potentials (ERP). ERP studies is extremely important as it reflects multitude of cognitive factors such as attention, memory and language. Thus assessment of its components is very valuable in disorders accompanied with attention impairment including ADHD. The use of P3 for clinical assessment of various neurological diseases is recommended by International Federation of clinical neurophysiology [11]. ERP studies in ADHD started in 1970s with the work of Satterfield and his group [48].

ERP is recorded under certain conditions like using of certain modality stimulus. It is known that its latency increases as a categorization of the stimulus becomes more difficult [15,18,23] while others have reported that ERP latency remains unaffected by task difficulty [24]. The simplest way for auditory ERP to be recorded is during performing auditory oddball paradigm [27]. The core feature is to give series of stimuli with randomized consequence. Those stimuli used for recording of ERP are divided into two ways: non- target and target which has to be recognized by patient. The ERP response recorded during recognition of relatively rare target stimulus differs from others by morphology as it appears with positive wave within latency range of 300 ms. This wave is called P3.

The response on target stimulus can be divided into two ways:
1. Earlier response P1-N1-P2 connected to simple auditory stimulus.
2. Relatively later N2-P3-N3-complex related to cognition like recognition and differentiation of stimulus and decision making which patient can express by pushing the button when hearing and recognizing target stimulus.

The earlier component like N1 - a first discernible peak is a negativity around 80 ms with a frontocentral maximum present for both rare and frequent tones [11]. It generally thought to represent the initial extraction of information from sensory analysis of the stimulus [36] and represents the correct recognition of stimulus [6].

The most significant component of later response is P3. It is proposed that amplitude and latency of P3 reflect the extent and timing of a distribution-specific cognitive process, while scalp distribution is indicative of which cognitive process is activated during the performance of a task [17].

The P3 reflects multiple cognitive processes, specifically attentional resource allocation [12]. P3 amplitude is thought to be a reflection of effortfulness of the stimulus response and the intensity of processing whereas P3 latency is taken as a reflection of the speed of information processing [43]. The assessment of P3 is important in ADHD children for several reasons: The first it is known that most important aspect of executive functioning frequently affected in ADHD children is engagement operation [27]. This process from neurophysiologic point of view is associated with the activation of cortical and subcortical structures that are involved in execution of the selected action which is disturbed in ADHD children. From psychological, functional point of view the engagement operation is associated with combining all brain resources for the action to be accomplished [27]. This operation is manifested in the P3 components. And the second according to Desmedt and Debecker's hypothesis the occurrence of P3 corresponds to the termination of the decision-making process which is taking place during the categorization of the target stimulus [10].

There are several studies concerning clinical values of ERP in children with ADHD. In spite of enormous studies in this field the unified consensus about morphology and clinical value of P3 in ADHD children is still absent. According to various authors P3 in ADHD does not differ from that of control group [19] whereas others detected significant changes in amplitude and latency of P3 in ADHD vs controls [27,4]. According to Alexander and colleagues [1] P3 can serve as a valid marker of attention disorders in ADHD and predictor of pharmacological treatment [45-47].

As for non pharmacological intervention less is known about impact of EEG Biofeedback (neurofeedback-NF) on P3 characteristics although NF becomes evidence based treatment option for ADHD in recent years. According to evidence-based practice in biofeedback and neurofeedback recommended by international society for mind-body research, health care and education, the efficacy of NF in ADHD has satisfied the upper level of efficacy (level 4 efficacy) [54].. Such popularity of NF can be explained by the fact that stimulants frequently used for the treatment of ADHD can cause various side effects including growth suppression. In addition, estimates indicate that as many as 30% of children with ADHD either do not respond to stimulant treatment or cannot tolerate the treatment secondary to side effects. This has lead to the consideration of treatment with both non stimulant medications as well as alternative therapies, including diet, iron supplementation and NF [5]. Only several papers are devoted to impact of NF on ERP measures [27,51]. According to Wangler and colleagues [51], the decrease of P3 latency was observed after NF therapy but according to these authors these evidence is less valid as 18 units for a single NF pro-

tocol might have been to small to obtain specific ERP effects. Besides this study is not consistent because of absence of comparative analysis as it did not include non - treated ADHD children as a control group.

Thus assessment of ERP parameters before- and after NF treatment is extremely important in ADHD children.

Materials and methods. We prospectively studied 93 children with ADHD of combined subtype (ADHD-com) without any kind of pharmacological treatment. Age range 9-12 years. All children met the diagnostic criteria for ADHDcom according to the DSM-IV [2]. ADHD was diagnosed by board certified experienced neurologist and a paediatric neurologist based on the child's detailed neurological and neuropsychological examination. This group was divided into two subgroups: The first ADHDcom-1 (48 children) were children where NF treatment was carried out and the second subgroup of ADHDcom-2 (45 children) were non treated children. Such distribution of patients can be explained by the fact that P3 [40] as well as N1 [52] can exhibit habituation by repetition after certain time interval.

We obtained informed written consent from parents or guardians of all children. The study protocol was approved by the Biomedical Research Ethic Committee in Tbilisi State Medical University.

A neuropsychological assessment was conducted in all group of children, including IQ testing by the Raven's progressive matrices. The inclusion criteria were IQ>70. All other children assessed were determined to be intellectually disabled and were excluded from study.

ERP was also carried out in both group of children .The parameters of ERP assessed were polarity (positive or negative), timing (latency) and amplitude. Omission (misses) and commission (false alarms) errors were also investigated as they are thought to index impulsivity [29]. EEG was recorded using with silver plated electrodes placed at area according to the international 10-20 system. We have chosen only Cz-A1 derivation for the analysis for two reasons:
1. It is known that amplitude of N1 as well as P3 at target stimuli is the largest in the midline [11], [4].
2. In order to avoid interregional effect frequently observed in ERP studies as it was out of scope of our study.

Cap electrodes were referenced to linked ears. Impedance was kept below 5 kμ for the cap electrodes. The subject was grounded by the cap ground electrodes located midway between Fpz and Fz. EEG was amplified 20 000 times with a bandpass down 3dB at 0.1 and 25 Hz and was sampled through a 12-bit analog-to-digital converter at 200 Hz. In the laboratory each child was familiarized with the testing equipment and procedure. All tasks were completed in a sound-attenuated air-conditioned room. Seated on a comfortable chair children were presented with auditory stimuli binaurally through headphones. Conditions of stimulations were:

- Stimulation-binaural
- Duration of stimulus-50ms.
- Intensiveness - 80Db
- Interstimulus period-1 second
- Tone frequency:

- For target stimulus-2000Hz, reliability 20-30%,
- For non-target stimulus-1000Hz, reliability 70-80%.

Non-target and target stimuli were given in an absolutely randomized way 1-2 target stimulus appears after each 5 non-target stimuli.

For more refinement of study we have chosen only two components of ERP: N1 as an earlier electrical correlate of cortical activity reflecting correct choice of task and P3 as a later one reflecting complex act of executive functions including attention.

NF was carried out in ADHDcom-1 children according to protocol previously developed by Lubar [30]. It was conducted over a period of 6 weeks (30 sessions, five training per week). Training was divided into two phases (15 sessions in each phase): in the first phase children were trained to enhance the amplitude of SMR (12-15) Hz and decrease the amplitude of theta activity (4-7Hz); In the second phase beta/theta training was used which required children to decrease the amplitude of theta waves (4-7Hz) and reward their beta 1 waves (15-18 Hz). During the first phase EEG was recorded from Cz, with reference placed on the left earlobe and ground electrode on the right earlobe. During the second phase EEG was recorded from Fz-Pz derivations with the same localization of the reference and ground electrodes. It is known that SMR enhancement reduces hyperactivity problems. As for beta/theta training the basic assumption guiding this

approach is that suppressing theta activity diminishes attention problems [29]. Each session was subdivided into 2 min periods (that were gradually increased up to 10 min). During the training sessions children were attempting to work with puzzles on the screen, solve mathematical problems and maintain a state relaxation by watching cartoons.

Data were analyzed by different descriptive and inferential statistical methods using SPSS 10.0. The 2 groups × 2 conditions repeated measures ANOVA was used to determine the effect of treatment on ERPs parameters for the study groups The correlation analysis was made by the Spearman's rho and the Pearson correlations. The independent-sample t test was used to make the between group comparisons. The nonparametric Mann Whitney U test was used to make between group comparisons for independent samples. The nonparametric Mann Whitney U test was used to compare ADHD groups with and without treatment.

Results and their discussion. The mean amplitude N_1 before treatment was significantly higher t (23.676)=2.219, p<.036 for the ADHD treated group (mean=5.31, SD=2.7) compared to the ADHD non treated group (mean=3.61, SD=1.75) (Fig. 2). The mean amplitude P_3 after treatment was significantly higher t(47)=4.376, p<.0001 for the ADHD treated group (mean=9.81, SD=1.87) compared to the ADHD non treated group (mean=7.3, SD=1.69) (Fig. 4). The mean omission errors rate after treatment was significantly higher t(33.979)=-5.338, p<.0001 for the ADHD non treated group (mean=4.7, SD=1.79) compared to the ADHD treated group (mean=2.38, SD=.89) (Fig. 5). The mean commission errors rate after treatment was significantly higher t(27.518)=-6.18, p<.0001for the ADHD non treated group (mean=4.87, SD=2.91) compared to the ADHD treated group (mean=.88, SD=.89) (Fig. 6). The same results were obtained for these variables using the nonparametric Mann Whitney U test.

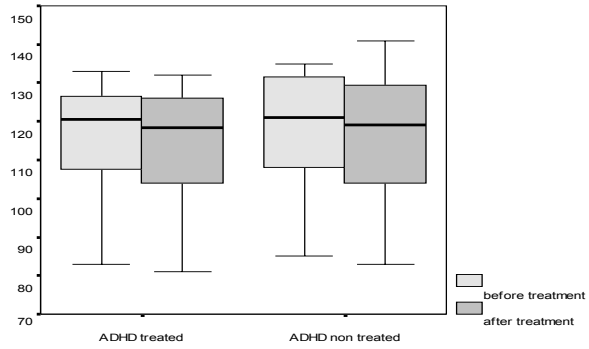

Fig. 1. The mean performance of latency N1

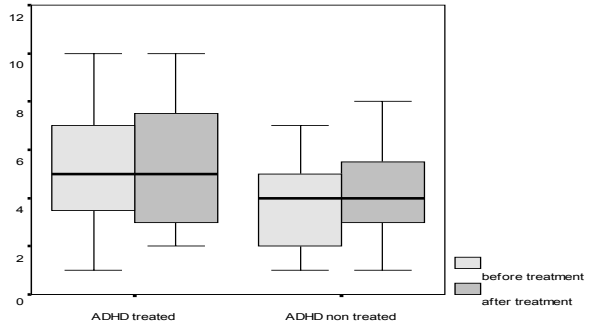

Fig. 2. The mean performance of amplitude N1

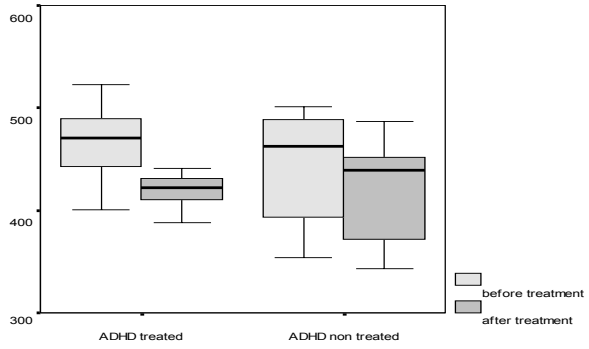

Fig. 3. The mean performance of latency P3

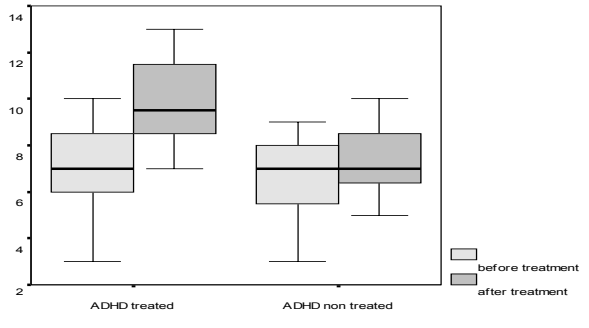

Fig. 4. The mean performance of amplitude P3

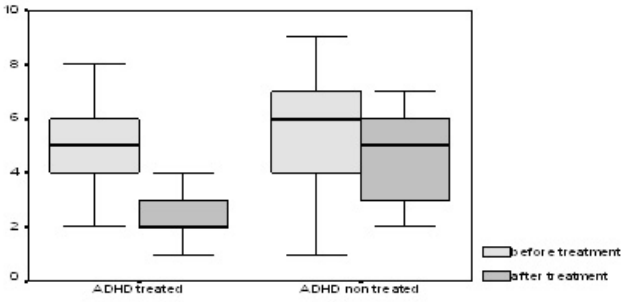

Fig. 5. The means of omission errors

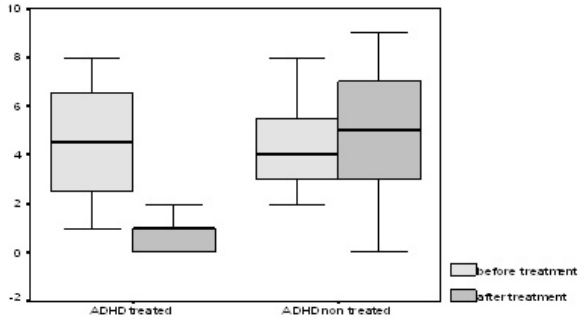

Fig. 6. The means of commission errors

To determine the effect of treatment on latency N_1, the data from the latency N_1 before treatment and latency N_1 after treatment were entered separately into a 2 (group) × 2 (condition – latency N_1 before treatment vs. latency N_1 after treatment) ANOVA. The ANOVA showed a significant effect of condition F(1,37)=6.282, MSE=4.879, p<.017, partial eta squared =.145 represents a large effect size. The effects of group (F<1) and interaction between group and condition (F<1) were not significant. The effect of age was significant F(1,36)=182.252, MSE=86, p<.0001, partial eta squared =.835 represents a large effect size, but the interaction between age and condition wasn't significant (F<1). The taking of age as covariate change relationships between the study variables and the effect of condition became not significant.

To determine the effect of treatment on amplitude N_1, the data from the amplitude N_1 before treatment and amplitude N_1 after treatment were entered separately into a 2 (group) × 2 (condition – amplitude N_1 before treatment vs. amplitude N_1 after treatment) ANOVA. The ANOVA showed a significant effect of condition F(1,37)=4.829, MSE=.333, p<.034, partial eta squared =.145 represents a large effect size, and of group F(1,37)=4.399, MSE=9.323, p<.043, partial eta squared =.106 represents a close to medium effect size. The effects of interaction between group and condition was significant at one tail F(1,37)=2.984, MSE=.333, p<.092. The effect of age was significant F(1,36)=23.655, MSE=5.782, p<.0001, partial eta squared =.397 represents a large effect size, but the interaction between age and condition wasn't significant (F<1) (Fig. 7).

To determine the effect of treatment on latency P_3, the data from the latency P_3 before treatment and latency P_3 after treatment were entered separately into a 2 (group) × 2 (condition – latency P_3 before treatment vs. latency P_3 after treatment) ANOVA. The ANOVA showed a significant effects of condition F(1,37)=223.69, MSE=114.735, p<.0001, partial eta squared =.858 represents a large effect size and of interaction between group and condition F(1,37)=22.698, MSE=114.735, p<.0001, partial eta squared =.38 represents a large effect size. The effect of group was not significant (F<1). The ANOVA showed a significant effects effect of age F(1,36)=40.62, MSE=1612.812, p<.0001, partial eta squared =.53 represents a large effect size, and interaction between age and condition F(1,36)=26.96, MSE=67.427, p<.0001, partial eta squared =.428 represents a large effect size (Fig. 8). The taking of age as covariate didn't change relationships between the study variables.

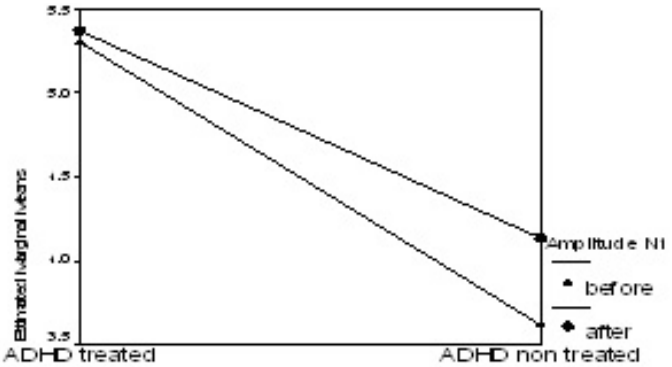

Fig. 7. The means of amplitude N_1 before and after treatment for study groups

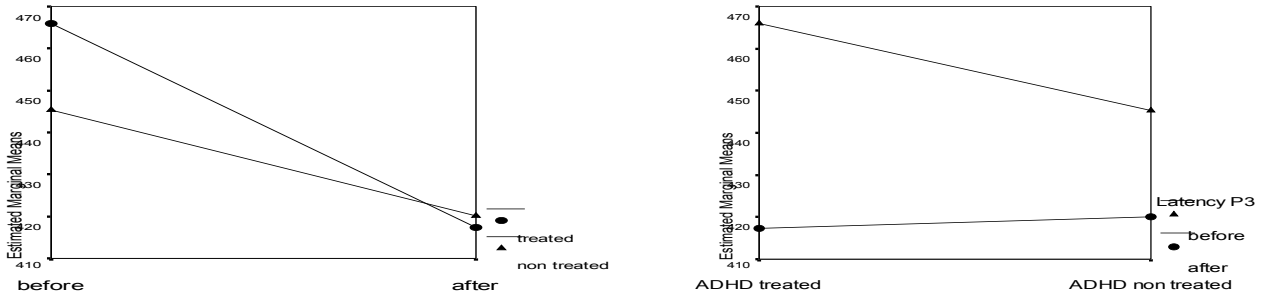

Fig. 8. The means of latency P_3 before and after treatment for study groups

To determine the effect of treatment on amplitude P_3, the data from the amplitude P_3 before treatment and amplitude P_3 after treatment were entered separately into a 2 (group) × 2 (condition – amplitude P_3 before treatment vs. amplitude P_3 after treatment) ANOVA. The ANOVA showed a significant effects of condition F(1,37)=157.263, MSE=.443, p<.0001, partial eta squared =.81 represents a large effect size; of group F(1,37)=7.07, MSE=6.008, p<.012, partial eta squared =.16 represents a large effect size, and of interaction between group and condition F(1,37)=44.044, MSE=.443, p<.0001, partial eta squared =.543 represents a large effect size. The effect of age was significant F(1,36)=7.721, MSE=5.085, p<.009, partial eta squared =.177 represents a large effect size but the interaction between age and condition wasn't significant (F<1) (Fig. 9). After taking of age as covariate the effect of condition became not significant but didn't change other relationships between the study variables.

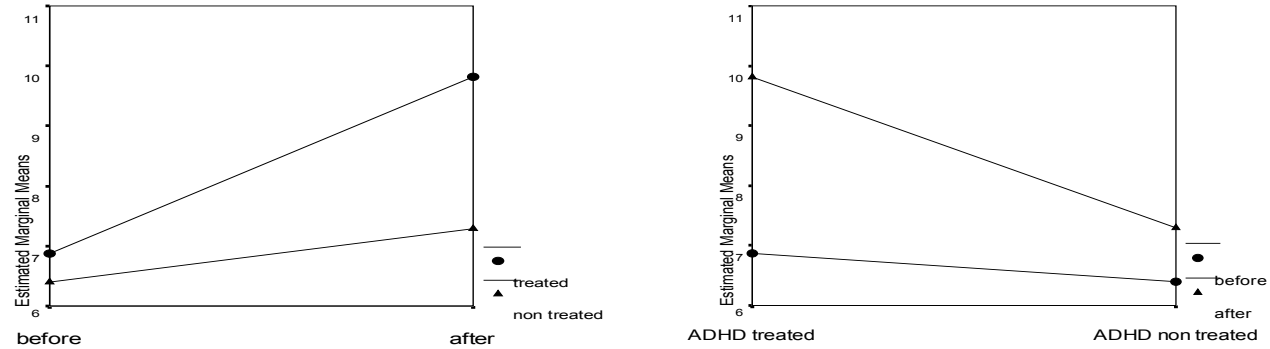

Fig. 9. The means of amplitude P_3 before and after treatment for study groups

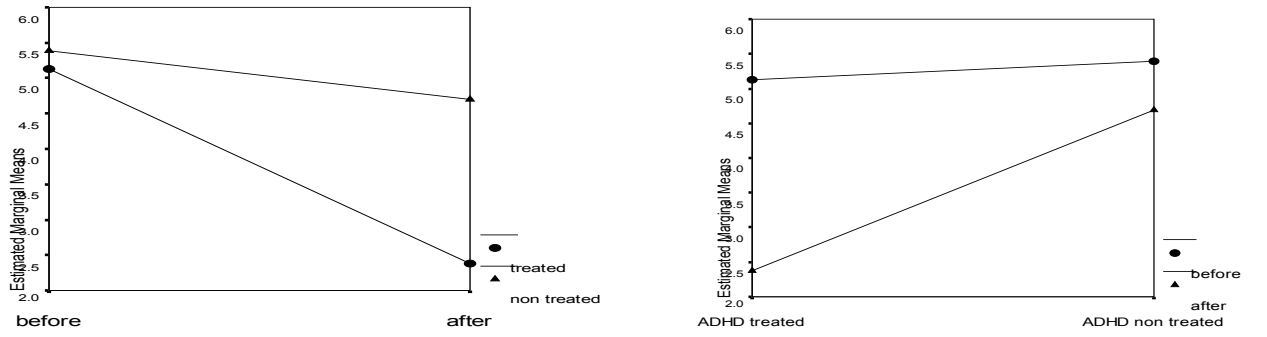

Fig. 10. The means of omission error rate before and after treatment for study groups

To determine the effect of treatment on omission error rate, the data from the omission error rate before treatment and omission error rate after treatment were entered separately into a 2 (group) × 2 (condition – omission error rate before treatment vs. omission error rate after treatment) ANOVA. The ANOVA showed a significant effects of condition F(1,37)=54.634, MSE=1.025, p<.0001, partial eta squared =.596 represents a large effect size; of group F(1,37)=6.422, MSE=4.917, p<.016, partial eta squared =.148 represents a large effect size and of interaction between group and condition F(1,37)=19.421, MSE=1.025, p<.0001, partial eta

squared =.344 represents a large effect size. The ANOVA showed a significant effects effect of age F(1,36)=61.727, MSE=1.861, p<.0001, partial eta squared =.632 represents a large effect size, and interaction between age and condition F(1,36)=9.672, MSE=.831, p<.004, partial eta squared =.212 represents a large effect size (Fig. 10). The taking of age as covariate didn't change relationships between the study variables.

To determine the effect of treatment on commission error rate, the data from the commission error rate before treatment and commission error rate after treatment were entered separately into a 2 (group) × 2 (condition – commission error rate before treatment vs. commission error rate after treatment) ANOVA. The ANOVA showed a significant effects of condition F(1,37)=20.004, MSE=2.208, p<.0001, partial eta squared =.351 represents a large effect size; of group F(1,37)=9.937, MSE=6.852, p<.003, partial eta squared =.212 represents a large effect size, and of interaction between group and condition F(1,37)=37.515, MSE=2.208, p<.0001, partial eta squared =.503 represents a large effect size. The effects of age (F<1) and interaction between age and condition were not significant (F<1) (Fig. 11). After taking of age as covariate the effect of condition became not significant but didn't change other relationships between the study variables.

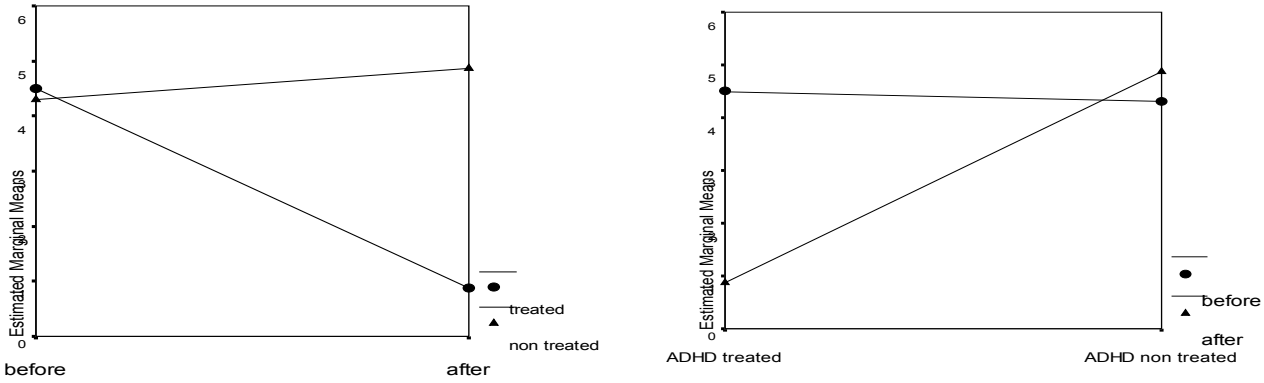

Fig. 11. The means of commission error rate before and after treatment for study groups

As we explained above N1 reflects the simple process of recognition of stimuli. Our study replicate the position of Barry [4] and Oades [37] who confirmed that N1 latency on target stimuli showed tendency to be smaller in ADHD than controls during oddball task. According to our results it was obvious that NF does not affect on N1 parameters. Thus it means that NF serving the improvement of attention parameters can not change the auditory information recognition process in the brain. As for later response like P3 as it was mentioned in the results that the mean amplitude of P_3 after treatment was significantly higher (F(1,37)=44.044, MSE=.443, p<.0001) for the ADHD treated group compared to the ADHD non treated. The mean latency of P3 before- and after treatment in ADHD treated group showed statistically significant reduction of latency compared to non treated ones (F(1,37)=22.698, MSE=114.735, p<.0001).

Our study confirms once more the facts that in ADHD children younger than 12 years of age the amplitude of P3 on target stimuli is reduced compared to controls [16] but latency is increased [28], [42]. But the most important finding of our study was that NF training causes significant increase of amplitude and decrease of latency of P3. This point is very important as we mentioned above P3 amplitude reflects effortfulness of the stimulus response and the intensity of processing whereas P3 latency is taken as a reflection of the speed of information processing. Thus decreasing of effortfulness of mental activity and improvement of speed of information processing is one of the most significant domain of activity in ADHD children.

Modification of ERPs components is extremely important in ADHD children as it is known that dysfunctions in cortical as well as subcortical structures plays the key role in the pathogenesis of ADHD [13]. As for psychological point of view the disorder of selection of adequate action is frequently expressed in ADHD population thus causing the impairment of executive attention. The effectiveness of NF on P3 can be explained by the following fact. It is known that NF influences neural networks that support attention, executive functions and motor regulation. According to Makris and colleagues [33] this complex network consists of several parallel networks: cortico-striatal, cortico-pallidal and cortico-cerebellar. The effective-

ness of NF in the change of P3 parameters can be explained by the fact that structures functioning of which is changed during NF treatment participate in the electrogenesis of P3.

1. The role of prefrontal cortex in the pathogenesis of ADHD is evidence based [44]. It was suggested that during the occurrence of P3 the prefrontal cortex temporarily inhibits the mesencephalic activating system [35]. According to Knight the cessation of this inhibition, following the lesion of the prefrontal area could account for the P3 changes [20] detected in our study. Thus it can be marker of functioning of prefrontal areas which are extremely important in the pathogenesis of ADHD.

2. The role of parietal lobes in the pathogenesis of ADHD is confirmed by Makris and collegues [32]. According to Simson [49] although existence of a frontal P3 generator could not be excluded, the generator of the P3 could most likely be localized to the inferior parietal lobe. Knight detected that [22] upper part of the parietal lobe does not play significant role in the genesis of the auditory P3 component. On the other hand, the auditory association cortical areas at the junction of the temporo-parietal lobes seem to be very important. The anatomical connections of this area with the prefrontal cortex may be significant as it is most important part of ADHD pathogenesis. Temporal lobe and parts of limbic system are also considered as generators of P3. Halgren and colleagues [14] recorded auditory ERP from the amygdala, hippocampus and vertex using oddball paradigm. The author detecting large amplitude components from these structures suggested that they can be considered as generators of P3. The role of the hippocampus and amygdala in attention-processing has been elucidated by various clinical studies. According to Plessen and colleagues [41] connectivity of the prefrontal regions with the hippocampus and amygdala regulates a variety of attentional, memory and emotional processes implicated in the pathophysiology of ADHD. The same authors detected larger hippocampal volumes in ADHD children and reported that, among children with hippocampal dysfunction, larger volumes tended to accompany less severe ADHD symptoms. The significance of hippocampus in NF effectiveness is huge as it is proved that frontal midline theta rhythm in human EEG is often associated with hippocampal theta activity. As it is obvious that Papez circle structures like hippocampus, mammilary body of hypothalamus and anterior nucleus of thalamus all together generate theta rhythm which was the basis of attention training during NF therapy [27]. The role of temporal lobes in P3 generation was described by various authors. According to Knight [21] after unilateral temporal lobe lesion (involving area 22, area 40, and the lower part of area 39) the P3 disappear. Daruna and colleagues found that [8] in epileptic patients following unilateral temporal lobectomy the amplitude of the recorded P3 was smaller over the affected side.

3. As for basal ganglias their role in the generation of P3 was explained by Yingling [53] and Kropotov [25], [26] where striatum, globus pallidus, the ventro-lateral nucleus of the thalamus and adjacent areas were considered as a possible generators of P3 together with cortex. The fact that basal ganglia play the important role in the pathogenesis of ADHD is obvious. A growing number of neuroimaging studies have demonstrated smaller size of nucleus caudatus [7] and globus pallidus [39], [3] in ADHD children. Lubar [31] suggested that during NF therapy the basis of which is EEG activity generated by thalamus the thalamic pacemaker generates different brain rhythms depending on which cortical loops they activate but changes in cortical loops can modify the firing rate of thalamic pacemakers and hence alter their firing pattern which is the basis of NF training used in our study. Thus thalamus together with other subcortical plays the key role in ADHD.

Another important finding of our study was improvement is the rate of omission and commission errors which as we mentioned above are thought to be the index of impulsivity which together with inattentiveness is the most prominent feature of ADHD . The mean omission errors rate after treatment was significantly higher ($p<.0001$) for the ADHD non treated group compared to the ADHD treated group. The mean commission errors rate after treatment was significantly higher ($p<.0001$) for the ADHD non treated group compared to the ADHD treated group. Thus the fact that NF can improve the rate of commission errors in the treated group whereas in untreated group it increases after time interval means that it can positively affect on hyperactivity expression.

In spite of several successful findings our work need further confirmation as the follow-up study is needed to observe how consistent is improvement of P3 parameters and how long it persists. Besides it will be very interesting to identify the profile of P3 parameters in various subtypes of ADHD and level of effectiveness of NF in these subtypes of children.

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SUMMARY

CHANGES IN COGNITIVE EVOKED POTENTIALS DURING NON PHARMACOLOGICAL TREATMENT IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER

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Attention deficit/hyperactivity disorder (ADHD) is one of the most widely spread condition of school aged children affecting 5% of children of this age. The unified consensus of the precise diagnosis of this condition is still absent. This fact encourages the researchers to seek the alternative neurometric tools which will help the clinicians in diagnosis making process of ADHD. The neurophysiologic approaches especially event-related potentials (ERPs) are mostly important from this point of view. The later response of ERPs (P3) reflects the most important parts of executive functioning frequently affected in ADHD children - the process of mental effortfullness to select the appropriate behavior and decision making. Besides the diagnosis the treatment of ADHD is also the point of concern of neurologists and neurophyschologists. In recent years EEG biofeedback (Neurofeedback-NF) have become the alternative treatment as in some cases pharmacological drugs are non effective. The positive impact of NF was based on improvement detected by various questionnaires which are less valid but its effectiveness on ERPs parameters is still unknown. Thus we aimed to study the changes of ERPs after NF therapy. Methods: We have studied 93 children with ADHD of combined subtype (ADHDcom) without any kind of pharmacological treatment. Age range 9-12 years. The children were divided into two subgroups: The first ADHDcom-1 (48 children) were children where NF treatment was carried out and the second subgroup of ADHDcom-2 (45 children) were non treated children. Results: We have observed statistically significant improvement of parameters of later response like P3 in ADHD-1 compared with ADHD-2 whereas NF was non effective for earlier component like N1. Conclusions: NF can positively affect on the P3 parameters which is very important in ADHD children as P3 reflects the speed of information processing as well as selection of appropriate action and decision making which are frequently affected in ADHD children.

Key words: Attention deficit hyperactivity disorder (ADHD), neurofeedback, cognitive evoked potentials, P3, N1.

РЕЗЮМЕ

ИЗМЕНЕНИЯ КОГНИТИВНЫХ ВЫЗВАННЫХ ПОТЕНЦИАЛОВ ПРИ НЕФАРМАКОЛОГИЧЕСКОЙ ТЕРАПИИ СИНДРОМА ДЕФИЦИТА ВНИМАНИЯ И ГИПЕРАКТИВНОСТИ У ДЕТЕЙ

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Синдром дефицита внимания и гиперактивности (СДВГ) представляет собой наиболее часто встре-

чающееся состояние детского возраста и составляет в среднем 5% среди школьников. Нет единого мнения относительно диагностики данного синдрома; исследователи стараются разработать альтернативные нейрометрические диагностические методы. С этой целью важное значение придается нейрофизиологическим методом обсследования, в частности изучению когнитивных вызванных потенциалов (КВП). За последние годы методу ЭЭГ-биообратной (нейрообратной) связи придается важное значение в свете альтернативной немедикаментозной терапии. В тоже время влияние нейрообратной связи на КВП до конца не выяснено. Целью исследования явилось изучение влияния нейрообратной связи на показатели когнитивных вызванных потенциалов у детей с синдромом дефицита внимания и гиперактивности.

Наблюдались 93 детей, 48 из них проводилось лечение методом нейрообратной связи (группа СДВГ-1), 45 больным лечение не проводилось (группа СДВГ-2). Проведённые исследования выявили статистически достоверное улучшение позднего коркового ответа (Р3) среди детей с СДВГ-1 (по сравнению с СДВГ-2), тогда как такое улучшение раннего коркого ответа (N1) не наблюдалось. Сделан ряд выводов, наиболее значительным из которых является тот факт, что метод нейрообратной связи положительно влияет на показатели Р3, что является особенно важным у детей с СДВГ, так как он отражает скорость восприятия информации, позволяет сделать выбор адекватного действия и обеспечивает процессы принятия решений.

რეზიუმე

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ყურადღების დეფიციტის და ჰიპერაქტივობის სინდრომი (ყდჰს) წარმოადგენს ბავშვთა ასაკის ერთ-ერთ ყველაზე უფრო გავრცელებულ მდგომარეობას. მისი გავრცელება შეადგენს სკოლის ასაკის ბავშვთა 5%-ს. ამ მდგომარეობის დიაგნოსტიკისადმი ერთიანი მიდგომა ჯერ კიდევ არ არსებობს. ამის გამო მკვლევარები დღემდე ცდილობენ შეიმუშავონ ალტერნატიული ნეირომეტრული დიაგნოსტიკის მეთოდები. ამ მიზნით მნიშვნელოვანი იქნება ნეიროფიზიოლოგიური კვლევის მეთოდების, განსაკუთრებით კი მოვლენებთან დაკავშირებული კოგნიტური გამოწვეული პოტენციალების (კგპ) შესწავლა. კგპ-ების მოგვიანებითი ქერქული პასუხი (Р3) ასახავს აღმასრულებელი ფუნქციების ისეთ მნიშვნელოვან ასპექტებს როგორიცაა შესაბამისი ქცევის შერჩევისთვის მენტალური ძალდატანება და გადაწყვეტილების მიღება. ყდჰს-ის მკურნალობა წარმოადგენს თანამედროვე ნევროლოგიისა და ნეიროფსიქოლოგიის მნიშვნელოვან პრობლემას. ბოლო წლებში ეეგ ბიოუკუკავშირი (ნეიროუკუკავშირი) წარმოადგენს მედიკამენტური მკურნალობის ალტერნატიულ მეთოდს. ნეიროუკუკავშირის ზეგავლენა კგპ-ების პარამეტრებზე ჯერ კიდევ უცნობია. აქედან გამომდინარე ჩვენი კვლევის მიზანს წარმოადგენდა ნეიროუკუკავშირის კგპ-ების მაჩვენებლებზე ზემოქმედების შესწავლა. მეთოდები: ჩვენს მიერ შესწავლილი იქნა ყდჰს-ის კომბინირებული ფორმის მქონე 9-12 წლის 93 ბავშვი ფარმაკოლოგიური მკურნალობის გარეშე. აღნიშნული ბავშვები დავყავით 2 ჯგუფად: ყდჰს-1 (48 ბავშვი), სადაც ჩავატარეთ ნეიროუკუკავშირით მკურნალობა და ყდჰს-2 (45 ბავშვი), სადაც მკურნალობა არ ჩატარებულა. შედეგები: ჩვენს მიერ ნანახი იქნა მოგვიანებითი ქერქული პასუხის (Р3) სტატისტიკურად სარწმუნო გაუმჯობესება ყდჰს-1 ჯგუფში ყდჰს-2 ჯგუფთან შედარებით, მაშინ როდესაც ეს ეფექტი ადრეულ პასუხზე (N1) აღმოჩენილი არ იქნა. დასკვნა: ნეიროუკუკავშირი დადებით ზეგავლენას ახდენს Р3-ის მახასიათებლებზე, რაც ძალიან მნიშვნელოვანია ყდჰს-ის მქონე ბავშვებში, რადგანაც იგი ასახავს როგორც ინფორმაციის აღქმის სიჩქარეს, ისე შესაბამისი მოქმედების შერჩევისა და გადაწყვეტილების მიღების პროცესებს.

IDENTIFICATION, MANAGEMENT AND COMPLICATIONS OF INTRA-ABDOMINAL HYPERTENSION AND ABDOMINAL COMPARTMENT SYNDROME IN NEONATAL INTENSIVE CARE UNIT (A SINGLE CENTRE RETROSPECTIVE ANALYSIS)

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Compartment syndrome occurs when the pressure within a closed anatomic space (a compartment) becomes so elevated that capillary perfusion is compromised and tissue ischemia develops. The abdominal compartment syndrome (ACS) is a result of increased intra-abdominal pressure (IAP), due to tissue edema or free fluid collecting in the abdominal cavity. Elevated pressure in the abdomen is referred to as intra-abdominal hypertension (IAH). This clinical spectrum dramatically impacts patient outcome: The end result of ACS, if undetected and untreated, is multisystem organ failure and patient death [4-6,14,16].

Critically ill patients requiring resuscitation with fluids and/or vasopressors suffer tissue ischemia/reperfusion injuries. This cycle of ischemia/reperfusion results in microvascular permeability, capillary leakage of fluid and tissue edema. An especially susceptible organ to tissue ischemia/reperfusion injury, capillary leak and edema is the bowel. Since the abdominal wall limits the total volume of intra-abdominal space, as bowel expands, the pressure within the abdomen also increases. This causes occlusion of capillary blood flow and ultimately ends in compromise of venous return and arterial flow. The resulting ischemia triggers a cycle of further inflammation, capillary leak, bowel edema and increasing intra-abdominal pressure. Normal intra-abdominal pressure is 0-5 mm Hg. Physiologic compromise begins when the pressure rises above 8-10 mm Hg. Once the pressures increase beyond 20 mm Hg, irreversible tissue injury occurs, ultimately resulting in ACS and multiple organ failure. Early recognition of rising abdominal pressure is critically important when it is still relatively occult (intra-abdominal hypertension) because it allows prompt intervention, which will prevent ACS from developing, leading to a much better prognosis for the patient [3-5].

Traditionally, ACS was considered a traumatic surgical disease. However, ACS is a problem in many critically ill patients who have suffered no trauma, especially those suffering systemic inflammatory response syndromes (SIRS). Any patient with an inflammatory response causing capillary leak and requiring volume resuscitation or vasopressor support is at risk for developing bowel edema, intra-abdominal hypertension and ACS. Intra-abdominal pressure monitoring should be strongly considered in all patients with this clinical presentation [3,4,6,7].

Abdominal compartment syndrome affects various organ systems and their functions.
(1) The early effects of IAH on pulmonary function are largely mechanical. As intra-abdominal pressure increases, it pushes the diaphragms cephalad. This results in reduced intra-thoracic volume (reduced functional residual capacity, total lung capacity and residual volume), reduced chest wall compliance and increased intra-pleural pressure. Simultaneously there is alveolar collapse due to the smaller intra-thoracic space and the higher intra-thoracic pressure. This leads to atelectasis, ventilation-perfusion mismatching, hypoxia, hypercarbia and respiratory acidosis. The combination of elevated intra-thoracic pressure and hypoxic pulmonary vasoconstriction can also lead to pulmonary hypertension [13,20].

(2) The combination of increased intra-abdominal and pleural space pressures cause: reduced venous return, increased afterload with resultant direct compression of heart chambers, especially to the right heart [3,6].

(3) Renal dysfunction is a common early presentation of elevated intra-abdominal pressure. Significant renal hypoperfusion develops at IAP levels of 8-12 mm Hg, oliguria is seen at intra-abdominal pressures over 15 mm Hg and anuria is common once pressures exceed 25-30 mm Hg. The causes of renal dysfunction includes reduced cardiac output, increased renal vascular resistance, decreased glomerular filtration gradient, higher levels of renin and aldosterone, as well as significant renal injury from high circulating cytokine levels [1,10,12,17,18].

(4) Intra-abdominal hypertension leads to serious pathophysiologic changes in the gut and the retroperitoneal space. Critical illness and the resulting inflammatory changes lead to profound capillary permeability that manifests primarily with edema in the bowel wall and mesentery. This edema leads to compression of the venous structures of the bowel causing venous and lymphatic obstruction and congestion with increasing tissue edema and ischemia. As the pressure continues to rise to the level of capillary perfusion pressure (15-25 mm Hg) the capillary structures begin to become compressed – a point at which severe ischemic injury will develop. As the gut becomes increasingly more hypoxic due to the cardiovascular effects of IAH, inflammatory mediators are produced and bacterial translocation from the gut lumen to the lymphatic and circulatory systems occur. If untreated, these events may lead to multiple organ dysfunction syndromes. Hypoxia and congestion of the liver also result in reduced clotting factor production and coagulopathies may develop [5-7,15].

(5) Intra-abdominal hypertension impacts intracranial pressure. As intra-abdominal pressure goes up, it pushes up the diaphragm, reducing intra-thoracic volume and causing elevated intra-thoracic pressure. Elevated intra-thoracic pressure results in elevated central venous pressure and subsequent elevated internal jugular venous pressure. The result is a functional obstruction of cerebral venous outflow, resulting in increases in intra-cranial pressure and reduction in cerebral perfusion pressure. [8,9,11].

The exact critical threshold of elevated intra-abdominal pressure in neonatal population is not established. It is the subject for future researches. Various sources give us the various thresholds for intra-abdominal hypertension:

1. Intra-abdominal pressure >10 mmHg
2. Intra-abdominal pressure >12 mmHg
3. Intra-abdominal pressure 10-15 mmHg [2,22].

Although the definition for IAH and ACS in adults requires pressures of 12-20 mm Hg, these are really just guidelines and the individual patient's organ function must be considered. It is especially important in children to not just look at a number, but look at the patient since their underlying mean arterial pressure is lower than adults and varies with age. The point - due to lower baseline MAP, the splanchnic perfusion of a small child will be more impacted at a lower abdominal pressure. In fact – neonates can have a compartment syndrome at levels of IAP in the range of 9-13 mm Hg. Beck found a pressure of 15 mm Hg high enough to cause compartment syndrome [2,22].

The goal of the study: 1) detection of abdominal compartment syndrome in newborns with clinically suspicious intra-abdominal hypertension; 2) identification of intra-abdominal pressure numbers presented with clinical manifestation; 3) measurement and detection of intra-abdominal pressure numbers presented with abdominal compartment syndrome; 4) find correlation between intra-abdominal hypertension grade and patient outcome.

Material and methods. We selected and reviewed medical records of 155 neonatal patients from 2008 to 2010, who stayed in surgical neonatal intensive care unit for more than 7 days. IAP monitoring was performed in 32 patients, which confirmed intra-abdominal hypertension (IAP>10 mmHg) in 28 patients (Table).

Table. Number of patients is surgical ICU with IAP monitoring and confirmed hypertension

Patients (n)	Mean age	Weight of patients	IAH	ACS IAP≥25mmHg	Abdominal surgery (number of patients)	Thoracic surgery (number of patients)	Non-surgical cases (number of patients)
32	<28 days	mean 2186g ±SD 826g	28 (87.5%)	11 (34.38%)	20 (62.5%)	6 (18.75%)	6 (18.75%)

The inclusion criteria for IAP monitoring were: increased abdominal circumference, reduced abdominal wall compliance and presence of fluid in abdominal cavity. Selected patients presented with different combinations of: illeus and/or necrotizing enterocolitis (NEC) and/or septic shock and/or renal

failure and/or low cardiac output and/or high central venous pressure (CVP) (mean 13,125 mmHg±SD 3,28 mmHg), delayed capillary refill time (>2 sec) and/or acute respiratory failure, increased arterial carbon dioxide partial pressure ($PaCO_2$>50mmHg Mean 61,43 mmHg±SD 13,18 mmHg) and decreased arterial oxygen partial pressure (PaO_2<60mmHg, mean 53,15 mmHg±SD 10,24 mmHg), and/or oligo/anuria (oliguria-urine output<0,5 ml/kg/hr in 12 hr, anuria-urine output<0,3 ml/kg/hr in>12 hr) and/or weak/absent pulse on femoral artery.

In order to distinguish IAH from ACS, we subdivided clinical presentation into I and II grade signs.
I grade signs include: increased abdominal circumference, reduced abdominal wall compliance and ultrasound confirmation of fluid presence in abdominal cavity.

II grade signs include: NEC, septic shock, renal failure, low cardiac output, increased CVP, delayed capillary refill time, acute respiratory failure, increased arterial carbon dioxide partial pressure, decreased arterial oxygen partial pressure, oligo/anuria and weak or absent pulse on femoral artery.

Presence of IAH was considered in all cases with IAP>10 mmHg, increased abdominal circumference, reduced abdominal wall compliance, ultrasound confirmation of fluid in abdominal cavity and presentation of at least 2 symptoms of II grade signs.

Presence of ACP was considered in all cases with IAP>20 mmHg, increased abdominal circumference, reduced abdominal wall compliance, ultrasound confirmation of fluid in abdominal cavity and presentation of at least 3 symptoms of II grade signs.

All patients with intra-abdominal hypertension (IAP>10 mmHg) and ultrasound confirmation of fluid in abdominal cavity were managed by insertion of peritoneal drain for decompression, even if amount of fluid in abdominal cavity was minimal.

The average weight of patients was 2234 gr, minimal of - 800 gr and maximal of – 4100 gr (mean 2186g±SD 826g).

Intra-abdominal pressure was measured as follows:
- Foley catheter was inserted in urinary bladder
- Connector with 18Ga needle or catheter and stop-cock was inserted between urine collection bag and Foley catheter (in some circumstances connector was fixed on urine collection bag)
- Needle or catheter was connected to invasive pressure monitor via transducer
- After urine collection bag was occluded, 2 ml/kg of sterile normal saline was injected via stop-cock in Foley catheter
- Monitor was zeroed on mid-axillary line
- Received figure on monitor was considered as intra-vesicular pressure corresponded to intra-abdominal pressure
- At the end of procedure urine collection bag was opened [21,22].

Results and their discussion. We revealed marked intra-abdominal hypertension of different grades in 28 cases. Obtained data was sorted according to World Society of Abdominal Compartment Syndrome (WSACS) classification [22]:
- I Grade IAP = 10-15 mmHg (7 patients)
- II Grade IAP = 16-25 mmHg (10 patients)
- III Grade IAP = 26-35 mmHg (8 patients)
- IV Grade IAP > 35 mmHg (3 patients)

Before insertion of peritoneal drain for decompression all patients presented with: low cardiac output, normal arterial blood pressure or hypertension with tachycardia, delayed capillary refill time (> 2 sec), increased abdominal circumference, presence of fluid in abdominal cavity and/or intestinal lumen. According to increased level of intra-abdominal pressure, we observed increased CVP, hypotension, oligo/anuria, respiratory distress, altered level of consciousness, decompensate mixed acidosis (II-III-IV grade of IAH).

Insertion of peritoneal drain for decompression was conducted in 28 cases. Indications for procedure were as follows: IAP > 10 mmHg and ultrasound confirmation of fluid in abdominal cavity. In 4 cases with IAP < 10 mmHg ultrasound revealed presence of small amount of fluid, which was managed by administration of diuretics.

Increased CVP was detected in 93% of patients (mean 13,125 mmHg±SD 3,28 mmHg), decreased PaO_2 in 71,5% of patients (PaO_2<60mmHg, mean 53,15 mmHg±SD 10,24 mmHg), increased $PaCO_2$ in 71,5% ($PaCO_2$>50 mmHg Mean 61,43 mmHg±SD 13,18 mmHg). 71,5% of patients were presented with high airway pressure (mean 30,5 mmHg±SD 7,95

mmHg). Oligo/anuria developed in 71,5% of patients (oliguria-urine output <0,5 ml/kg/hr in 12 hr, anuria-urine output <0,3 ml/kg/hr in >12 hr).

After insertion of peritoneal drain for decompression we observed the resolution of symptoms in all patients, but in different ways: In 20% of patients from I and II grade group, renal function was corrected without performing of peritoneal dialysis. In 80% dialysis became necessary for renal replacement therapy of various duration. Draining and decompression of peritoneal cavity was followed by correction of some measurements and clinical presentation: hemodynamic improvement, decreased abdominal circumference, increased tidal volume, decreased $PaCO_2$, increased PaO_2 and normalization of pH. In IV-grade group peritoneal dialysis was not performed, due to massive destruction of intestines.

According to our research we may come to the following conclusion:

- Intra-abdominal hypertension was confirmed in 87, 5% of all suspected cases.
- Intra-abdominal pressure of >10 mmHg in patients with clinical suspicion may be considered as intra-abdominal hypertension.
- Intra-abdominal hypertension is in close correlation with presence of fluid in abdominal cavity proved by ultrasound investigation.
- Intra-abdominal pressure of ≥20 mmHg can be considered as a point of development of abdominal compartment syndrome.
- The grade of hypertension is in close correlation with patient outcome:

I-II Grade IAP: 14 patients from 17 recovered (mortality rate 17%)
III Grade IAP: 3 patients from 8 recovered (mortality rate 37.5%)
IV Grade IAP: From 3 patients none of them survived (mortality rate 100%).

Review of the literature and results of other researches were approximately the same as results received from our small retrospective analysis [16,20-22].

This research represents a retrospective overview of only infant patients mostly with surgical diseases. Therefore the results cannot have high evidence. However, the evident clinical correlations were discovered and measurable results achieved. This allows us to analyze and plan more expanded and advanced multi-central research with modern methods of planning, data analyze and patients' selection, which will give us an opportunity to come to more reliable and important conclusions.

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SUMMARY

IDENTIFICATION, MANAGEMENT AND COMPLICATIONS OF INTRA-ABDOMINAL HYPERTENSION AND ABDOMINAL COMPARTMENT SYNDROME IN NEONATAL INTENSIVE CARE UNIT (A SINGLE CENTRE RETROSPECTIVE ANALYSIS)

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The abdominal compartment syndrome (ACS) is a result of increased intra-abdominal pressure (IAP) due to tissue edema or free fluid collecting in the abdominal cavity. Elevated pressure in the abdomen is referred to as intra-abdominal hypertension (IAH). The end result of ACS, if undetected and untreated, is multisystem organ failure and patient death. Intra-abdominal pressure monitoring should be strongly considered in all patients with this clinical presentation. Normal intra-abdominal pressure is 0-5 mm Hg. Physiologic compromise begins when the pressure rises above 8-10 mm Hg. Once the pressures increase beyond 20 mm Hg irreversible tissue injury occurs, ultimately resulting in ACS and multiple organ failure. Early recognition of rising abdominal pressure is critically important, because it allows prompt intervention which will prevent ACS from developing, leading to a much better prognosis for the patient.

The purpose of the research was to: 1) Detect abdominal compartment syndrome in newborns with clinically suspicious intra-abdominal hypertension; 2) Identify intra-abdominal pressure numbers presented with clinical manifestation; 3) Measure and detect intra-abdominal pressure numbers presented with abdominal compartment syndrome; 4) Find correlation between intra-abdominal hypertension grade and patient outcome.

For completion of our goal we selected and reviewed medical records of 155 neonatal patients from 2008 to 2010, who stayed in surgical neonatal intensive care unit for more than 7 days. We monitored IAP in patients with suspected ACS and different clinical presentation.

According to our research we may come to the following conclusion:

- Intra-abdominal hypertension was confirmed in most suspected cases.
- Intra-abdominal pressure of >10 mmHg in patients with clinical suspicion may be considered as intra-abdominal hypertension.
- Intra-abdominal hypertension is in close correlation with presence of fluid in abdominal cavity proved by ultrasound investigation.
- Intra-abdominal pressure of ≥20 mmHg can be considered as a point of development of abdominal compartment syndrome.
- The grade of hypertension is in close correlation with patient outcome.

Key words: Abdominal compartment syndrome (ACS), intra-abdominal pressure (IAP), intra-abdominal hypertension (IAH).

РЕЗЮМЕ

ИДЕНТИФИКАЦИЯ, УПРАВЛЕНИЕ И ОСЛОЖНЕНИЯ АБДОМИНАЛЬНОЙ ГИПЕРТЕНЗИИ И АБДОМИНАЛЬНОГО КОМПАРТМЕНТ СИНДРОМА В ИНТЕНСИВНОЙ ТЕРАПИИ НОВОРОЖДЕННЫХ (РЕТРОСПЕКТИВНЫЙ АНАЛИЗ ОДНОГО ЦЕНТРА)

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Абдоминальный компартмент синдром является результатом повышенного внутрибрюшного давления вследствие отека тканей или накопления жидкости в брюшной полости. Повышение давления в брюшной полости ведет к развитию внутрибрюшной гипертензии, что, в свою очередь, оказывает значительное влияние на исход заболевания. При отсутствии соответствующего лечения или в нераспознанных случаях конечным результатом абдоминального компартмент синдрома является полиорганная недостаточность и смерть больного. Мониторинг внутрибрюшного давления необходимо проводить всем больным с клиническими симптомами внутрибрюшной гипертензии. Нормальным показателем внутрибрюшного давления является 0-5 мм рт.ст. Физиологические нарушения выявляются при давлении свыше 8-10 мм рт.ст. Когда внутрибрюшное давление превышает 20 мм рт.ст., происходит необратимое повреждение тканей, что, в конечном счете, приводит к абдоминальному компартмент синдрому и полиорганной недостаточности. Раннее выявление повышенного внутрибрюшного давления и проведение соответствующих превентивных мероприятий весьма необходимо для предотвращения развития абдоминального компартмент синдрома, что сказывается на благоприятном исходе заболевания.

Целью исследования явилось: 1) выявление абдоминального компартмент синдрома у новорожденных с клиническим подозрением на наличие внутрибрюшной гипертензии; 2) определение показателей внутрибрюшного давления, при которых развивается клиническая картина внутрибрюшной гипертензии; 3) измерение и определение показателей внутрибрюшного давления, при которых развивается абдоминальный компартмент синдром; 4) определение корреляции между степенью внутрибрюшной гипертензии и исходом заболевания.

Для достижения цели нами изучены истории болезни 155 новорожденных, проходивших курс лечения в отделении хирургической реанимации и интенсивной терапии, рожденных в 2008-2010 г.г. с продолжительностью пребывания в стационаре свыше 7 дней. Мониторинг внутрибрюшного давления проводился больным с подозрением на наличие абдоминального компартмент синдрома.

Данные исследования позволяют заключить, что:
- наличие внутрибрюшной гипертензии обнаруживается в большинстве случаев с клиническим подозрением;
- внутрибрюшное давление >10 мм рт.ст. при клиническом подозрении можно считать наличием внутрибрюшной гипертензии;
- внутрибрюшная гипертензия находится в тесной корреляции с наличием жидкости в брюшной полости, подтвержденным ультразвуковым методом обследования;
- внутрибрюшное давление >20 мм рт.ст. является показателем наличия абдоминального компартмент синдрома;
- отмечается тесная корреляционная связь заболевания со степенью гипертензии и исходом заболевания.

რეზიუმე

აბდომინალური ჰიპერტენზიისა და აბდომინალური კომპარტმენტ სინდრომის იდენტიფიკაცია, მართვა და გართულებები ახალშობილთა ინტენსიურ თერაპიაში (ერთი ცენტრის რეტროსპექტული ანალიზი)

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გ. ჟვანიას სახელობის პედიატრიული კლინიკის ახალშობილთა და ბავშვთა კრიტიკული მედიცინის დეპარტამენტი, თბილისი, საქართველო

აბდომინალური კომპარტმენტ სინდრომი წარმოადგენს მომატებული ინტრააბდომინალური

წნევის პათოფიზიოლოგიურ შედეგს, რაც განპირობებულია ქსოვილთა შეშუპებით ან მუცლის ღრუში თავისუფალი სითხის დაგროვებით. მუცლის ღრუში წნევის მომატება განიხილება,როგორც აბდომინალური ჰიპერტენზია, რომელიც მნიშვნელოვან გავლენას ახდენს პაციენტის გამოსავალზე. ამოუცნობი და უმართავი აბდომინალური კომპარტმენტ სინდრომის საბოლოო შედეგს მულტიორგანული უკმარისობა და პაციენტის სიკვდილი წარმოადგენს. აბდომინალური წნევის მონიტორინგი აუცილებელია აბდომინალური კომპარტმენტ სინდრომის კლინიკური გამოვლინებისთვის. ინტრააბდომინალური წნევის ნორმალური მაჩვენებელია 0-5 მმ ვც.ს. ფიზიოლოგიური დარღვევები ვითარდება, როდესაც წნევა აღემატება 8-10 მმ ვც.ს. წნევის 20 მმ ვც.ს-ზე მეტად მომატების პირობებში ვითარდება ქსოვილების შეუქცევადი დაზიანება, რომლის საბოლოო შედეგს აბდომინალური კომპარტმენტ სინდრომისა და მულტიორგანული უკმარისობის განვითარება წარმოადგენს. მომატებული აბდომინალური წნევის ადრეული გამოვლენა და სწორი მართვა განსაკუთრებით მნიშვნელოვანია აბდომინალური კომპარტმენტ სინდრომის თავიდან ასაცილებლად, რაც მკვეთრად აისახება პაციენტის მდგომარეობის გამოსავალზე.

კვლევა მიზნად ისახავდა: 1) ახალშობილებში ინტრააბდომინალურ ჰიპერტენზიაზე კლინიკური ეჭვისას აბდომინალური კომპარტმენტ სინდრომის არსებობის დადგენას; 2) ინტრააბდომინალური წნევის მაჩვენებლების განსაზღვრას, რომლებიც განაპირობებენ ჰიპერტენზიის კლინიკური სურათის განვითარებას; 3) ინტრააბდომინალური წნევის იმ მაჩვენებლების გამოვლენა, რომლებიც მონაწილეობენ აბდომინალური კომპარტმენტ სინდრომის ჩამოყალიბებაში; 4) ინტრააბდომინალური ჰიპერტენზიის ხარისხსა და კლინიკური სურათის შორის კორელაციური კავშირის დადგენას.

მიზნის მისაღწევად ავტორებმა შეისწავლეს 2008-2010 წლებში ახალშობილთა და ჩვილ ბავშვთა ქირურგიულ რეანიმაციაში მყოფი 155 ახალშობილი პაციენტის ისტორია,რომელთა დაყოვნება განყოფილებაში შეადგენდა 7 დღეზე მეტს. ინტრააბდომინალური წნევის მონიტორინგი წარმოებდა აბდომინალურ კომპარტმენტ სინდრომზე ეჭვის შემთხვევაში.

კვლევის შედეგები უფლებას გვაძლევს დავადგინოთ:

- ინტრააბდომინალური ჰიპერტენზია დასტურდება კლინიკურად საეჭვო თითქმის ყველა შემთხვევაში;
- ინტრააბდომინალური წნევა >10 მმ ვც.ს კლინიკური ეჭვის დროს შეიძლება ჩაითვალოს როგორც ინტრააბდომინალური ჰიპერტენზია;
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- ინტრააბდომინალური წნევის მაჩვენებელი ≥20 მმ ვც.ს მიუთითებს აბდომინალური კომპარტმენტ სინდრომის არსებობაზე;
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СТРАТИФИКАЦИЯ ФАКТОРОВ РИСКА ПРОГРЕССИРОВАНИЯ ОСТРОЙ РЕСПИРАТОРНОЙ ИНФЕКЦИИ У ДЕТЕЙ

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Острые респираторные инфекции (ОРИ) характеризуются высокими эпидемиологическими показателями, большим числом осложнений и госпитализации среди детской популяции [1-4,7].

Исходя из вышеуказанного, оценка и анализ патогенетических механизмов и факторов риска осложнений острых респираторных инфекций являются весьма актуальными, так как могут быть заложены в основу прогнозирования клинического течения заболевания [6,8,9] и, тем самым, его профилактики.

Целью исследования явилась комплексная оценка эндогенной интоксикации, угнетения тканевой гипоксии и функции защитной системы, клиническая и лабораторная стратификация риск-факторов, способствующих прогрессированию заболевания и осложнению пневмонией.

Материал и методы. Проведено одномоментное исследование. Подбор исследуемой популяции был осуществлен на основе амбулаторно-стационарного обращения. Наблюдались 36 пациентов в возрасте от 1 до 7 лет с острой респираторной инфекцией. Контрольная группа составила 19 практически здоровых детей. Исследование проводилось с информированного согласия родителей. На каждого пациента заполнялся стандартный специализированный вопросник, который содержал демографические данные, информацию о перинатальном периоде, степени наследственной нагрузки, ретроспективных анамнестических данных, о наличии других заболеваний, эффективности проведенного лечения, социальных данных и др.

Изучались изменение оптической плотности плазмы и эритроцитов; эндотельная система и тканевая гипоксия ферментными и фотоспектрометрическими методами, антиоксидантная система - SOD (супероксиддисмутаза) и активность каталазы, определение NAD (окисленный никотинамидаденин-динуклеотид), NADH (восстановленный никотинамидаденин-динуклеотид), цитохром-С, активность цитоплазмической RNA-азы (рибонуклеаза) и активность кислых катефсинов производилось флюоросцентным методом.

С целью выявления прогнозируемых негативных факторов риска нами учитывались возраст, пол, ранний анамнез, степень наследственной нагрузки, тяжесть основного заболевания пациентов, длительность и особенности течения болезни, сочетанная патология, проведенное лечение и его эффективность. Проводился сравнительный анализ данных вышеуказанных параметров и лабораторных исследований. В отношении стандартных и специфических риск-факторов определено соотношение шансов (OR) с применением тетрахорической таблицы. Определение количественных данных риск-факторов осуществлялось с учетом 95% интервала (CI) доверия.

Статистическая обработка полученных данных производилась на основе программного пакета SPSS v.12.

Результаты и их обсуждение. При острой респираторной инфекции, протекающей без осложнений, на второй день после выявления симптомов болезни в спектрограмме плазмы выявлено достоверное увеличение максимума экстинкции эритроцитов и повышение оптической плотности плазмы.

На третий день, после выявления симптомов острой респираторной инфекции вместе с повышением оптической плотности эритроцитов отмечено достоверное увеличение экстинкции плазмы по сравнению с нормой (таблица 1).

Таблица 1. Изменение оптической плотности плазмы и эритроцитов (интегральный показатель эндогенной интоксикации при острой респираторной инфекции)

Заболевание	Плазма/ эритро-циты	Продолжительность болезни (дни)				
		2	3	5	7	30
ОРИ	плазма λ=282 нм норма 0,24±0,05 ед.опт. плотности	0,33±0,04	0,78±0,04**	0,58±0,12***	0,35±0,08	0,32±0,100
	λ=258 нм норма эритроцит 0,56±0,05 ед.опт. плотности	0,78±0,08*	1,61±0,08**	1,24±0,18***	0,88±0,05**	0,63±0,04
ОРИ +пневмония	плазма λ=282 нм	0,55±0,04*#	0,88±0,04**	0,98±0,12***##	0,85±0,08**##	0,42±0,10
	эритроци-ты λ=258 нм	1,12±0,13***##	1,89±0,18***#	1,63±0,15***#	0,43±0,05*	0,67±0,04

*примечание: средняя разность * - по сравнению с нормой при ОРИ, протекающей без осложнений: * - p<0,001; ** - p<0,01; *** - p<0,05;*
 # - при ОРИ, осложненной пневмонией, по сравнению только с ОРИ: # - p<0,001; ## - p<0,01

Таблица 2. Диагностические критерии угнетения антиоксидантной системы организма в динамике при ОРИ и ОРИ, осложненной пневмонией

Показатель		норма	груп-па	продолжительность болезни (дни)			
				2	3	7	30
система антиоксидантной защиты	SOD,пир. одна/мин. мг. белка	28,9±2,6	ОРИ	42,9±2,3*	41,5±2,2**	31,6±1,2	22,6±1,9***
			ОРИ + пнев.	44,7±1,5*	31,6±4,2**#	30,5±1,0**	25,6±1,2***
	каталаза,нмолл H_2O_2-/мг белка мин.	77±9	ОРИ	79,5±4,3**	83,4±4,2+	74±2+	74,5±1,6
			ОРИ + пнев.	72,8±2,5***	51,6±3,2**	67±6**	72,9±2,2***
система лизосомов	катепсин D н.молл.тиро-зин л	21,4±1,4	ОРИ	24,6±0,6	26,9±1,2*	26,9±1,4*	21,9±0,0
			ОРИ + пнев.	27,9±1,5	31,6±1,2***	31,6±1,3**	22,6±1,2
	RNA-аза м/ммол.мин.	2,1±0,2	ОРИ	1,7±0,4	2,6±0,1*	2,4±0,2	2,0±0,1
			ОРИ+ пнев.	2,9±0,5	3,6±0,2***	3,6±0,2***	2,4±0,2

*примечание: средняя разность по сравнению с нормой при ОРИ, протекающей без осложнений: * - p<0,001; ** - p<0,01; *** - p<0,05*

При острой респираторной инфекции, осложненной пневмонией, в начале болезни достоверно повышается экстинкция плазмы и эритроцитов по сравнению с нормой.

Степень эндотоксемии указывает на нарушение равновесия между образованием эндотоксинов и возможностями их биологической трансформации и системы элиминации [8]. На седьмой день болезни на спектрограмме отмечалось резкое понижение экстинкции эритроцитов, указывающий на нарушение структуры эритроцитов и понижение оптической плотности плазмы. При острой респираторной инфекции, осложненной пневмонией (таблица 2), зафиксировано развитие ярко выраженной токсемии, отмечена также высокая активность антиоксидантной системы (SOD и каталаза) и лизосомных ферментов (катепсин, RNA-аза).

Таблица 3. Показатели тканевой гипоксии в динамике

Показатель	Норма	Продолжительность болезни (день)			
		2	3	7	30
АТР	75±3	69±9	66±5	70±4	76±4
		67±8	63±5*	61±4*	75±4
СР	86±6	82±4	80±4	83±2	87±2
		79±2	73±5*	71±4*	84±4
цитохром С, нмолл /мл.	0,65±0,05	0,60±0,03	0,59±0,02	0,63±0,04	0,62±0,03
		0,63±0,03	0,65±0,03	0,72±0,04	0,65±0,04
NAD	3,4±0,4	3,55±0,08	3,62±0,05	3,60±0,05	3,38±0,03
		3,6±0,1	3,5±0,1	2,8±0,2*#	3,2±0,1
NAD/NADH	1,06±0,12	0,94±0,03	0,88±0,04*	0,98±0,04	1,0±0,1
		0,93±0,06	0,83±0,6*	0,78±0,04*#	0,92±0,08

*примечание: средняя разность * - по сравнению с нормой при ОРИ, протекающей без осложнений: *- p<0,001; **- p< 0,01; ***- p<0,05; # - при ОРИ, осложненной пневмонией, по сравнению только с ОРИ: # - p<0,001*

На завершающем этапе исследования по отношению клинических, лабораторных и специфических риск-факторов были определены шансы соотношения [5] и на основании полученных данных осуществлена стратификация прогнозирования риска течения острой респираторной болезни. Для больных ОРИ была проведена риск-стратификация осложнения пневмонией.

Для риск-стратификации при ОРИ нами были определены следующие прогнозируемые параметры:
- возраст детей;
- наследственная нагрузка с патологией распираторного тракта;
- частое заболевание острой респираторной инфекцией;
- употребление табака в семье;
- низкий уровень информированности родителей;
- характер и продолжительность лечения;
- изменение оптической плотности плазмы и эритроцитов;
- снижение редокс-потенциала системы энергетического обеспечения.

Определен прогноз достоверных данных риск-факторов по следующим показателям: возраст ребенка (до трех лет) - OR=2.8 (CI-0.93-8.3); наследственная нагрузка с патологией дыхательной системы - OR= 3,68 (CI-1.22-11.1); частое заболевание острой респираторной инфекцией - OR=3,68 (CI-1,22-11,1); употребление табака в семье - OR= 6.31 (CI-1.1-35.3); низкий уровень информированности родителей - OR= 2.3(CI-0.6-9.1); неполное

лечение - OR=2.62 (CI-0.8-8.5); изменение оптической плотности плазмы и эритроцитов - OR=1.37 (CI-0.4-4.1); понижение (уменьшение) редокс-потенциала системы энергетического обеспечения - OR=1.58 (CI- 0.5-4.6).

Нами разработана прогнозтическая модель, которая позваляет предположить вероятность ожидаемых осложнений со стороны респираторной системы среди детей.

Группа низкого риска: ОРИ - транзиторные изменения лабораторных данных.

Группа среднего риска: ОРИ, частые респираторные инфекции с длительным течением - изменения оптической плотности плазмы и эритроцитов.

Группа высокого риска: ОРИ, частые респираторные инфекции; активные курильщики в семье; наследственная нагрузка с патологией респираторного тракта; низкая информированность родителей - изменение оптической плотности плазмы и эритроцитов; понижение редокс-потенциала, сопровождаемое осложнением пневмонией.

Таким образом, нами осуществлена риск-стратификация прогрессирования острой респираторной инфекции, что может лечь в основу разработки целенаправленных превентивных терапевтических мероприятий.

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SUMMARY

STRATIFICATION OF RISK FACTORS OF PROGRESSING OF ACUTE RESPIRATORY INFECTION IN CHILDREN

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The work purpose is the complex estimation of endogenous intoxication (change of optical density of plasma and erythrocytes), depressions of tissue hypoxia and functions of protective system, clinical and laboratory stratification of the risks-factors promoting progressing of disease and complication of pneumonia. There was carried cross-section study. The study included 36 patients from 1 to 7 years with an acute respiratory infection. The control group was made up of 19 healthy children. The comparative analysis of results of the specified factors and laboratory research set as the purpose to reveal the predictable negative risk factors. Evaluation of the quantitative findings of risks-factors was carried out in 95 % taking into account the confidence interval (CI). For the acute respiratory infection complicated with pneumonia, was determined strongly marked toxemia, and also high activity of antioxidant systems (SOD and catalase) and lysosomal enzymes (catepsin, RNA) was noted. The prognosis of the authentic risks-factors of acute respiratory disease was defined with following indicators: age of the child - before three years; hereditary background with a

respiratory system pathology; the tobacco use in a family; low level of knowledge of parents; incomplete treatment; change of optical density of plasma and erythrocytes; fall (reduction) of redox-potential of the system of energy maintenance. We developed predictable model on probability of expected complications of respiratory system and groups of low, average and high risk were allocated.

Key words: respiratory infections, pneumonia, tissue hypoxia, catalasa, SOD, NAD NADH.

РЕЗЮМЕ

СТРАТИФИКАЦИЯ ФАКТОРОВ РИСКА ПРОГРЕССИРОВАНИЯ ОСТРОЙ РЕСПИРАТОРНОЙ ИНФЕКЦИИ У ДЕТЕЙ

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Цель исследования - комплексная оценка эндогенной интоксикации (изменение оптической плотности плазмы и эритроцитов), угнетения тканевой гипоксии и функции защитной системы, клиническая и лабораторная стратификация риск-факторов, способствующих прогрессированию заболевания и осложнению пневмонией. Проведено одномоментное исследование. Было охвачено 36 пациентов в возрасте от 1 до 7 лет с острой респираторной инфекцией. Контрольная группа составила 19 практически здоровых детей. Определение количественных данных риск-факторов осуществлялся с учётом 95% интервала (CI) доверия. При острой респираторной инфекции, осложненной пневмонией, зафиксировано развитие ярко выраженной токсемии, отмечена высокая активность антиоксидантной системы (SOD и каталаза) и лизосомных ферментов (катепсин, RNA-аза). Определен прогноз достоверных данных риск-факторов острой респираторной болезни по следующим показателям: возраст ребенка - до трех лет; наследственная нагрузка с патологией дыхательной системы; частое заболевание острой респираторной инфекцией; употребление табака в семье; низкий уровень информированности родителей; неполное лечение; изменение оптической плотности плазмы и эритроцитов; понижение редокс-потенциала системы энергетического обеспечения. Нами разработана прогнозтическая модель с учетом вероятности ожидаемых осложнений со стороны респираторной системы и выделны группы низкого, среднего и высокого риска.

რეზიუმე

მწვავე რესპირატორული ინფექციის პროგრესირების რისკ-ფაქტორების სტრატიფიკაცია ბავშვებში

ნ. მანჯავიძე, ლ. ჟორჟოლიანი, თ. ბარბაქაძე, რ. გუჯაბიძე, მ. კაჭკაჭიშვილი

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი; ივ. ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი

კვლევის მიზანი იყო მწვავე რესპირატორული ინფექციის დროს ენდოგენური ინტოქსიკაციის (პლაზმისა და ერითროციტების ოპტიკური სიმკვრივის ცვლილება), ქსოვილოვანი ჰიპოქსიის და დაცვითი სისტემების ფუნქციის დათრგუნვის კომპლექსური შეფასება, დაავადების პროგრესირებისა და პნევმონიით გართულების ხელშემწყობი კლინიკური და ლაბორატორიული რისკ-ფაქტორების სტრატიფიკაცია. ჩატარდა ერთმომენტიანი კვლევა. კვლევამ მოიცვა 1-დან 7 წლამდე ასაკის მწვავე რესპირატორული ინფექციით დაავადებული 36 პაციენტი. საკონტროლო ჯგუფი შეადგინა 19 პრაქტიკულად ჯანმრთელმა ბავშვმა. რისკის ფაქტორების რაოდენობრივი მონაცემების განსაზღვრა ხდებოდა 95% სანდოობის ინტერვალის (CI) გათვალისწინებით. მწვავე რესპირატორული ინფექციის პნევმონიით გართულებულ შემთხვევებში დაფიქსირდა გამოხატული ტოქსემიის განვითარება, აღი-ნიშნა ანტიოქსიდანტური სისტემის (SOD და კატალაზა) და ლიზოსომური ფერმენტების (კათეფსინი, RNA-აზა) მაღალი აქტივობა.

განისაზღვრა მწვავე რესპირატორული ინფექციების დროს პროგნოზულად მნიშვნელოვანი რისკ-ფაქტორები: ბავშვის ასაკი 3 წლამდე; მემკვიდრული დატვირთვა სასუნთქი სისტემის პათოლოგიით; ხშირი რესპირატორული ინფექციები; თამბაქოს მოხმარება ოჯახში; მშობლების ინფორმირებულობის

დაბალი დონე; არასრული მკურნალობა; პლაზმისა და ერითროციტების ოპტიკური სიმკვრივის ცვლილება; ენერგეტიკული უზრუნველყოფის სისტემის რედოქს-პოტენციალის დაქვეითება.

შემუშავდა რესპირატორული სისტემის მხრივ მოსალოდნელ გართულებათა ალბათობის სამი პროგნოზული მოდელი და გამოიყო დაბალი, საშუალო, მაღალი რისკის ჯგუფები.

ENVIRONMENTAL SAFETY RISK RESEARCH

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Georgia has experienced very rapid economic and infrastructural change since the collapse of the former USSR in 1992 and the so-called "rose revolution" in 2003. A high percentage of population has moved from rural to urban centers, where they are self-employed in small businesses with little income. Universal access to health care no longer exists and the government insurance system is critically under-funded. In general, the standard of living of the population has declined markedly and lifestyles appear to have become less healthy. The citizens of Georgia are no longer protected by a centralized health sector that provided free universal access to services for everyone.

That the environment is an instrument of disease is a long held concept in environmental health and medicine. The ecological situation in Georgia is still a problem [8]. The renewing of manganese extraction increased the risk of different diseases as a result of economic crisis and infrastructural changes in the health care system. The sanitary condition of the territories has an important hygienic significance for proper living conditions of the population. No ecological risk assessments that describes soil air, water, or food products exist, so manganese concentrations in Zestaforni are not well characterized. We do not have reliable data on human health outcomes from manganese exposures in these regions. There is no real system for protection and insurance for citizens of these regions during pregnancy [1-4].

The principal aim of the proposed research is to study workers health in ecologically polluted regions of the Republic of Georgia. A survey will be conducted in Imareti district - Zestaponi (where a manganese refinery factory is located). The proposed research provide preliminary data and form the basis for a large-scale epidemiologic investigation to identify risk factors for Mn and population health.

Material and methods. Overall 102 workers have been surveyed. They were selected from the list circulating in the plant ambulance. Selected workers have been surveyed through a standard questionnaire. The survey revealed that prevalence of such diseases as Radiculitis, hypertension, bronchitis, gastritis, and ulcer, ocular and nasal-pharyngeal diseases are high among the workers of the Zestafoni Processing Plant.

By SPSS software was analyzed database of Pilot epidemiology survey conducted within the Zestaponi manganese Factory workers research.

Results and their discussion. When was asked to evaluate their health, 4,9% of workers estimated their health as a "poor", 15,7% - as a "good" and other 79,4% noted that their health was "satisfactory". More than half workers 62,7% think their health problems are associated to working conditions. Workers' sincerity when self-evaluating their health conditions may raise doubts, as during similar surveys workers usually avoid speaking about their health problems in fear of losing their jobs. 95,2% of comparison surveyed individuals consider their health condition as good or satisfactory.

Like all Georgia in general, among the respondents the prevailing are families with two children (50%), com-

paratively less are families with one and three children. 2,0 % of respondents do not have children yet.

Chronic inhalation of manganese and its compounds from air, soil and waste, first of all, affects respiratory organs, nervous and reproductive systems.

The characteristic features of the spread of certain diseases and complaints among the workers were studied using the descriptive epidemiology study methods. Since manganese has a distinct cumulative capacity, of particular interest is the spread of these diseases among the surveyed individuals, who for different periods of time were engaged in manganese production. According to the years of working at the factory were defined five groups of workers: individuals with the length of experience up to 2 years; 2-10; 11-20; 21-30 and more than 30. We studied the characteristic features of spread of diseases and complaints among each of them. Apart from the length of service, the respondents differ according to the characteristics of the performed work. Obviously those, who work directly in the Factory, are exposed to particular risk. It is interesting to what extent the diseases in the afore said surveyed individuals differ from those of the rest of employees engaged in manganese production. For that purpose we compared the spread of diseases and complaints among simple workers (44,1%) and smelter workers (52,0%) of the factory.

According to the survey findings, the prevalence of Radiculitis, high blood pressure and eye disease is rather high among smelter workers then others. The aforesaid problems are especially widespread among the male population. Gastrointestinal, throat-noise diseases (gastritis, ulcer), and bronchitis have low distribution. The most respondents in our survey are males, thus, further analytical survey will show, whether the prevalence of gastritis and ulcer reflects the general tendency in the country or is connected with occupational factors.

Radicullitis is the second widely spread disease among the workers in the world. In our survey 25,5% of workers and 32,1% of smelter workers were suffer from Radicullitis –it means that every third of smelter workers had radicullitis. Based on etiology typical for Radiculitis we may say that widespread of this disease is related to the working conditions – damp environment, heavy manual labor.

Hypertension is widespread not only among the workers but also in the entire population of Georgia and it is the main cause of morbidity and mortality. Thus, the aforesaid disease is not related to occupational factors. But among smelter workers it has high distribution (24,5%) and it seems every the forth of smelter workers have high blood pressure.

The survey results revealed that upper respiratory diseases such as pneumonia, bronchitis, bronchial asthma are not widely distributed among the workers. Inhalation of manganese dioxide and trioxide causes inflammatory processes in lungs. The symptoms and signs that may occur as a result of lung damage are cough, bronchitis, pneumonia and weakening of pulmonary function. Lung intoxication increases its sensitivity to infections and sometimes manganese pneumonia is developed.

So the most part of factory workers have problems with above mentioned diseases, listed in order of prevalence: Radiculitis; Hypertension; Eye diseases; Bronchitis; Gastritis; Throat-Nose; Ulcer.

It Needs to mention among selected group of smelter workers was found low frequency of the diseases – Pneumonia, Cancer (Not lung cancer – 2,2%), Parkinson and nervous system disorders. According current research data other workers have not several disease - dermatitis, diabetes, mental diseases – it may be result of small number of cases, but otherwise this disease seems to be not problematic among workers.

Research ratio distribution of diseases between the smelter workers and other factory workers – Gastritis, Radiculitis and vascular diseases more frequently in smelter workers – ratio – more than 2. But Bronchial asthma and throat-nose diseases – in other workers – ratio up to 2). But in both cases they are significantly more than for non Factory workers,

Radiculitis, High blood pressure, Eye Diseases, Bronchitis, Hearth diseases, Gastritis, Throat - Nose, Ulcer are widely distributed among Zestaponi workers. The prevalence of radicualities among respondents living within 1 km around the factory is only 4,9%. Prevalence of diseases is higher among the workers that lived within 2-5 km around the factory, then among the workers living within 5-10 km. The Most high prevalence detected for throat-nose diseases within 2-5 km of residence from the factory. So there is

primary correlations between the risk of developing disease and distance from the Factory. High prevalence of these disease is related to air pollution and to the working conditions – damp environment, heavy manual labor, as well.

The respondents living near MMT – gasoline station have defined additional risk of high blood pressure (ratio - 3,8), For other diseases additional risk was not registered.

Radiculitis, High blood pressure, Eye Diseases, Bronchitis, Hearth diseases, Gastritis, Throat - Nose, Ulcer are the most frequent among the workers of factory who have been working in Zestaponi manganese Factory for 20-30 years. 50,0% of workers with 20-30 year of experience are suffer from Hearth diseases, 48% - from Radiculitis, 44,4% – from eye diseases, 37,5% - from Bronchitis . We can see primary dependence and correlation between length of experience and mentioned diseases prevalence. Study revealed high prevalence of Eye and Throat-Nose diseases among factory workers, who have been working for a long time period. The main cause of those diseases is high air pollution and absents of smelter filters.

Radiculitis, High blood pressure, Eye Diseases, Bronchitis, Hearth diseases, Gastritis, are the most frequent among old workers. According study results there is no correlation between Throat – Nose and Ulcer diseases and ages.

It is need to be mentioned, that the hypertension is generally high among all Georgian population as well as at Zestaponi.

It is a common knowledge, that there is high risk of nervous system damages among the workers who are exposed to high concentration of manganese at their working place smelter workers. As a result of prolonged exposure to manganese functional changes in central nervous system and symptoms of autonomic dysfunction develop, which further promotes the formation of encephalopathy or amyostatic syndrome (syndromum amyostaticum). At the initial stage, there is a general weakness, headache, difficulty walking, tremor of fingers, psycho-emotional lability, pathological laughing and crying.

Statistical analyses show, that there are high level of complaints typical for damage of central nervous system – sleep disorders, Supper from sweat, Back pain walking difficulties. 73,4% and 45,9% of respondents noted about sleep disorders and sleep during the day occurs at, and have high prevalence among smelter workers. Sweat problems are highly distributed among smelter workers also.

Comparatively small percent of respondents indicated complaints characterized for functional changes of central nervous system with vegetative dysfunction - weakness in hands and feet or swelling. Swelling appears among 22,4% of respondents. Low prevalence of memory impairment was revealed among the respondents.

Back pain and walking difficulties were more distributed Among Manganese Factory workers, than Zestaponi those are correlated to the high risk of Radiculitis among workers.

Correlations were revealed between diseases and type of work. High prevalence of sweat– up to 75% was determined among smelter workers, when among other workers it is about 25% - 3 times less. Cough had especially high distribution among smelter workers – 32,1% and was approximately 4 times higher than among the other workers!

So factory workers mostly have above mentioned professional problems and diseases symptoms. Professional problems below are listed in the order of prevalence: Sleep disorders; Sleeping during the day; Sweat problems; back pain; walking difficulties at ladder; Swilling; Noise at hear; Cough.

Mainly these are professional disease symptoms. Only walking difficulties - go up a ladder can considered as a problem caused from cardio-vascular disorders, Cough and high-intensity noise also seems problematic; Respiratory system problems, those are distributed widely, include bronchitis and throat -Nose diseases.

It needs to mention, among smelter workers was found very low distribution of symptoms related to the memory disorders and was not found calligraphy problems, otherwise the diseases cause this symptoms seems to be not problematic among workers.

Respondents living within 1 km around the factory is small. The prevalence of the central nervous

system symptoms is higher among the workers that lived within 2-5 km around the factory than those lived far more than 5 km. High prevalence were detected for caught, sleep disorders and swelling. So there were negative correlations between risk of developing symptoms and distance from the Factory. High prevalence of these symptoms are related to the working conditions – damp environment, heavy manual labor.

Swelling, Cough and sleep disorders have the most frequent distribution among workers who have worked in Zestaponi Manganese Factory for 20-30 years. Swelling had the most high prevalence - up to 50,0% among the workers with 10-20 years of experience.

Walking up on ladder causes difficulties for up to 75% of workers among 50-69 of age – that correlated with High blood pressure and Bronchitis. Cough also problematic among the older workers. Symptoms, those are characterized for occupational disorders, have high prevalence at 50-59 years of age. However the cardiovascular system diseases have high prevalence at the same age group in population. High percentage of the sleep problems among the workers may be reason of nervous system disorders.

The results proven correlation between occupational factors and diseases and different symptoms are of great importance. Though, it should be mentioned that this study was only pilot study, and desirable, more comprehensive, larger scale and prospective study has to be undertaken in the future, with focus on the above health problems.

As it has been stated above, the primary objective of our survey was to study the adverse affect of occupational exposures on Zestaponi manganese Factory workers'. There is no distinct connection between the intensity of intoxication and manganese concentration in the working air.

Diseases such as Radiculitis, Hypertension, Eye diseases, Bronchitis, Gastritis, Throat-Nose, Ulcer – have high prevalence among workers of Zestaponi manganese Factory.

According study results there was primary correlations between the risk of developing some diseases and distance from the factory. Prevalence of Hypertension, Eye diseases, Bronchitis, Throat-Nose diseases among the workers that liИed within 2-5 km around the factory was higher, then among the others.

Study results show primary correlation between length of experience and prevalence of Bronchitis, Eye diseases, Radiculitis, Hypertension, Heart diseases and Gastritis.

Study revealed high prevalence of symptoms characterized for central and vegetative nervous system such as Sleep disorders, sleep during a day, swilling, back pain, walking difficulties at ladder, sweat.

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SUMMARY

ENVIRONMENTAL SAFETY RISK RESEARCH

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Pilot epidemiology survey has been conducted with the aim to study the effect of occupational factors on workers in the Zestafoni Manganese Processing Plant. Overall 102 workers have been surveyed. They were selected from the list circulating in the plant ambulance. Selected workers have been surveyed through a standard questionnaire. The survey revealed that prevalence of such diseases as Radiculitis, hypertension, bronchitis, gastritis, and ulcer, ocular and nasal-pharyngeal diseases are high among the workers of the Zestafoni Processing Plant. Study results have shown direct correlation between development of diseases and distance residence from the plant. Prevalence of hypertension, ocular and nasal-pharyngeal diseases, bronchitis was higher among workers lived within distance of 2-5 kilometers from the plant. Positive correlation revealed between length of job and prevalence of bronchitis, ocular diseases, Radiculitis, hypertension, cardiac diseases and gastritis. Among plant workers revealed high prevalence of symptoms characterized the central nervous system disorders such as sleep disorder, insomnia, backache, walking disorders. The results proven correlation between occupational factors and diseases and different symptoms.

Key words: manganese, survey, risk factor, environment.

РЕЗЮМЕ

ОЦЕНКА РИСКОВ ОКРУЖАЮЩЕЙ СРЕДЫ

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Проведены эпидемиологические исследования с целью изучения влияния производственных факторов на рабочих Завода ферросплавов г. Зестафони. Обследовано 102 рабочих из числа находящихся на учете в поликлинике завода. Опрос рабочих проведен по стандартному опроснику. Выявлено, что распространенность ряда заболеваний (хронический радикулит, артериальная гипертензия, бронхит, хронический гастрит, язвенная болезнь желудка и 12-перстной кишки, ЛОР-органов и органов зрения) среди рабочих Зестафонского завода ферросплавов высока. Прослеживается прямая взаимосвязь между частотой выявления заболеваний и расстоянием от места жительства до завода. В частности, распространенность артериальной гипертензии, глазных и ЛОР-заболеваний, хронического бронхита оказалась выше среди рабочих завода, проживающих на расстоянии от 2 до 5 км от производства. Положительная корреляция выявлена между стажем рабочих и частотой заболеваемости хроническим бронхитом, болезней органов зрения, хроническим радикулитом, артериальной гипертензией и другими сердечно-сосудистыми заболеваниями, хроническим гастритом. Среди рабочих завода выявлена высокая распространенность симптомов поражения центральной нервной системы: расстройство сна, боли в области поясницы, затруднение в ходьбе. Результаты исследования свидетельствуют о связи между факторами производственной среды изученного предприятия и выявленными заболеваниями (симптомами).

რეზიუმე

გარემოს რისკების უსაფრთხოების შეფასება

მ. ფირცხალავა, რ. ჯავახაძე, მ. მირცხულავა, ნ. ჩაკვეტაძე

სამედიცინო უნივერსიტეტი «გეომედი», თბილისი, საქართველო

ზესტაფონის ფეროშენადნობთა ქარხნის მუშებზე პროფესიული ფაქტორების მოქმედების შესწავლის მიზნით ჩატარდა პილოტური ეპიდემიოლოგიური კვლევა. გამოკითხული იქნა ქარხნის 102 მუშა, რომელთა შერჩევა მოხდა საქარხნო პოლიკლინიკაში არსებული სიიდან. შესწავლილ კონტინგენტში გამოვლინდა ქრონიკული რადიკულიტის,ჰიპერტენზიული დაავადების, ქრონიკული ბრონქიტის, ქრონიკული გასტრიტის, კუჭისა და 12-გოჯა ნაწლავის წყლულოვანი დაავადებების, თვალისა და ყელ-ყურ-ცხვირის დავადებების მაღალი პრევალენტობა. აღინიშნა პირდაპირი კორელაცია მუშთა დაავადებათა პრევალენტობასა და ქარხნამდე საცხოვრებელი ადგილის მანძილს შორის. კერძოდ, არტერიალური ჰიპერტენზია, ქრონიკული ბრონქიტი, თვალისა და ყელ-ყურ-ცხვირის დავადებების განვითარების რისკი უფრო მაღალია იმ მუშებს შორის, რომლებიც ქარხნიდან 2-დან 5 კმ-ის მოშორებით ცხოვრობენ. დადებითი კორელაცია გამოვლინდა სამუშაო სტაჟსა და რიგ დაავადებების სახეშირეს შორის (ქრონიკული ბრონქიტის, ქრონიკული რადიკულიტის, არტერიალური ჰიპერტენზიასა და სხვა გულ-სისხლძარღვთა სისტემის პათოლოგია, ქრონიკული გასტრიტის,თვალის) ასევე გამოვლინდა ცენტრალური ნერვული სისტემის დაზიანებისათვის დამახასიათებელი სიმპტომებიც: ძილის ფორმულის დარღვევები, ტკივილი წელის არეში, მოძრაობის კოორდინაციის დარღვევები და სხვა. კვლევის შედეგები მეტყველებენ პირდაპირ კავშირზე პროფესიულ ფაქტორებსა და ცალკეულ დაავადებებს (სიმპტომებს) შორის.

PANCREATIC D-CELLS IN AGING AND INTRAISLET EFFECTS OF PANCREATIC SOMATOSTATIN

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The interest expressed by the scientific world toward the pancreatic D-cells still is highly active [6,8-12,14]. D-cells produce somatostatin, which is known as an universal inhibitor (inhibits secretion of growth hormone, gastrin, insulin, glucagon, renin). The fact, that D-cells are not the only source of somatostatin in the human body, provokes the high interest toward the mentioned cells and its endocrine and paracrine influences on organisms; To study and determine the autocrine and intracrine effects of somatostatin is of great scientific importance as well.

It should be emphasized as well, that scientists' view regarding the role of D-cell somatostatin in pancreatic intraislet (local) regulatory processes not infrequently is controversial. The specific intraislet function of D-cell somatostatin remains uncertain [2].

As the rate of development of such disorders as diabetes mellitus (type 2) and the other metabolic disturbances are more frequent at old ages, to reveal D-cells acting mechanisms in pancreatic islets, especially in aging process, is of great interest. Involution aging

processes in pancreatic B- and A-cells at old ages have been studied on animals [4,5]. At the same time it was noted that the number of D-cells doesn't change in accordance with the aging process [3,5].

The aim of the study was the revelation of morphological peculiarities of pancreatic D-cells in aging, which will serve as the background for carrying out the judgment on functional activity and local significance of the mentioned cells in aging.

Material and methods. For study 40 male white rats were used. It was selected four ages: pubertatic period of life (10 animals), adult period of life (10 animals), early period of senescence (10 animals) and late period of senescence (10 animals). Under the ether narcosis the animals were sacrificied.The tissue taken from pancreas has been processed for electron microscopy. Ultrastereometrical study was performed by the test-system expressed on translucent tapes which were put on the electronograms, taken at magnification x 4000 and printed at magnification x 10000. In each experimental case have been studied 100 D-cells [16]. The obtained quantitative data has been analyzed statistically by Student's criterium (t).

Results and their discussion. The results of the study have shown (table 1), that in adult period of life, in comparison with the animals in pubertatic period of life, the average volume indices of mitochondria in the D-cells of pancreatic islets are elevated by 35.8% (t=3,7); The above-mentioned index in the early period of senescence is increased by 25.0% (t=4,4) in comparison with the animals of adult period of life and is not changed in the late period of senescence (t<2,0). The average volume indices of granular endoplasmatic reticulum (GER) in animals of adult period of life do not undergo changes to compare the same indices in pubertatic period (t < 2,0), while in the early period of senescence in comparison with adult period elevates by 11.6% (t=2,5) and remains on the same level in the late period of senescence. The average volume indices for Golgi apparatus is not changed (t=0,5; t=0,6; t=0,9), though reveals the tendency to elevation during the aging. The average volume index of secretory granules in adult period of life in comparison with pubertatic period is increased by 19.3% (t=3,2); the mentioned parameter does not change in the animals of early period of senescence (t < 2,0), while in the late period of senescence is reduced by 15.4% (t=3,1) in comparison with the animals of early senescence and by 23.8% (t=4,6) – in adult period of life.

Table 1. Volume part (in %) of pancreatic D-cells organelles of white rats during the different ages

Age	Organelles	Average volume indices of organelles
Pubertatic period of life	Mitochondria	2,15±0,19
	GER	13,12±0,31
	Golgi Apparatus	1,22±0.04
	Secretory Granules	35,75±1,31
Adult period of life	Mitochondria	2,92±0,09
	GER	14,05±0,41
	Golgi Apparatus	1,26±0.05
	Secretory Granules	42,67±1,71
Early period of senescence	Mitochondria	3,65±0,14
	GER	15,86±0,51
	Golgi Apparatus	1,31±0.05
	Secretory Granules	8,46±1,31
Late period of senescence	Mitochondria	3,65±0,14
	GER	15,86±0,51
	Golgi Apparatus	1,38±0,05
	Secretory Granules	32,53±1,38

Visually, in the pancreatic D-cells of old ages – in the early and late periods of life (in comparison with the pubertatic and adult periods of life) the volume and number of mitochondria, as well as the number and size of mitochondrial crysts are increased; the number of membranes of granular endoplasmatic reticulum is increased as well together with the elevation of number and sizes of membrane-attached and free ribosomes and polisomes; the Golgi apparatus is well defined; the number of secretory granules is decreased. Besides, destructive processes absent and disorganization of cells' structures are not prominent (Figs. 1-7).

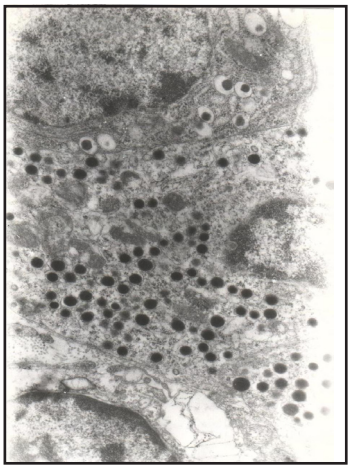

Fig. 1. Ultrastructures of normal pancreatic B-, A-, D-cells. Electron microscopy: x 36 000, JEM-1200ex. White rat (Pubertatic period of life)

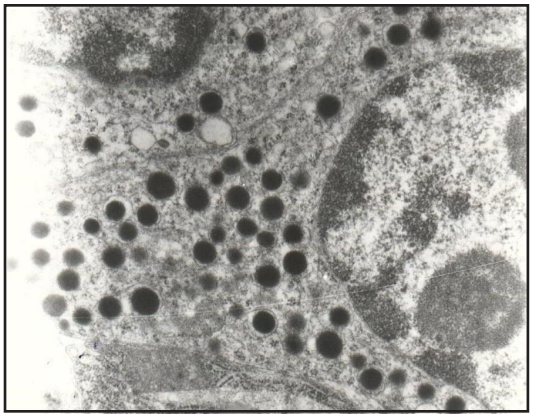

Fig. 2. Ultrastructures of normal pancrearic D-cells. Electron microscopy x 36 000, JEM-1200ex. White rat (Pubertatic period of life)

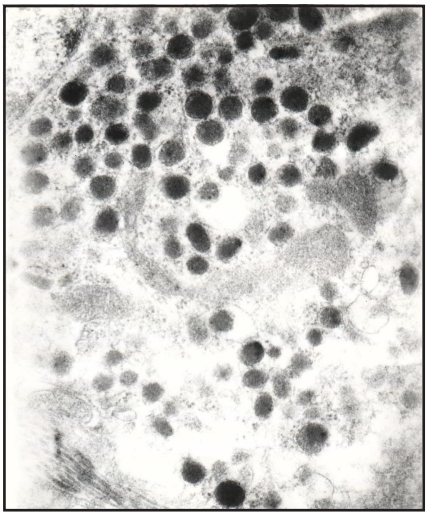

Fig. 3. Ultrastructures of normal pancrearic D-cells. Electron microscopy x 75 000 JEM-1200ex. White rat (Adult period of life)

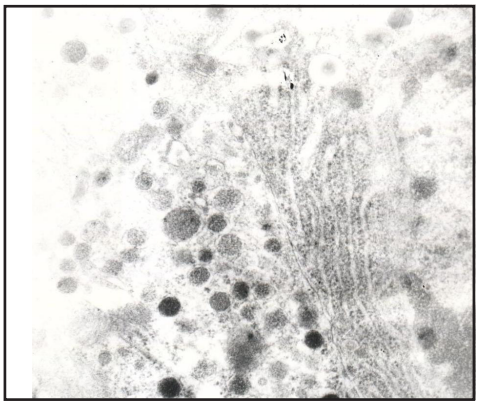

Fig. 4. In the pancreatic D-cells the number of membranes of granular endoplasmatic reticulum is increased as well together with the elevation of number and sizes of membrane-attached and free ribosomes and polisomes; the volume and number of mitochondria are increased as well; the number of secretory granules is decreased. Electron microscopy: x 75 000, JEM-1200ex. White rat (Early period of senescence)

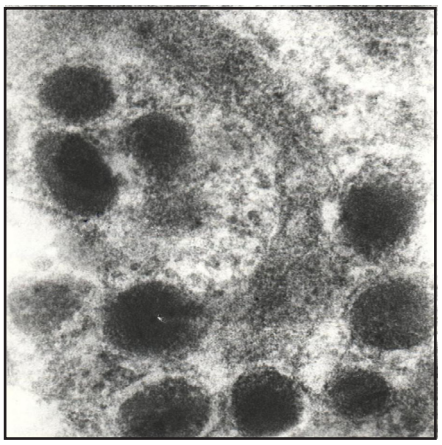

Fig. 5. Secretory granules in the pancreatic D-cells. Electron microscopy: x 240 000, JEM-1200ex. White rat (Early period of senescence)

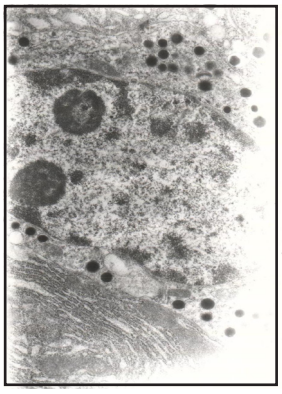

Fig. 6. In the pancreatic D-cells the number of membranes of granular endoplasmatic reticulum is increased; the number of secretory granules is decreased. Destructive processes absent and disorgani-

zation of cells' structures are not prominent. Electron microscopy: x 36 000, JEM-1200ex. White rat (Late period of senescence)

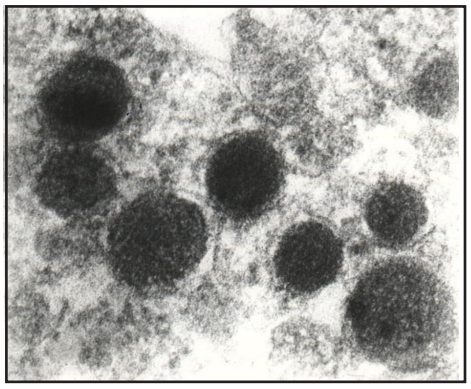

Fig. 7. Secretory granules in the pancreatic D-cells. Electron microscopy: x 240 000, JEM-1200ex. White rat (Late period of senescence)

According to the above-mentioned, the number of D-cells in the white rats of early and late senescent periods of life in comparison with the young organisms does not undergo changes, while functional activity is enhanced, reflected by the elevation of volume and number of organelles involving in secretion of pancreatic D-cells and decrease of number of secretory granules, damage is not revealed. Respectively, intensification of secretory and extrusive functions are more prominent in old organisms then in young ones.

For making definite conclusion concerning to D-cells' local intraislet regulating influences (as in young as in aging bodies), comprehensive analysis of the searched materials and scientific literature is needed. In this respect a great attention should be paid to the cytotopographic and vascular features of pancreatic islets. Excessive number of capillaries is fixed in the central part of the islet, where creation of sinusoidal nets from them is considered as a frequent process. Human beings and rodents are characterized by so called "Mantle" type islets – with the heart of B-cells in it (disposed along the capillaries in the islets) and the mantle of A- and D-cells peripherally. Content of D-cells in the islets is low and equals to 3-10%. Pancreatic islet has its own microcirculation and investigation of blood flow direction in the islet microvasculature is of great importance as well. Firstly, it was thought that in the islet capillaries blood flowed from periphery to center i.e. from mantle to heart. Consequently, majority of the authors were pointing to the local influence of Somatostatin, secreted by D-cells disposed peripherally, on as A-cells as B-cells through the microcirculation. According to the obtained data, in case if we share the mentioned point of view indicating to D-cells functional activation in aging, it would be possible to explain the impairing of insulin and glucagon extrusion processes in B- and A-cells and stagnation of secret granules.

But the studies showed that microcirculation in islets [12, 14] is directed from center to periphery and in "Mantle" type islets, for example in human beings and rodents, by vector is expressed like B→ A→ D. That is: D-cells are on periphery; B-cells, suppress A- and D-cells [7] locally through the microcirculation; A-cells, through the microcirculation locally activate D-cells [1]; microcircularly D-cells are neutral for island cells and their main target might be only acinar cells of exocrine part in pancreas – due to the existence of insulo-acinar portal system [9]. In mammals, less characterized by the islets of "Mantle" type and having more heterogeneous structure, the inter-effects intermediated by microcirculation appeared to be less expressed [11].

Taking into the account the afore-mentioned, stagnation of the secretory granules in pancreatic A- and B-cells in old ages could not be caused by influence of paracrine effect of somatostatin. The given process could be considered as a result of reduction of energo-potentials and suppression of signal ways for initiation of insulin and glucagon secretion. Respectively, extrusion impediment of secretory granules resulted in their stagnation could be explained by suppression of exocytosis as an energy- and signal-dependent process. On the one hand, the assumption that [13, 11] D-cells are supposed to be the local regulators (inhibitors) of A- and B-cells, might be believed as A-cells contain Somatostatin-14 (type of Somatostatin produced in D-cell) receptors, though B-cells are lack of these receptors. Despite of this, some authors [10] emphases that those single B-cells, located directly alongside D-cell, contain more secret granules (supposedly – due to the impaired extrusion), in comparison with the rest of B-cells. On this regard Taborsky's experiments [15], made on the dogs as if proving paracrine effect of D-cells on A- and B-cells were very interesting. It is known that in dogs D-cells are located in the center of pancreatic islets; therefore, according to the modern point of view Somatostatin effect on A- and B-cells in Taborsky's experiment was mainly determined by the microcirculation (from center to periphery) and not through the paracrine way [13]. Despite of the

mentioned facts, science is still involved in the process a serious experimental substantiation of Somatostatin intraislet or local effects.

Taking into consideration the obtained results and the general data we suppose that cytotopographic and microvascular peculiarities of pancreatic islets in human beings and rodents is a reflection of intensification of insulin apparatus and is directed to loose the B-cells from the local (microvascular or paracrine) influences (effects of D- or A-cells). B-cells themselves will be able to suppress A- and D-cells not only indirect but in direct way as well. The mentioned is of high physiological importance (especially in the process of aging) for the organisms of above-presented taxonomic groups due to rich amount of carbohydrates in their food ration. The above-mentioned fact gains the special importance in human beings, where evolutionary "solitary" (represented by single B-cells) insulinar apparatus is faced with evolutionary "rooted" strong and diverse contrainsulinar apparatus, leading to development of diabetes mellitus (type 2) in late ages.

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SUMMARY

PANCREATIC D-CELLS IN AGING AND INTRAISLET EFFECTS OF PANCREATIC SOMATOSTATIN

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In old organisms pancreatic D-cells are not changed in number. During the aging in mentioned cells takes place the intensification of secretory and extrusive functions, which are more prominent in old organisms than in young ones. Peripherally situated D-cells are vascularly ineffective within the pancreatic islet and do not suppress locally B- and A-cells. D-cells' major target tissue may be pancreatic acinar cells. Functionally activated D-cells in old organisms may play the main role in the development of involutive processes

in exocrine pancreas and in its atrophy. Stagnation of the secretory granules in pancreatic A- and B-cells in old ages could not be caused by influence of paracrine effect of somatostatin. The given process could be considered as a result of reduction of energopotentials and suppression of signal ways for initiation of insulin and glucagon secretion. Respectively, extrusion impediment of secretory granules resulted in their stagnation could be explained by suppression of exocytosis as an energy- and signal-dependent process. We suppose that cytotopographic and microvascular peculiarities of pancreatic islets in human beings and rodents is a reflection of intensification of insulin apparatus and is directed to loose the B-cells from the local (microvascular or paracrine) influences (effects of D- or A-cells). The mentioned is of high physiological importance (especially in the process of aging) for the organisms of above-presented taxonomic groups due to rich amount of carbohydrates in their food ration. The above-mentioned fact gains the special importance in human beings, where evolutionary "solitary" (represented by single B-cells) insulin apparatus is faced with evolutionary "rooted" strong and diverse contrainsulin apparatus, leading to development of diabetes mellitus (type 2) in late ages.

Key words: pancreatic D cells, aging, somatostatin.

РЕЗЮМЕ

ПАНКРЕАТИЧЕСКИЕ D-КЛЕТКИ В ПРОЦЕССЕ СТАРЕНИЯ ОРГАНИЗМА И ВНУТРИОСТРОВКОВЫЕ ЭФФЕКТЫ ИНСУЛЯРНОГО СОМАТОСТАТИНА

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В старых организмах число панкреатических D-клеток не меняется, хотя в процессе старения в этих клетках происходит интенсификация секреторных и экструзивных процессов: отмеченная интенсификация более выражена в старшем, чем в молодом возрасте. В панкреатических островках периферически расположенные D-клетки не являются васкулярно-эффективными и не влияют на островки B- и A-клеток. Основной тканью для воздействия D-клеток являются ацинарные клетки экзокринного панкреаса. Функционально активные D-клетки в стареющих и старых организмах могут сыграть роль в развитии инволюционных процессов и атрофии экзокринной части поджелудочной железы. В старших возрастах стагнация секреторных гранул в островковых A- и B-клеток, скорее всего, вызвана не паракринным эффектом соматостатина, а обусловлена редукцией энергопотенциалов и супрессией сигнальных путей инициации секреции инсулина и глюкагона. Соответственно, подавление процесса экструзии, которая вызывает стагнацию секреторных гранул, можно обяснить заторможением экзоцитоза, так как он является энерго- и сигнал-зависимым процессом. Полагаем, что цитотопографические и микроваскулярные особенности панкреатических островков в организме человека и грызунов являются проявлением усиления инсулинного аппарата, а также защиты B-клеток от локальных (микроваскулярных или паракринных) влияний D- и/или A-клеток. Отмеченное имеет большое физиологическое значение, особенно в процессе старения, для организмов таксономических групп, рационы которых в большом количестве содержат углеводы. Этот факт особо важен для защиты эволюционной «одиночки» инсулинного аппарата, который представлен только B-клетками, от влияния эволюционно «коренастого», сильно и многообразно развитого контраинсулинного аппарата с целью природной превенции развития сахарного диабета (типа 2), столь часто встречающегося в старшем возрасте.

რეზიუმე

პანკრეასის კუნძულების D-უჯრედები ორგანიზმის დაბერების პროცესში და პანკრეასული სომატოსტატინის კუნძულშიდა ეფექტები

დ. კასრაძე, რ. ბერიაშვილი, მ. კასრაძე, ა. თავართქილაძე, პ. ნოზაძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, კლინიკური ჩვევების ლაბორატორია; ციტოპათოლოგიის მიმართულება; კლაიპედის უნივერსიტეტი, ჯანმრთელობის დაცვის

მეცნიერებათა ფაკულტეტი,ლიტვა; წმ. ლუკა მახარებლის სახელობის ქართულ-ჰოლანდიური კლინიკა, თბილისი, საქართველო

უფროსი ასაკის ორგანიზმებში პანკრეასული D-უჯრედების რიცხვი არ იცვლება, თუმცა აღნიშნულ უჯრედებში დაბერების პროცესთან ერთად ადგილი აქვს სეკრეციისა და ექსტრუზიის ინტენსიფიკაციას. კუნძულის პერიფერიაზე მდებარე D-უჯრედები ვასკულარულად ნეიტრალურია კუნძულშიდა უჯრდებისათვის და ლოკალურად გავლენას არ ახდენს B- და A-უჯრედებზე, მათი ძირითადი სამიზნე უნდა იყოს პანკრეასული აცინური უჯრედები, და ფუნქციურად აქტიური D-უჯრედები მაღალ ასაკში უნდა განაპირობებდეს ეკზოკრინული პანკრეასის ინვოლუციასა და ატროფიას. უფროს ასაკში პანკრეასულ B- და A-უჯრედებში სეკრეციული გრანულების სტაგნაცია არ უნდა იყოს სომატოსტატინის პარაკრინული ეფექტით გამოწვეული, არამედ ეს პროცესი უფროს ასაკში B- და A-ინსულოციტებში ენერგოპოტენციალების შემცირებისა და ინსულინისა თუ გლუკაგონის სეკრეციის ინიციაციის სასიგნალო გზების დათრგუნვისა და, შესაბამისად, ეგზოციტოზის დაბრკოლების (როგორც ენერგო- და სიგნალდამოკიდებული პროცესის) შედეგი უნდა იყოს, რასაც სეკრეციული გრანულების ექსტრუზიის შეფერხება და მათი სტაგნაცია მოჰყვება. ვფიქრობთ, ადამიანსა და მღრღნელებში პანკრეასის კუნძულების ციტოტოპოგრაფიული და მიკროცირკულაციური თავისებურებანი ინსულინური აპარატის გაძლიერების გამოხატულებაა და მიმართულია B-უჯრედების განთავისუფლებისკენ ადგილობრივად – D- ან A-უჯრედების ზემოქმედებისაგან. ამ ფაქტს, თავის მხრივ, უდიდესი ფიზიოლოგიური მნიშვნელობა უნდა ჰქონდეს ხსენებული ტაქსონომიკური ჯგუფების ორგანიზმებისათვის, ვინაიდან მათი რაციონები უხვად შეიცავს ნახშირწყლებს. განსაკუთრებულ მნიშვნელობას იძენს აღნიშნული ფაქტი ადამიანებში,სადაც ევოლუციურად "მარტოხელა" (მხოლოდ B-უჯრედებით წარმოდგენილ) ინსულინურ აპარატს უხდება გამკვლავება ევოლუციაში "ფესვებგადგმულ" მძლავრ და მრავალფეროვან კონტრაინსულინურ აპარატთან, რასაც სწორედ უფროს ასაკში მოჰყვება ხოლმე შაქრიანი დიაბეტის (ტიპი 2) აღმოცენება.

THE SPECTRUM OF HEMISPHERAL CORTEX LESIONS IN INTRAUTERINE ALCOHOLIC INTOXICATION

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The given study provides the evidence of embryotoxic effect of alcohol, which is demonstrated by the complex morphological and functional changes, including severe damage to fetal and neonatal CNS, which subsequently determines the mental lag, oligophrenia, craniocephal shifts and decline in neurological state. Teratogenic effect of alcohol on embryonic cells and human gonads through interrupting methylation process of DNA in regions HIG and IG – DMR of male gametes were also shown [10].

Mother alcohol consumption (toxic effect of alcohol) leads to intranatal death of foetus in the phase of organogenesis and placentation, accounting for the fact

that sterilization or premature abortion are indicated in a number of countries, for the risk of developing alcoholic syndrome for foetus at the time of mother alcoholism equals to 40-50% in total [7,9].

On the other side, despite of the fact that the problem has considerable medical-social and economical implications, the systematic and goal-seeking studies on brain in alcoholic embryopathy have not been performed so far. There are only solitary studies which aimed to determine the alcohol effect on embryonal brain structure. Slowdown in the maturation of neuroblasts and glia and the interruption of neuroorganogenesis have been observed [1]. Though the basic processes contributing to formation of neurological and psychopathological syndromes in alcoholic embryopathy have not been studied yet using the latest scientific technologies.

We consider that the experimental-morphological tests, including electronic microscopy and immunohistochemical studies will make possible to observe the morphogenesis of lesions to various brain regions dynamically, in different models of alcohol consumption.

CNS lesions primarily account for the core picture in fetal alcoholic syndrome. Prenatal alcohol consumption is characterized by teratogenic effect with delayed growth [5,6,11]: formation of adequate associative connections in CNS, memory phenomenon and the sympathetic activity of the neuron depends on the number of spinelets of dendrites and the level of it's branching, as the latter determines the possibility of contacts between the neurons [4]. The toxic effect of alcohol lies exactly in this point, resulting in the disturbance of structural integration of CNS and reduced number of dendrite processes, which was demonstrated in the studies with animal alcoholic intoxication models in vivo and in vitro [15]. The studies of motor neurons in the cortex and hippocampal neurons, also those in substantia nigra in the condition of pre- and postnatal exposure to alcohol, which may elucidate the mechanism of damage to dendrites, especially to apical dendrites, are very actual for present.

As clarified from the results of specialized neurophysiological and psychological tests, exactly the loss of synaptic contacts and their breakage presumably due to the lesion of mitochondrial membranes in active zone of synapses [13] refer to the main reasons of neurodygenesis (ARND) and behavioral pathologies. Analysis of 2700 cases with familial alcohol consumption carried out by Wattendorf et al. [14] puts the study of fetal alcholoic syndrome on agenda, as one of the top tools for epilepsy prevention.

In the study on rats, Schilko V.I. et al. [5] showed that the main inhibiting effect on cytomorphological (cytoarchitectonic) development of the CNS is laid by the toxic influence of alcohol on neurons, which subject to lysis and degenerative changes; the latter especially refers to cortical and hypothalamic neurons. Authors studied expression of transforming growth factor TGF-β1 on the target cell receptors, demonstrating the delayed development of the forebrain. Godin, Dehart, Parnell [8] suppose that ventromedial dysgenesis of the forebrain represents itself the earliest sign of prenatal alcohol effect. The experiments by Rout and Dhossche [12] show that the simultaneous consumption of alcohol and water result in the loss of weight of the animal (female), foetus and placenta, thereby causing the reduced expression of signal protein integrin in the neurons of fetal cortex as well.

It should be mentioned that the animal alcoholic intoxication is also applied as the adequate biological model in the studies on alcohol-induced dementia [11].

All above mentioned indicates that the detailed study of morphological structures of CNS in fetal alcoholic syndrome (FAS) by application of the latest technologies refers to an actual and timely subject, representing itself one of the most considerable directions in the study of abnormal juvenile behavioral reactions, epilepsy and dementia.

Aim of the study is to assess the lesions of morphological (molecular – biological) components of blood-brain barier and neurons in the central gyri of hemispheres in the setting of intrauterine alcohol effect.

Material and methods. experiments were carried out in Spring period, on white laboratory non-linear rats of both sexes, weighting up to 180-200 g., which were kept at the room temperature, giving free access to food. In the separate chambers, via 50 ml teated vessel, the animals were given 15% ethyl alcohol solution instead of water during 1 month (females n=10, males n=10) [5]. After a month, each male was roomed with 3 females during 7 days in the aim of fertilization. After establishing pregnancy (by vaginal smear), the females were transfered to individual chambers. According to specific goal, 7 females were kept on the alcohol during the whole period of preg-

nancy (21 days) – corresponding to I group. The II group – animals were receiving alcohol with the same concentration during the last week of pregnancy (days 14-21) (after completion of placentation stage).

The samples of brain tissues from the progeny of intact animals of the same age and body weight served as the control group (n=10).

24 experimental and 10 control rats were subjected to the study overall. The present study demonstrates the results of the I series of observation.

Rat euthanasia was performed by decapitation under light ether narcosis. The skull was opened immediately after evacuation of the foetus from uterus and macroscopic evaluation of the brain was performed.

Part of the progeny of alcoholized rats were euthanatized on the 5th day of life. In both cases, the tissue samples taken from convexital surface of sensomotor cortex were fixed in 10% buffered solution of neutral formalin with the ratio of not less than 1:10. The samples from paraffin-embedded blocks were dyed by hematoxylin eosin and by the method of Nissle. Material intended for study of ultrastructures from specific identified regions were fixed by the immersion method recommended by Popov E.N. et al. [3]. Electronograms were obtained by the microscope Tesla BS 500, with the voltage-accelerating device 70 kwt.

Study results and discussion: Morphological and histological studies of brain tissue samples from the progeny of intact rats did not demonstrate any changes or deviations in the normal brain structure. Cytoarchitectonics of all cortical layers were visualized clearly, perivascular spaces of Virchov-Robin were exposed in the form of small clarifications.

Macroscopic examination of brain samples from experimental group showed hyperemia of pia with partial incorporation. Disordered neuroorganogenesis in brainstem structures, poor development of gyri and leptomeningeal heterotopia were revealed in most of cases with various severity, and microcephaly was observed in 6 cases from 20.

Rarefaction foci in the cortex were observed in the structure of sensomotor region histologically, which were especially prominent in the layers IV-V, so-called "crystal-like" nuclei with the signs of pycnosis and chromatosysis were also found (Fig. 1a).

Fig. 1. Sensomotor region of brain cortex of the newborn animal in intrauterine alcohol intoxication:
a) "Crystal-like" nuclei of neurocytes, pycnosis and partial chromatolysis. Stain by Nissle x200;
b) Electronmicrogram – edema of astrocyte pedicles in blood-brain barrier, edema in neuropil, stasis of erythrocyte in the lumen x12 000;
c) lectronmicrogram – hyperosmophylia of nuclei and cytoplasm, clumping and aggregation of chromatin x16 000

On the 5th day of life, the progeny of alcoholized rats revealed dyscirculatory changes in the cortex, expressed by dystonic vessels and aggregation of blood formed elements in the capillary lumina. Perivascular edema and diapedetic haemorrhages were also frequently observed. Neurophages and proliferation of neuroglia was prominent everywhere.

Results of the study of blood-brain barrier ultrastructure demonstrated substantial edema of cytoplasmic processes of perivascular astrocytes with the appearance of pericapillary "clutches", also a "cribleur" around the vessels of bigger calibre.

Neuroglial structure shows the areas of sparseness, depletion of organelles in neurocyte cytoplasm, acute swelling of matrix and fragmentation of mitochondrial membranes, increased number of multivesicular bodies and lysis in non-pyramidal cells (Fig. 16). Swelling of dendrites and their vacuolization with reduction of microtubules is also denotable, simultaneously with the reduced number of vesicles in axon terminals. Part of the neurons underwent the changes, evaluated as hypersmophylia of nuclei and cytoplasm, mitochodrial destruction in both pyramidal and other neurons of sensomotor cortex (Fig. 1 c). Deformation, swelling and vacuolization of dendrite branches with the destruction of mitochondria and microtubules were also observed in these neurons.

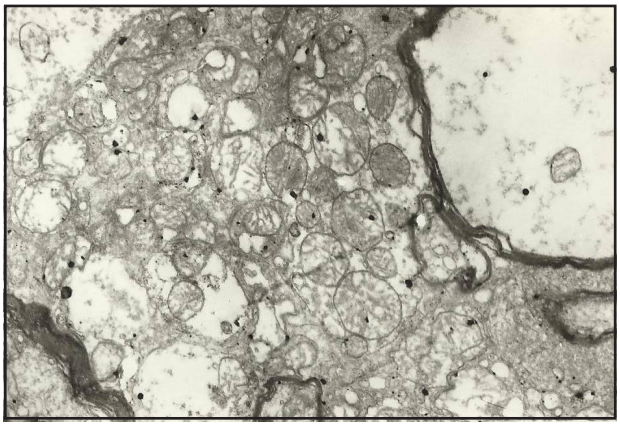

Fig. 2. Sensomotor cortex of the animal brain in intrauterine alcohol intoxication. 5th day of life. Destruction of mitochondrial structure with vacuolization, edema of the axoplasm x 16 000

Comparing the picture of brain of newborn subjects to those euthanized on the 5th day of life demonstrated the clear progression of alterations right up to the irreversible forms of destruction of structural elements of the nervous tissue, accumulation of the large lysosomes not only in pericarion, but also in the apical dendrites (Fig. 2). Nearly complete disappearance of mitochondria in normal structure, acquiring the vacuole-like appearance and fragmentation of cysterns on granular cytomplasmic reticulum also deserves attention.

The glial reaction develops through the proliferation of neuroglia, phagocytosis of neurons and perivascular edema with narrowing of the capillary lumen.

The increasing dynamics of pathological changes indicates on continued alcoholic intoxication with steadily progressive submicroscopic and tissue destructive processes. Obviously, the pathogenesis of lesions of nervous elements in intrauterine alcohol intoxication is diverse, provided by the different structures involved in the whole picture of pathology: vessels, glial and nervous elements. Schilko V.I. et al. [5] consider that the injured differentiation and intensified apoptosis of neurons can be resulted from the premature transformation of radial astroglia in astrocytes under the alcohol influence, which is related to blocking of the receptors of transforming growth factor (TGF-β1) in developing cells. Defective structure of the receptor unit during differentiation [2] is demonstrated in our experiments as well, confirmed by the involution of dendrite structures, their processes and vacuolization of axon terminals. Neuroanatomical studies by Wei-Jung Chen, Susan E. Maier et al. [15] give the evidence about the importance of intracellular energy production and integrity of structural integration of mitochondria in developing components of the cortex; alcohol affects the adhesion molecules (L1CAM), which, in turn, distort the formation of cellular cooperation mechanisms.

By observing the lesions of dendrites and visually seen reduction in the number of their spineless, we may make conclusion about the disturbed transmission of nervous impulse. Extrapolation of the given data relatively on human analogue can provide the explanation for cognitive problems developing in children with fetal alcoholic syndrome.

Thus, the morphogenesis of structural lesions of brain cortex is substantiated by the destruction of structural integration of neurons, glia and intraneuronal organizational changes on one side, and proliferation of neuroglia, phagocytosis of neurons and edema of

astrocytic component of blood-brain barrier on the other, which in sum, lead to postnatal progression of neurodysgenesic processes.

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SUMMARY

THE SPECTRUM OF HEMISPHERAL CORTEX LESIONS IN INTRAUTERINE ALCOHOLIC INTOXICATION

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Aim of the study was to examine the specific morphological changes of brain cortex in fetal alcoholic intoxication model. The latter was performed in male and female animals by substituting water with 15% ethyl alcohol during 1 month period, which was followed by putting pregnant females on alcohol of the same concentration for the duration of the whole period of pregnancy (21 days). 24 experimental and 10 control (intact) animals were subjected to study overall. The study material applied the samples of brain convexital cortex from foetus and newborn rats. Paraffin-embedded slices (films) were dyed by the method of Nissle and hematoxylin eosin. After immersion fixation in 2.5% glutaraldehyde and 1% osmium acid solutions followed by double contrasting, the ultrathin slices were studied in the electron microscope Tesla BS 500.

Macroscopic study demonstrated the hyperemia of pia with partial incorporation, different types of neuroorganogenesis disturbance, also, leptomeningeal heterotopia and microcephaly in 6 cases from 24 (25%) in the experimental group.

Morphology of cortical damage to fetal brain in

alcoholic intoxication was demonstrated by progressive massive destruction of neuronal mitochondria, involutional changes in dendrites and their processes and glial proliferation, which possibly account for the structural basis of energetic and informational deficit in neurons. Acquired data may be extrapolated on human model of alcoholic embryopathy with subsequent cognitive problems.

Key words: fetal alkogol syndrome, brain cortex morphology, ultrustructure.

РЕЗЮМЕ

СПЕКТР ПОРАЖЕНИЯ СТРУКТУРЫ КОРЫ БОЛЬШИХ ПОЛУШАРИЙ ГОЛОВНОГО МОЗГА ПРИ ВНУТРИУТРОБНОЙ АЛКОГОЛЬНОЙ ИНТОКСИКАЦИИ

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Целью настоящего исследования является изучение особенностей морфологических изменений коры больших полушарий головного мозга при алкогольной интоксикации плода. Для моделирования алкогольной интоксикации белые беспородные крысы (самки -10, самцы - 10) массой тела 180-200 г получали 15% раствор этилового спирта вместо воды в условиях свободного доступа к пище, в дальнейшем беременные самки получали алкоголь в течение всего периода беременности (21 день). Работа выполнена на материале 24 опытных и 10 контрольных образцов ткани головного мозга потомства новорожденного и на 5-ый день жизни. Парафиновые срезы окрашивались по Нисслю и гематоксилином и эозином. Ультратонкие срезы исследовались в электронном микроскопе Tesla BS 500.

Исследовались структурные компоненты конвекситальной коры из сенсомоторной области больших полушарий мозга. Макроскопически – различные проявления нарушения нейроорганогенеза, частичная инкорпорация мягкой мозговой оболочки, лептоменингеальная гетеротопия, в 6 случаях из 24 (25%) – микроцефалия.

Повреждения структуры коры головного мозга плода проявлялись в прогрессирующей деструкции митохондрий нейронов, дендритов и их отростков на фоне признаков инволюции, а также в пролиферации глии, что возможно, составляет структурную основу энерго- и информационного дефицита нейронов

Условно экстраполируя данные изменения на аналогичные у человека, можно объяснить возникновение когнитивных проблем у детей с фетальным алкогольным синдромом.

რეზიუმე

თავის ტვინის დიდი ჰემისფეროების სტრუქტურათა დაზიანების სპექტრი ნაყოფის ალკოჰოლური ინტოქსიკაციის დროს

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ნაშრომის მიზანს წარმოადგენს თავის ტვინის დიდი ჰემისფეროების ქერქის მორფოლოგიურ ცვლილებათა თავისებურებების კვლევა ნაყოფის ალკოჰოლური ინტოქსიკაციის პირობებში. ალკოჰოლური ინტოქსიკაცია განხორციელდა მამრ და მდედრ ცხოველებში წინასწარ 1 თვის განმავლობაში 15% ეთილის სპირტით წყლის ჩანაცვლებით და შემდგომ მდედრის მიერ ამავე კონცენტრაციის სპირტის მოხმარებით მაკეობის პერიოდში (21 დღე). საკვლევ მასალას წარმოადგენდა 24 საცდელი და 10 საკონტროლო ჯგუფის (ინტაქტური) ვირთაგვას ნაყოფის და ახალშობილის თავის ტვინის კონვექსიტალური ქერქის ქსოვილის ნიმუშები. პარაფინის ანათლები იღებებოდა ნისლის მეთოდით და ჰემატოქსილინითა და ეოზინით. ულტრათხელი ანათლები შესწავლილია გლუტარალდე-

გიდის 2,5% სხნარისა და ოსმიუმის მჟავას 1% ხსნარში იმერსიული ფიქსაციის და ორმაგი კონტრასტირების შემდგომ Tesla BS 500 ტიპის ელექტრონულ მიკროსკოპზე.

მაკროსკოპულად საცდელ ჯგუფში აღინიშნა რბილი გარსის სისხლსავსეობა ნაწილობრივი ინკორპორაციით, ნეირო-ორგანოგენეზის მოშლის სხვადასხვა ხარისხი, აგრეთვე ლეპტომენინგური ჰეტეროტოპია და მიკროცეფალია 6 (25) შემთხვევაში 24 დან. ნაყოფის თავის ტვინის ქერქის დაზიანების მორფოლოგია ალკოჰოლური ინტოქსიკაციის დროს გამოიხატა ნეირონთა მიტოქონდრიების პროგრესირებადი მასიური დესტრუქციით, დენდრიტებისა და მათი მორჩების ინვოლუციური ცვლილებებით, გლიის პროლიფერაციით, რაც ნეირონთა ენერგო- და ინფორმაციული დეფიციტის სავარაუდო სტრუქტურულ ბაზისს წარმოადგენს. შესაძლებელია, მიღებული მონაცემების ექსტრაპოლაცია ადამიანის ალკოჰოლური ემბროპათიაზე შემდგომი კოგნიტიური პრობლემებით.

ИССЛЕДОВАНИЕ ТОКСИЧНОСИТИ ПРОТЕЗНОГО МАТЕРИАЛА PROTHYL HOT НА МОДЕЛИ КЛЕТОК JURKAT

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На современном этапе развития ортопедической стоматологии восстановление дефектов зубного ряда связано с внесением в полость рта чужеродного тела – протеза [1,3,9]. В результате взаимодействия протеза с тканями ротовой полости возможно физическое повреждение слизистой оболочки, деструкция эпителия [4,7,10], образование язв и фиброзной соединительной ткани. Используемые в съемных протезах биоактивные соединения (например, смола - Polimethylmethacrylate) способствуют массивной гибели фибробластов [2], развитию аллергических, воспалительных или травматических повреждений, что, в свою очередь, может стать причиной интервенции микроорганизмов и нарушения иммунного и оксидационного баланса в организме. Вышеизложенное обуславливает изменение метаболизма (интенсификация окислительного стресса, пролиферация или апоптоз клеток, плоидизм ДНК) [8], развитие воспалительных процессов (стоматит, гингивит), деструкции (ткани пародонта), отмиранию эпителиальных и мезенхимальных тканей ротовой полости [5]. Во всех этих процессах активно участвуют иммунокомпетентные клетки (Т-лимфоциты и макрофаги), которые скапливаются в очагах поражения и обуславливают локальную интенсификацию синтеза провоспалительных цитокинов, факторов роста и реактивных соединений кислорода (РСК) [6].

Устранение и предотвращение повреждающих воздействий стоматологических материалов на ткани ротовой полости является одной из важнейших и, по сей день нерешенных проблем современной стоматологии. Исследования в этой области проводятся как в направлении поиска новых атравматических протезных материалов, так и разработки методов эффективной коррекции постпротезных повреждений. Для достижения последнего необходимо установление татогенетических механизмов повреждающего действия различных компонентов протезов на ткани и клетки организма.

Целью нашего исследования явилось установление токсической провоспалительной активности протезных материалов на модели человеческих лейкемия-трансформированных Т-клеток (Jurkat клетки).

Культура клеток Jurkat, полученная из интенсивно пролиферирующих лейкемия-трансформированных Т-клеток широко приме-

няется в научных и клинических исследованиях в качестве модели человеческих Т-лимфоцитов.

Материал и методы. *Клеточная культура:* Человеческие лейкемия-трансформированные зрелые клетки Jurkat (DSMZ-Deutshe Sammulung von Mikroorganismen und Zellkulturen, Germania), размножались в суспензии, содержащей биологически активную среду RPMI 1640 (GIBSO), инактивированную телячью сыворотку (Sigma), L-глутамин (4 mM), пенициллин (100 ед.мл) и стрептомицин (100 ед/мл), во влажной, 5% CO_2 в атмосфере при температуре 37^0. Эксперименты проводились при концентрации клеток 0,3-0,6x10^6 клеток в 1 мл среды.

Стимуляция клеток Jurkat: в инкубационную среду клеток Jurkat добавлялись компоненты исследуемого протезного материала Prothyl Hot, в дозах, применяемых в практике (рассчитанных 10^6 клеток); инкубация продолжалась в течение 24 часов.

Сравнительная оценка токсичности протезных материалов: с целью ***с***равнительной оценки токсичности протезных материалов после инкубации определялись активность митохондриальных дегидрогеназ клеток Jurkat посредством МТТ теста (стандартная методика) и значение митохондриального потенциала (жизнеспособность клеток).

МТТ тест: для каждого компонента протезного материала рассчитывался коэффициент пролиферации по формуле:

$$K = A_{экс}/A_{контроль}$$

где $A_{экс}$, $A_{контроль}$ - интенсивность поглощения образцами излучения длиной волны 570 нм (в случае инкубации с протезным материалом и без).

Измерение митохондриального потенциала $\Delta\Psi$ проводилось методом проточной цитометрии с использованием липофильного флуоресцентного катионового зонда 3,3'-dihexyloxacarbocyanine iodide - $DiOC_6$.

Определение активности антиоксидантных ферментов: с целью определения активности супероксиддисмутазы (СОД) в культуре клеток Jurkat проводили предварительную гомогенизацию клеток посредством обработки ультразвуком в течение 50 минут при температуре льда.

Активность СОД: инкубационная среда содержала 50 mM фосфата калиума, 50 μM синего нитротетразолиума (NBT), 150 μM NADPH и 50 μM метилсульфата феназониума (PMS) при pH 7,4. Реакция начиналась после добавления 50 μl лизата клеток. Определялось спектрофотометрическое поглощение излучения длины волны 540 нм. Показатели изменения концентрации восстановленного синего нитротетразолиума рассчитывались в международных единицах на 1 г белка.

Глутатион редуктаза (ГР): инкубационная среда содержала 67 mM фосфата натриума, 27 μM окисленного глутатиона, 20 μM NADPH при pH 6,6. Реакция начиналась после добавления 50 μl лизата клеток. Определялось спектрофотометрическое поглощение излучения длины волны 340 нм. Изменения концентрации окисленного NADPH рассчитывались в международных единицах на 1 г белка.

Каталаза: инкубационная среда содержала 50 mM фосфата калиума, 0,06% перекиси водорода при pH 6,6. Реакция начиналась после добавления 20μl лизата клеток. Определялось спектрофотометрическое поглощение излучения длины волны 240 нм. Показатели изменения концентрации расщепленного H_2O_2 рассчитывались в международных единицах на 1 г белка.

Содержание реактивных соединений кислорода и липидов определяли методом электронного парамагнитного резонанса на радиоспектрометре РЭ-1307 (Россия) с использованием спин-меток.

Экспрессия цитокинов ILL-2, ILL-10 клетками Jurkat определялась методом ELISA.

Статистическая обработка результатов исследования проводилась с помощью программного пакета SPSS (версия 10).

Результаты и их обсуждение. В таблице 1 представлены данные изменений активности антиоксидантных ферментов в клетках Jurkat, инкубированных с жидкостью, порошком и комплексом Prothyl Hot в течение 24 часов. Из данных таблицы следует, что в случае инкубации клеток с порошком Prothyl Hot активность СОД и ГР не изменялась по сравнению с контрольными значениями, а каталазы в 2 раза превышала контрольные

значения. В случае инкубации клеток с жидкостью Prothyl Hot активность СОД возрастала на 150%, активность ГР - на 116%, а каталазы - на 50% по сравнению с контрольными значениями. В случае инкубации клеток с протезным материалом Prothyl Hot, полученным в результате полимеризации порошка и жидкости, активность СОД увеличивалась на 250%, активность ГР - на 33%, а каталазы - на 130% по сравнению с контрольными значениями.

Таблица 1. Активность антиоксидантных ферментов клеток Jurkat

Образцы	ГР (ед = нМ NADPH/ мин/1мг белка)	СОД (ед = нМ NADPH/ мин/1мг белка)	каталаза
Jurkat	277,8±20,0	22,2±2,0	1,8±0,9
Jurkat+Prothyl Hot жидкость 0,013 μg	600,2±29,0*	56,3±2,1*	2,7±0,6*
Jurkat+Prothyl Hot порошок 31 μg	294±12,0	22,0±2,7	3,5±0,8*
Jurkat+Prothyl Hot комплекс 35 μg	369±22,0*	77,6±2,9*	4,2±0,5*

** - статистически достоверные изменения по сравнению с контролем (p<0,001)*

Активация антиоксидантных ферментов клеток Jurkat на фоне совместной инкубации с компонентами протезного материала Prothyl Hot указывает на интенсификацию окислительных процессов в клетках, особенно, при инкубации с жидкостью Prothyl Hot.

Об интенсификации окислительного метаболизма и увеличении продукции РСК в клетках Jurkat, инкубированных совместно с компонентами протезного материала Prothyl Hot, свидетельствуют также результаты ЭПР спектроскопического исследования (таблица 2). Согласно данным таблицы 2 в образцах клеток, инкубированных совместно с отдельными компонентами или комплексом Prothyl Hot, выявлены ЭПР сигналы РСК (супероксидрадикалов) липопероксидов ($LOO\cdot$).

Таблица 2. Реактивные соединения кислорода и липидов в культуре клеток Jurkat

Образцы	супероксидрадикалы (O_2^-)	липопероксиды ($LOO\cdot$)
Jurkat	-	-
Jurkat + Prothyl Hot жидкость 0,013 μg	2,0±0,5	2,8±0,3
Jurkat + Prothyl Hot порошок 31 μg	1,8±0,3	2,2±0,4
Jurkat + Prothyl Hot комплекс 35 μg	2,2±0,4	2,4±0,5

С целью определения насколько опасна индуцированная протезным материалом Prothyl Hot интенсификация окислительного метаболизма для жизнеспособности клеток, нами изучены параметры энергетического метаболизма клеток, отражающих их жизнеспособность.

В таблице 3 представлены данные цитотоксичности протезных материалов (результаты МТТ теста). Согласно данным МТТ теста на фоне добавления жидкости, порошка и продукта полимеризации компонентов Prothyl Hot в инкубационную среду клеток Jurkat, активность митохондриальных дегидрогеназ по сравнению с контрольными значениями (K=0,93, K=1, K=1, соответственно) меняется незначительно.

Таблица 3. Показатели жизнеспособности клеток Jurkat

Образцы		K
среда	0,3	
Jurkat	0,3	1
Jurkat + Prothyl Hot жидкость 0,013 μg	0,28	0,93
Jurkat + Prothyl Hot порошок 31 μg	0,3	1
Jurkat + Prothyl Hot комплекс 35 μg	0,32	1

** - статистически достоверные изменения по сравнению с контролем (p<0,001)*

Результаты исследований методом проточной цитометрии также свидетельствуют о стабильности значения потенциала (ΔΨ) клеток Jurkat, инкубированных совместно с жидкостью, порошком и цельным полимером Prothyl Hot.

Результаты проведенных спектрофотометрических и цитометрических исследований свидетельствуют о стабильности жизнеспособности клеток Jurkat после добавления в среду их инкубации компонентов и полимера Prothyl Hot. Таким образом, можно заключить, что протезный материал Prothyl Hot не обладает токсичностью, и вызванную комплексом Prothyl Hot и его компонентами интенсификацию окислительного метаболизма клеток Jurkat (таблица 1,2) можно отнести к числу компенсаторно-адаптационных реакций, развивающихся в клетках в ответ на внесение в инкубационную среду чужеродного соединения, а в частности, токсичной жидкости.

Таблица 4. Экспрессия цитокинов

Образцы	IL-1β	IL-10
Jurkat	0,5±0,08	10,3±1,9
Jurkat + Prothyl Hot жидкость 0,013 μg	0,8±0,2	11,3±2,1
Jurkat + Prothyl Hot порошок 31 μg	0,6±0,09	10,8±1,5
Jurkat + Prothyl Hot комплекс 35 μg	0,5±0,06	12,3±2,9

** - статистически достоверные изменения по сравнению с контролем (p<0,001)*

Результаты иммунологических исследований не выявили значительных изменений интенсивности экспрессии про- и антивоспалительных цитокинов (IL-1β, IL-10) клетками Jurkat после внесения в среду их инкубации компонентов протезного материала Prothyl Hot (таблица 4).

Таким образом, на основании анализа проведенных исследований можно заключить, что протезный материал Prothyl Hot:

- не оказывает токсического влияния на жизнеспособность клеток Jurkat, что проявляется в стабильности активности митохондриальных дегидрогеназ и митохондриального потенциала.
- не влияет на баланс про- и антивоспалительных цитокинов, экспрессируемых клетками.
- способствует некоторой интенсификации окислительного метаболизма клеток Jurkat, что можно отнести к числу компенсаторно-адаптационных реакций, развивающихся в клетках.

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SUMMARY

STUDY OF TOXICITY OF DENTURE PROSTHETIC APPLIANCE PROTHYL HOT ON THE JURKAT CELL MODEL SYSTEM

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The aim of our study was the investigation of toxicity of denture prosthetic appliance Prothyl Hot on the model system of Jurkat cell culture.

As a result of our study it was revealed that denture prosthetic appliance Prothyl Hot:
- hadn't manifested toxic effects the viability Jurkat cells (that reviled by stability of activity of mitochondrial dehydrogenises and mean of mitochondrial membrane potential;
- didn't influence on the balance of pro-and antyinflammatory cytokines, expressed by Jurkat cells;
- induces intensification of oxidative metabolism in Jurkat cells, which may be considered as compensatory reaction developing in the cells.

Key words: Prothyl Hot, toxicity.

РЕЗЮМЕ

ИССЛЕДОВАНИЕ ТОКСИЧНОСИТИ ПРОТЕЗНОГО МАТЕРИАЛА PROTHYL HOT НА МОДЕЛИ КЛЕТОК JURKAT

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Восстановление дефектов зубов - важнейшая задача современной стоматологии. Трудности осуществления этой задачи обусловлены аллергически-воспалительными, травматическими и дистрофическими осложнениями, возникающими вследствие взаимодействия чужеродного тела со слизистыми тканями полости рта после установления протеза пациенту. Превенция и коррекция отрицательных эффектов протезных материалов на ткани полости рта является актуальной проблемой стоматологии.

Целью нашего исследования явилась оценка токсичности протезного материала Prothyl Hot на модели клеточной культуры Jurkat.

На основании анализа проведенных исследований можно заключить, что протезный материал Prothyl Hot:
- не оказывает токсического влияния на жизнеспособность клеток Jurkat, что проявляется в стабильности активности митохондриальных дегидрогеназ и митохондриального потенциала.
- не влияет на баланс про- и антивоспалительных цитокинов, экспрессируемых клетками.
- способствует интенсификации окислительного метаболизма клеток Jurkat, что можно отнести к числу компенсаторно-адаптационных реакций, развивающихся в клетках.

რეზიუმე

საპროთეზო მასალის Prothyl Hot-ის ტოქსიურობის შეფასება ჟურკატ უჯრედების სამოდელო სისტემაზე

ზ. ნაკუდაშვილი, ს. მღებრიშვილი, ნ. ნაკუდაშვილი, თ. მჭედლიშვილი, თ. სანიკიძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, თბილისი, საქართველო

ორთოპედიული სტომატოლოგიის განვითარების თანამედროვე ეტაპზე მნიშვნელოვან ამოცანას წარმოადგენს კბილთა რკალის დეფექტების აღდგენა. აღნიშნულის სირთულე დაკავშირებულია კბილთაპროთეზირების უარყოფით ზემოქმედებასთან საპროთეზო ველის ქსოვილებზე და პირის ღრუს ლორწოვან ქსოვილში ალერგიულ-ანთებითი, ან ტრავმული, დისტროფიული პროცესების განვითარებასთან. სტომატოლოგიური საპროთეზო მასალების პირის ღრუს ქსოვილებზე მავნე (უარყოფითი) ეფექტის პრევენცია და კორექცია სტომატოლოგიის ერთ-ერთი გადაუწყვეტელი და აქტუალური პრობლემაა. გამოკვლევის მიზანს წარმოადგენდა საპროთეზო მასალის Prothyl Hot-ის ტოქსიური აქტივობის დადგენა Jurkat უჯრედების მოდელურ სისტემაზე.

კვლევების შედეგები საშუალებას იძლევა დასკვნისა,რომ საპროთეზო მასალა Prothyl Hot:

• არ ავლენს ტოქსიურ ზემოქმედებას Jurkat უჯრედის სიცოცხლისუნარიანობაზე, რაც ვლინდება მიტოქონდრიალური დაჰიდროგენაზების აქტივობისა და მიტოქონდრიული პოტენციალის მაჩვენებლის სტაბილობით;

• არ ზემოქმედებს უჯრედების მიერ ექსპრესირებული პრო- და ანტიანთებით ციტოკინების ბალანსზე;

• ხელს უწყობს Jurkat უჯრედების ოქსიდაციური მეტაბოლიზმის ინტენსიფიკაციას (უკანასკნელი ატარებს კომპენსატორულ-ადაპტაციურ ხასიათს).

GUMMI ARMENIACAE ИЗ АБРИКОСОВЫХ ДЕРЕВЬЕВ, ПРОИЗРАСТАЮЩИХ В АРМЕНИИ - ПЕРСПЕКТИВНЫЙ ИСТОЧНИК АРАБИНОГАЛАКТАНА

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В последнее время в производстве чаще применяются такие заменители, как желатин, модифицированная целлюлоза, декстрины и их синтетические аналоги, которые не универсальны и имеют противопоказания к применению.С этой точки зрения представляют особый интерес растительные гетерополисахариды, которые все чаще привлекают внимание исследователей [3,4]. Они составляют основную часть пищевого рациона человека и, в связи с этим, широко используются в пищевой и кондитерской промышленности. Это - многочисленная широко распространенная группа органических соединений, которые наряду с белками и жирами необходимы для жизнедеятельности всех живых организмов [1]. Среди древесных камедоносов флоры Армении (абрикос, персик, слива, миндаль, а из других семейств - лох и трагакант) представляют интерес абрикосовые деревья, которые являются одной из важнейших плодовых культур Республики Армения (РА) и занимают значительные площади в Араратской долине, Котайке, Арагацотне, предгорном поясе Вайка.

В связи с этим особый интерес представляют камеди абрикосов (Gummi armeniacae) флоры Республики Армения, которые, являясь экологически чистым продуктом, могут полностью заменить дорогостоящий гуммиарабик, а также его синтетические аналоги в пищевой промышленности [8].

Периодически проводимые нами ресурсоведческие исследования в разных регионах Армении позволяют подтвердить имеющиеся предположения о биологических и эксплуатационных запасах камедей в республике [7].

Химический состав и физико-химические свойства камеди абрикосовых деревьев, культивируемых в различных районах Средней Азии, были впервые изучены З. М. Уманским (1943). В состав камеди, по его данным, входят глюкуроновая кислота - до 16%, галактоза - до 44%, арабиноза - до 41%; примесь белковых веществ не превышает 0,6% [5]. Особое место среди полисахаридов в связи со значительным содержанием и уникальными свойствами в растительном сырье занимает водорастворимый арабиногалактан (АГ). Арабино-3,6-галактаны составляют основу камедей покрытосеменных растений, например, акации, а также голосеменных, особенно лиственницы (р. *Larix*). Так, ядровая древесина некоторых видов лиственницы содержит до 35% АГ, а одно дерево акации (гуммиарабик) может ежегодно продуцировать более 2 кг камеди [2,6].

Целью данного исследования явилось изучение химического состава камеди абрикоса, произрастающего на территории РА и возможностей ее применения в качестве источника водорастворимого арабиногалактана.

Материал и методы. Объектами исследования явились камеди абрикосовых деревьев (Armeniaca vulgaris Lam.), собранные во время сокодвижения в Армавирском и Эчмиадзинском регионах. После сбора, камеди очищались обычным физическим методом - без химического и энзимного воздействия.

Приготовление стандартных растворов: 20,0 мг (точная навеска) арабиногалактана переносили в мерную колбу, емкостью 20 мл, добавляли воду до метки, перемешивали и диспергировали в ультразвуковой бане в течение 5 минут.

Объем вводимой пробы равнялся 20 мкл. Время анализа – 7 минут. Пики на хромаграммах идентифицировали по времени удерживания (tR).

Количественное определение проводили методом внешнего стандарта. В качестве внешних стандартов использовали растворы стандартного образца арабиногалактана с известной концентрацией. Чистота соединений по данным высокоэффективной жидкостной хроматографии составляла не менее 95%.

Приготовление калибровочных растворов: 20,0 мг (точная навеска) стандарта арабиногалактана взвешивали в мерной колбе емкостью 25 мл, добавляли 10 мл воды и добавлением растворителя доводили до метки. Затем путем последовательного разбавления раствора стандарта готовили градуированные растворы арабиногалактана с концентрациями 0,2; 0,4; 1; 1,5; 2 мг/мл. Каждый раствор хроматографировали не менее трех раз при длине волны 200-254 нм. На основании полученной хроматографической информации рассчитывали градуированные коэффициенты – коэффициенты пропорциональности между соотношением площадей пиков и концентраций арабиногалактана.

Анализируемые образцы камеди абрикоса исследовали методом высокоэффективной жидкостной хроматографии на приборе фирмы Shimadzu (Shimadzu LC 20 AD, Япония), с детектором диодной матрицы (Detector SPD20A) в следующих условиях: инжекция 20 мкл, колонка (MN NUCLEOGEL 300ION 7A) размерами 300/7.8мкм, фаза 0.01N H2SO4. Скорость потока 0,8 мл/мин, детекция при 200нм.

Содержание арабиногалактана в образцах рассчитывали по следующей формуле:

$$A = C_{взжх} \times K, \text{ где}$$

A – содержание арабиногалактана в 1 г камеди (мг);
$C_{взжх}$ – концентрация арабиногалактана в стандартном образце (мг/мл);
K - фактор разбавления анализируемого образца.

Результаты и их обсуждение. В результате исследования методом ВЭЖХ в составе камеди был обнаружен арабиногалактан, что позволило провести качественную и количественную характеристику абрикосовой камеди по содержанию арабиногалктана.

Согласно полученным данным, время удерживания стандартного образца при детектировании 254 нм арабиногалактана составило 4,2 мин (рис. 1). Построение калибровочной кривой с использованием различных растворов с известными концентрациями стандарта арабиногалактана выявило прямолинейную зависимость между концентрацией арабиногалактана и площадью пика (рис. 2), что позволило проведение количественного определения в исследуемом растворе абрикосовой камеди.

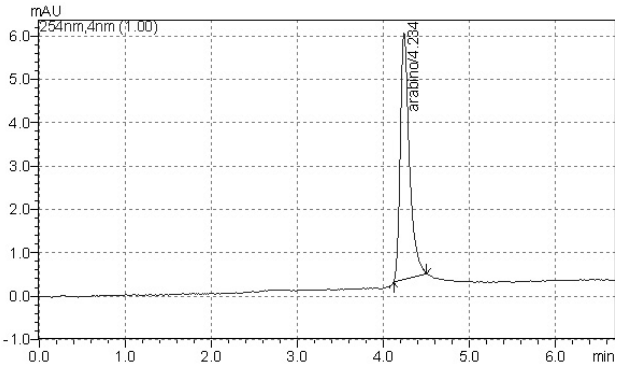

Рис. 1. Хроматограмма арабиногалактана в стандартном образце

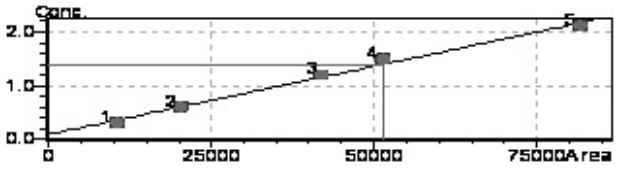

Рис. 2. Калибровочный график различных растворов с известными концентрациями стандарта арабиногалактана

Так, при хроматографировании время удерживания арабиногалактана в растворе абрикосовой камеди составило 4,17 мин., что соответствует времени удерживания стандартного образца (рис. 3,4).

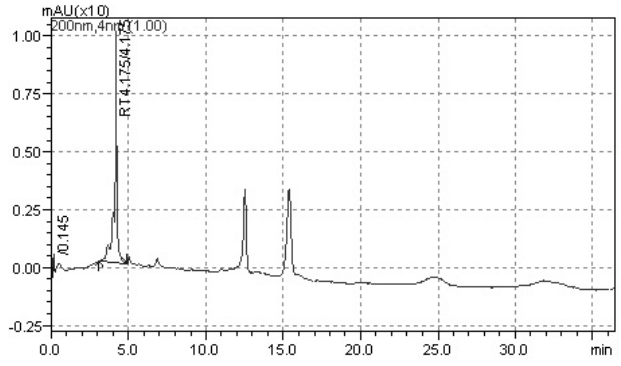

Рис. 3. Хроматограмма абрикосовой камеди

RT4.175 Ch1 200nm 2 98048 9987 3.08 98.1895

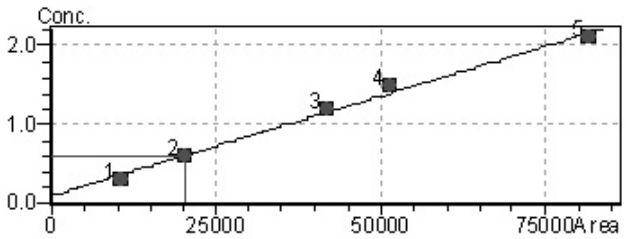

Рис. 4. Калибровочный график различных растворов с известными концентрациями абрикосовой камеди

Согласно данным количественного анализа, содержание арабиногалактана в 1 г абрикосовой камеди составило 99,8 мг/мл. Данный показатель позволит стандартизировать абрикосовую камедь флоры РА.

Несмотря на разнообразие практически ценных свойств арабиногалактана и доступность, в Армении отсутствует его промышленное производство.

С этой точки зрения выделение и очистка АГ из абрикосовой камеди представляется вполне перспективной и актуальной.

Результаты исследований позволяют предположить, что в ближайшее время арабиногалактан абрикосовой камеди займет достойное место в медикофармацевтической практике.

Таким образом, учитывая наличие достаточных сырьевых ресурсов абрикосовой камеди во флоре Армении, использование его в качестве естественного источника водорастворимого арабиногалактана представляется вполне перспективным.

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SUMMARY

GUMMI ARMENIACAE COLLECTED FROM APRICOT TREES IN ARMENIA – PERSPECTIVE SOURCE OF ARABINOGALACTAN

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The subjects of this inquiry were apricot tree gums - Gummi armeniacae, collected from different regions

of Republic Armenia. The samples of gums were analyzed by the method of gas-liquid chromatography. As a result arabinogalactans were revealed in apricot tree gums. Due to the presence of sufficient resources of Gummi armeniacae in Armenian flora their usage in the water soluble arabinogalactan's obtaining process is quite perspective.

Key words: gummi armeniacae, arabinogalactan.

РЕЗЮМЕ

GUMMI ARMENIACAE ИЗ АБРИКОСОВЫХ ДЕРЕВЬЕВ, ПРОИЗРАСТАЮЩИХ В АРМЕНИИ - ПЕРСПЕКТИВНЫЙ ИСТОЧНИК АРАБИНОГАЛАКТАНА

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Целью данного исследования явилось изучение химического состава камеди абрикоса, произрастающего на территории Республики Армения и возможностей ее применения в качестве источника водорастворимого арабиногалактана. В результате исследований в составе камеди был обнаружен арабиногалактан, что позволило провести качественную и количественную характеристику абрикосовой камеди по содержанию арабиногалктана. Таким образом, учитывая наличие достаточных сырьевых ресурсов абрикосовой камеди во флоре Армении, использование ее в качестве естественного источника водорастворимого арабиногалактана представляется вполне перспективным.

რეზიუმე

სომხეთის ჭერამის ხის Gummi Armeniacae არაბინოგალაქტანის პერსპექტიული წყაროა

ნ. ჩიჩოიანი

მ. გერაცის სახ. ერევნის სახელმწიფო სამედიცინო უნივერსიტეტი,ფარმაკოგნოზიის კათედრა, ერევანი, სომხეთი

შრომის მიზანს წარმოადგენდა სომხეთის რესპუბლიკაში გაშენებულ-გაზრდილი ჭერამის ხის გუმფისის ქიმიური შემადგენლობისა და მისი წყალში ხსნადი არაბინოგალაქტანის წყაროს სახით გამოყენების შესწავლა წარმოადგენდა.

კვლევის შედეგად გუმფისში აღმოჩენილ იქნა არაბინოგალაქტანი და განისაზღვრა ჭერმის ხის გუმფისის თვისობრივი და რაოდენობრივი მახასიათებლები.

ავტორის დასკვნით, სომხეთის ფლორას საკმარისი რაოდენობით გააჩნია ჭერმის გუმფისის ნედლეულის მარაგი და, ამდენად, სავსებით პერსპექტიულია მისი ფამოყენება წყალში ხსნადი არაბინოგალაქტანის ბუნებრივი წყაროს სახით.

* * *