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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

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

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CONTACT ADDRESS IN TBILISI

GMN Editorial Board
7 Asatiani Street, 3th Floor
Tbilisi, Georgia 0177

Phone: 995 (32) 254-24-91
995 (32) 222-54-18
995 (32) 253-70-58
Fax: 995 (32) 253-70-58

CONTACT ADDRESS IN NEW YORK

NINITEX INTERNATIONAL, INC.
3 PINE DRIVE SOUTH
ROSLYN, NY 11576 U.S.A.

Phone: +1 (917) 327-7732

WEBSITE

www.geomednews.org

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

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

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

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

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

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

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

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რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

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

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5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

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

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

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

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

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

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

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

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

НАУКА

APLASIA CUTIS CONGENITA TYPE I – A CASE SERIES

[1]Wollina U., [2]Chokoeva A., [3]Verma Sh., [4]Tchernev G., [5]Handjani F.

[1]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [2]Onkoderma - Policlinic of Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [3]Nirvana Skin Clinic, Vadodara, Gujarat, India; [4]Medical Institute of MVR, Department of Dermatology and Venereology, Sofia, Bulgaria; [5]Molecular Dermatology Research Center, Department of Dermatology, Shiraz University of Medical Sciences, Shiraz, Iran

Aplasia Cutis Congenita (ACC, [MIM 107600]) is a rare congenital disease characterized by local absence of skin (epidermis, dermis) and sometimes subcutaneous tissue. The most common affected site is scalp. Frieden (1986) has proposed a classification of the disease into 9 subtypes which may occur in association with genetic defects, malformations or non-syndromic [5].

The incidence rate is about 3 per 10,000 births with a female dominance of 7:5 [12]. The etiology of ACC is unknown, although various factors are discussed in medical literature, such as teratogenic substances during pregnancy (i.e. therapeutic or illicit drugs), trauma injury, vascular disease, thrombotic events, viral infections and chromosomal aberrations [5,10].

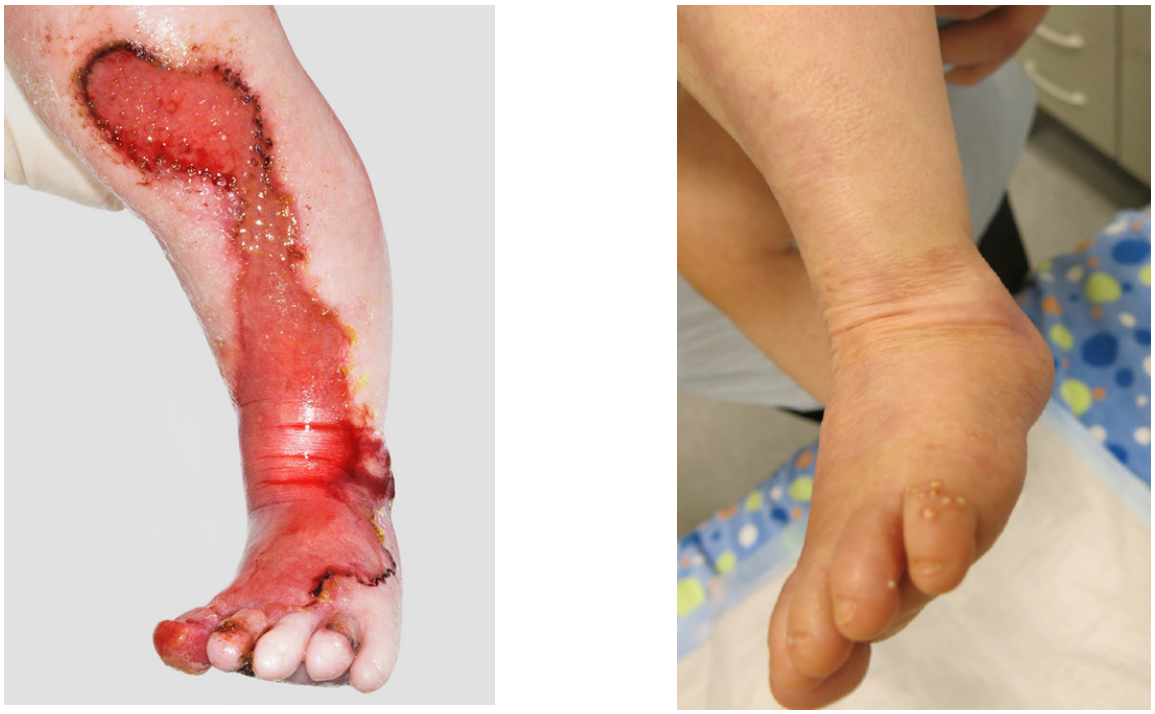
We report on a series of patients presenting with ACC type I, non-syndromic ACC, and the hitherto unreported occurrence of milia in association with ACC.

Material and methods. Case reports.

Case 1. A 3-month-old male was brought to the clinic by his parents for treatment of congenital ulcers on the right foot and lower leg. He was the first child of a non-consanguineous couple. Pregnancy was uneventful and childbirth was on term. At birth, the boy had a large skin defect on the left foot involving the heel and in the pretibial area of the left lower leg in a linear orientation (total area about 30 cm^2). Pediatric investigations ruled out any known chromosomal aberrations or other medical problems. A conservative treatment with application of petrolatum gauze and moisturizing ointments was recommended by the dermatologist. Six months later, all lesions were healed with a slight hyperpigmentation. On the 4th and 5th left toes milia were noted (Fig. 1). The lesions on the toes healed with secondary anonychia. The diagnosis of ACC type I was confirmed.

Case 2. A 6-weeks old male newborn was referred to the dermatologic clinic for diagnosis of a congenital scalp lesion. The patient was a well-developed infant born on term and first child of a young non-consanguineous couple. Pediatric investigations ruled out any other medical problem.

On physical examination, an irregularly shaped atrophic area on the scalp skin with a size of 1.2 x 1.0 cm was noted. The area was slightly depressed, completely hairless, and covered by a thin epi-



A B

Fig. 1. Case 1. (A) Aplasia cutis of the foot and lower leg. (B) Six month later, ulcers healed completely. Milia on the foot

dermal layer (Fig. 2). Based on the clinical findings and absence of any other medical problems, ACC type I was diagnosed. Parents were advised to perform conservative skin care with moisturizers.

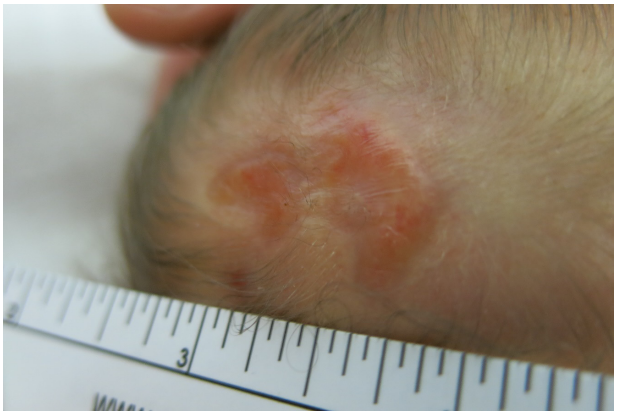


Fig. 2. Case 2 with atrophic, erythematous scalp lesions

Case 3. A 2-month-old female newborn was brought by her parents due to a non-healing birth lesion of scalp. She was the second child of the non-consanguineous couple. The pregnancy was uneventful. Childbirth was on term. The development of the child was normal and no medical problems had occurred to date.

On physical exam, the lesion which had been hemorrhagic at birth healed by conservative treatment within 2 months leaving a 2x2 cm round hairless area on the vertex (Fig. 3). Magnetic Resonance Imaging, neurologic and ophthalmologic investigations revealed no abnormalities. Histolopathology examination of a punch biopsy specimen showed absence of skin appendages and slight epidermal atrophy. The diagnosis of ACC I was confirmed.

This case had been published before [3].

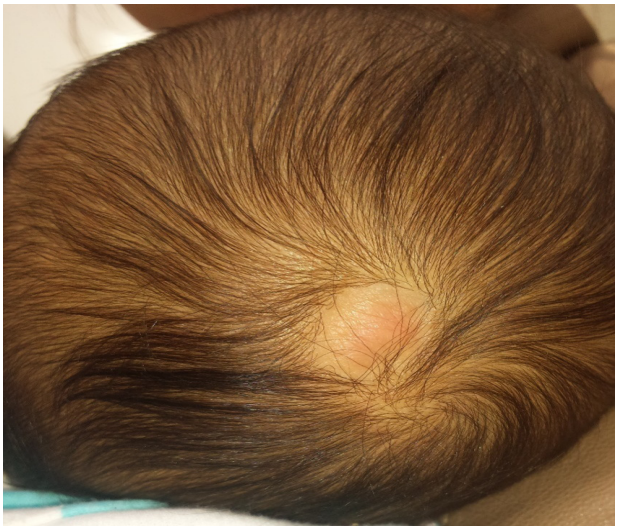


Fig. 3. Case 3 with a hairless scalp lesion on the vertex

Case 4. A 12–week old male newborn exhibiting a hairless area on the scalp was brought into the clinic by his parents. He was the first child of a young non-consanguineous couple and was born on the 33rd gestation week. The parents noticed the scalp lesion at birth. Pediatric workup provided no evidence of any other medical conditions or malformations. The lesion was treated conservatively by topical wound care remedies. On physical examination, the boy had a hairless area, measuring 5 cm in diameter, on the vertex region. At three months of age there was atrophy of soft tissue, but ulceration was no longer present (Fig. 4). The diagnosis of ACC type I was confirmed and the parents were advised to continue with appropriate skin care.

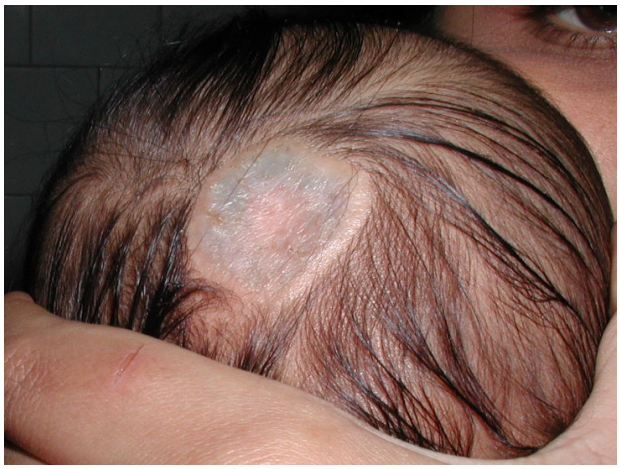


Fig. 4. Case 4 with a slightly erythematous and atrophic hairless scalp lesion

Case 5. A 5-weeks old male newborn was brought for dermatology consultation by his non-consanguineous parents. He had a 1 cm hairless skin depression on the scalp with irregular borders. Childbirth was on term. There were no other anomalies. The lesion was already epithelialized. The parents were advised to use a gentle skin care with moisturizer.

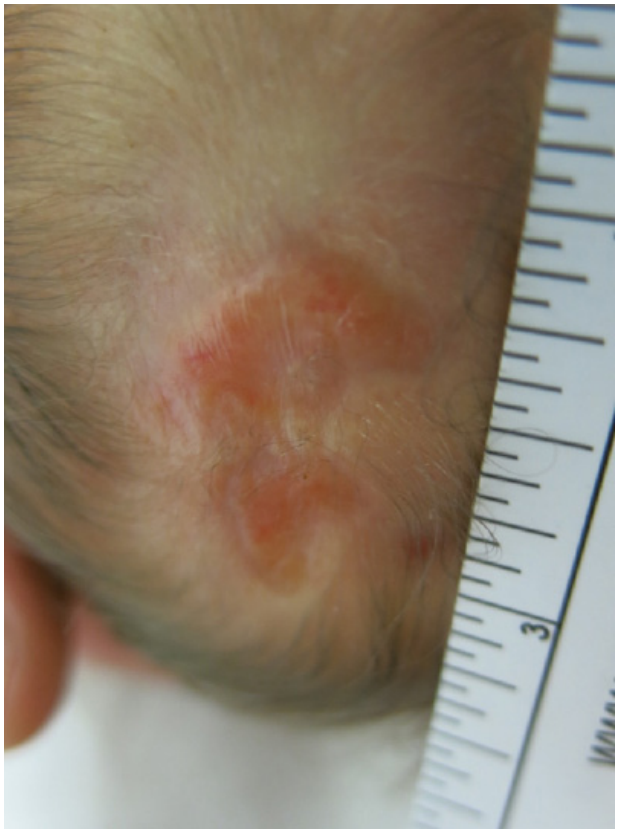


Fig. 5. Case 5 with an irregular shaped, hairless patch of the scalp. Epithelialization was already complete

Results and their discussion. ACC is a congenital malformation of soft tissue (skin and subcutaneous tissue) occurring in about 20% of scalp lesions with associated underlying skull defects. The clinical workup aims to identify possible associated genetic defects such as trisomy 13, fetus papryraceus, epidermolysis bullosa, Adams-Oliver syndrome, Barth syndrome, Goltz syndrome, Wolf-Hirschhorn syndrome, Delleman syndrome, Scalp-Ear-Nipple syndrome or Johanson-Blizzard syndrome, and embryologic malformations [3,5,01,12,13]. The most common type of ACC is type I without syndrome-related features [5,16]. This type often occurs with sporadic inheritance, though autosomal dominant inheritance has also been reported.

Our series of four patients consisted of sporadic inheritance only. Recently, a mutation in the ribosomal GTPase BMS1 has been identified in autosomal dominant ACC that is associated with a p21-mediated G1/S phase cell cycle transition delay and results in a reduced cell proliferation rate [16]. Missense variants in UBA2 are involved in scalp defects in 19q13.11 deletion syndrome and have been detected as a syndrome characterized by ACC, Duane anomaly, hip dysplasia [10]. In sporadic ACC type I no genetic defect could be identified so far.

While the most common site is scalp vertex, trunk and limbs, any other part of the body can be affected [5,7,13]. In our series, four patients suffered from the common type and one newborn had affected foot and lower leg. The occurrence of milia in the latter case of ACC is being reported for the first time. Milia represent small keratin-filled cysts that develop after occlusion of hair follicles or eccrine sweat glands. The occlusion might have been provoked by topical treatment and wound dressings.

The approach to treatment of ACC is controversial. Some authors prefer skin grafts or flaps to cover larger areas (> 4 cm^2) and skull defects of ACC that may result in faster epithelialization [1,4,8]. Sagittal sinus or large vein exposure is an indication for urgent surgical treatment to prevent possible fatal hemorrhages and infections [6,9,16,17].

However, most authors advocate conservative treatment for defects regardless of their size to avoid the risk of surgery [5,7,12,13,15]. Those lesions not affecting vital structures can be treated with topical wound and skin care products easily and cost-effectively. Parents can be guided to perform daily dressing changes and application of topical treatments [2]. Recently topical application of basic fibroblast growth factor has been described as an experimental approach to facilitate epithelialization in large scalp defect of ACC [14].

In our series, no bony defects were observed and no larger vessels were exposed. Conservative treatment was effective in all our cases.

Acknowledgements. We wish to express our gratitude to the parents.

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SUMMARY

APLASIA CUTIS CONGENITA TYPE I – A CASE SERIES

[1]Wollina U., [2]Chokoeva A., [3]Verma Sh., [4]Tchernev G., [5]Handjani F.

[1]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [2]Onkoderma - Policlinic of Dermatology and Dermatologic Surgery, Sofia, Bulgaria; [3]Nirvana Skin Clinic, Vadodara, Gujarat, India; [4]Medical Institute of MVR, Department of Dermatology and Venereology, Sofia, Bulgaria; [5]Molecular Dermatology Research Center, Department of Dermatology, Shiraz University of Medical Sciences, Shiraz, Iran

Aplasia Cutis Congenita is a rare disorder with circumscribed, partial or widespread absence of skin and subcutaneous soft tissue; in about 20% it also causes skull defects. The disease is heterogeneous in its clinical presentation with nine major subtypes. Type I represents nonsyndromic Aplasia Cutis Congenita.

We report 5 infants with skin defects of the scalp and limbs presented to dermatologists. Pediatric workup ruled out any other malformations or genetic disorders. All patients were treated by conservative wound and skin care without complications. In one case the formation of milia has been observed – an outcome not described before. Therapeutic approach and differential diagnoses are described.

Topical wound and skin care resulted in complete closure of the defects. Skin appendages did not recover, leaving hairless areas on the scalp and limbs.

Aplasia Cutis Congenita type I is a rare disorder in newborns with >85% of all solitary lesions occurring on the scalp. Conservative treatment is a simple and safe option in many cases. Exposed large veins and sagittal plexus demand urgent surgical approaches to prevent fatal hemorrhages or infections.

Key words: aplasia cutis congenita; treatment; genetic disorders; newborns.

РЕЗЮМЕ

ВРОЖДЕННАЯ АПЛАЗИЯ КОЖИ I ТИПА - СЕРИЯ КЛИНИЧЕСКИХ СЛУЧАЕВ

[1]Воллина У., [2]Чокоева А., [3]Верма Ш., [4]Чернев Г., [5]Ханджани Ф.

Академический клинический госпиталь Дрезден-Фриедрихштадт, отделение дерматологии и аллергологии, Дрезден, Германия; [2]Онкодерма - Поликлиника дерматологии и кожной хирургии, София, Болгария; [3]Дерматологическая клиника «Нирвана», Вадодара, Гужарат, Индия; [4]Медицинский институт Министерства внутренних дел, отделение дерматологии и кожной хирургии, София, Болгария; [5]Научно-исследовательский центр молекулярной дерматологии, отдел дерматологии, Шираз Университет Медицинских Наук, Шираз, Иран

Врожденная аплазия кожи (Aplasia Cutis Congenita) - редкое заболевание с чётко ограниченными краями, частичным или распространенным отсутствием кожи и подкожной мягкой ткани; приблизительно в 20% случаев также присутствуют дефекты черепа. Заболевание гетерогенно по своей клинической картине с девятью основными подтипами. Тип I представляет собой несиндромную врождённую аплазию кожи (ВАК).

Авторами представлены 5 клинических случаев дефекта кожи головы и конечностей у новорожденных, лечившихся в дерматологической клинике. Педиатрическое обследование исключало наличие пороков развития или других генетических нарушений. Всем пациентам проведено консервативное лечение ран; осложнений не наблюдалось. В одном случае наблюдалось образование милий (белая сыпь наподобие “просяного зерна”, возникшая в результате закупорки сальных желез), что ранее не было описано в литературе. В статье описаны терапевтический подход и дифференциальная диагностика.

Поверхностная обработка раны и кожи привела к полному закрытию дефектов. Кожные придатки не восстановились, оставляя лысины на волосистой части головы и конечностях. Врожденная аплазия кожи I типа - редкое заболевание у новорожденных с более чем 85% всех одиночных поражений, возникающих на коже головы. Консервативное лечение во многих случаях является простым и наиболее безопасным подходом. Вены крупного калибра и сагиттальное сплетение, обнаженные в результате данного дефекта, являются показанием к срочному хирургическому вмешательству с целью предотвращения жизненно опасных кровотечений или инфекций.

რეზიუმე

კანის I ტიპის თანდაყოლილი აპლაზია –კლინიკური შემთხვევების სერია

[1]უ. ვოლინა, [2]ა. ჩოკოევა, [3]შ. ვერმა,
[4]გ. ჩერნევი, [5]ფ. ხანდჟანი

[1]დრეზდენ-ფრიედრიხშტადტის აკადემიური კლინიკური ჰოსპიტალი, დერმატოლოგიისა და ალერგოლოგიის განყოფილება, დრეზდენი, გერმანია; [2]ონკოდერმა – დერმატოლოგიისა და კანის ქირურგიის პოლიკლინიკა, სოფია,ბულგარეთი; [3]დერმატოლოგიური კლინიკა “ნირვანა”,ვადოდარა,გუჯარატი,ინდოეთი; [4]შინაგან საქმეთა სამინისტრო,სამედიცინო ინსტიტუტი,დერმატოლოგიის და კანის ქირურგიის განტოფილება, სოფია, ბულგარეთი; [5]მოლეკულური დერმატოლოგიის სამეცნიერო-კვლევითი ცენტრი, დერმატოლოგიის განყოფილება, შირაზის სამედიცინო მეცნიერებათა უნივერსიტეტი, შირაზი, ირანი

კანის თანდაყოლილი აპლაზია (Aplasia Cutis Congenita) იშვიათი დაავადებაა,მკაფიოდ შემოფარგლული კიდეებით,კანის და კანქვეშა რბილი ქსოვილის ნაწილობრივი ან განვრცობილი არარსებობით; შემთხვევათა დაახლოებით 20%-ში, ასევე, აღინიშნება თავის ქალას დეფექტებიც. დაავადება კლინიკური სურათის მიხედვით ჰეტეროგენულია და აქვს ცხრა ძირითადი ქვეტიპი. ტიპი 1 წარმოადგენს კანის თანდაყოლილ არასინდრომულ აპლაზიას (კთა). კანის თანდაყოლილი I ტიპის აპლაზია ახალშობილთა იშვიათი დაავადებაა, რომლის დროსაც ერთეული დაზიანებების 85%-ზე

მეტი ვითარდება თავის კანზე. ხშირ შემთხვევაში კონსერვატიული მკურნალობა მარტივი და ყველაზე უსაფრთხო მიდგომაა. ამ დეფექტის შედეგად გაშიშვლებული მსხვილი კალიბრის ვენები და საგიტალური წნული, სიცოცხლისათვის საშიში სისხლდენისა და ინფექციების თავიდან აცილების მიზნით,წარმოადგენს ჩვენებას სასწრაფო ქირურგიული ჩარევისათვის.

ავტორების მიერ წარმოდგენილია ახალშობილების თავისა და კიდურების კანის დეფექტის 5 კლინიკური შემთხვევა, რომლებიც მკურნალობდნენ დერმატოლოგიურ კლინიკაში. პედიატრიულმა კვლევამ გამორიცხა განვითარების მანკებისა და სხვა გენეტიკური დარღვევების არსებობა. ყველა პაციენტს ჩაუტარდა ჭრილობების კონსერვატიული მკურნალობა; გართულებები არ განვითარებულა. ერთ შემთხვევაში, ქონის ჯირკვლების სადინრების დახშობის გამო,წარმოიქმნა "გაცრილი მარცვლის" ტიპის თეთრი გამონაყარი,რაც ადრე ლიტერატურაში აღწერილი არ ყოფილა. სტატიაში აღწერილია თერაპიული მიდგომა და დიფერენციული დიაგნოსტიკა.

ჭრილობისა და კანის ზედაპირულმა დამუშავებამ განაპირობა დეფექტების სრული დახურვა. კანის დანამატები არ აღდგა, დატოვა რა სიმელოტე თავისა და კიდურების თმიან ნაწილზე.

NEOADJUVANT CHEMOTHERAPY FOR LOCALLY ADVANCED BREAST CANCER

[1]Fomenko Y., [1]Sirota V., [2]Omarova I., [1]Kabildina N., [1]Amanov A.

[1]Karaganda State Medical University; [2]Karaganda Regional Cancer Center, Kazakhstan

Treatment of locally advanced breast cancer (LABC) is complex with the use of local and general methods of influence on the tumor. Up to 40% of breast cancer patients at the time of treatment initiation are locally advanced [5]. Therefore, neoadjuvant chemotherapy is currently gained recognition among clinicians in most countries [15]. Some researchers recommend neoadjuvant chemotherapy before surgery [9,13], other authors - before preoperative radiotherapy [8], and others - on the background of radiotherapy followed by surgery [12].

Neoadjuvant chemotherapy contributes to the transfer of the irresectable into resectable tumor status, eliminates micrometastases, thereby improves both immediate and long-term outcomes. Neoadjuvant chemotherapy increases the number of pathological complete response (pCR), the rate of breast conserving surgery and reduces the risk of tumor recurrence in young women. In locally advanced breast cancer (LABC) standard neoadjuvant protocols in Kazakhstan are CMF, FAC and AC, but nowadays new anticancer agents with a new range of action (taxanes, vinorelbine) are put into practice [10].

"Arglabin" is registered in the Republic of Kazakhstan as an antitumor agent (Registration Certificate RK-LS-5-№003950). Arglabin was created in the Republic of Kazakhstan (the developer - "International research and production holding "Phytochemistry). It is based on the eponymous sesquiterpene lactone isolated from a plant endemic to Central Kazakhstan - wormwood smooth. Preclinical studies of the drug in monotherapy and in combination with other anticancer drugs have shown the presence of cytostatic and immunomodulating activities. Arglabin is a farnesyl protein transferase inhibitor which stops the processing of Ras-oncoproteins responsible for tumor cell mitotic activity [2,4,6].

The estimation of efficiency of Arglabin in the neoadjuvant treatment of LABC compared with standard neoadjuvant chemotherapy and in combination with it is a point of interest. The goal of the trial - a comparative analysis of the effectiveness of different protocols of neoadjuvant chemotherapy for LABC by estimation of the clinical efficacy, degree of tumor and metastatic lymph nodes regression, pathological response, hematologic and non-hematological toxicity.

Material and methods. The clinical study was conducted in accordance with ethical principles, based on the Declaration of Helsinki, GCP and the applicable laws. It was approved by the Central Ethics Committee of the Ministry of Health of the Republic of Kazakhstan from 09.10.2012, № 24 (5). All patients gave the written informed consent to participate in a clinical trial.

The study included 93 patients with newly diagnosed and histologically confirmed nodular form of breast cancer of the stages T2 N1-2 M0 and T3 N0-2 M0 treated in the regional oncologic center in Karaganda. Exclusion criteria were as follows: allergy to Artemisia, other malignancies, anemia, leukopenia, thrombocytopenia, renal failure, uncompensated heart disease, diabetes mellitus, acute inflammation and other diseases that hinder chemotherapy, radiation therapy, and radical mastectomy.

The age of patients ranged from 35 to 75 years. The third part of patients aged 41 - 50 years, about half of patients aged 51 – 70 years. 31 patients had stage T2 N1-2 M0 and 62 patients – stage T3 N0-2 M0.

All patients were randomized into 3 groups: two investigative groups and one control group.

The I control group included 36 patients with LABC who received four cycles of neoadjuvant chemotherapy according to AC-protocol: doxorubicin - 50 mg/m^2, cyclophosphamide - 500 mg/m^2 on day 1 every 21 days followed by radical mastectomy, 4 courses of adjuvant chemotherapy (AC), radiotherapy and adjuvant antihormonal therapy if indicated.

I investigative group included 30 patients who received four cycles of neoadjuvant chemotherapy according to AC-protocol in combination with Arglabin: doxorubicin - 50 mg/m^2, cyclophosphamide - 500 mg/m^2 on day 1 + Arglabin 370 mg/m^2 on 7 days, every 21 days. Further adjuvant therapy was identical to the control group.

II investigative group included 27 patients who received four cycles of Arglabin as monotherapy (370 mg/m^2 on seven days, repeated every 21 days) in the neoadjuvant and adjuvant setting. Further adjuvant therapy was identical to the control group.

Evaluation of the direct results was carried out immediately after the four courses of neoadjuvant chemotherapy. The effectiveness of the combined treatment was assessed according to standard WHO criteria (1978), using clinical examination, ultrasound and mammography. Evaluation of hematological toxicity was conducted according to the recommendations of the WHO (Geneva, 1979, 1985).

Statistical analyses of the results were carried out by methods of parametric statistics to estimate the significance of differences between the control and test groups per Student's t-test. Statistical analyses were performed using "STATISTICA 10" and EXCEL.

Results and their discussion. It has been revealed that the complete clinical response is not received in any of the three groups. Partial responses were obtained in 63,3±8,8% with AC-protocol + Arglabin, 58,3±8,2% - in the control group ($p\geq0,05$) and 25,9±8,4% - in the group treated with Arglabin as monotherapy ($p\leq0,05$). There are no statistically significant differences between the three groups of patients in assessing the stable disease - 38,9%, 33,3% and 51,9%, respectively ($p\geq0,05$). The progressive disease was significantly higher ($p\leq0,05$) in the II investigative group - 22,2±8,0% in comparison to the control group - 2,8±2,6% and the I investigative group - 3,3±3,3% ($p\geq0,05$). Table 1 shows the immediate results of neoadjuvant treatment of patients with LABC.

Table 2 shows the characteristics of tumor patients with locally advanced breast cancer according to tumor volume by breast ultrasound. Sample Testing for normality of the distribution is made on indicators of "asymmetry" and "excesses" and the median was chosen for analysis. The extent of tumor regression is most expressed in control group - 71.7±7.5% ($p\leq0.05$). Patients in I investigative group were investigated the largest tumor volume (61.5) and the degree of regression was 67.2±8.6% ($p\leq0.05$). The extent of tumor regression in patients of the II investigative group was 10.8±5.9%. AC-protocol and its combination with Arglabin comparable in efficiency. Adding Arglabin to AC-protocol is not increased degree of regression of breast cancer.

Highest regression of metastatic lymph nodes marked in patients of I investigative group - 73,0±8,1%, further in patients of Control group - 56,4±8,3%, in II investigative group – 54,6±9,6%, a statistically significant regression of lymph nodes was revealed in patients of all three groups ($p\geq0,05$). Adding Arglabin to AC-protocol showed a tendency to increase the regression of lymph nodes. Table 3 shows the volume of axillary lymph nodes in patients with locally advanced breast cancer in the dynamics of neoadjuvant treatment by ultrasound.

There was no statistically significant difference in the pathological response of the tumor in patients of all three groups ($p\geq0,05$). Table 4 shows the pathological response of the tumor after neoadjuvant therapy.

Table 1. Immediate results of preoperative treatment of locally advanced breast cancer

Groups of patients according to the method of treatment	Number of patients	Clinical tumor response			
		CR	PR	SD	PD
I control group (AC)	36	0	21 (58,3±8,2)*	14 (38,9±8,1)	1 (2,8±2,8)*
II investigative group (AC+Arglabin)	30	0	19 (63,3±8,8)*	10 (33,3±8,6)	1 (3,3±3,3)*
II investigative group (Arglabin)	27	0	7 (25,9±8,4)	14 (51,9±9,6)	6 (22,2±8,0)

*note: * - statistically significant PR and PD in the Control group and I Investigative group in relation to the II Investigative group ($p\leq0.05$)*

Table 2. The dynamics of tumor volume before and after neoadjuvant treatment on medians

Groups of patients according to the method of treatment	Number of patients	Tumor volume before treatment (cm^3)	Tumor volume after treatment (cm^3)	The degree of tumor regression in %
I control group (AC)	36	56,7	16,1	71,7±7,5*
II investigative group (AC+Arglabin)	30	61,5	20,2	67,2±8,6*
II investigative group (Arglabin)	27	57,6	51,4	10,8±5,9

*note: * - statistically significant regression in the Control group and I Investigative group in relation to the II Investigative group ($p \leq 0.05$)*

Table 3. The volume of axillary lymph nodes in patients with locally advanced breast cancer before and after neoadjuvant treatment (by ultrasound)

Groups of patients according to the method of treatment	Number of patients	Volume of lymph nodes before treatment (cm3)	Volume of lymph nodes after treatment (cm3)	The degree of lymph nodes regression in %
I control group (AC)	36	2,75	1,2	56,4±8,3
II investigative group (AC+Arglabin)	30	3,74	1,01	73,0±8,1
II investigative group (Arglabin)	27	7,26	3,3	54,6±9,6

*note: * - there is no statistically significant regression in any of the three groups (p≥0,05)*

Table 4. Pathological response of the tumor after neoadjuvant therapy

Groups of patients according to the method of treatment	Number of patients	Pathological response degrees					
		0	1	2	3	4	3+4
I control group (AC)	36	-	15 41,7±8,2	12 33,3±7,9	6 16,7±6,2	3 8,3±4,6	9 25,0±7,2
II investigative group (AC+Arglabin)	30	-	12 40,0±8,9	8 26,6±8,1	7 23,3±7,7	3 10,0±5,5	10 33,3±8,6
II investigative group (Arglabin)	27	3 11,1±6,0	15 55,6±9,6	5 18,5±7,5	4 14,8±6,8	-	4 14,8±6,8

*note: * - there is no statistically significant difference in any of the three groups (p≥0,05)*

Table 5. Hematological toxicity of neoadjuvant chemotherapy and arglabin in patients with breast cancer (M±m)

Hematological toxicity	Groups of patients according to protocols		
	AC – protocol (patients -36, cycles -144) absolute value (%)	AC – protocol + Arglabin (patients-30, cycles -120) absolute value (%)	Arglabin (patients -27, cycles -108) absolute value (%)
Neutropenia total 1 degree 2 degree 3-4 degrees	28 (19,5±3,3%) 16 (11,1±2,6%) 8 (5,6±1,9%) 4 (2,8±1,4%)	13 (10,8±2,8%)* 8 (6,7±2,3%) 4 (3,3±1,6%) 1 (0,8±1,0%)	1 (0,9±0,9%)** 1 (0,9±0,9%) - -
Anemia total 1 degree 2 degree 3-4 degrees	8 (5,6±1,9%) 8 (5,6±1,9%) - -	6 (5,0±2,0%) 6 (5,0±2,0%) - -	2 (1,9±1,3%) 2 (1,9±1,3%) - -
Thrombocytopenia total 1 degree 2 degree	9 (6,3±2,0%) 9 (6,3±2,0%) -	6 (5,0±2,0%) 6 (5,0±2,0%) -	5 (4,6±2,0%) 5 (4,6±2,0%) -

*note: * - statistically significant lower neutropenia in patients in the I investigative group with respect to control group (p≤0,05);*
*** statistically significant lower neutropenia in patients in the II investigative group in relation to the patients of the control group and the I investigative group (p≤0,05)*

In patients with LABC treated with neoadjuvant multiagent chemotherapy, we also defined hematologic and non-hematological toxicity (Table 5).

The most severe hematologic toxicity was in the control group of patients. In this group of patients neutropenia was observed in 19,5±3,3% of patients. It was 10,8±2,8% in patients treated with

Table 6. Non-hematological toxicity of neoadjuvant chemotherapy and arglabin in patients with breast cancer (M±m)

Non-hematological toxicity	Groups of patients according to protocols		
	AC – protocol (patients -36, cycles -144) absolute value (%)	**AC – protocol + Arglabin (patients-30, cycles -120) absolute value (%)**	**Arglabin (patients -27, cycles -108) absolute value (%)**
Nausea, vomiting total	28 (19,5±3,3%)	16 (13,3±3,1%)	-
1-2 degrees	28 (19,5±3,3%)	16 (13,3±3,1%)	-
3-4 degrees	-	-	-
Mucositis total	14 (9,7±2,5%)	6 (5,0±2,0%)	-
1-2 degrees	14 (9,7±2,5%)	6 (5,0±2,0%)	-
3-4 degrees	-	-	-
Hepatotoxity total	16 (11,1±2,6%)*	5 (4,2±1,8%)	3 (2,8±1,6%)
1-2 degrees	16 (11,1±2,6%)*	4 (3,3±1,6%)	3 (2,8±1,6%)
3-4 degrees	-	1 (0,8±0,8%)	-
Nephrotoxicity total	2(1,4±0,98%)	-	-
1-2 degrees	2(1,4±0,98%)	-	-
3-4 degrees	-	-	-
Allergic reactions total	-	5 (4,2±1,8%)	3 (2,8±1,6%)
1-2 degrees (transient rash, urticaria)	-	5 (4,2±1,8%)	3 (2,8±1,6%)
3-4 degrees (bronchospasm, anaphylaxis)	-	-	-

*note: * - statistically significant higher hepatotoxicity in patients in the control group with respect to the I and II investigative groups(p≤0,05)*

neoadjuvant AC-protocol + Arglabin and 0,9±0,9% in patients treated with Arglabin as monotherapy. Arglabin does not cause neutropenia, including Arglabin to AC-protocol causes a leveling of the toxic effect of its agents.

Anemia I degree detected in patients of the control group and the I investigative group, it was observed in 5,6±1,9% and 5,0±2,0% of patients respectively, and it is less expressed in patients of the investigative group 2 (1,9±1,3%, but the difference is statistically insignificant (p≥0,05).

Thrombocytopenia I degree is expressed in patients of all groups equally with low rates.

Non-hematological toxicities include nausea, vomiting, mucositis, hepatotoxicity, nephrotoxicity, and allergic reactions.

Nausea and vomiting are equally common in patients in the control group and the I investigative group - in 19,5±3,3% and 13,3±3,1% of cases, respectively (p≥0,05). Mucositis similarly constituted 9,7±2,5% and 5,0±2,0%, respectively (Table 6). Arglabin as monotherapy does not cause nausea and vomiting.

The most hepatotoxic was AC-protocol 11,1±2,6% of cases (p≤0,05). In I and II investigative groups - 4,2±1,8% and 2,8±1.6%, respectively. Nephrotoxicity was observed only in the control group patients - 1,4±0,98% (p≥0,05).

Among patients who received Arglabin, allergic reactions such as skin rashes were observed in 4,2±1,8)% of cases in the I investigative group and in 2,8±1,6% of cases in the II investigative group (p≥0,05).

Chemotherapy is one of the principal methods of cancer treatment, which allows not only to prolong the patient's life, but also to improve its quality. That is why clinicians have such an interest to chemotherapy tolerability [4,14].

Currently, the use of phytoagents is quite promising direction in the complex treatment of cancer patients. It has been established that Arglabin prevent farnesylation of cellular proteins. Ras-protein is a proto-oncogene of about 30% of human cancers, including breast cancer. It is synthesized in the cytosol as a proto-oncogene and then undergoes posttranslational modification, which includes farnesylation by the enzyme farnesyl protein transferase, elimination of the three carboxy-terminal amino acid residues with a protease. Ras-modified protein binds to the inner side of the plasma membrane and participates in the mitogenic signal transduction [17]. Arglabin is a competitive inhibitor of farnesyl transferase [10], which contributes to the inhibition of the mitotic activity of tumor cells.

Furthermore, Arglabin, reducing the level of ATP tumor cell [1], can cause destabilization of cell mitochondria that begins with the fall of the transmembrane potential of the inner mitochondrial membrane and is accompanied by the release of apoptogenic factors: proapoptotic bcl 2 protein, Bax protein, - causing cell apoptosis.

The effectiveness of chemotherapy is evaluated not only from the point of view of immediate cytotoxic effects, but also taking into account immunomodifying effects, which are inherent in many chemotherapy drugs. Different immunocompetent cells react unequally to the same chemotherapy drugs, which probably determines the immunomodulatory effects. Arglabin has been shown to have an immunomodulatory effect [14], is low-toxic and well tolerated by patients.

Conclusions.

1. Clinical efficacy of neoadjuvant chemotherapy according to AC-protocol and AC-protocol + Arglabin were similar and was significantly superior to Arglabin monotherapy. The addition of Arglabin to AC might help lowering side effects of chemotherapy but further inverstigation in larger collectives is necessary.
2. The degree of regression of the tumor is the same in patients receiving neoadjuvant chemotherapy according to the scheme of AC and AC + Arglabin, which significantly exceeds the degree of regression in patients who received Arglabin monotherapy.
3. The highest rates of regression of metastatic lymph nodes are observed in patients who received chemotherapy according to AC + arglabin (73.0±8.1%). The introduction of Arglabin in the AC-protocol revealed a tendency to increase the degree of regression of the lymph nodes. There was no statistically significant degree of regression of the lymph nodes in patients of all three groups.
4. There was no statistically significant difference in the pathological response of the tumor in patients of all three groups.
5. The most severe hematologic toxicity was in the control group, neutropenia was observed at (19,5±3,3)% of patients. Arglabin as monotherapy does not cause neutropenia. Adding Arglabin to AC-protocol causes a leveling of the toxic effect of its agents. Arglabin has very low toxicity and eliminates the toxic effects of standard chemotherapy.

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SUMMARY

NEOADJUVANT CHEMOTHERAPY FOR LOCALLY ADVANCED BREAST CANCER

[1]Fomenko Y., [1]Sirota V., [2]Omarova I.,
[1]Kabildina N., [1]Amanov A.

[1]Karaganda State Medical University; [2]Karaganda Regional Cancer Center, Kazakhstan

93 patients with LABC (T2N1-2M0, T3N0-2M0) at the age from 35 to 75 years were included in the trial. With 2 stage - 60 patients, with the third stage - 33 patients. All patients were randomized into 3 groups: The I control group (n=36) received 4 courses of neoadjuvant chemotherapy according to AC-protocol (doxorubicin 50 mg/m^2, cyclophosphan-500 mg/m^2 on day 1, repeated every three weeks) followed by radical mastectomy, 4 courses of adjuvant chemotherapy (AC), radiotherapy and hormone therapy if indicated. II investigative group (n=30) received the same CTX but in combination with Arglabin at a dose of 370 mg/m^2 for 7 days. III investigative group (n=27) received Arglabin as monotherapy. The clinical efficacy of neoadjuvant chemotherapy according to the scheme of AC and AC + arglabin was the same and significantly exceeded Arlabine monotherapy. There was no statistically significant difference in pathological response in patients of all three groups. Arglabin has very low toxicity and eliminates the toxic effects of standard chemotherapy.

Keywords: breast cancer, neoadjuvant chemotherapy, efficacy, toxicity of chemotherapy.

РЕЗЮМЕ

НЕОАДЪЮВАНТНАЯ ХИМИОТЕРАПИЯ МЕСТНОРАСПРОСТРАНЕННОГО РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ

[1]Фоменко Ю.М., [1]Сирота В.Б., [2]Омарова И.М.,
[1]Кабилдина Н.А., [1]Аманов А.С.

[1]Карагандинский государственный медицинский университет; [2]КГП «Областной онкологический диспансер», Караганда, Казахстан

В исследование включены 93 больных местнораспространенным раком молочной железы (МР РМЖ). Больные

разделены на 3 группы: 2 исследуемые и контрольная. I (контрольную) группу составили 36 больных МР РМЖ, которые получали 4 курса неоадъювантной химиотерапии по схеме АС (доксорубицин 50 мг/м^2, циклофосфан 500 мг/м^2), 30 пациенток II исследуемой группы получали 4 курса химиотерапии по схеме АС + арглабин (арглабин 370 мг/м^2 7 дней), 27 пациенток III исследуемой группы - 4 курса монотерапии арглабином.

Клиническая эффективность неоадъювантной химиотерапии по схеме АС и АС+арглабин оказалась одинаковой и достоверно превосходила монотерапию арглабином. Статистически значимой разницы лекарственного патоморфоза опухоли у пациентов всех трех групп не выявлено. Арглабин обладает самой низкой токсичностью и нивелирует токсическое действие стандартной полихимиотерапии.

რეზიუმე

სარძევე ჯირკვლის ადგილობრივად გავრცელებული კიბოს ნეოადიუვანტური ქიმიოთერაპია

[1]იუ. ფომენკო, [1]ვ. სიროტა, [2]ი. ომაროვა, [1]ნ. კაბილდინა, [1]ა. ამანოვი

[1]ყარაგანდის სახელმწიფო სამედიცინო უნივერსიტეტი;
“სამხარეო ონკოლოგიური დისპანსერი”, ყარაგანდა, ყაზახეთი

კვლევის მიზანს შეადგენდა სარძევე ჯირკვლის ადგილობრივად გავრცელებული კიბოს ნეოადიუვანტური ქიმიოთერაპიის ეფექტურობის შეფასება. კვლევაში ჩართული იყო 93 ავადმყოფი სარძევე ჯირკვლის ადგილობრივად გავრცელებული კიბოთი. ავადმყოფები დაიყო სამ ჯგუფად – საკონტროლო და ორი საკვლევი. საკონტროლო ჯგუფი (I) წარმოდგენილი იყო 36 ავადმყოფით, რომელთაც ჩაუტარდა ნეოადიუვანტური ქიმიოთერაპიის 4 კურსი АС სქემით (დოქსორუბიცინი - 50 მგ/მ^2, ციკლოფოსფანი - 500 მგ/მ^2); II საკვლევი ჯგუფი შეადგინა 30 პაციენტმა,რომლებსაც ჩაუტარდა ქიმიოთერაპიის 4 კურსი სქემით АС+არგლაბინი (არგლაბინი - 370 მგ/მ^2, 7 დღის განმავლობაში); 27 ავადმყოფმა შეადგინა III საკვლევი ჯგუფი. აღნიშნული ჯგუფის ავადმყოფებს ჩაუტარდა მონოთერაპია არგლაბინით – 4 კურსი.

АС და АС+არგლაბინით სქემებით ჩატარებული ნეოადიუვანტური ქიმიოთერაპიის კლინიკური ეფექტურობა იყო ერთნაირი და უფრო მაღალი,ვიდრე მონოთერაპია არგლაბინით.

სამივე ჯგუფის პაციენტებში სიმსივნის მედიკამენტური პათომორფიზმის მაჩვენებლებს შორის სტატისტიკურად მნიშვნელოვანი განსხვავება არ გამოვლინდა. არგლაბინი ხასიათდება ყველაზე დაბალი ტოქსიკურობით და, ამავე დროს, ახდენს სტანდარტული პოლიქიმიოთერაპიის ტოქსიკურობის ნიველირებას.

DINAMICS OF KNEE JOINT SPACE ASYMMETRY ON X-RAY AS A MARKER OF KNEE OSTEOARTHRITIS REHABILITATION EFFICACY

Sheveleva N., Minbayeva L., Belyayeva Y.

Karaganda State Medical University, Department of Medical Rehabilitology, Visual Diagnostics and Physical Training, Karagandy, Kazakhstan

The knee joint is a complex anatomical structure, consisting of a tibiofemoral and patellofemoral joints, formed with 4 bones (femur, tibia, fibula and patella). Joint stabilization is provided by menisci, strong capsular-ligamental and musculotendinous complexes. Anatomical structure of the knee joint allows wide range of motions in sagittal (flexion-extension ranged 140^0-145^0), frontal (abduction-adduction within 5^0) and horizontal planes (internal/ external rotation in flexion position 15-20^0). Extension of the joint in the range of 90^0-180^0 is accompanied with external rotation and anterior displacement of the tibia [7].

An excessive axial and rotational load on the knee joint occurs as a result of flat feet presence, valgus/varus installation of feet, asymmetry of the limbs length, and violations axial and angular positions of the pelvis. Uneven distribution of pressure on medial, lateral, anterior and posterior portions of the joint inevitably leads to traumatization of intra- and/or periarticular tissues, dysfunction of connective tissue and muscle structures, violation of the lower limb axis, which promotes formation of functional overload of the knee. As a result, conditions for development and progression of degenerative changes in the knee joint are created [1,5,10]. Thus, functional well-being of the knee depends on tendons, ligaments and muscles of the entire lower extremity providing the correct biomechanics, as well as the state of hip and ankle joints.

According to the data presented in the National Institute of Clinical Excellence (NICE) recommendations on osteoarthritis care and management in adults (United Kingdom, 2014), osteoarthritis (OA) is the leader among the causes of disability in older people. In accordance with the prognostic data on the increase of osteoarthritis incidence provided in 2013 by the United Nations (UN), number of people aged over 60 years suffering from OA would triple during the next 40 years and would affect about 20% of the world population by 2050 (about 130 millions). 30% of the patients would have severe forms of disability [13]. About 25% of the population aged 50 years and older have radiological

evidence of knee joint OA. The high prevalence of the disease and progressive increase in the incidence of osteoarthritis [13], necessitate continuous improvement of therapeutic and preventive measures. Frequently revealed discrepancy of clinical and radiological symptoms of knee joint osteoarthritis and long-lasting relative stability of the characteristic X-ray symptoms [8], makes it difficult to assess progression of the process and motivates professionals improving the diagnostic search procedure.

Radiography is one of the most accessible and informative diagnostic method of joints examination, allowing to assess precisely enough typical for osteoarthritis pathological changes of bone structures and to determine the extent of its severity. The most common radiological classifications used to identify the severity of pathological changes in knee joints are the Kellgren-Lawrence Grading Scale (1957) and classification of Kosinskaya N.S. (1961) [3,4,11]. However, in international practice of knee joint osteoarthritis diagnostics, as well as in the Clinical Protocols of Diagnostics and Treatment of Gonarthrosis (M17) by the Health and Social Development Ministry of the Republic of Kazakhstan (2015), it is recommended to determine the degree of pathological changes severity by Kellgren-Lawrence classification with mandatory standard X-ray examination of the knee in direct and lateral projections [2].

On the frontal X-ray it is possible to determine the size of joint space. The joint space narrowing along with development of subchondral osteosclerosis and formation of bone boundary growths (osteophytes), is a specific radiological symptom of knee joint osteoarthritis. Analysis of the dynamics of X-ray joint space allows evaluating changes in the functional volume of the articular cartilage and judging about progression of the process [8]. According to the recommendations of the World Health Organisation/ International League of Associations for Rheumatology (WHO/ ILAR), standardized measurement of interarticular knee joint space is carried out by direct projection roentgenogram in the place of maximal narrowing between femur and tibia (place of the greatest mechanical load) on medial edge, which is normally consist 4-8 mm [8]. Anatomical reference point for X-ray joint space measuring are cortical endplate of the articular surface of the femoral condyle and the articular surface of the proximal edge of the tibia condyle at the base of articular recess [8].

However, decrease of joint cartilage, regardless of underlying causes of knee joint OA, frequently occurs unevenly on different areas of the articular surface [8], that leads to the joint space asymmetry on medial and lateral contours. The use of standardized methods for X-ray knee joint space determining does not provide an assessment of joint space symmetry. Nevertheless, considering characteristic for the knee joint osteoarthritis biomechanical imbalances of lower limbs and relatively long-lasting stability of radiographic symptoms, analysis of the X-ray joint space variability expressed through quantitative index of X-ray joint space asymmetry, seems to be informative. Thus, to calculate this index, measurements should be carried out both in the place of the largest narrowing and expanding with following calculating of the difference between obtained values. Determination of the X-ray knee joint space asymmetry index (X-ray KJSAI) allows to assess precisely enough changes of the knee joint anatomical congruence in dynamics that can be used for statistical analysis and pathological process progression monitoring. It will help improving the advisory and diagnostic care for patients with knee OA.

Thus, the method of the X-ray KJSAI determining has been developed to optimize radiological examination of the knee.

Material and methods. To achieve this goal several changes to the standard procedure of knee joints radiological diagnostics have been made:
- standard position to perform an X-ray of the knee in direct projection (lying with straightened in the knee and hip joints legs, slightly turning feet inwards) [8] has been changed to standing position "with load";
- patient positioning "with load" has been upgraded by direct installation of the feet (parallel to each other) on the deck footboard, that differs from the standardized (with feet turning inwards) [9]. In this position it is possible to get a radiological picture of the axial load on the knee joint distribution, depending on the presence of valgus/varus position of the feet;
- an X-ray joint space was assessed by two parameters measured on the medial and lateral joint contours in areas of largest narrowing and expanding (edge surface of the lateral and medial condyle of femur and tibia bones at the anterior surface), respectively (Fig. 1);
- an asymmetry of X-ray joint space was evaluated by the difference of digital indicators (in cm), fixed in the areas of narrowing and expanding.

The direction of the central beam during radiographic examination was carried out 2 cm (one finger width) below the upper pole of the patella (in the middle of the articular surface), and then to the center of the sensing device, according to the standard technique [9].

Method of radiography in lateral projection was not a subject for modification and was not used for the analysis, because it is not informative for the X-ray knee joint space determination.

The proposed technique of radiological research was tested on 30 patients (22 women, 8 men) with verified diagnosis of knee joint osteoarthritis of 2-3 degrees in Kellgren-Lawrence classification. Digital X-ray system Luminos Fusion (Siemens) with a dynamic version of the flat panel detector and the ability to reduce the radiation exposure by up to 90% was used for diagnostics [15]. The software of the diagnostic equipment with advanced image processing algorithms allowed carrying out high-quality calculation of the X-ray KJSAI.

All patients received knee joint OA treatment with extracorporeal shock-wave therapy (ESWT), used as a monotherapy. Prior to each procedure, the shock-wave diagnostics of pain locus in bone, muscle, tendon and ligaments structures of femur and tibia (back and frontal surface) was conducted. Searching was also carried out in the area of sacroiliac joint and lumbar spine, with following therapeutic influence on the identified areas of hyperalgesia [14]. Areas of diagnostic search were determined according to the laws of pain propagation by Симонс Д.Г. et al. [6]. A feature of the applied ESWT methodology was implementation of individual biomechanical correction of ligament-tendon-muscular system of lower limbs of the patients that contributed to the creation of necessary conditions for full range of movement in knee joints at functional unload. The course of treatment consisted of 5 procedures carried out with 3-5 days interval. Thus, the time between the initial (before treatment) and secondary (within 2-3 days after the end of therapy) X-rays of the knee was, respectively, 3-4 weeks. Analysis of the X-ray KJSAI dynamics and the result of

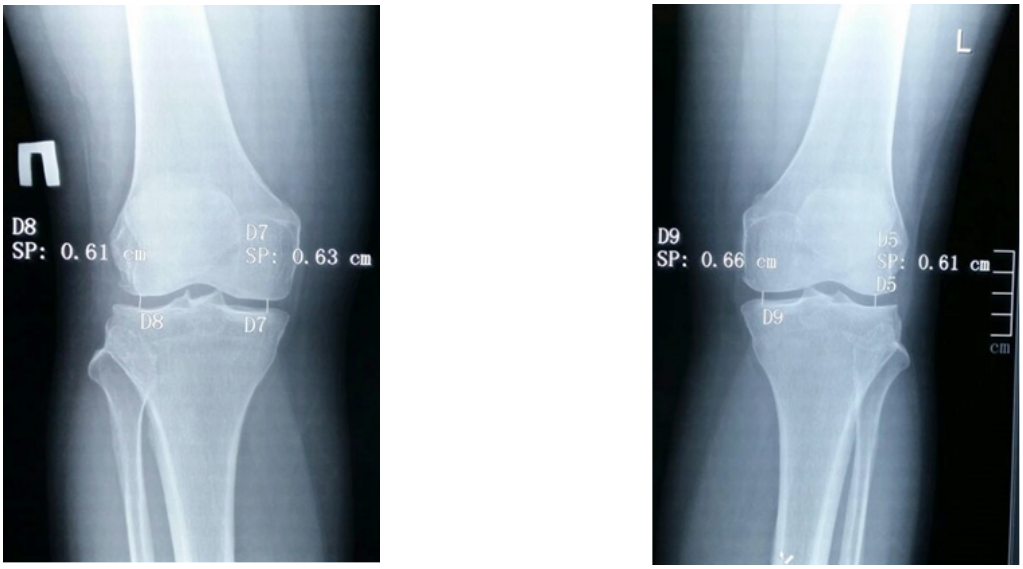
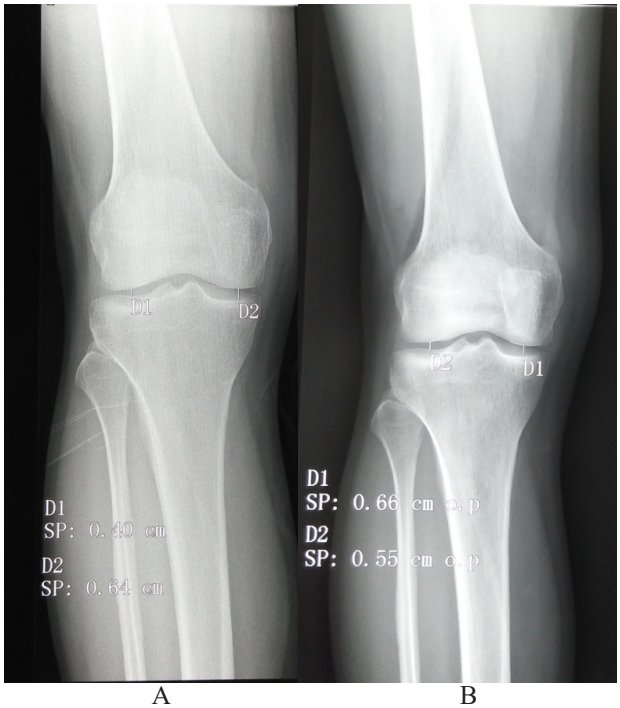


Fig. 1. Determination of the X-ray knee joint space in the areas of maximum narrowing and expanding

podometric survey in comparative assessment before and after extracorporeal shock-wave therapy was performed with the use of nonparametric paired Wilcoxon test for 2-affiliated groups, with representation of data in Me (Q1;Q3). Reducing of counted index and severity of load asymmetry between the front and rear part of the foot on the affected with knee joint osteoarthritis leg, indicated about biomechanical processes improvement and was seen as a positive trend. Evaluation of ESWT clinical efficacy was performed by Roles and Maudsley Granding Score at the end of therapy: 1 points (excellent) - complete functional recovery of patients with pathological changes of joints in the absence of pain; 2 points (good) - complete restoration of motor activity with the preservation periods of discomfort; 3 points (acceptable) - the appearance of discomfort sense in knee joint due to prolonged physical activity; 4 points (bad) - low efficiency of ESWT caused by persistence of pain, limiting motor activity. The treatment result, valued from 1 to 3 points was regarded as positive, 4 points - as the lack of clinical efficacy of the therapy.

Results and their discussion. In the primary knee joint X-ray examination an asymmetry of joint space was revealed in 100% of patients (n=30). As a result of course therapy with ESWT, the change in X-ray picture of the knee was observed in all patients. Statistically significant decrease of X-ray KJSAI defined by the proposed method was observed as a result of ESWT application (Z=5.20, p<0.001) and amounted 0.22 (0.18;0.24) before and 0.12 (0.10;0.14) after treatment. Statistically significant (Z=5.10; p=0.00001) dynamic change of podometric pattern was observed in all respondents and characterized by decrease of supporting area asymmetry and percentage index of load distribution on the front and rear aspects of foot from 24(12;30) to 6(4;30) (M(Q1;Q3)). By Roles and Maudsley Granding Score, all patients reported positive clinical effect of biomechanically based ESWT mode of application. Thus, 30% (n=9) of patients evaluated the results of treatment as “excellent” (1 point), 63% (n=19) - as “good” (2 points), and only 7% (n=2) - as “acceptable”(3 points).

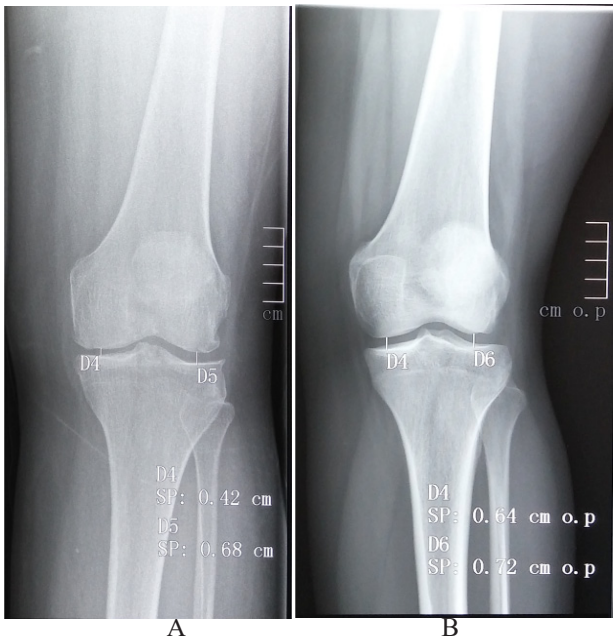
Figs. 2 and 3 shows the examples of x-ray joint space asymmetry definition in patients with knee OA before and after a course of ESWT application with calculation of asymmetry index. X-ray KJSAI on presented in Figures 2 and 3 roentgenograms was calculated by finding the difference between the size of joint space on the lateral (for both patients - a place of maximum expansion) and medial (for both patients - place of the greatest narrowing) contours.



A B

Fig. 2. Patient N., 39 years old. Determination of the X-ray joint space asymmetry index in areas of maximum narrowing and expansion: A - before treatment, B - after treatment

Thus, for the patient N., 39 years (Fig.2), calculation of X-ray KJSAI on presented X-ray images was as follows: D2-D1=0.64-0.40=0.24 cm (Fig.2A) - before treatment and D2-D1=0.66-0.55=0.11 cm (Fig.2B) - after treatment. As a result, comparative evaluation of the received data showed decrease of the X-ray joint space asymmetry index from 0.24 cm to 0.11 cm that means in percentage by 54%.



A B

Fig. 3. Patient K., 58 years old. Determination of the X-ray joint space asymmetry index in areas of maximum narrowing and expansion: A - before treatment, B - after treatment

For the patient K., 58 years (Fig.3) X-ray KJSAI calculated as follows: D5-D4=0.68-0.42=0.26 cm (Fig.3A) - before treatment and D6-D4=0.72-0.64=0.08 cm (Fig.3B) - after treatment. According to our measurements, the X-ray joint space asymmetry index changed from 0.26 cm to 0.08 cm, corresponding to the index decrease on 69%.

Reducing of the X-ray knee joint space asymmetry as a result of ESWT application in the absence of any signs of exacerbation of degenerative and destructive changes in the knee joints, was seen as a positive X-ray dynamics of knee joint OA, comparable with the improvement of clinical parameters. Decreasing of joint space asymmetry testified restitution of load uniformity on lateral and medial areas of the affected with osteoarthritis knee, contributing to the creation of conditions to facilitate joint functioning.

Thus, the proposed modification of standardized X-ray method of knee joint investigation allows expressing the joint space asymmetry in digital equivalent (X-ray KJSAI), estimating dynamics of changes of knee joint congruence, and providing differentiated approach to the treatment. It is recommended for implementation in healthcare practice.

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SUMMARY

DINAMICS OF KNEE JOINT SPACE ASYMMETRY ON X-RAY AS A MARKER OF KNEE OSTEOARTHRITIS REHABILITATION EFFICACY

Sheveleva N., Minbayeva L., Belyayeva Y.

Karaganda State Medical University, Department of Medical Rehabilitology, Visual Diagnostics and Physical Training, Karagandy, Kazakhstan

Reducing of articular cartilage functional volume in knee joint osteoarthritis occurs unevenly and accompanied with pathological changes of lower limb axis as a result of connective tissue and muscle structures dysfunction. Evaluation of X-ray knee joint space asymmetry seems to be informative to analyze the dynamics of lower extremities biomechanical imbalances characteristic for knee joint osteoarthritis. However, standardized method of X-ray joint space determining does not include its symmetry calculation.

The purpose of the study was optimization of knee joint radiological examination by developing of X-ray knee joint space asymmetry index calculation method.

The proposed method was used for comparative analysis of extracorporeal shock-wave therapy efficacy in 30 patients with knee joint osteoarthritis of 2-3 degrees (Kellgren-Lawrence, 1957). As a result of the conducted treatment statistically significant decrease of the X-ray knee joint space asymmetry index was observed (Me(Q1;Q3): Z=5.20, p<0.001) and amounted as 0.22 (0.18;0.24) before treatment and 0.12 (0.10;0.14) after. Also, statistically significant (Z=5.10; p=0.00001) changes of load asymmetry on front and rear foot sections were observed by the results of podometric survey in comparative assessment before (Me(Q1;Q3)=24(12;30)) and after (Me(Q1;Q3)=6(4;30)) course therapy. 30% (n=9) of the patients evaluated the outcome

of the treatment as "excellent" (1 point), 63% (n=19) - as "good" (2 points) and only 7% (n=2) - as "acceptable" (3 points) according to the Roles and Maudsley score. The listed above data was regarded as an X-ray positive dynamics comparable with clinical improvement.

Thus, the X-ray knee joint space asymmetry index, calculated according to the proposed method, allows to evaluate dynamics of articular surfaces congruency changes and provide differentiated approach to the treatment of knee joint osteoarthritis.

Keywords: knee joint osteoarthritis, radiography, joint space, shock-wave therapy.

РЕЗЮМЕ

ДИНАМИКА АСИММЕТРИИ СУСТАВНОЙ ЩЕЛИ КОЛЕННОГО СУСТАВА НА РЕНТГЕНОГРАММЕ КАК МАРКЕР ЭФФЕКТИВНОСТИ РЕАБИЛИТАЦИИ ГОНАРТРОЗА

Шевелева Н.И., Минбаева Л.С., Беляева Я.В.

Карагандинский государственный медицинский университет, кафедра медицинской реабилитологии, лучевой диагностики и физического воспитания, Караганда, Казахстан

Уменьшение функционального объема суставного хряща при гонартрозе происходит неравномерно и сопровождается нарушением оси нижней конечности вследствие дисфункции соединительнотканных и мышечных структур. Оценка симметричности рентгеновской суставной щели коленных суставов является информативным материалом для анализа динамики биомеханического дисбаланса нижних конечностей, однако, стандартизированная методика определения рентгеновской суставной щели не предусматривает проведение расчета ее симметричности. Поэтому, с целью оптимизации рентгенологического исследования коленных суставов нами разработана методика расчета показателя асимметричности рентгеновской суставной щели коленных суставов.

Предложенная методика была использована для проведения сравнительного анализа эффективности экстракорпоральной ударно-волновой терапии у 30 пациентов с гонартрозом 2-3 степени по Келлгрен-Лоуренсу (1957). В результате проведенного лечения наблюдалось статистически значимое уменьшение показателя асимметричности рентгеновской суставной щели коленных суставов - Me(Q1;Q3): Z=5,20; p<0,001), что составило 0,22 (0,18;0,24) до лечения и 0,12 (0,10;0,14) после. Статистически значимо (Z=5,10;p=0,00001) изменилась асимметрия нагрузки на передний и задний отделы стопы по результатам подометрического исследования в сравнительном аспекте - до Me(Q1;Q3)=24(12;30) и после Me(Q1;Q3)=6(4;30) курсовой терапии. По шкале Роулза и Модсли 30% обследуемых результат лечения оценили как «отличный» (1 балл), 63% - как «хороший» (2 балла) и только 7% - как «приемлемый» (3 балла). Вышеперечисленное расценивалось как положительная рентгенологическая динамика, сопоставимая с улучшением других клинико-диагностических показателей.

Таким образом, рассчитанный по предложенной методике показатель асимметричности рентгеновской суставной щели позволяет оценить изменения конгруэнтности суставных поверхностей в динамике и обеспечить дифференцированный подход к терапии гонартроза.

რეზიუმე

მუხლის სახსრის რენტგენოლოგიური სასახრე ნაპრალის ასიმეტრიის დინამიკა, როგორც გონართროზის რეაბილიტაციის ეფექტურობის მარკერი

ნ. შეველიოვა, ლ. მინბაევა, ი. ბელიაევა

ყარაგანდის სახელმწიფო სამედიცინო უნივერსიტეტი, სამედიცინო რეაბილიტაციის,სხივური დიაგნოსტიკისა და ფიზიკური აღზრდის კათედრა,ყარაგანდა,ყაზახეთი

მუხლის სახსრის რენტგენოლოგიური გამოკვლევის ოპტიმიზაციის მიზნით ავტორების მიერ შემუშავებულია მუხლის სახსრის რენტგენოლოგიური სასახსრე ნაპრალის ასიმეტრიულობის მაჩვენებლის გამოთვლის მეთოდიკა.

შემოთავაზებული მეთოდიკა გამოყენებული იყო გონართროზიანი პაციენტების (n=30; გონართროზის 2-3 ხარისხი კალგრენ-ლოურენსის მიხედვით, 1957) დარტყმით-ბგერითი ექსტრაკორპორული მკურნალობის ჩატარების ეფექტურობის შედარებითი ანალიზისათვის. ჩატარებული მკურნალობის შედეგად აღინიშნა რენტგენოლოგიური სასახსრე ნაპრალის ასიმეტრიულობის მაჩვენებლის მნიშვნელოვანი შემცირება - Me(Q1;Q3): Z=5,20; p<0,001, რამაც შეადგინა 0,22 (0,18;0,24) მკურნალობამდე და 0,12 (0,10;0,14) მკურნალობის შემდეგ. ასევე,შედარებითი პოდომეტრიული კვლევის შედეგების მიხედვით, სტატისტიკურად სარწმუნოდ (Z=5,10;p=0,00001) შეიცვალა დატვირთვის ასიმეტრია ტერფის წინა და უკანა ნაწილებზე - Me(Q1;Q3)=24(12;30) და Me(Q1;Q3)=6(4;30) მკურნალობის კურსამდე და შემდეგ. როულზის და მოდსლის შკალის მიხედვით გამოკვლეულთა 30% მკურნალობის შედეგი შეაფასა, როგორც “შესანიშნავი” (1 ქულა), 63% – როგორც “კარგი” (2 ქულა), მხოლოდ 7% – როგორც “მისაღები” (3 ქულა). ზემოაღნიშნული შეფასდა,როგორც დადებითი რენტგენოლოგიური დინამიკა.

ამრიგად, შემოთავაზებული მეთოდიკით გამოთვლილი მუხლის სახსრის რენტგენოლოგიური სასახსრე ნაპრალის ასიმეტრიულობის მაჩვენებელი იძლევა სასახსრე ზედაპირების კონგრუენტულობის ცვლილების დინამიკის შეფასების და გონართროზის მკურნალობისადმი დიფერენციული მიდგომის უზრუნველყოფის საშუალებას.

PROGNOSTIC RISK OF OBSTETRIC AND PERINATAL COMPLICATIONS IN PREGNANT WOMEN WITH THYROID DYSFUNCTION

Morchiladze N., Tkeshelashvili B., Gagua T., Gagua D.

"David Gagua Clinic" Ltd., Tbilisi, Georgia

It is known that thyroid hormones regulate the fetal growth and nervous system development process, mineralization of bones, metabolic activity in cells and protein synthesis [2,8,20]. Dysfunction of thyroid gland accounts for dysembryogenesis and placentation pathology, deteriorates the labor and perinatal outcome. 17% of pregnant women demonstrate pathologies, including: pre-eclampsia in 30%, fetoplacental insufficiency in 86%, labor abnormalities – in 30% of cases, respectively [2,5,9]. Inadequate treatment of thyroid pathology significantly increases the incidence of spontaneous abortions, cessation of pregnancies and premature deliveries [10,12,21].

There is a consideration, that incomplete adaptive capacity of thyroid functions in pregnancy can lead to complicated course of gestation, labor and post-partum period, especially under Iodine deficit conditions [3,13,16]. According to other authors, the risk of specific complications in pregnancy is decreased to minimum provided the adequate treatment and compensation of thyroid pathology [7,17,22].

Pregnant women with thyroid pathology demonstrate perinatal encephalopathy (68.2%), frequently during gestation, anema (27.8%), also chronic hypoxia (22.5%), hypotrophy (23.4%) and different types of developmental abnormalities (25%) [1,13,15], as for the perinatal mortality, it keeps high accounting for 24 cases per 1000 newborns. Target risks include CNS and endocrine organs of the fetus. In 12% of cases, congenital dysfunction of thyroid gland develops [4,6,19].

All above mentioned unequivocally indicates on important role of maternal thyroid pathology in obstetric and peri-neonatal morbidity structure. A number of studies have been dedicated to the research of thyroid gland dysfunction in pregnant women.

Although these issues still remain actual, especially those considering the influence of thyroid dysfunction on maternal and neonatal health. Moreover, there is no uniform hypothesis about complications of pregnancy and prognostication of unfavorable outcome.

Study Aim - To clarify the specificities of gestational process, also to define the prognostic risk of obstetric and perinatal complications in pregnant women with thyroid pathology.

Material and methods. The study was performed on the basis of "David Gagua Clinic" Ltd. The design was prospective, open controlled study. According to the referral to the clinic, 292 pregnant females were recruited and involved into the main group, who had been diagnosed thyroid pathology based on the clinical and laboratory/instrumental (ulstrasound) findings. The quantity changes in normal limits to thyroid hormones for pregnancy profile were taken into account during the assessment of hormonal status (TSH - 0,1-2,5 mIE/L, FT4 - 10,3-24,5 pmol/L, Anti-tpo<40 IE/L).

The study inclusion criteria considered the following: reproductive age, between 16-44 years; I trimester of pregnancy; testified diagnosis of thyroid pathology.

The study exclusion criteria involved the presence of comorbid chronic somatic pathology. The control group involved 58 "conditionally" healthy pregnant females, who were not diagnosed neither for thyroid nor for other somatic pathologies and had not been under the follow-up with endocrinologist before pregnancy.

Monitoring of thyroid status was performed according to the trimesters. Overall health was assessed according to international protocols, Apgar scale and anthropometric data. In case if neded, neuroscopy study was used. National clinical practice guideline / recommendation for "Early age pediatric physical development and its assessment" (2009) was used to evaluate the neonate's weight.

The retrieved data was statistically treated by application of SPSS v.12 program package.

Pearson's value - χ^2 and P were calculated to define the confidence range between quantitative data for comparable groups. 0.05 value was considered as critically siginificant. Risks ratio (RR) was determined for obstetric and perinatal complications, using the table (2x2), and considering the 95% confidence interval.

Results and their discussion. 350 pregnant women (292+58) and their neonates were studied under the research. The mean age of pregnant females was 25±3,9 years. In both main and control groups first-time pregnancies were prevailing (50.7% and 51.7%, respectively). Overweight before pregnancy was prevailing in patients involved in main group (29,4%,χ^2=1.903, P=0.168). In the same group, 31.8% of pregnant females had dysmenorrhea in the history, 11.6% - spontaneous abortion and premature delivery, and 14.4% of pregnants females were using hormonal contraception before pregnancy. The control group showed dysmenorrhea in history of 22.4% of cases (χ^2=1,618,P=0.204), spontaneous abortion and premature delivery in 13.8% (χ^2=0,057,P=0.811), and the previous use of hormonal contraception was found in 8.6% of patients (χ^2=0,931,P=0.335).

According to thyoid status, 41.4% of pregnants demonstrated hypothyroidismus, 35.6% - isolated hypothyroxinemia, and 4.5% - hypothyroidismus. High level of antibodies were found in 18.5% of cases; nodular goiter was diagnosed in 38 patients, 12.3% from which was associated with hypothyroidismus and 23% - with isolated hypothyroxinemia. All patients in the main group devecoped treatment during pregnancy period mainly targeting on thyroid stimulation (Iodine preparationg, L-thyroxin).

Relative risk (RR) to complications observed in the ongoing pregnancy was defined in the study process (Table 1).

According to obtained results, the nausea/vomiting of pregnancy was observed in 60.9% of the main group, which was 1.5 times higher than control group data (χ^2=16.153, P=0,0001). In addition, this finding was found to be confidently high in pregnants with hypothyroidismus (61,9%, χ^2=5,926, P=0,015) and (62,5%, χ^2=5,883, P=0,015), respectively. The prevalence index for iron deficiency anemia was 2 times higher in the main group (χ^2=24.881, P=0,0001). Similar to the nausea/vomiting,

Table 1. Pregnancy complications in the studied cohort (n=350)

Clinical signs	Main group (n=292)	Control group (n=58)	RR	CI	χ^2	P
Nausea/vomiting of pregnancy	178(60,9%)	24 (41,4%)	3.36	1.79-6.31	16.153	0.000
Iron deficiency anemia	122(41,8%)	14 (24,1%)	2.25	1.13-4.53	5.619	0.018
Chronic lower limb veins disease	44(15,1%)	10(17,2%)	0.85	0.38-1.94	0.048	0.826
Preeclampsia	15(4,5%)	3(5,2%)	0.99	0.25-4.47	0.000	1.000
Overweight	99(33,9%)	14(24,1%)	1.61	0.80-3.25	1.688	0.194
Arterial hypertension	16(5,5%)	2(3,4%)	1.62	0.34-10.51	0.099	0.753
Vaginal bleeding	30(10,2%)	6(10,3%)	0.99	0.37-2.80	0.000	1.000

Table 2. Ddelivery complications and outcomes in the studied group (n=350)

Clinical signs	Main group (n=292)	Control group (n=58)	RR	CI	χ^2	P
The risk of spontaneous abortion	45(15,4%)	6(10,3%)	1.57	0.60-4.35	0.632	0.427
Premature delivery	28(9,6%)	4(6,9%)	1.43	0.45-5.02	0.160	0.688
Ealy rupture of fetal sac	31(10,6%)	3(5,2%)	2.17	0.60-9.27	1.073	0.301
Abnormal labor activity	67(22.9%)	14(24,1%)	0.93	0.46-1.91	0.001	0.979
Drug-stimulated delivery	47(16,1%)	5(8,6%)	2.03	0.73-6.11	1.587	0.208
Obstetric surgery procedures	78(26,7%)	8(13,8%)	2.27	0.98-5.45	3.688	0.054
Late pregnancies	8(2,7%)	3(5,2%)	0.51	0.11-2.52	0.322	0.507
Postpartum bleeding	30(10,3%)	6(10,3%)	0.99	0.37-0.80	0.000	1.000

the prevalence of iron deficiency anemia was statistically significant and high in pregnants with hypothyroidismus (45,5%, χ^2=6.648, P=0,010) and isolated hypothyroxinemia (41,3%, χ^2=4.110, P=0,042).

The study results match are in accordance with the literature data [3,4] about development of thyroprive anemia in pregnants with thyroid pathology, which indicates on metabolic activity and stimulating effect on erythropoiesis decreasing.

The study of comparative risk for complications in pregnancy revealed confidently high indicis of pregnancy-related nausea/vomitting (RR-3,36, CI-1.79-6.31) and iron-deficiency anemia (RR-2.25, CI-1.13-4.53). Relative risk >1 was demonstrated in cases of abnormal weight gain (RR-1.61, CI-0.80-3.25) and arterial hypertension (RR-1.62, CI-0.34-10.51), though the mentioned hypothesis was not testified by χ^2 and P data.

The complications and outcomes of delivery are seen in Table 2. The Table 2 shows that the risk for spontaneous abortion (RR-1.57, CI-0.60-4.35) and premature delivery (RR-1.43, CI-0.45-5.02) are both high, especially in hypothyroidismus and high levels of anti-thyroid peroxidase antibodies.

Under the above mentioned circumstances, the risk (27,8%, χ^2=4,493, P=0,034) of premature delivery (14,3%,χ^2=1.099, P=0,295) was twice as high as control group data (10.3% and 6.9%, respectively). In patients with thyroid dysfunction the prognostical risk for obstetric surgeries (episio-perineotomy, induced rupture of fetal sac, also the use of obstetric forceps and vaccum extraction procedures) was proved to be statistically significant (RR-2.27, CI-0.98-5.45). One case in main group demonstrated spontaneous abortion and in one case there was a delivery with stillborn neonate.

The comparative risk of cesarean section was equally high in both groups of pregnant females (33.6% in main group, 29.3% in control group, respectively). We believe that cesaean section was frequently performed not by medical indication but mostly by requirement of pregnant subjects, due to which this indices were not considered in the results.

The assessment data by Apgar scale was identical in compared groups. Timely normal neonates with weight of 2500 – 4000 gr. were born in 91.4% of pregnant females group with thyroid pathology. The average weight of neonates was 3400±323,5 gr., with length of 50,9±11,9 cm. Overweight at birth (>4000 gr.) was observed in 6.5% of neonates (RR-2.65, CI -0,35-56.16), and low weight (1500-2500 gr.) – in 4.5% (RR-0.60, CI-0.21-1.78). The number of timely neonates in control group was 93.1% (average weight - 3400±0,80, average length – 50.0+0.16). The number of premature neonates in main group was 7.9%, and in control group – 6.8%, respectively (RR-1.15,CI-0.35-4.11).

Postpartum iron deficiency anemia was observed in 23.3% of main group of females after delivery, which was 1.5 times higher than the control group data (15,5%, χ^2=1.419, P=0,234). The relative risk for iron deficiency anemia was 1.69 (CI-0.75-3.90). Abnormal weight gain was demonstrated in 16.8% of main group, which was 3 times higher than the control group data (5,2%, χ^2=4.449, P=0,035), the relative risk also was respectively high (RR-3.77,CI-1.07-15.78).

The risk for chronic venous diseases of lower limbs was shown to be statistically significant in postpartum period (RR-7.15, χ^2=3,926, P=0.047).

Cjnclusion: The analysis of the obtained results demonstrated the high risk of pregnancy-related nausea/vomitting and iron deificiency anemia in the pregnant population with thyroid pathology, especially in hypothyroidism and isolated hypothyroxinemia conditions. The prognostical risk for spontaneous abortion, premature delivery and the need for obstetric surgeries was statistically significant in pregnants with hypothyroidismus.

The risk of delivery with low weight neonates was high in the aspect of perinatal outcomes. High relative ratio of iron deficiency anemia, abnormal weight gain and chronic venous diseases of lower limbs was alarming in postpartum period.

Thus, the results of conducted study demonstrated that thyroid pathology in pregnant females, regardless of obstetric and perinatal complications, is related with particular risk for development of obstetric and perinatal complications in general. All of the above indicates on absolute necessity of pre-gravid preparation and achievement of euthyroid state at the stage of planning of the pregnancy. At the same time, adequate treatment allows to remit the thyroid pathology diagnosed during pregnancy in compensatory phase, in order to decrease significantly its negative effects on both maternal and fetal organism.

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SUMMARY

PROGNOSTIC RISK OF OBSTETRIC AND PERINATAL COMPLICATIONS IN PREGNANT WOMEN WITH THYROID DYSFUNCTION

Morchiladze N., Tkeshelashvili B., Gagua T., Gagua D.

"David Gagua Clinic" Ltd., Tbilisi, Georgia

Maternal thyroid pathology takes important role in obstetric and peri-neonatal morbidity structure. Despite of the number of studies conducted in the field of thyroid disorders of pregnant females, the definition of influence of thyroid gland dysfunction on maternal and neonatal health still remains actual. The mentioned topics draw specific interest in the aspect of prognosticaiton of complications and unfavorable outcome.

Aim of the study - to define the specificities of gestation period and determine the prognostic risk of obstetric and perinatal complications in pregnant females with thyroid pathology.

The study was performed at the base of "David Gagua Clinic" Ltd. Prospective, open controlled study design was applied. Based upon the referral to the clinic, 292 pregnant females with thyroid pathology were involved in the main group.

The control group involved 58 conditionally healthy pregnant females of reproductive age. Thyroid status had been monitored accoding to trimesters during the whole period of prgnancy and 1 month following the delivery. The health state of neonates was assessed by international protocols.

To define the confidence interval for relative ratio between quantitative data of compared groups, χ^2, P and RR indices were calculated, and its critical level was considered to be 0.05. The risks ratio with defining of the data was determined for obstetric and perinatal complications.

120 (41.4%) of pregnant subjects demonstrated hypothyroidism, 104 (35.6%) - isolated hypothyroxinmia, and 13 (4.5%) - hyperthyroidism. High levels of anti-thyroid peroxidase antibodies were observed in 54 (18.5%) of cases, nodular gout was found in 38 (13%) patients, 5 (12.3%) of which was associated with hypothyroidism and 9 (23%) - with isolated hypothyroxinemia. Correcting treatment was administered to all pregnant subjects during the pregnancy period.

Based on the analysis of acquired data, the high probability of prengancy-related nausea/vomiting and iron-deficiency anemia was demonstrated in the population of pregnant females with thyroid pathology, especially in those with hypothyroidism and isolated hypothyroxinemia. The prognostic risk of early spontaneous abortion, premature delivery and obstetric surgical interventions was statistically significant in pregnant females with hypothyroidism. The relative ratio for low neonatal weight, maternal iron deficiency anemia in postpartum period, abnormal weight gain and chronic lower limb venous disorders were high in the aspect of perinatal outcomes.

Thus, despite of timely diagnosis and adequate treatment, thyroid pathology revealed in the gestational period is related with particular risk for development of obstetric and perinatal complications, which indicates on absolute necessity of pregravid preparation and achievement of euthyroid state at preliminary stage of pregnancy planning.

Keywords: pregnancy, thyroid pathology, obstetric and perinatal complications.

РЕЗЮМЕ

ПРОГНОЗ РИСКА АКУШЕРСКИХ И ПЕРИНАТАЛЬНЫХ ОСЛОЖНЕНИЙ У БЕРЕМЕННЫХ С ТИРЕОИДНОЙ ДИСФУНКЦИЕЙ

Морчиладзе Н.А., Ткешелашвили Б.Д., Гагуа Т.Д., Гагуа Д.А.

ООО «Клиника Давида Гагуа», Тбилиси, Грузия

В структуре акушерских и перинеонатальных заболеваний значительное место принадлежит тиреоидной патологии матери. Несмотря на множество исследований, проведенных в тиреологии беременных, по сей день остается актуальным установление влияния дисфункции щитовидной железы на состояние здоровья матери и новорожденного с точки зрения прогнозирования осложнений и неблагонадежных исходов.

Целью исследования явилось определение особенностей протекания гестации и риска акушерских и перинатальных осложнений у беременных с тиреоидной дисфункцией.

Исследование выполнено на базе ООО «Клиника Давида Гагуа». Проведено проспективное, открыто-контролируемое исследование 292 беременных с установленной тиреоидной патологией (основная группа). Контрольную группу составили 58 условно здоровых беременных репродуктивного возраста. Мониторинг тиреоидного стасуса по триместрам производился в течение всего периода беременности и на протяжении месяца после родов. Состояние здоровья новорожденных оценивалось в соответствие с международными протоколами.Для установления достоверности связи между количественными показателелями сравниваемых групп рассчитаны χ^2 и RR, за уровень достоверности принято значение $p<0,05$. Что касается акушерских и перинатальных осложнений определено соотношение рисков с определением показателей.

У 120 (41,1%) беременных обнаружен гипотириоз, у 104 (35,6%) изолированная гипотироксинемия, а у 13 (4,5%) - гипертиреоз. Высокий титр антител по отношению к тиреоидному пероксидазму зафиксирован у 54 (18,5%) женщин, узловой зоб - у 38 (13%) пациентов, из которых 5 (12,3%) были ассоциирован с гипотериозом, а 9 (23%) с изолированной гипотироксинемией. У всех пациентов основной группы в течение беременности проводилось корригированное лечение. Анализ полученных данных выявил высокую вероятность развития железо-дефицитной анемии в популяции беременных с тиреоидной патологией, особенно во время гипотериоза и изолированной гипотирексинемии, а также статистически достоверный прогноз риска преждевременного прекращения беременности, преждевременных родов и акушерского вмешательства у больных с гипотериозом. С точки зрения перинатального исхода родов высоким был риск рождения детей с малым весом, развития железо-дефицитной анемии матерей в послеродовом периоде, патологический рост веса и хроническое венозное заболевание нижних конечностей. Результаты проведенного исследования озволяют заключить, что несмотря на своевременную диагностику и адекватное лечение тиреоидной патологии, выявленной во время беременности, часто развиваются акушерские и перинатальные осложнения, что диктует необходимость прегравидной подготовки на этапе планирования беременности и достижения эутироидного состояния.

რეზიუმე

სამეანო და პერინატალური გართულებების რისკის პროგნოზირება ორსულებში თირეოიდული დისფუნქციით

ნ. მორჩილაძე, ბ. ტყეშელაშვილი, თ. გაგუა, დ. გაგუა

შპს „დავით გაგუას კლინიკა“ თბილისი, საქართველო

დედის თირეოიდულ პათოლოგიას მნიშვნელოვანი როლი განეკუთვნება სამეანო და პერინეონატალური ავადობის სტრუქტურაში. ორსულთა თირეოიდოლო-

გიაში ჩატარებულ კვლევათა სიმრავლის მიუხედავად, კვლავ აქტუალური რჩება ფარისებრი ჯირკვლის დისფუნქციის გავლენის დადგენა დედისა და ახალშობილის ჯანმრთელობის მდგომარეობაზე. აღნიშნული საკითხები განსაკუთრებულ ყურადღებას იმსახურებს გართულებებისა და არაკეთილსაიმედო გამოსავალის პროგნოზირების თვალსაზრისით.

შრომის მიზანი იყო გესტაციის მიმდინარეობის თავისებურებების, აგრეთვე სამეანო და პერინატალური გართულებების პროგნოზული რისკის დადგენა თირეოიდული პათოლოგიის მქონე ორსულებში.

შრომა შესრულდა შპს „დავით გაგუას" კლინიკის ბაზაზე. ჩატარდა პროსპექტული, ღია კონტროლირებადი კვლევა. კლინიკაში მომართვიანობის საფუძველზე ძირითად ჯგუფში ჩაერთო 292 ორსული დადგენილი თირეოიდული პათოლოგიით.

საკონტროლო ჯგუფში გაერთიანდა რეპროდუქციული ასაკის 58 პირობითად ჯანმრთელი ორსული. თირეოდუ-ლი სტატუსის მონიტორინგი ტარდებოდა ტრიმესტრების მიხედვით ორსულობის განმავლობაში და მშობიარობიდან ერთი თვის შემდეგ. ახალშობილთა ჯანმრთელობის მდგომარეობა ფასდებოდა საერთაშორისო პროტოკოლების მიხედვით.

შესადარებელი ჯგუფების რაოდენობრივ მაჩვენებლებს შორის კავშირის სანდოობის დასადგენად გამოთვლილია χ^2, P და RR, რომლის კრიტიკულ მნიშვნელობად მიჩნეულია 0,05. სამეანო და პერინატალური გართულებების მიმართ განსაზღვრული იყო რისკების შეფარდება მაჩვენებლების განსაზღვრით.

120 (41,4%) ორსულს აღენიშნებოდა ჰიპოთირეოზი, 104 (35,6%) - იზოლირებული ჰიპოთიროქსინემია, 13 (4,5%) - ჰიპერთირეოზი. თირეოიდული პეროქსიდაზის მიმართ ანტისხეულების მაღალი ტიტრი დაფიქსირდა 54 (18,5%) შემთხვევაში, კვანძოვანი ჩიყვი გამოუვლინდა 38 (13%) პაციენტს, მათგან 5 (12,3%) ასოცირებული იყო ჰიპოთირეოზთან, 9 (23%) - იზოლირებულ ჰიპოთიროქსინემიასთან. ძირითადი ჯგუფის ყველა პაციენტს ორსულობის პერიოდში უტარდებოდა მაკორეგირებელი მკურნალობა.

მიღებული მონაცემების გაანალიზების საფუძველზე გამოვლინდა ორსულთა რკინადეფიციტური ანემიის განვითარების მაღალი ალბათობა თირეოიდული პათოლოგიით ორსულთა პოპულაციაში, განსაკუთრებით ჰიპოთირეოზისა და იზოლირებული ჰიპოთიროქსინემიის დროს. ჰიპოთირეოზით დაავადებულ ორსულებში გამოვლინდა ორსულობის ადრეულ ვადაზე შეწყვეტის, ნაადრევი მშობიარობისა და სამეანო ჩარევების სტატისტიკურად სარწმუნო რისკი. პერინატალური გამოსავლის თვალსაზრისით მაღალი იყო მცირე წონის ახალშობილთა დაბადების, მშობიარობის შემდგომ პერიოდში დედის რკინადეფიციტური ანემიის, წონის პათოლოგიური მატებისა და ქვედა კიდურების ქრონიკული ვენური დაავადების ხვედრითი წილი.

ამრიგად, ორსულობის დროს გამოვლენილი თირეოიდული პათოლოგია, დროული დიაგნოსტიკისა და ადექვატური მკურნალობის მიუხედავად, დაკავშირებულია სამეანო და პერინატალური გართულებების ფორმირების გარკვეულ რისკთან, რაც ორსულობის დაგეგმარების ეტაპზე პრეგრავიდური მომზადების და ეუთიროიდული მდგომარეობის მიღწევის აუცილებლობაზე მეტყველებს.

ЭПИДЕМИОЛОГИЯ, СТРУКТУРА И АЛГОРИТМ ВЕДЕНИЯ БЕРЕМЕННЫХ ЖЕНЩИН С ЭКСТРАГЕНИТАЛЬНОЙ ПАТОЛОГИЕЙ ТЕРАПЕВТИЧЕСКОГО ПРОФИЛЯ

[1]Бачева И.В., [1]Умбеталина Н.С., [2]Брегвадзе-Табагари Н.С., [1]Шалыгина А.А., [1]Байдильдина Б.Н.

[1]Карагандинский государственный медицинский университет, кафедра внутренних болезней № 3, Республика Казахстан;
[2]Медицинский университет им. Давида Твилдиани, Тбилиси, Грузия

Ежедневно около 800 женщин во всем мире умирают по причинам, связанным с беременностью и родами. 99% всех случаев материнской смерти зафиксировано в развивающихся странах [8]. Эта проблема не решена и актуальна в экономически развитых странах: в США, где ежегодно расходуется около 60 миллиардов долларов на акушерскую службу, от тяжелых осложнений беременности и родов в 2014 г. погибло 1200 женщин. Еще 60 000 беременных нуждались в экстренной госпитализации в связи с развитием или обострением тяжелых заболеваний [17,26]. В структуре причин летальных исходов акушерских (прямых) и экстрагентиальных заболеваний/состояний значительную роль играет экономическое и социальное развитие страны. В Западной Кении, где материнская смертность высокая (488 случаев на 100 000 живых детей в 2013 г.), а доступность акушерской службы крайне низкая, 1/3 смертельных исходов связана с прямыми акушерскими причинами. Остальные случаи обусловлены заболеваниями внутренних органов (печень, почки, сердечно-сосудистая система, анемии различного генеза) и инфекциями (СПИД/ВИЧ, малярия, туберкулез) [18]. Авторами [19,20] выявлено, что в Мексике с уровнем материнской смертности 230 на 100 000 живых детей в 2013 г. 86,9% случаев обусловлены акушерскими причинами, из них на гестозы приходится 36,2%, остальные связаны с заболеваниями внутренних органов: 42% - кардиомиопатии, 15% - эндокринопатии, 10% - пневмопатии, гастропатии и нефропатии по 8%, 6% - нарушения кровообращения, 4% составили ревматические заболевания и осложнения анестезии, анафилаксия и травма - по 2%. Шувалова М.П. и соавт. [10], изучая гестозы как причину материнской смертности в Российской Федерации, выявили, что подавляющее большинство умерших женщин (80-84%) имели экстраге-

нитальную патологию (ЭГП), а своевременная диагностика помогла бы предотвратить порядка 50% осложнений [22].

Согласно Bulletin of the World Health Organization [14], во всем мире наметился прогресс в снижении материнской смертности, однако ее показатель продолжает оставаться весьма высоким. Наличие хронических терапевтических заболеваний у беременных (сахарный диабет, артериальная гипертензия, ожирение) оказывает значимое влияние на течение гестационного процесса и развитие осложнений при родах. Campbell K.H. и соавт. [15], исследовавшие в 1995-2003 гг. в Нью-Йорке влияние материнской заболеваемости на материнскую смертность при родах, выявили ряд заболеваний, повышающих ее риски: легочная гипертензия (скорректированное отношение шансов - ОШ 65,1; 95% доверительный интервал - ДИ 15.8-269.3), преэклампсия или эклампсии (скорректированное ОШ 8,1; 95% ДИ, 5.5-12.1), хроническая гипертония (скорректированное ОШ 7,7; 95% ДИ 4.7-12.5), ожирение (скорректированное ОШ 2,9 ; 95% ДИ 1.1-8.1), предгестационной диабет (скорректированное ОШ 3,3; 95% ДИ 1.3-8.1), ВИЧ (скорректированное ОШ 7,7; 95% ДИ 3.4-17.8). Таким образом, легочная гипертензия, как исход заболеваний сердечно-сосудистой и бронхо-легочной систем, в 65 раз увеличивала шанс смерти матери во время родов. Small M.J. и соат. [23], изучавшие причины развития критических состояний у беременных, требовавших их нахождение в отделении реанимации и интенсивной терапии с 2005 по 2009 гг. в Duke University Medical Center показали, что заболевания сердца являлись основной причиной направления женщин в отделение интенсивной терапии. Авторы считают, что этому способствует доступность передовых технологий в кардиохирургии, рост числа случаев наступления беременности в позднем возрасте, наличие врожденных пороков, сахарного диабета, ожирения, артерильной гипертензии у женщин. Подобные данные о широком распространении и негативном влиянии материнской заболеваемости на течение и исходы гестационного процесса получены и в других эпидемиологических исследованиях [12,13,16].

Интересны результаты наблюдений за беременными в Российской Федерации: по данным родовспомогательных учреждений г. Витебска за 2007-2011 гг., в 73% случаев беременность протекала на фоне ЭГП. Наиболее часто обнаруживались заболевания щитовидной железы, анемии, инфекции мочевыводящих путей, реже - артериальная гипертензия. Наблюдалась тенденция к увеличению клапанной патологии за счет улучшения диагностики малых аномалий развития сердца [6].

Исеновой С.Ш. и соавт. [2] при проведении анализа случаев оперативного родоразрешения («кесарево сечение») выявлено, что в 26,6% случаев присутствовал хронический пиелонефрит, в 16,5% – метаболические нарушения, в 8,9% – хронические заболевания желудочно-кишечного тракта (хронический гастрит, хронический холецистит, вирусный гепатит В и С), 7,6% составили патологию щитовидной железы (эндемический зоб, аутоимунный тиреоидит) и органов дыхания. Во время беременности у этих же пациенток в 46,8% случаев диагностирована умеренная анемия, в 15,25% – артериальная гипертензия, в 8,9% – острая респираторная вирусная инфекция, в 1,3% случаев – гестационный диабет. Согласно результатам исследований Кенжебаевой Г.Ю. и соавт. [3] по распространенности ЭГП в Республике Казахстан, 68,6% беременностей протекают с железодефицитной анемией, 30% приходится на анемию тяжелой степени, на фоне которой 14,5% случаев родов протекали с несвоевременным отхождением околоплодных вод, 9,1% - со слабостью родовой деятельности.

В 2013 г. под эгидой ВОЗ выпущен бюллетень, в котором ведущими специалистами обсуждаются вопросы материнской заболеваемости и смертности. Все эксперты едины во мнении о значимости снижения материнской смертности, и опасности игнорирования материнской заболеваемости, которая является не только предтечей развития неблагоприятных исходов беременности, но и причиной инвалидности и низкого качества жизни женщин. И если термин материнская смертность унифицирован, то к понятию материнской заболеваемости не найден единый подход. Экспертам было предложено разработать единый инструмент оценки материнской заболеваемости, с этой целью сформирован международный проект EURO-PERISTAT [21].

Большая часть используемых для статистического анализа данных предоставляется акушерско-гинекологической службой, тогда как лечение экстрагенитальной патологии проводится преимущественно специалистами терапевтического профиля, к сожалению, эти данные включаются в итоговые отчеты ограниченно.

Целью данного исследования явилось получение более точной информации о превалентности и структуре экстрагенитальной патологии у беременных.

Материал и методы. Для решения поставленной цели проведено исследование среди находящихся на учете женщин и/или обратившихся за медицинской помощью к специалистам терапевтического и акушерско-гинекологического профиля на амбулаторном и стационарном этапах.

Исследование проводилось в 2 этапа:
I этап: поперечное/скрининговое когортное обследование беременных, состоящих на учете и/или обратившихся за амбулаторной и стационарной помощью в лечебные учреждения г. Караганды (Областная клиническая больница, Поликлиника № 3, Городской центр первичной медико-санитарной помощи) за 2012-2014 гг.
- ретроспективное исследование обращений беременных за скорой медицинской помощью (СМП) в 2012-2013 гг. (данные Областной станции скорой медицинской помощи г. Караганды);
II этап – разработка практических рекомендаций.

В скрининговом/поперечном исследовании первого этапа приняли участие 742 беременных, давших согласие на участие. Средний возраст составил 28,4±5,5 лет. 51% обследуемых находились на III триместре, 33,4% - на II. Когортное исследование проводилось по специально разработанной «Скрининг-программе выявления экстрагенитальной патологии у беременных» (далее Скринниг-программа) с применением метода анкетного опроса. Детальное описание методики проведения и обработки данных представлено Умбеталиной Н.С. и соавт. [1]. Скрининг-программа включала 6 профилей: нефрологический, гематологический, кардиоревматологический, гастроэнтерологический, эндокринологический, пульмонологический. Каждый профильный симптом оценивался в баллах от 0 до 6 как до, так и на фоне текущей беременности, которые суммировались

в пределах одного профиля и являлись критерием включения женщин в определенную группу риска: группа низкого риска – от 6 до 12 баллов, среднего – от 12 до 18, высокого – более 18. При сумме баллов менее 6 беременные считались относительно здоровыми. Среднее время анкетирования 20 минут, затруднений при ответах на вопросы у респондентов не возникало.

Ретроспективный анализ организации СМП беременным проводился по учетной форме №110/у «Карта вызова станции скорой медицинской помощи» (утверждена приказом и.о. Министра здравоохранения Республики Казахстан № 907 от 23.11.2010 года), с использованием компьютерной программы «АДИС». Для получения детального анализа вызовов СМП к беременным по нозологическим формам, в компьютерную программу «АДИС» первым диагнозом вводилось интересующее заболевание, вторым – беременность; затем первым диагнозом указывалась беременность, а вторым - данное заболевание, что позволило, суммируя два полученных результата, изучить число вызовов беременных по заболеванию.

На втором этапе, на основании результатов проведенного исследования и данных литературы, предложен алгоритм ведения беременных с ЭГП терапевтического профиля.

Результаты и их обсуждение. Полученные в результате исследования данные по распределению ЭГП по терапевтическим профилям скринингового исследования представлены в таблице 1.

Таблица 1. Структура ЭГП по терапевтическим профилям у беременных по данным скрининг-программы

Название профиля скрининговой программы	До беременности	На фоне беременности
Нефрологический	**44,2% (95% CI:40,6-47,7%)**	**39,1% (95% CI:35,6-42,6%)**
Низкий риск	37,2% (95% CI:33,7-40,8%)	23,7% (95% CI:20,7-26,9%)
Средний риск	6,7% (95% CI:5,1-8,9%)	8,7% (95% CI:6,9-11,1%)
Высокий риск	0,3% (95% CI:0,01-1,1%)	7% (95% CI:5,3-9,1%)
Гематологический	**39,8% (95% CI:36,2-43,4%)**	**41,2% (95% CI:37,7-44,9%)**
Низкий риск	25,7% (95% CI:21,1-28,3%)	27,2% (95% CI:24,1-30,6%)
Средний риск	13,8% (95% CI:11,4-16,5%)	11,5% (95% CI:9,3-14,1%)
Высокий риск	0,9% (95% CI:0,4-2,1%)	2,6% (95% CI:1,6-4%)
Гастроэнтерологический	**28,8% (95% CI:25,6-32,3%)**	**38,8% (95% CI:35,3-42,4%)**
Низкий риск	25,3% (95% CI:22,3-28,7%)	24,4% (95% CI:21,4-27,7%)
Средний риск	3,2% (95% CI:2,1-4,8%)	11,2% (95% CI:9,1-13,7%)
Высокий риск	0,2% (95% CI:0,01-1,1%)	3,2% (95% CI:2,1-4,8%)
Эндокринологический	**20,3% (95% CI:17,6-23,5%)**	**9,9% (95% CI:7,8-12,3%)**
Низкий риск	13,1% (95% CI:10,7-15,8%)	6,7% (95% CI:5,1-8,9%)
Средний риск	5,6% (95% CI:4,2-7,7%)	2,6% (95% CI:1,6-4,0%)
Высокий риск	1,6% (95% CI:0,9-2,9%)	0,5% (95% CI:0,2-1,5%)
Кардиоревматологический	**10,7% (95% CI:8,6-13,2%)**	**19,7% (95% CI:16,9-22,8%)**
Низкий риск	9,6% (95% CI:7,6-12%)	13,8% (95% CI:11,4-16,5%)
Средний риск	0,7% (95% CI:0,3-1,7%)	4,5% (95% CI:3,1-6,3%)
Высокий риск	0,5% (95% CI:0,2-1,5%)	1,4% (95% CI:0,7-2,6%)
Пульмонологический	**8,4% (95% CI:6,5-10,7%)**	**7,3% (95% CI:5,6-9,5%)**
Низкий риск	9,6% (95% CI:7,6-11,9%)	13,8% (95% CI:11,4-16,5%)
Средний риск	0,6% (95% CI:0,3-1,7%)	4,5% (95% CI:3,1-6,3%)
Высокий риск	0,5% (95% CI:0,2-1,5%)	1,4% (95% CI:0,7-2,6%)

52 женщины (7%; 95% CI:5,4-9,1%) вошли в группу здоровых по всем профилям как до, так и во время беременности. Наиболее распространенными терапевтическими профилями на фоне беременности по данным скрининг-программы являлись гематологический 41,2%, нефрологический 39,1%, гастроэнтерологический 38,8%. Такая динамика гематологического профиля обусловлена анемическим синдромом. В 52% анемия встречается в развивающихся странах, в 23% - в развитых. Плохое питание, недостаточное поступление железа и других микроэлементов, малярия, анкилостомоз и шистосомоз являются наиболее частыми причинами анемии; ВИЧ-инфекция и гемаглобинопатии - дополнительные факторы её возникновения. В развивающихся странах, где анемический синдром достигает 75%, эндемические проблемы вместе с неадекватным питанием способствуют развитию анемии - самой распространенной патологии среди беременных [11,24]. Среди заболеваний нефрологического профиля одним из грозных заболеваний является пиелонефрит, встречаемость которого у беременных согласно данным разичных авторов наблюдается от 9% до 12%, а по данным акушерско-гинекологического стационара – в 33,8%, являясь одним из наиболее серьезных осложнений беременности [7,25].

Среди всех профилей, согласно Скрининг-программе, превалировали категории «низких рисков». На фоне беременности частота встречаемости более высоких рисков увеличивалась, за исключением эндокринологического профиля. Некоторые лица из категории «низкого риска» и «среднего риска» до беременности, во время беременности переходили в группу более высокого риска или в группу «здоровых». У 20% обследуемых встречалась патология двух профилей, у 5% – трех, у 2% – четырех и более.

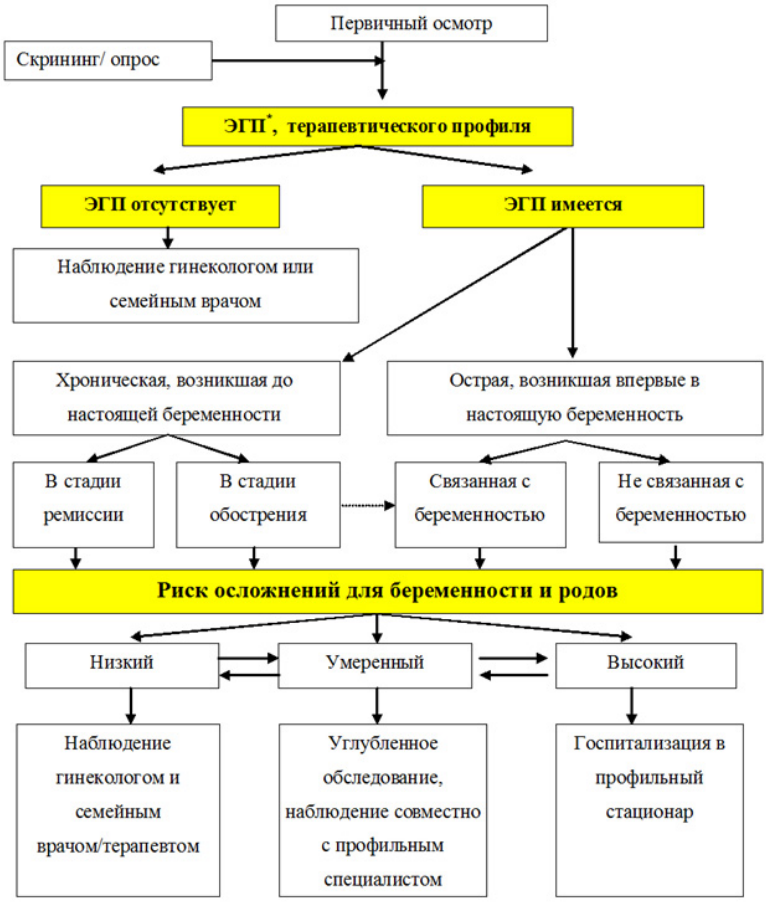
Исследование обращаемости беременных за СМП показало, что за 2012 г. зафиксировано 10159 случаев (41% от числа всех беременных Карагандинской области – 24536), за 2013 г. – 10690 случаев (45% от 23505). За 2012 и 2013 гг. за СМП по поводу заболеваний терапевтического профиля обратилось 1070 (4,3%) и 1646 (7%) беременных женщин, соответственно. Среди всех вызовов первое место занимали болезни органов дыхания (Рис. 1): 2012 г. – 28% случаев, 2013 г. – 30%. Среди болезней органов дыхания скорую медицинскую помощь чаще оказывали по поводу ОРЗ, ОРВИ и их осложнений. Имеются данные о негативном влиянии ОРВИ на течение беременности: в 1,3 раза чаще регистрировалось перинатальное поражение центральной нервной системы с различной степенью нарушения мозгового кровообращения и выраженностью церебральной ишемии; в 1,3 раза чаще - врожденные пороки развития у плода; в 1,4 раза чаще - задержка внутриутробного развития плода; в 1,6 раз чаще – незрелость плода [9]. В Украине в 2009 и 2010 годах на фоне ОРВИ погибло 53 и 39 беременных женщин, соответственно [4,5].

На втором месте – болезни мочевыводящей системы: 2012 г. – 19,6%, 2013 г. –17,2%. Причинами обращений за СМП при патологии мочевыводящих путей являлись пиелонефрит (острый, хронический), почечная колика, цистит, мочекаменная болезнь. Болезни органов пищеварения в общей нозологической структуре обращений беременных в 2013 г. находились на третьем месте (14%), что на в 3,6% больше, чем в 2012 г. При этом, значительная доля среди причин обращаемости приходилась на гастрит, дуоденит, острый холецистит, острый панкреатит. Число обращений по поводу заболеваний нервной системы уменьшилось на 1,6%.

Учитывая полученные данные, с целью улучшения консультативно-диагностической и лечебной помощи беременным, нами составлен алгоритм выявления рисков и оказания медицинской помощи беременным с ЭГП (Рис. 2).

Острая ЭГП в предложенной схеме определена как впервые возникшая у ранее здоровой женщины и делится на две группы: связанную и несвязанную с беременностью. Не связанная с беременностью патология может относиться к любому классу болезней. Особую группу составляет острая ЭГП, связанная с беременностью, обусловленная анатомическими, физиологическими, биохимическими изменениями, присущими самой беременности.

Рис. 1. Структура причин обращения беременных за СМП по нозологическим группам в динамике за 2012-2013 гг в Карагандинской области в %



** ЭГП-Экстрагенитальная патология*

Рис. 2. Алгоритм выявления рисков и оказания медицинской помощи беременным

Использование разработанного алгоритма выявления рисков и ведения беременных женщин с ЭГП (острые и хронические заболевания и состояния, связанные и несвязанные с беременностью), позволит систематизировать имеющиеся данные, определить группу риска, осуществить дифференцированный подход к ведению беременных и избежать развития осложнений. Обоснованным является осуществление мультидисциплинарного подхода: акушер-гинеколог - семейный врач (терапевт) – специалист – пациентка.

Выводы: В структуре ЭГП по данным проведенного скринингового исследования в Республике Казахстан лидируют причины, связанные с гематологическими и нефрологическими профилями как в виде монопрофильных, так и в сочетании. Болезни органов дыхания, мочевыделительной системы являются наиболее частой причиной обращений беременных за скорой медицинской помощью. Анализ полученных данных позволил разработать алгоритм выявления рисков и оказания медицинской помощи беременным с ЭГП.

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SUMMARY

EPIDEMIOLOGY, STRUCTURE AND ALGORITHM OF MANAGEMENT OF PREGNANT WOMEN WITH EXTRAGENITAL PATHOLOGY OF THERAPEUTIC PROFILE

[1]Bacheva I., [1]Umbetalina N., [2]Bregvadze-Tabagari N., [1]Shalygina A., [1]Baidildina B.

[1]Karaganda State Medical University, Kazakhstan; [2]D. Tvildiani Medical University, Tbilisi, Georgia

Purpose of the study - the study of the extragenital pathology (EGP) structure in pregnant women according to the requests for medical help.

The screening survey was attended by 742 pregnant women. Average age was 28,4±5,5 years. A retrospective analysis of the causes of calls to pregnant ambulance carriages was carried out for 2012-2013. On the basis of obtained data was suggested an algorithm of pregnant women with EGP management. In the structure of EGP in one profile led hematology - 306 cases (41.2%), followed by nephrology - 290 (39.1%) and gastroenterology (38.8%) - 288 cases, respectively. In the structure of requests for emergency medical care for pregnant first place occupied by respiratory diseases (2012 r - 28%, 2013- 30%), followed by urinary system diseases (2012 - 19.6% 2013 - 17.2% r). Obtained data formed the basis for the algorithm to identify risks and provide medical care for pregnant women with extragenital pathology. In the structure of the screening study prevailed hematology profile diseases, and respiratory system diseases often were the reason for emergency medical care. The result of this study became the creating of the algorithm for medical care delivery.

Keywords: prevalence, structure, extragenital pathology in pregnant women, emergency medical care.

РЕЗЮМЕ

ЭПИДЕМИОЛОГИЯ, СТРУКТУРА И АЛГОРИТМ ВЕДЕНИЯ БЕРЕМЕННЫХ ЖЕНЩИН С ЭКСТРАГЕНИТАЛЬНОЙ ПАТОЛОГИЕЙ ТЕРАПЕВТИЧЕСКОГО ПРОФИЛЯ

[1]Бачева И.В., [1]Умбеталина Н.С., [2]Брегвадзе-Табагари Н.С., [1]Шалыгина А.А., [1]Байдильдина Б.Н.

[1]Карагандинский государственный медицинский университет, кафедра внутренних болезней №3, Республика Казахстан; [2]Медицинский университет им. Давида Твилдиани, Тбилиси, Грузия

Целью исследования явилось изучение превалентности и структуры экстрагенитальной патологии у беременных женщин по данным обращений за медицинской помощью.

В скрининговом обследовании принимали участие 742 беременных. Средний возраст составил 28,4±5,5 лет. Проведен ретроспективный анализ причин вызовов к беременным кареты скорой медицинской помощи г. Караганды за 2012-2013 гг. На основании полученных данных предложен алгоритм ведения беременных женщин с экстрагенитальной патологией (ЭГП).

По данным скринингового исследования в структуре ЭГП по одному профилю лидировал гематологический профиль - 306 (41,2%) случаев, затем нефрологический – 290 (39,1%) и гастроэнтерологический - 288 (38,8%) случаев. Сочетанная патология более чем по двум профилям выявлена от 2 до 20%.

На основании проведенного исследования следует заключить, что в структуре ЭГП по данным скринингового исследования в Республике Казахстан лидируют причины, связанные с гематологическими и нефрологическими профилями как в виде монопрофильных, так и сочетанных. Болезни органов дыхания, мочевыделительной системы явились наиболее частой причиной обращений беременных за скорой медицинской помощью. Анализ полученных данных позволил разработать алгоритм выявления рисков и оказания медицинской помощи беременным с ЭГП.

რეზიუმე

თერაპიული პროფილის ექსტრაგენიტალური პათოლოგიის მქონე ორსულთა ეპიდემიოლოგია,სტრუქტურა და მართვის ალგორითმი

[1]ი. ბაჩევა, [1]ნ. უმბეტალინა, [2]ნ. ბრეგვაძე-თაბაგარი,
[1]ა. შალიგინა, [1]ბ. ბაიდილდინა[1]

[1]ყარაგანდის სახელმწიფო სამედიცინო უნივერსიტეტი, შინაგან დაავადებათა №3 კათედრა,ყაზახეთის რესპუბლიკა; [2]დავით ტვილდიანის სახ. სამედიცინო უნივერსიტეტი, თბილისი, საქართველო

კვლევის მიზანს შეადგენდა ორსულთა ექსტრაგენიტალური პათოლოგიის პრევალენტობისა და სტრუქტურის შეფასება სამედიცინო დახმარებისათვის მიმართვიანობის მონაცემების საფუძველზე.

სკრინინგულ კვლევაში მონაწილეობა მიიღო 742 ორსულმა,საშუალო ასაკი – 28,4±5,5 წელი. ჩატარებულია 2012-2013 წლებში ქ. ყარაგანდაში ორსულებთან სასწრაფო დახმარების ბრიგადის გამოძახების მიზეზების რეტროსპექტული ანალიზი. მიღებული შედეგების საფუძველზე შემოთავაზებულია ექსტრაგენიტალური პათოლოგიის (ეგპ) მქონე ორსულთა მართვის ალგორითმი.

სკრინინგული კვლევის მოანაცემების მიხედვით, ეგპ-ის სტრუქტურაში ერთი პროფილით დომინირებდა ჰემატოლოგიური პროფილი – 306 შემთხვევა (41,2%), შემდეგ ნეფროლოგიური - 290; 39,1% და გასტროენტეროლოგიური - 288 (38,8%). შერწყმული პათოლოგია ორზე მეტი პროფილით გამოვლინდა შემთხვევათა 2-20%-ში.

კვლევის შედეგების საფუძველზე დადგენილია, რომ ყაზახეთის რესპუბლიკაში სკრინინგული კვლევების მიხედვით ეგპ-ის სტრუქტურაში ლიდერობს ჰემატოლოგიურ და ნეფროლოგიურ პროფილთან დაკავშირებული მიზეზები (როგორც მონოპროფილური, ასევე, შერწყმული სახით). სასუნთქი ორგანოების და შარდის გამომყოფი სისტემის დაავადებები აღმოჩნდა ორსულებთან სასწრაფო დახმარების გამოძახების ქვედაზე ხშირი მიზეზი.

მიღებული შედეგები საფუძვლად დაედო ექსტრაგენიტალური პათოლოგიის მქონე ორსულთა რისკების გამოვლინებისა და სამედიცინო დახმარების აღმოჩენის ალგორითმს.

RISK FACTORS OF CLEFT LIP AND PALATE IN GEORGIA

[1,2]Chincharadze S., [1]Vadachkoria Z., [2]Mchedlishvili I.

Tbilisi State Medical University, [1]Department of Surgery Direction of Child and Adult Stomatology (Dentistry) and Prevention of Stomatological (Dental) Diseases; [2]Department of Epidemiology and Biostatistics Direction of Public Health, Georgia

Maxillofacial congenital malformations take distinguished place in congenital abnormalities by their occurrence and severity. From this group of malformations cleft lip and palate (orofacial clefts) are the most common. Risk factors having influence on the development of such pathologies are divided into several groups: genetic, behavioral and unfavorable environmental factors. The latter two include tobacco and alcohol excessive consumption, contracting infectious diseases in the first trimester of pregnancy, presence of chronic diseases, use of various therapeutic drugs before or in the early period of pregnancy, unfavorable ecology, exposure to chemicals, etc. [2,5,10,12,14]. From the above-mentioned factors the genetic factor should be mentioned first. The major role of the factor in the development of thesemalformations is demonstrated through: more intensive distribution of orofacial clefts among individuals of Caucasian race in comparison with Negro race [4], high probability of its occurrence when the birth defect is present in one of the parents [3], or in cases of close relative marriages [6].

There is no consensus with regard to behavioral and unfavorable environmental factors and their impact on the frequency of cleft lip and palate. Role of smoking in the development of this pathology before and during the first trimester of pregnancy can be brought as an example. According to many scientists, there is a close statistical association between these two events [1,9,15]. However, based on a number of studies, other scientists have not revealed any association [11,13]. The situation is similar with regard to other risk factors.

We consider that one and the same factor has influence of different intensity on the development of cleft lip and palate that is likely to be attributed to genetic peculiarities of population, living conditions, social and economic status, traditions, etc. Therefore, we consider it important to identify a factor or a set of factors, which along with the genetic factor contribute to the development of orofacial clefts. Knowledge of the factors contributing to the development of this pathology is fundamental for implementation of effective preventive measures.

The aim of our study was to identify those risk factors, which are in correlation with the occurrence of cleft lip and palate in Georgia.

Material and methods. In order to pursue the set-up goal, we carried out a case-control study. The main group was composed of 41women who gave birth to newborns with orofacial clefts (cleft lip and/or palate) in Tbilisi maternity houses during 2015-2016. Upon receipt of a notification from the maternity house about the birth of a child with this malformation, the information regarding the possible risk factors was collected using a special form. At the same time in the same maternity house similar information was collected from 61 healthy newborns' mothers who served as controls.

The following information was collected from the newborns' mothers: consumption of tobacco and alcohol and its intensity a month prior to and during I trimester of pregnancy, contracting of infectious diseases in the same period, concomitant chronic diseases or other pathologies, parental drug use, use of treatment medicines, history of stressful situations, parental age, social status and level of education. If parents or close relatives had birth defects, parents of such children did not participate in the study.

In case of parental smoking intensity of tobacco consumption was divided into three levels: mild smoker – if a parent smoked 1-5 cigarettes daily, moderate smoker - from 6 to 10 cigarettes per day, and heavy smoker–when parent smoked 11 or more cigarettes per day. Intensity of alcohol consumption by parents was divided into 3 levels as well: mild - if a parent consumed any kind of alcohol once a week, moderate - if consumed twice a week, and heavy consumer - when alcohol was consumed 3 or more times per week.

Family economic status was divided into two groups: unsatisfactory and satisfactory. Families, which were on social care and received support from the state, or their income was less than the average consumer basket, belonged to the unsatisfactory group.

In order to assess a role of possible risk factors on the development of cleft lip and palate, bivariate analysis was conducted at the first stage of the study. Odds ratio (OR) was calculated for each factor. Statistical significance of the results was evaluated by 95% confidence interval (95% CI). The next stage was the identification of those risk factors, which statistically significantly correlated with congenital defects. Multivariate analysis was conducted using a multiple logistic regression model. Conclusions were based on the standardized (adjusted) odds ratio.

Statistical analysis was performed with SPSS v.16.

Results and their discussion. We have studied impact of 11 risk factors on the development of cleft lip and palate. Results of the bivariate analysis of the data are shown in Table 1. Statistically significant association was found between contracting of infectious disease during the first trimester of pregnancy and orofacial clefts in newborns: OR = 2.56, 95% CI: 1.05-6.24. History of influenza and upper respiratory tract infections was the most frequent among mothers of children with cleft lip and palate; herpes and cytomegalovirus infections, enteroviral infection, chlamydia and others were identified as well.

The second factor, which also had a statistically significant effect, is presented by noncommunicable diseases, especially chronic diseases, such as goiter, diabetes mellitus, hypertension (OR = 2.43, 95% CI: 0.82-7.77). Use of medicine during the first trimester of pregnancy had a statistically significant impact on the development of cleft lip and palate (OR= 3.65, 95% CI: 1.30-10.20). Pregnant women most often consumed antibiotics, followed by *L-Thyroxine*, medications against diabetes mellitus and hypertension.

Strong positive correlation was revealed between the development of congenital clefts and stressful situations in families (OR = 8.82, 95% CI: 2.32-33.50) , as well as with regard to the risk factor - hard economic conditions (OR = 2.43, 95% CI: 1.04-9.23). These two factors often interrelate, as unfavorable economic conditions quite often create conflicts and/or stressful situations in families. Besides, difficult economic conditions prevent a pregnant woman from balanced diet and consumption of protein- and vitamin-rich products.

In our cases maternal smoking during the first trimester of pregnancy had no effect on the development of cleft lip and palate. It should be noted that frequency of smoking was quite low among mothers of babies with birth defects as well as among mothers of healthy babies. Out of mothers of children with orofacial clefts only 2 indicated smoking during pregnancy, whilst out of healthy children's mothers – 4, nevertheless, all of them were

Table 1. Influence of various factors on the development of cleft lip and palate based on the case-control study results (Bivariate analysis)

Exposure factor	OR	95% CI
Infectious Diseases	2.56	1.05 - 6.24
Noncommunicable diseases	2.53	0.82 - 7.77
Use of medicine	3.65	1.30 – 10.20
Severe economic condition	2.43	1.04 – 9.23
Stress	8.82	2.32 – 33.50
Tobacco smoking by mother	0.72	0.13 – 4.11
Tobacco smoking by father	0.59	0.21 – 1.30
Alcohol consumption by mother	1.05	0.47 – 2.33
Alcohol consumption by father	0.68	0.31 – 1.51
Mother's age <20 and >30	0.57	0.25 – 1.30
Frequent abortions (3 and more)	1.10	0.34 - 3.66

Table 2. Influence of various factors on the development of cleft lip and palate based of the case-control study results (Multivariate analysis)

Exposure Factor	OR	95% CI
Infectious diseases	2.10	0.77 – 5.70
Noncommunicable diseases	2.88	0.83 – 9.97
Use of medicine	2.22	0.77 – 10.41
Severe economic condition	1.14	0.45– 2.84
Stress	7.76	1.93 – 31.33

mild smokers. These findings might be explained by the fact that an absolute majority of smokers in the country is presented by males, as well as the fact that the majority of women commonly try to refrain themselves from smoking while getting pregnant or beforehand.

Similar situation was observed when we studied the influence of alcohol. In our case, association was very weak (OR = 1.05, 95% CI: 0.47-2.33). In contrast to tobacco use, in the group of cases as well as in the group of controls, almost a half of the women indicated consumption of alcohol during the first 12 weeks of pregnancy. However, it should be emphasized that consumption of alcohol, as a rule, was common in both groups with a frequency of once a week or less, for example during holidays in a little amount. In such a case, women mainly consumed wine or beer. Thus, in our case all enrolled in the study women were mild alcohol consumers that led to the obtained results.

No significant effect was observed in the study of the infuence of fathers' smoking and alcohol intake habits on the development of the congenital pathologies under study (OR = 0.59, 95% CI: 0.21-1.30 and OR=0.68, 95% CI:0.31-1.51, correspondingly).

Similarly, no statistical association was revealed between maternal age and cleft lip and palate development (OR = 0.57, 95% CI: 0.25-1.30), though many authors have established such association in their studies. The same is applicable to the association between the number of abortions and the development of orofacial clefts, no significant association was revealed in our study.

Thus, based on the bivariate analysis of our study results it was determined that the following factors contribute to the development of cleft lip and palate: contracting diseases (both: infectious or noncommunicable) during the first trimester of pregnancy, taking medications during this period, hard economic condition and stressful situation in families.

At the second stage we conducted a multivariate analysis. We included in the analysis those factors, which were found to have association with the development of orofacial clefts based on the bivariate analysis, in particular: infectious and noncommunicable diseases, use of medicine, stress and hard economic condition. The results are shown in Table 2.

As we see, stressful situations in the families of pregnant women during the first trimester of pregnancy had the most significant impact on the development of orofacial clefts (standardized OR = 7.76, 95% CI: 1.93-31.33). There is a positive correlation between the birth defect and contracting of infectious or noncommunicable diseases during this period.

Thus, based on the multivariate data analysis of the case-control study results we can conclude, that stressful situations in the family of the pregnant woman play the most significant role in the development of orofacial clefts. Other factors such as contracting of infectious or noncommunicable diseases in the first trimester of pregnancy as well as the use of therapeutic drugs have some impact on the development of the pathology.

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SUMMARY

RISK FACTORS OF CLEFT LIP AND PALATE IN GEORGIA

[1,2]Chincharadze S., [1]Vadachkoria Z., [2]Mchedlishvili I.

Tbilisi State Medical University, [1]Department of Surgery Direction of Child and Adult Stomatology (Dentistry) and Prevention of Stomatological (Dental) Diseases; [2]Department of Epidemiology and Biostatistics Direction of Public Health, Georgia

A case-control study was conducted to reveal risk factors for cleft lip and palate. The main group consisted of 41mothers of infants with orofacial clefts (cleft lip and/or palate) who were born in Tbilisi maternity houses during 2015-2016. The control group was composed of 61 mothers who have given birth to healthy babies in the same maternity houses. Information on possible risk factors was collected using a special form. In order to evaluate a role of these risk factors, bivariate analysis was conducted at the first stage of the study. Odds ratio (OR) was calculated for each factor, significance of the results was evaluated by calculating 95% confidence intervals (95% CI). At the next stage of the study the factors significantly correlated with the development of orofacial clefts were identified and multivariate analysis was performed using a multiple logistic regression model.

According to the study results stressful situations in the families of pregnant women play the most significant role in the development of cleft lip and palate with standardized (adjusted) OR=7.76, 95% CI: 1.93–31.33. Other risk factors such as contracting infectious or noncommunicable diseases during the first trimester of pregnancy as well as use of medications during this period have some impact on the development of these malformations (OR=2.10, 95% CI: 0.77–5.70; OR=2.88, 95% CI: 0.83–9.97 and OR=2.22, 95% CI: 0.77–10.41, correspondingly).

Keywords: cleft lip and palate, pregnancy, stress.

РЕЗЮМЕ

РИСК-ФАКТОРЫ ВРОЖДЕННОЙ РАСЩЕЛИНЫ ВЕРХНЕЙ ГУБЫ И НЕБА В ГРУЗИИ

[1,2]Чинчарадзе С.Д., [1] Вадачкориа З.О., [2]Мчедлишвили И.М.

[1]Тбилисский государственный медицинский университет, департамент хирургии направления стоматологии детей и подростков и профилактики стоматологических заболеваний; [2]департамент эпидемиологии и биостатистики направления общественного здоровья, Грузия

Для выявления риск-факторов врожденной расщелины верхней губы и неба проведено исследование случай-контроль. Основную группу составила 41 мать, дети которых родились в родильных домах г. Тбилиси в 2015-2016 гг. с патологией - расщелина верхней губы, расщелина неба и сочетанные расщелины губы и неба. Контрольную группу составила 61 мать здоровых новорожденных, родившихся в тех же родильных домах в то же время. Сбор необходимой информации о факторах риска осуществлялся с помощью специальной анкеты. Для оценки роли этих факторов на первом этапе проведен бивариационный анализ и для каждого фактора рассчитаны соотношение шансов (OR) и доверительный интервал с 95% достоверностью. На следующем этапе выделены факторы, которые находились в корреляционной связи с врожденными расщелинами и проведен мультивариационный логический регресивный анализ полученного материала.

В результате проведенного анализа установлено, что развитие врожденной расщелины верхней губы и неба, в большинстве случаев вызвано стрессовой ситуацией в семье женщины во время ее беременности, стандартизированный (adjusted) OR=7.76, 95% CI: 1.93–31.33. В развитии данной патологии определенную роль играют также перенесенные инфекции в первом триместре беременности (OR=2.10, 95% CI: 0.77–5.70); наличие неинфекционных заболеваний (OR=2.88, 95% CI: 0.83–9.97) и медикаментозное лечение в этом периоде (OR=2.22, 95% CI: 0.77–10.41).

რეზიუმე

ზედა ტუჩისა და სასის თანდაყოლილი ნაპრალის განვითარების რისკ-ფაქტორები საქართველოში

[1,2]ს. ჭინჭარაძე, [1]ზ. ვადაჭკორია, [2]ი. მჭედლიშვილი

[1]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, ბავშვთა და მოზარდთა სტომატოლოგიისა და სტომატოლოგიურ დაავადებათა პროფილაქტიკის მიმართულების ქირურგიის დეპარტამენტი; [2]საზოგადოებრივი ჯანმრთელობის მიმართულების ეპიდემიოლოგიისა და ბიოსტატისტიკის დეპარტამენტი, საქართველო

ზედა ტუჩისა და სასის თანდაყოლილი ნაპრალის რისკის ფაქტორების გამოსავლენად ჩატარდა შემთხვევა-კონტროლით კვლევა. ძირითადი ჯგუფი შეადგინა 2015-2016 წწ. თბილისის სამშობიარო სახლებში აღნიშნული მანკით დაბადებული 41 ახალშობილის დედამ; მათ შორის იყო როგორც ზედა ტუჩის და სასის იზოლირებული, ასევე, კომბინირებული ნაპრალით დაავადებული ბაშვების დედები. საკონტროლო ჯგუფი შეადგინა ამავე სამშობიარო სახლებში დაბადებული 61 ჯანმრთელი ახალშობილის დედამ. ინფორმაციის შეგროვება ზედა ტუჩისა და სასის თანდაყოლილი ნაპრალის შესაძლო რისკის ფაქტორების შესახებ ხდებოდა სპეციალური ანკეტის მეშვეობით. მონაცემების შეფასების მიზნით პირველ ეტაპზე ჩატარდა ბივარიაციული ანალიზი და თითოეული ფაქტორისათვის გამოთვლილი იყო შანსების თანაფარდობა (OR). შედეგების სარწმუნობა შეფასდა 95%-იანი სარწმუნობის ინტერვალის გამოთვლით (95%CI). მომდევნო ეტაპზე გამოყოფილ იქნა ფაქტორები, რომელთა კორელაცია თანდაყოლილი მანკების არსებობასთან იყო სარწმუნო; ჩატარდა მულტივარიაციული ანალიზი მრავლობითი ლოჯისტიკური რეგრესიის მოდელის გამოყენებით.

მიღებული შედეგებზე დაყრდნობით, ავტორებს გამოტანილი იქვთ დასკვნა, რომ ზედა ტუჩისა და სასის თანდაყოლილი ნაპრალის განვითარებაზე მნიშვნელოვან ზეგავლენას ახდენს სტრესული სიტუაციების არსებობა ორსულის ოჯახში, სტანდარტიზებული (adjusted) OR=7.76, 95% CI: 1.93–31.33. ამ პათოლოგიის განვითარებაში, ასევე, გარკვეულ როლს ასრულებენ ორსულობის პირველ ტრიმესტრში გადატანილი ინფექციური დაავადებები,არაგადამდები დაავადებები და სამკურნალო პრეპარატების მოხმარება, შესაბამისად, სტანდარტიზებული OR=2.10, 95% CI: 0.77–5.70; OR=2.88, 95% CI:0.83–9.97; OR=2.22, 95% CI: 0.77–10.41.

DEPENDENCE OF MORPHOMETRIC PARAMETERS OF THE DENTAL OCCLUSION ON THE TYPE OF THE LOWER JAW GROWTH IN CHILDREN WITH CLASS II_1 DENTOFACIAL ANOMALIES WHO LINE IN THE NORTHERN UKRAINE

[1]Galich L.V., [2]Kuroedova V., [1]Lakhtin Yu., [2]Galich L.B., [1]Moskalenko P.

[1]Medical Institute at Sumy State University; [2]Higher State Educational Institution "Ukrainian Medical Dental Academy", Ukraine

Recently, specialists from many countries of the world have observed an increase in the prevalence of dentofacial anomalies in children and adolescents, which, in particular, is associated with urbanization processes and environmental degradation [4]. According to WHO, the incidence of dentofacial anomalies in the world is 92% [1]. One of the most common anomalies of the dentofacial apparatus in the late interchangeable occlusion is the violation of occlusion in the sagittal direction, namely, class II_1 according to Angle's classification [7]. For the timely treatment of this pathology in the pubertal period, the early detection is necessary [9]. However, the results of epidemiological studies in different regions and countries are contradictory [1,2,6-8,11], there is insufficient information on the structure of class II_1 anomalies according to Angle's classification with different types of lower jaw growth among 10-13 years old children. This necessitates a further study of the prevalence of dentofacial anomalies.

Purpose of the study - to study the structure of dentofacial anomalies in children and adolescents in Sumy city and Sumy oblast (Ukraine) by their applying. To identify the dentoalveolar morphological peculiarities of the occlusion in 10-13 years old patients with anomalies of class II_1 according to Angle's classification with different types of lower jaw growth.

Material and methods. A retrospective analysis of 2236 outpatient dental cards of urban and rural patients with orthodontic pathology, which applied to the regional children's clinical dental clinic (Ukraine), was conducted. Patients were divided into three age groups: 6-9 years old (early mixed occlusion) - 592 children; 10-13 years old (late mixed occlusion) - 1180 children; over 13 years old (permanent occlusion) - 464 persons (Fig. 1).

The form of dentofacial anomalies was established according to the Angle's classification. Open and cross occlusions were divided in separate groups.

In addition, 76 patients with class II_1 anomalies according to Angle's classification aged 10-13 years were examined in the clinic to determine the type of lower jaw growth. Children underwent an X-ray study, diagnostic models were made. In practical orthodontics, the most widely X-ray method of research is used [10], especially orthopantomography, which allows to carry out a detailed diagnosis, to select the strategy and tactics of orthodontic intervention, to control the stages and the final result of the treatment, depending on the direction of growth of the dentofacial apparatus, it allows the doctor to give a long-term prognosis [3,12].

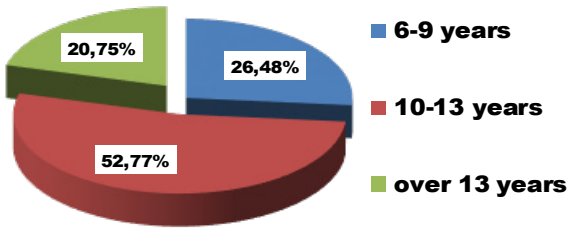

FIg. 1. The classification of patients by age

Orthopantomographic examination was performed to determine the type of lower jaw growth according to the procedure described by R. Reinhardt and others [13] (Fig. 2). All patients were divided into five groups, taking into account the type of lower jaw growth: group I - 21 patients with a neutral type of growth (∟Go = 123±5˚), group II - 11 children with vertical growth (∟Go> 128˚), group III - 9 patients with horizontal type of growth (∟Go <118˚), group IV - 9 children with combined (neutral with vertical) type of growth, group V consists of 5 children with a combination of neutral and horizontal type of lower jaw growth. Total 152 measurements were made.

On the diagnostic models of the jaws, to determine the degree of the severity of morphological changes, the biometric indicators were calculated, since they are an important criterion for choosing a treatment tactics [5]. Morphometric examinations were carried out on 55 control-diagnostic models of the jaws of patients with a late mixed occlusion with dentofacial anomalies of class II according to Angle's classification by the method of Linder-Hart, Korkhaus. Total 220 measurements were made.

The statistical processing of the material was carried out according to parametric criteria (mean value - M, standard error - m), statistical significance of the difference between the indices of two independent groups was carried out according to the parametric criterion (Student) using the statistical program package AtteStat 10.8.4. for MS Excel. Statistically significant differences were considered when $p < 0.05$.

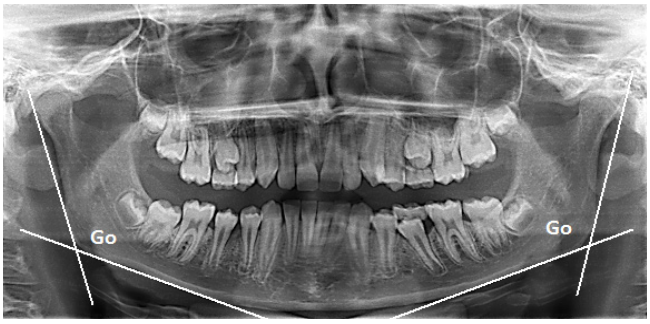

Fig. 2. Determination of the type of lower jaw growth

Results and their discussion. In the structure of dentofacial anomalies in patients of Sumy city and Sumy oblast, applying for orthodontic care, it is characteristic for all age groups that in a significant majority there are anomalies of individual teeth and dental curves (class I according to Angle's classification) and that is ranged from 67.95% to 77.87% of cases (Fig. 3).

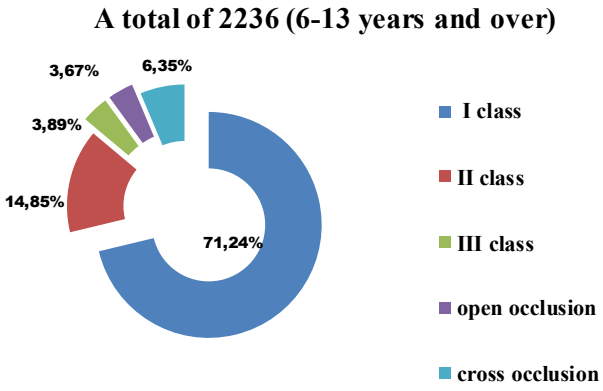

Fig. 3. The structure of dentofacial anomalies in 6 - 13 years old children

With regard to occlusion anomalies, in the age group of 6-9 years old patients (early mixed occlusion), the most common is an open occlusion (7.44%), which can be explained by the presence of a large number of various harmful habits at this age.

At a later age (late period of mixed and permanent occlusion), there is a decrease in the number of patients with open occlusion and class III anomalies according to Angle's classification, which is most likely due to the elimination of bad habits at an earlier age and the eruption of permanent teeth.

The occlusion anomalies of class II according to Angle's classification progress with age, and their percentage increases almost 9 times (from 2.87% up to 19.18%) both in 10-13 years old children and in patients older than 13 years in comparison with the early mixed occlusion.

On orthopantomograms it was found that in a significant number of examined patients the value of the jaw angles was 123±5˚, which corresponds to the neutral type of lower jaw growth (Table).

The neutral and combined types of growth were leading in boys, in girls more often the neutral (∟Go = 123 ± 5˚), vertical (∟Go> 128˚) and horizontal (∟Go <118˚) types of lower jaw growth were observed.

Among the patients with the combined growth types a combination of neutral and vertical types of lower jaw growth was revealed in 63.16%, and a combination of neutral and horizontal types of growth was revealed in 36.84% of cases.

In the biometric study of the control and diagnostic models of the jaws, a symptom complex of morphometric indices of dental curves with dentofacial anomalies of class II according to Angle's classification, depending on the type of lower jaw growth, was established.

For patients with a neutral type of lower jaw growth, the width of the upper dental curve between the canines averages 31.72±0.25 mm at a norm of 32.47±0.25 (p=0.05) and a lower one averages 25.86±0,43 mm at a norm of 24.40±0.40 mm (p<0.01); in the region of the first premolars on the upper jaw it averages 33.89±0.54 (p=0.001), on the lower jaw - 34.17±0.61 (p<0.001) at a norm of 37.05±0.58 mm and 37.05±0.58 mm respectively. It was found that the width in the region of the first permanent molars of the upper jaw is 45.05±0.78 mm at a norm of 48.35±0.78 mm (p=0.01), of the lower one it is 46.24±0.56 mm at a norm of 48.35±0.78 (p=0.05); the length of the frontal segment of the upper dental curve is 20.53±0.33 mm (p=0.001), of the lower dental curve - 15.1±0.4 mm (p=0.01) at a norm of 18.26 ± 0.26 mm and 16.29±0.25 mm respectively.

For patients with a vertical type of lower jaw growth, the following results were obtained: the width of the upper dental curve in the region of 3/3 teeth is 33.86±0.67 mm (N=32.44±0.47 mm) (p=0.05), upper dental curve - 26.25±0.49 mm (N=24.44±0.47 mm) (p<0.01); the width between 4/4 teeth on the upper jaw is 33.9±0.54 mm (N=36.36±0.60 mm) (p=0,01), on the lower jaw – 34.1±0.66 mm (N=36.36±0.60 mm) (p=0.05). Transversal dimensions in the region of 6/6 teeth on the upper jaw are 43.95±0.69 mm (N=46.69±0.84 mm) (p<0.01), on the lower jaw - 44.52±0.50 mm (N=47.25 ± 1.07 mm) (p = 0.05); the length of the frontal part of the upper jaw is 19.12 ± 0.52 mm (N = 47.25 ± 1.07 mm) (p <0.05), of the lower jaw - 13.9 ± 0.41 mm (N = 15.9 ± 0.35 mm) (p = 0.01).

Biometric study of the control and diagnostic models of the jaws of patients with horizontal growth showed that the width of the upper dental curve between the canines averaged 31.61

Table. Types of lower jaw growth in children according to orthopantomograms

Sex	Neutral growth type		Vertical growth type		Horizontal growth type		Combined growth type	
	n	%	n	%	n	%	n	%
Boys	17	22.37	5	6.58	4	5.26	12	15.79
Girls	11	14.47	10	13.16	10	13.16	7	9.21
Total	28	36.84± 5.53	15	19.74± 4.56	14	18.42±4.47	19	25± 4.98

± 0.53 mm at a morn of 32.90 ± 0.53 mm (p = 0.05) and of the lower one - 25.52±0.29 mm at a norm of 24.47 ± 0.43 mm (p <0.05); in the region of the first premolars on the upper jaw it is 33.59 ± 0.61 mm (p = 0.001), on the lower one - 32.28 ± 0.36 mm (p <0.001) at a norm of 36.99 ± 0.68 mm and 36.99 ± 0.68 mm respectively. It was established that the width in the region of the first permanent molars of the upper jaw is 43.42 ± 0.68 mm at a norm of 47.2 ± 1.41 mm (p = 0.01), of the lower jaw - 43.77 ± 0.17 mm at a norm of 47.2 ± 1.41 (p = 0.05); the length of the frontal segment of the upper dental curve is 20.97 ± 0.38 mm (p = 0.001), of the lower one it is 14.78 ± 0.39 mm (p = 0.01) at a norm of 17.73 ± 0.5 mm and 16.03 ± 0.44 mm respectively.

For children who have a combination of neutral and vertical type of lower jaw growth, it is typically the following: the width of the upper dental curve in the region of 3/3 teeth is 33.70 ± 0.14 mm (N = 32.92 ± 0.28 mm) (p = 0,05), of the lower one - 26,94 ± 0,46 mm (N = 24,76 ± 0,68mm) (p <0,01); between 4/4 teeth on the upper jaw - 34,84 ± 0,61 mm (N = 36,97 ± 0,74 mm) (p = 0,01), on the lower jaw – 34.77 ± 0.37 mm (N = 36.97 ± 0.74 mm) (p = 0.05). Transversal dimensions in the region of 6/6 teeth on the upper jaw are 45.37 ± 0.82 mm (N = 48.24 ± 0.97 mm) (p <0.01), at the lower jaw - 45.72 ± 0.51 mm (N = 48.24 ± 0.97 mm) (p = 0.05); the length of the frontal region of the upper jaw is 19.83 ± 0.62 mm (N = 18.34 ± 0.27 mm) (p <0.05), of the lower jaw -15.32 ± 0.25 mm (N = 16.23 ± 0.31 mm) (p = 0.01).

Under the combination of neutral and horizontal type of lower jaw growth, it was established the following: the width of the upper dental curve between the canines averages 32.44 ± 0.37 mm at a norm of 33.78 ± 0.59 mm (p = 0.05) and of the lower one it is 23, 1 ± 0.52 mm at a norm of 24.42 ± 0.57 mm (p <0.01); in the region of the first premolars on the upper jaw - 33.16 ± 0.69 mm (p = 0.001), at the lower jaw - 35.16 ± 0.63 mm (p <0.001) at a norm of 37.1 ± 0.57 and 37.1 ± 0.57mm respectively. It was found that the width in the region of the first permanent molars of the upper jaw is 44.28 ± 0.39 mm at a norm of 47.36 ± 0.63 mm (p = 0.01), of the lower one - 44.12 ± 0.61 mm at a norm of 47.36 ± 0.63 mm (p = 0.05); the length of the frontal segment of the upper dental curve is 20.66 ± 0.55 mm (p = 99.9), of the lower - 15.76 ± 0.37 mm (p = 0.01) at a norm of 18.22 ± 0.89 mm and 16.56 ± 0.24 mm, respectively.

Conclucion. Orthodontic care in the Sumy Oblast Children's Clinical Dental Clinic is mainly used by children from 10 to 13 years old. The anomalies of individual teeth and dental curves were leading in all age groups (71.24%).

Among the occlusion anomalies in 10-13 years old children, a significant proportion falls on the class II according to Angle's classification (19.18%).

A third of 10-13 years old patients, with class II anomalies according to Angle's classification, has a neutral type of lower jaw growth (36.84 ± 5.53%), horizontal and vertical types of growth are 18.42 ± 4.47% and 19.74 ± 4.56% respectively. The combination of neutral and vertical type of lower jaw growth occurs in 1.7 times more often than the combination of neutral and horizontal types.

In all groups, a characteristic symptom complex of morphological changes in the dental curves of the upper and lower jaws of different severity was established. The most pronounced morphological changes are observed in the group of patients with a horizontal type of lower jaw growth.

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SUMMARY

DEPENDENCE OF MORPHOMETRIC PARAMETERS OF THE DENTAL OCCLUSION ON THE TYPE OF THE LOWER JAW GROWTH IN CHILDREN WITH CLASS II_1 DENTOFACIAL ANOMALIES WHO LINE IN THE NORTHERN UKRAINE

[1]Galich L.V., [2]Kuroedova V., [1]Lakhtin Yu., [2]Galich L.B., [1]Moskalenko P.

[1]Medical Institute at Sumy State University; [2]Higher State Educational Institution "Ukrainian Medical Dental Academy", Ukraine

The aim of the work was to study the structure of dentofacial anomalies in children and adolescents in Sumy city and Sumy oblast, to identify dentoalveolar morphological peculiarities of the occlusion in 10-13 years old patients with class II_1 anomalies according to Angle's classification with different types of lower jaw bone growth.

A retrospective analysis of 2236 outpatient dental cards of urban and rural patients with orthodontic pathology was conducted. Patients were divided into three age groups: 6-9 years old (early mixed occlusion) - 592 children; 10-13 years old (late mixed occlusion) - 1180 children; over 13 years old (permanent occlusion) - 464 persons; besides 76 patients with class II_1 anomalies according to Angle's classification aged 10-13 years were examined. To determine the type of lower jaw growth, the children underwent orthopantomographic examination, diagnostic models were made and biometric indicators were calculated to determine the severity of the morphological changes.

It was established that anomalies of individual teeth and dental curve dominated in all age groups (71.24%). Among the occlusion anomalies, a large part falls to class II anomalies according to Angle's classification (19.18%). A third of these patients have a neutral type of lower jaw growth (36.84±5.53%), horizontal and vertical types of growth reach 18.42±4.47% and 19.74±4.56%, respectively. The combination of neutral and vertical type of growth of the lower jaw occurs in 1.7 times more than the combination of neutral and horizontal. The most pronounced morphological changes were observed in the group of patients with a horizontal type of lower jaw growth.

When planning treatment and prophylactic measures among patients of the orthodontic profile, it is necessary to take into account the peculiarities of both the prevalence of pathology in the region and the morphological changes of different severity in the dental curves of the jaws.

Keywords: dentofacial anomalies, prevalence of dentofacialr anomalies, class II according to Angle's classification, growth of jaws, types of jaw growth, orthopantomography, morphometry.

РЕЗЮМЕ

ЗАВИСИМОСТЬ МОРФОМЕТРИЧЕСКИХ ПАРАМЕТРОВ ПРИКУСА ОТ ТИПА РОСТА НИЖНЕЙ ЧЕЛЮСТИ У ПАЦИЕНТОВ СЕВЕРНОГО РЕГИОНА УКРАИНЫ С ЗУБОЧЕЛЮСТНЫМИ АНОМАЛИЯМИ II_1 КЛАССА ПО ЭНГЛЮ

[1]Галич Л.В., [2]Куроедова В.Д., [1]Лахтин Ю.В., [2]Галич Л.Б., [1]Москаленко П.А.

[1]Медицинский институт Сумского государственного университета;
[2]Высшее государственное учебное заведение "Украинская медицинская стоматологическая академия", Украина

Целью исследования явилось изучение структуры зубочелюстных аномалий у детей и подростков города Сумы и Сумской области и выявление зубоальвеолярных морфологических особенностей прикуса у пациентов 10-13 лет с аномалиями II_1 класса по Энглю с разным типом роста нижней челюсти.

Проведен ретроспективный анализ 2236 амбулаторных стоматологических карточек городских и сельских пациентов с ортодонтической патологией. Пациенты были разделены на три возрастные группы: дети в возрасте от 6-9 лет (ранний смешанный прикус) - 592; 10-13 лет (поздний смешанный прикус) - 1180 детей; выше 13 лет (постоянный прикус) - 464; кроме того, обследовано 76 пациентов с аномалиями II_1 класса по Энглю в возрасте 10-13 лет. Для определения типа роста нижней челюсти детям проведено ортопантомографическое исследование, изготовлены диагностические модели и по ним рассчитаны биометрические показатели для выявления степени тяжести морфологических изменений.

Установлено, что во всех возрастных группах доминировали аномалии отдельных зубов и зубных рядов (71,24%). Среди аномалий прикуса значительная часть приходится на II класс по Энглю (19,18%). У трети этих пациентов наблюдается нейтральный тип роста нижней челюсти (36,84±5,53%), горизонтальный и вертикальный типы роста составили 18,42±4,47% и 19,74±4,56%, соответственно. Сочетание нейтрального и вертикального типов роста нижней челюсти встречается в 1,7 раза больше, чем сочетание нейтрального с горизонтальным. Наиболее выраженные морфологические изменения наблюдались в группе пациентов с горизонтальным типом роста нижней челюсти.

При планировании лечебно-профилактических мероприятий среди пациентов ортодонтического профиля необходимо учитывать особенности как распространенности патологии в регионе, так и морфологические изменения зубных рядов челюстей разной степени тяжести.

რეზიუმე

თანკბილვის მორფოლოგიური პარამეტრების დამოკიდებულება ქვედა ყბის ზრდის ტიპზე უკრაინის ჩრდილოეთ რეგიონის კბილ-ყბის ენგლიუს მიხედვით II_1 კლასის ანომალიებით მოზარდებში

[1]ლ.ვ. გალიჩი, [2]ვ. კუროედოვა, [1]ი.უ. ლახტინი, [2]ლ.ბ. გალიჩი, [1]პ. მოსკალენკო

[1]სუმის სახელმწიფო უნივერსიტეტი,სამედიცინო ინსტიტუტი; [2]უმაღლესი სახელმწიფო სასწავლო დაწესებულება "უკრაინული სამედიცინო სტომატოლოგიური აკადემია", უკრაინა

ნაშრომის მიზანს წარმოადგენდა კბილ-ყბის ანომალიების სტრუქტურის შესწავლა ქალაქ სუმისა და სუმის ოლქში ბავშვებსა და მოზარდებში, 10-13 წლის პაციენტების თანკბილვის კბილალვეოლური მორფოლოგიური თავისებურებების გამოვლენა, ენგლიუს მიხედვით II_1 კლასის ანომალიების ქვედა ყბის ზრდის სხვადასხვა სახით.

ჩატარდა ორთოდონტური პათოლოგით ქალაქში და სოფელში მცხოვრებ 2236 პაციენტის ამბულატორიული სტომატოლოგიური ბარათების რეტროსპექტიული ანალიზი, ასევე 10-13 წლის ასაკის 76 პაციენტის გამოკვლევა ენგლიუს მიხედვით II_1 კლასის ანომალიით. ქვედა ყბის ზრდის ტიპის განსაზღვრის მიზნით ბავშვებს ჩაუტარდათ ორთოპანტომოგრაფიული კვლევა, დამზადებული იყო დიაგნოსტიკური მოდელი და მორფოლოგიური ცვლილებების სიმძიმის დონის გამოვლენის მიზნით მის მიხედვით გამოთვლილი იქნა ბიომეტრიული მაჩვენებლები.

დადგენილია,რომ ყველა ასაკობრივ ჯგუფებში დომინირებს ცალკეული კბილებისა და კბილების რიგების (71,24%) ანომალიები. თანკბილვის ანომალიებს შორის მნიშვნელოვანი ნაწილს შეადგენს ენგლიუს მიხედვით II კლასი (19,18%). ამ პაციენტების მესამედს შეინიშნება ქვედა ყბის ზრდის ნეიტრალური ტიპი (36,84±5,53%), ზრდის ჰორიზონტალური და ვერტიკალური ტიპები შეადგენს 18,42±4,47% და 19,74±4,56%, შესაბამისად. ქვედა ყბის ნეიტრალური და ვერტიკალური ზრდის ტიპების თანხვედრა გამოვლინდა 1,7-ჯერ უფრო ხშირად, ვიდ-რე ნეიტრალურის და ჰორიზონტალურის. ყველაზე გამოხატული მორფოლოგიური ცვლილებები დაფიქსირდა პაციენტთა ჯგუფში ქვედა ყბის ზრდის ჰორიზონტალური ტიპით.

ავტორებს გამოტანილი აქვთ დასკვნა,რომ ორთოდონტური პროფილის პაციენტებისთვის სამკურნალო პროფილაქტიკური ღონისძიებების დაგეგმ-ვისას აუცილებელია გათვალისწინებული იყოს როგორც რეგიონში პათოლოგიის გავრცელება,ასევე სხვადასხვა სიმძიმის დონის ყბათა კბილების რიგების ცვლილებები.

MICROBIOLOGICAL ASPECTS OF THE ORTHODONTIC TREATMENT

Zharmagambetova A., Tuleutayeva S., Akhmetova S., Zharmagambetov A.

Karaganda State Medical University, Department of Childhood Dentisrty and Surgical Dentistry, Faculty of General Medicine and Dentistry, Kazakhstan

Today, the prevalence of dental diseases remains high [6,9,13]. Dentoalveolar anomalies are one of the first places for the prevalence after dental caries and periodontal disease [1,4,14,18]. The high prevalence of dentoalveolar anomalies requires detailed diagnostics and rational treatment and prevention. To treat dentoalveolar anomalies, both removable and non-removable treatment methods are used. Orthodontic devices applied eliminate dentoalveolar anomalies, normalize the dental system function, provide the aesthetic needs of the patient, increase the life quality in general. However, the orthodontic appliance in the mouth worsens conditions for its self-cleaning, complicates the teeth care and makes an environment favorable to the soft tooth deposit. In this regard, there is a high microbial contamination of teeth surfaces and orthodontic appliances covering their extensive soft deposit that, in turn, leads to a demineralization of tooth enamel. In addition, there is change in the mouth microflora composition, which presents an increase in the number of pathogenic and opportunistic microorganisms, disbacteriosis mouth events. These factors contribute to the high prevalence of dental caries and inflammatory periodontal diseases. Therefore, being a panacea to treat dentoalveolar anomalies, the orthodontic appliance at the same time, have an adverse impact on the oral cavity state, but also on the organism as a whole, which requires further and careful study. On this basis, at the orthodontic treatment, various fundamental researches are held such as cytological, microbiological and others [2,8,10,15].

In modern dentistry, preventing dental caries is very important, which is aimed at reducing the number of bacteria and increasing the tooth resistance to various influences, as the major causative agent of dental caries is the opportunistic pathogenic oral microflora and its metabolic products. The research results show that the orthodontic treatment changes the qualitative and quantitative oral microflora composition: increases the number and frequency of the isolation rate of particular species, finds mouth atypical microbial strains, the symbiotic microflora ceases to perform barrier role for non-residents, pathogenic staphylococci and yeast-like fungi actively vegetate. According to Patack N.E. et al, and Pramod S. et al. [16,17] the microbial contamination creates conditions for developing inflammation in paradontium edge. It is also known that when wearing orthodontic appliances in the oral cavity, there is an increased amount of Streptococcusmutans, Candidaalbicans, Lactobacillusspp., Enterobacteriaceaespp., which are a key link in developing teeth demineralization and periodontal diseases.

Clinical and microbiological studies by several authors have shown that using orthodontic appliances leads to a statistically significant increase in the percentage of bacteria containing the

black pigment, a change in the environmental oral situation, a domination of periodontal microorganisms. The orthodontic appliances have changed the mouth microflora. It is confirmed the intensive propagation of yeast-like fungi on the oral cavity mucosa when wearing appliances [5,7].

Researchers [12] have found that by using removable appliances Candida, in particular Candidaalbicans are prevalent in the mouth. It is known that when treating with a removable appliance, streptococci, staphylococci, anaerobic bacteria have been identified on tooth biofilms. Nevertheless, most of them have Enterobacteriaceae met and Lactobacillusspp family [5]. It is also shown that the growth of microorganisms during wearing removable appliances is contributed by the lack of oral hygiene, that is timely mandatory tooth brushing has not been carried out, the appliance care rules have not been respected - no cleaning of the machine [11].

In the literature, the majority of works is devoted to the study of the microbial landscape with fixed orthodontic treatment. Despite the obvious relevance, the formation problem of opportunistic and pathogenic microorganisms when treating dentoalveolar anomalies with a removable orthodontic appliance remains understudied. Determining the obligate and facultative oral microflora during the orthodontic treatment with a removable orthodontic appliance in its various phases is still relevant to prevent dental caries and periodontal disease.

The research aim was to investigate the influence of the removable type of orthodontic treatment of patients aged 12 with dentoalveolar anomalies on the mouth microbiocenosis.

To achieve this aim the following objectives were identified:
- Examine the oral hygiene state in orthodontic patients
- Study the microbial oral landscape at all stages of the orthodontic treatment on the basis of microbiological examination methods.

Material and methods. The dental examination was performed in 100 patients aged 12 with dentoalveolar anomalies.

The dental examination was carried out by polling and survey using a standard set of dental tools at artificial light.

The dental examination included assessment of the oral hygiene state by the OHI-S index (Green J.C., Vermillion J.R., 1964) [19]. In determining the oral hygiene state, teeth were stained with the Schiller-Pisarev solution to identify plaque, and a visual assessment of the availability of hard dental plaque on the teeth and the surface covered by them were carried out. The hygienic state was determined at all stages of the orthodontic treatment.

The microbiological examination was performed in 100 patients at all stages of the orthodontic treatment. The microbiological examinations included determining obligate and facultative plaque microflora in the lateral and anterior dental arcades, and in paragraphs of orthodontic appliances retention.

Sampling material were taken by warning the patient not to clean the teeth and aids in day of sampling taking. Delivery of sampling to the bacteriological laboratory was carried out in the transport medium Amies (Himedia), followed by inoculation of the following culture media: blood agar (staphylococci, streptococci); egg yolk high salt agar (staphylococci, bacilli); Endo's medium (enterobacteria, non-fermentative Gramm-negative bacteria); Sabouraud medium (yeast-like fungi, yeast); MPC-2 medium (lactobacillus, streptococcus lactic acid); thioglycolic medium (clostridium, bacteroides, fusobacterium). Cultures were incubated during 18-24 hours at a temperature of 37°C, Saburo medium - about 3-5 days at 28°C. Staining was carried out by the method of Gram-Gins and Storm, with evaluation of morphological and tinctorial properties of microorganisms.

For identification of microorganisms bacteriological research method was used. The initial culture was carried out according to the Gould's method on meat-and-peptone agar, blood agar, Sabouraud agar, Lacto agar, Endo agar. Identification of isolated microorganisms was conducted up to genus on MALDI apparatus (Germany).

Statistical analysis was performed using standard software SPSSv22.0 for Windows. Descriptive statistics was performed for all analyzed parameters, depending on the type of the variable. Qualitative characteristics were presented in the form of shares (%) and absolute numbers. Quantitative features were described as the average value and standard deviation.

Results and their discussion. During the dental examination of 100 children with dentoalveolar anomalies before orthodontic treatment it was found that the average hygienic index OHI-S (Green J.C., Vermillion J.R.) [19] was M=1,2, SD=0,4, which says about satisfactory oral hygiene. During orthodontic treatment worsening state of oral hygiene was noted - M=2,1, SD=0,3, after orthodontic treatment of children the improvement in parameters was observed (Fig. 1).

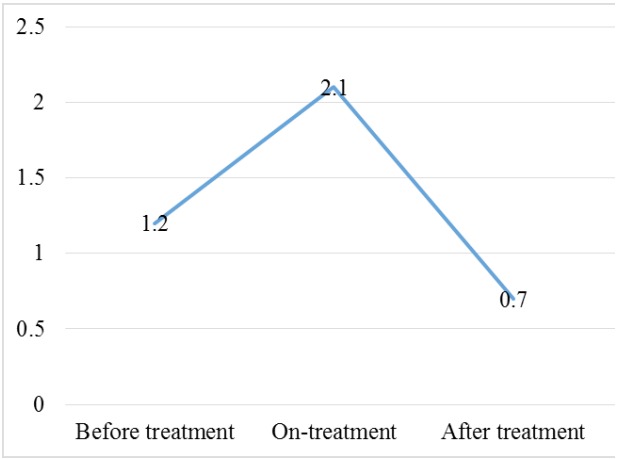

Fig. 1. Indicators of oral hygiene during orthodontic treatment

Analysis of microscopy results showed that the quantitative composition in smears of all patients surveyed varied depending on the period of orthodontic treatment. During the treatment there was an increase of certain strains of microorganisms. At all stages of the treatment permanent contaminants such as Lactobacillus spp., Streptococcus spp. and Staphylococcus spp were allocated (Figs. 2,3,4).

As shown in the figures 2,3,4, during the orthodontic treatment, in surveyed smears in addition to the reducing the number of permanent contaminants Lactobacillus spp., Streptococcus spp. and Staphylococcus spp., the representatives of Candida albicans, Staphylococcus aureus, Streptococcus mutans genera prevailed in

the amount compared to the beginning of orthodontic treatment, which corresponds to the literature. Also during that period of treatment Streptococcus piogenius, neisserial and others were seeded. The structure of the microbial landscape of the oral cavity in the surveyed children in carriage of the resident flora was manifested by increase in quantitative and qualitative indicators of Staphylococcus aureus. During research of the degree of colonization of pathological niches formed during wearing removable orthodontic appliances by staphylococci the high isolation rate of Staphylococcus aureus in oral cavity was set. The frequency of isolation of bacteria by Staphylococcus aureus, which is an important component of the microflora of the mouth and a significant etiological factor in the development of dental caries and periodontal disease, was M=16,1% SD=4,3.

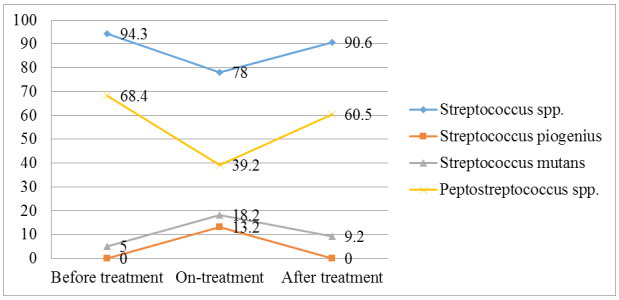

Fig. 2. Microbial landscape during orthodontic treatment: change of streptococci

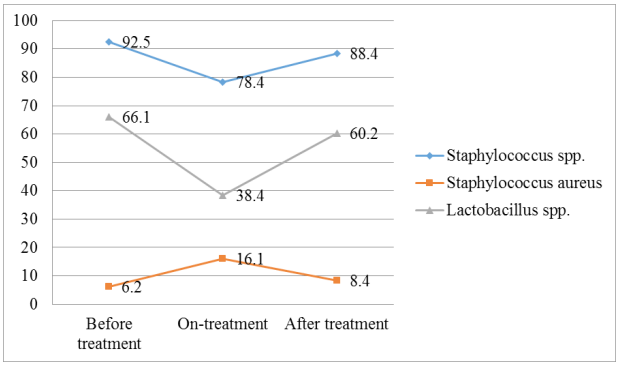

Fig. 3. Microbial landscape during orthodontic treatment: a change of staphylococci and lactobacilli

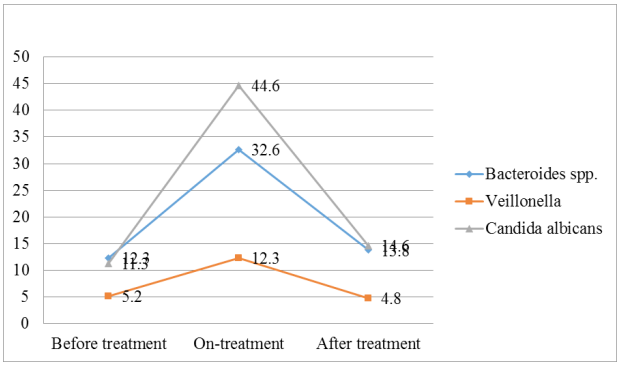

Fig. 4. Microbial landscape during the orthodontic treatment: a change of bacteroides, veylonella and candida

Oral health condition after orthodontic treatment was improved to M=0,7, SD=0,2, which corresponds to a satisfactory level.

Conclusions. It was found that in the surveyed children with dentoalveolar anomalies the microbial associations were represented by lactobacilli, various types of streptococci, staphylococci, yeast-like fungi. In the oral microflora during orthodontic treatment there was a sharp increase in the dominance of opportunistic and pathogenic microorganisms representatives, and a high level of colonization of aerobic and anaerobic microorganisms. The quantitative and qualitative analysis of the composition of the isolated bacteria revealed a significant increase in the number of Candida albicans. Also Streptococcus mutans and Staphylococcus aureus were dominant. Thus, the results of microbiological studies indicate a change of oral microbiocenosis in patients undergoing orthodontic treatment, which indicates that during orthodontic treatment the risk of dental caries development and periodontal disease is increasing.

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SUMMARY

MICROBIOLOGICAL ASPECTS OF THE ORTHODONTIC TREATMENT

Zharmagambetova A., Tuleutayeva S., Akhmetova S., Zharmagambetov A.

Karaganda State Medical University, Department of Childhood Dentistry and Surgical Dentistry, Faculty of General Medicine and Dentistry, Kazakhstan

An orthodontic appliance in the mouth worsens conditions for its self-cleaning, complicates the teeth care and makes an environment favorable to the soft tooth deposit, in turn, leads to the teeth enamel demineralization. In literature, the majority of works are devoted to the study of the microbial landscape with fixed orthodontic treatment. Despite the obvious relevance, the formation problem of opportunistic and pathogenic microorganisms when treating dentoalveolar anomalies with a removable orthodontic appliance remains understudied.

The research aim was to investigate the influence of the removable type of orthodontic treatment of patients aged 12 with dentoalveolar anomalies on the mouth microbiocenosis.

The dental examination and microbiological study was conducted to 100 children aged 12 with dentoalveolar anomalies. The dental examination included assessment of the oral hygiene state by the OHI-S index.

The microbiological research was conducted in the following sequence: the bacterioscopy smear of plaque, stained by the Gram and Burri method with the assessment of morphological and tinctorial properties of microorganisms.

The statistical data analysis was performed using SPSS v22.0 forWindows program.

The dental examination showed that the oral hygiene state varied according to the orthodontic treatment stage. During the orthodontic treatment the OHI-S Index was 2.1 score, indicating a satisfactory oral hygiene level.

The microbiological study showed that persistent contaminants were lactobacilli, streptococci, staphylococci, and yeast-like fungi. However, the treatment showed a decrease of normal flora level and the increase in number of Candidaalbicans, Staphylococcusaureus and Streptococcusmutans, that was a trigger in the development of dental caries and periodontal disease.

During the orthodontic treatment, children with dentoalveolar anomalies are at high risk of dental caries and periodontal disease.

Keywords: orthodontic treatment, microbiocenosis, tooth deposit, microorganisms.

РЕЗЮМЕ

МИКРОБИОЛОГИЧЕСКИЕ АСПЕКТЫ ОРТОДОТИЧЕСКОГО ЛЕЧЕНИЯ

Жармагамбетова А.Г., Тулеутаева С.Т., Ахметова С.Б., Жармагамбетов А.Г.

Карагандинский государственный медицинский университет, кафедра стоматологии детского возраста и хирургической стоматологии, факультет общей медицины и стоматологии, Республика Казахстан

Наличие в полости рта ортодонтического аппарата ухудшает условия ее самоочищения, осложняет уход за зубами и создает условия, благоприятствующие отложению мягкого зубного налета, что, в свою очередь приводит к деминерализации эмали зубов. Большинство исследований посвящены изучению микробного пейзажа при несъемном ортодонтическом лечении. Несмотря на очевидную актуальность, проблема распространения условно-патогенных и патогенных микроорганизмов при лечении зубочелюстных аномалий на съемной ортодонтической аппаратуре остается недостаточно изученной.

Целью исследования явилось изучение влияния съемного вида ортодонтического лечения пациентов в возрасте 12 лет с зубочелюстными аномалиями на микробиоценоз полости рта.

Стоматологическое обследование и микробиологическое исследование проводилось 100 детям с зубочелюстными аномалиями в возрасте 12 лет. Стоматологическое обследование включало оценку состояния гигиены полости рта по индексу OHI-S.

Микробиологическое исследование проводилось в следующей последовательности: бактериоскопия мазка из зубного налета, окрашенного по методу Грама и Бурри с оценкой морфологических и тинкториальных свойств микроорганизмов.

Статистическая обработка данных осуществлялась с использованием программы SPSS v22.0 for Windows.

Стоматологическое обследование показало, что состояние гигиены полости рта менялось в зависимости от этапа ортодонтического лечения. Во время ортодонтического лечения индекс OHI-S составил 2,1 балла, что свидетельствует о неудовлетворительном уровне гигиены полости рта.

Микробиологическое исследование показало, что постоянными контаминантами являются лактобактерии, стрептококки, стафилококки и дрожеподобные грибы. Однако, во время лечения отмечалось снижение уровня нормофлоры и увеличение количества Candida albicans, Staphylococcus aureus и Streptococcus mutans, что является пусковым механизмом в развитии кариеса зубов и заболеваний пародонта.

Во время ортодонтического лечения у детей с зубочелюстными аномалиями имеется высокий риск развития кариеса зубов и заболеваний пародонта.

რეზიუმე

ორთოდონტული მკურნალობის მიკრობიოლოგიური ასპექტები

ა. ჟარმაგამბეტოვა, ს. ტულეუტოვა, ს. ახმეტოვა, ა. ჟარმაგამბეტოვი

ყარაგანდის სახელმწიფო სამედიცინო უნივერსიტეტი, ბავშვთა ასაკის და ქირურგიული სტომატოლოგიის კათედრა, საერთო მედიცინის და სტომატოლოგიის ფაკულტეტი, ყაზახეთის რესპუბლიკა

ორთოდონტული აპარატის არსებობა პირის ღრუში არახელსაყრელ პირობებს უქმნის პირის ღრუს ჰიგიენის ჩატარებას, ართულებს კბილების მოვლას და იწვევს კბილის ემალის დემინერალიზაციას და კბილის რბილი ნადების განვითარებას. გამოკვლევათა დიდი რაოდენობა სტომატოლოგიაში ეძღვნება მიკრობული პეიზაჟის შესწავლას მოუხსნელი აპარატებით ორთოდონტულ მკურნალობის დროს. მიუხედავად აღნიშნული საკითხის განსაკუთრებული აქტუალობისა, პირობით-პათოგენური და პათოგენური მიკროორგანიზმების გავრცელება მოსახსნელ ორთოდონტულ აპარატებზე სადღეისოდ საკმაოდ არ არის შესწავლილი.

ზემოაღნიშნულიდან გამომდინარე, კვლევის მიზანს წარმოადგენდა მოსახსნელი სახეობის ორთოდონტული მკურნალობის ზეგავლენის შესწავლა პირის ღრუს მიკრობიოცენოზზე 12 წლის ბავშვებში კბილების ანომალიებით.

სტომატოლოგიური გასინჯვა და მიკრობიოლოგიური გამოკვლევა ჩაუტარდა 12 წლის 100 ბავშვს კბილ-ყბის ანომალიებით. სტომატოლოგიური გასინჯვა მოიცავდა პირის ღრუს მდგომარეობის შეფასებას OHI-S ინდექსის მეშვეობით. მიკრობიოლოგიური კვლევა ჩატარდა შემდეგი თანმიმდევრობით: კბილის ნადების ნაცხის ბაქტერიოსკოპია, გრამა და ბურის შეღებვის მეთოდით, მიკროორგანიზმების მორფოლოგიური და ტენკტორული თვისებების შეფასებით.

მონაცემების სტატისტიკური დამუშავება განხორციელდა SPSS პროგრამით v 22.0.

სტამატოლოგიურმა კვლევამ გამოავლინა, რომ პირის ღრუს ჰიგიენა ცვალებადობას განიცდიდა ორთოდონტული მკურნალობის ეტაპების მიხედვით. ორთოდონტული მკურნალობის დროს OHI-S ინდექსი შეადგენდა 2,1 ქულას, რაც მიუთითებს პირის ღრუს ჰიგიენის არადამაკმაყოფილებელ დონეზე.

მიკრობიოლოგიურმა კვლევამ აჩვენა, რომ მუდმივ კონტამინანტებს წარმოადგენენ ლაქტობაქტერიები, სტრეპტოკოკები, სტაფილოკოკები და საფუარისმაგვარი სოკოები. მკურნალობის დროს აღინიშნებოდა ნორმოფლორის დონის დაქვეითება და Candida albicans, Staphylococcus aureus и Streptococcus mutans რაოდენობის მომატება, რაც წარმოადგენს კბილის კარიესის და პაროდონტის განვითარების ამოსავალ მექანიზმს.

ჩატარებული კვლევის შედეგებზე დაყრდნობით ავტორებს გამოტანილი აქვთ დასკვნა, რომ კბილ-ყბის ანომალიებით ბავშვების ორთოდონტული მკურნალობის დროს არსებობს კბილის კარიესისა და პაროდონტის დაავადების განვითარების მაღალი რისკი.

ACUTE VIRAL BRONCHIOLITIS IN INFANTS (REVIEW)

[1]Chkhaidze I., [2]Zirakishvili D.

[1]Tbilisi State Medical University; [2]M. Iashvili Central Children Hospital, Tbilisi, Georgia

Bronchiolitis is the most common reason for hospitalization of children in many countries, challenging both economy, area and staffing in pediatric departments. Bronchiolitis is an acute lower respiratory tract infection in early childhood caused by different viruses, with coughing, wheeze and poor nutrition as the major symptoms. A substantial proportion of children will experience at least one episode with bronchiolitis, and 2- 3% of all children will be hospitalized with bronchiolitis [34,37].

There is no uniform definition of bronchiolitis, and no definite age limitation. The American Academy of Pediatrics (AAP) underlined that bronchiolitis is a clinical diagnosis, recognized as “a constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort and wheezing in children less than 2 years of age” [34].

Epidemiology

RSV is the most frequent cause of bronchiolitis in infants and young children and accounts in the United States alone for approximately 125,000 hospitalizations and 250 infant deaths every year. Global estimates by the World Health Organization indicate that RSV accounts overall for more than 60% of acute respiratory infections in children. Furthermore, RSV is responsible for more than 80% of lower respiratory tract infections (LRTIs) in infants younger than 1 year. [32]

RSV infection is the second largest cause of mortality, after malaria, in infants outside the neonatal period and causes up to 200,000 deaths per year worldwide [20, 27]. In the UK there are approximately 30,000 hospitalizations (1-3% of the entire birth cohort) and over 900 pediatric intensive care unit (PICU) admissions per year [13].

However, the epidemiology of RSV differs widely across latitudes and meteorological conditions. For example, at sites with persistently warm temperatures and high humidity, RSV activity tends to be continuous throughout the year, peaking in summer and early autumn. In temperate climates, RSV activity is maximal during winter and correlates with lower temperatures. In areas where temperatures remain colder throughout the year, RSV activity again becomes nearly continuous. Thus, RSV activity in communities is affected by both ambient temperature and absolute humidity, perhaps reflecting meteorologic combinations that allow greater stability of RSV in aerosols. Morbidity and mortality of RSV disease are higher in premature infants and in infants with chronic lung disease (eg, bronchopulmonary dysplasia, cystic fibrosis, and interstitial lung diseases) or hemodynamically significant congenital heart disease. Because preterm infants miss the third trimester window during which the placenta expresses Fc receptors mediating the transfer of maternal IgG to the fetus, they are born with reduced humoral protection against infection and reach lower nadir concentrations of maternal IgG. This is compounded by T-cell–mediated responses that are inefficient because T cells also mature primarily during the last trimester of pregnancy [32].

Approximately 20% of children develop bronchiolitis during their first year of life, and studies from the USA have found increasing rates of bronchiolitis (188/1000 infants in 1996/97 to 265/1000 in 2002/03) in this age group [16, 39]. In a large study from England the admission rate for all infants with bronchiolitis below 12 months of age was 24.2 per 1000 [25]. Another study from the UK underlines that the mortality rate for bronchiolitis in children below 12 months is low and falling, from 21.5 to 1.8 per 100 000 children (age 1 to 12 months) from 1979 to 2000, reflecting improvements in paediatric intensive care [31].

The most common etiologic agent is RSV (60–80% of cases), but rhinovirus, adenovirus, coronavirus, influenza and parainfluenza virus, and human metapneumovirus, as well as *Mycoplasma pneumonia, Chlamydophyla pneumoniae* can also be responsible [22, 34, 41, 45]. Dual infections are reported in 20–30% of children, most commonly with RSV and either HMPV or rhinovirus, but whether concomitant infection modifies the severity of bronchiolitis is not known [4].

Pathogenesis and Pathophysiology

Transmission of RSV infection occurs through inoculation of the nasopharyngeal or conjunctival mucosa with respiratory secretions from infected individuals. The virus remains viable on hard surfaces for up to 6 hours, on rubber gloves for 90 minutes, and on skin for 20 minutes. This prolonged survival highlights the need for hand washing and contact precautions as an essential (and cost-effective) practice to limit the spread of infection, especially in clinic settings. The incubation period ranges from 2 to 8 days, and immunocompetent individuals can shed the virus for up to 3 weeks, although on average this is limited to approximately 8 days. However, viral shedding from immunocompromised individuals can continue for several months because intracellular replication is not effectively contained by specific cell-mediated immunity. RSV infection starts in the nasopharyngeal epithelium but then spreads rapidly by intercellular transmission through the lower airways, reaching the terminal bronchioles, where the replication of this virus is most efficient. Direct pathologic consequences of lytic viral replication include sloughing of necrotic epithelial cells, which exposes the dense subepithelial network of nociceptive nerve fibers, forming the afferent limb for the cough reflex. Mucous secretions increase in quantity and viscosity and tend to pool because of the loss of ciliated epithelium, resulting in widespread mucous plugging. This constellation of acute inflammatory changes that form the immediate response to exponential viral replication in the bronchioles leads to airway obstruction and air trapping, producing the classic clinical triad of polyphonic wheezing, patchy atelectasis, and bilateral hyperinflation. However, disease severity and duration are primarily a function of the immune response mounted by the host. Innate immune mechanisms provide the respiratory tract with a first barrier against the establishment of a productive infection. Subsequently, specific humoral and cell-mediated immunity play a critical role in clearing the infection and attenuating its course. Although this response does not result in complete protection against subsequent infection, it decreases their severity. In infants, higher titers of maternally derived RSV neutralizing antibody are associated with a much lower risk of hospitalization due to RSV, and this protective effect can be replaced or enhanced in high-risk infants by passive prophylaxis. Cytotoxic T lymphocytes are central in the control of active infection and viral clearance, which explains why immunocompromised individuals with deficient cell-mediated immunity experience more severe and prolonged RSV disease and shed the virus much longer.[32]

Clinical Manifestations

After RSV infects the upper respiratory tract there is an incubation period of 2-8 days before clinical symptoms occur. Viral replication in the nasopharyngeal epithelium usually leads to mild coryzal symptoms. Within 1-3 days RSV infection spreads to the lower respiratory tract causing cough, dyspnoea and cyanosis. It is not clear why some infants go on to develop lower respiratory tract signs while others do not, but there is some evidence that reduced lung function or a genetic predisposition may play a role in both term and prematurely born infants [9, 46.]. Clinical examination findings include prolonged expiration, wheeze, crepitations and signs of respiratory distress. In addition, infants may present with only apnoea, especially those born prematurely, those with bronchopulmonary dysplasia or those less than 3 months old [34]. Risk factors for more severe disease include premature birth, chronic lung disease, haemodynamically significant congenital heart disease, age less than 3 months, neuromuscular disorders and immunodeficiency. Infants seen in primary care with marked respiratory distress, oxygen saturations less than 92% on air, significantly reduced feeding, clinical dehydration or a history of apnoea require referral to hospital for consideration of hospital admission [5].

Typically, the infection starts with signs and symptoms of mucosal inflammation and irritation of the upper respiratory tract (congestion, rhinorrhea, and sneezing). In the next few days, the clinical status evolves with involvement of the lower respiratory tract manifested by cough and increased work of breathing with use of accessory respiratory muscles to overcome the increased resistance of obstructed airways. Many of the clinical manifestations of airway obstruction are driven by the immune response against

the virus rather than by viral replication and direct cytotoxicity. Therefore, wheezing and other typical signs of bronchiolitis may be reduced or even absent in immunosuppressed patients and be replaced by rapidly evolving parenchymal infiltrates that can lead to acute respiratory distress syndrome. Inspection reveals respiratory distress ranging from minimal to profound respiratory failure associated with a variable degree of nasal flaring and intercostal retractions. Auscultation reflects the vibration of conducting airways generated by turbulent airflow and is remarkable for a prolonged expiratory phase, diffuse polyphonic wheezing, and coarse crackles (rales) scattered throughout the lung fields. Pulse oxymetry and arterial blood gas analysis detect moderate to severe hypoxemia derived primarily from the perfusion of respiratory units that are poorly ventilated because of mucous plugging (ventilation-perfusion mismatch). Progressive carbon dioxide retention and respiratory acidosis signal the development of respiratory muscle fatigue and evolving respiratory failure that require ventilator assistance. Infants are usually more severely affected and may also develop lethargy, fever, poor feeding, and otitis media, whereas older children typically manifest symptoms of the upper respiratory tract but may also develop tracheobronchitis. Apnea is a well-known complication of RSV infection in infants, and its incidence is as high as 20% in infants younger than 6 months who require hospitalization. When present, apnea usually is an early event that precedes lower respiratory tract signs and symptoms, suggesting the involvement of reflex neural activity triggered in the upper airways. The highest incidence of apnea occurs in premature infants and in infants younger than 1 month, probably because of the relative immaturity of ventilatory control. In most cases, however, apnea is self-limited and does not recur with subsequent infections [33].

No formal scoring system for the severity of bronchiolitis exists, but a suggestion for the grading into mild, moderate and severe bronchiolitis based on guidelines from New Zealand and Scotland [2, 6, 40]. In a study including children with bronchiolitis from an out-patient clinic, the resolution of symptoms took more than 14 days in 40% of the children, and approximately 10% had symptoms after 4 weeks [39]. The median length of hospitalization in a large study including children below 12 months was only one day [25], and in a Norwegian study the mean length of hospitalization was 80 hours [36].

Risk factors for bronchiolitis are male gender, a history of prematurity, young age, being born in relation to the RSV season, preexisting disease such as bronchopulmonary dysplasia, underlying chronic lung disease, neuromuscular disease, congenital heart disease, exposure to environmental tobacco smoke, high parity, young maternal age, short duration/no breastfeeding, maternal asthma and poor socioeconomic factors. However, the majority of children hospitalized for bronchiolitis have no underlying condition [25, 39]. The same conditions may also be risk factors for a more severe course.

Work-up

Acute bronchiolitis usually does not require investigations [34]. Viral antigen tests usually have only a small predictive value, the identification of specific agents can be limited to the hospital setting, where it can reduce use of antibiotics, number of investigations and length of hospitalization [10]. RSV infection should be confirmed by a nasopharyngeal aspirate and can be useful for infection control purposes [7]. A positive viral test could be useful to exclude bacterial infections in infants with bronchiolitis and fever during the first few months of life. However, a prospective study of 218 patients excluded serious bacterial infections in young infants with fever [21]. In the majority of cases, the diagnosis of bronchiolitis is clinical. Blood gas measurement to detect hypercapnia is indicated only in critical cases [6].

Mansbach et al. demonstrated that a pulse oximetry level of 94% could be related to an increased likelihood of hospitalization [22]. All the admitted infants should receive barrier nursing, to avoid nosocomial spread of infection [7]. Chest radiography is not usually recommended as a routine test, but it can be more useful in children with high or prolonged fever, low oxygen saturation, underlying cardiopulmonary disease or mechanical ventilation [8]. Differential diagnosis may include gastroesophageal reflux, laryngotracheobronchomalacia, pertussis, foreign body aspiration, vascular ring and other mediastinal obstructions or other congenital lung diseases, but it is very seldom necessary.

Management

Despite relentless attempts to identify pharmacologic strategies to improve the clinical course and outcomes of this infection, the most effective management remains limited to the supportive care measures discussed above. There is no solid scientific evidence supporting the use of any pharmacologic agent currently available.

A conservative approach to treatment seems adequate in the majority of children, especially for the youngest ones (<3 months) and treatment is mainly supportive [26]. Patients can deteriorate for 2–3 days after the onset of the disease but then start to improve, therefore hospital admission could be arranged if there is no improvement and supplemental treatments should then be considered [36.]. An important decision is whether to admit the patient to hospital and what are the indications for admission, candidates being severe disease, very young age, or important comorbidities. Apnea is a very important aspect of the management of young infants with bronchiolitis.

Low values of oxygen saturation are representative of a higher risk of hospitalization and, in these cases, hospitalization itself can be more prolonged, so administration of oxygen is recommended for values of SpO2 <90% [35]. It is crucial to monitor oxygen saturation continuously during treatment, but monitoring can be slowed down or suspended as the child improves [34].

Maintaining hydration is an important part of the care of infants with bronchiolitis. The respiratory distress due to increased work of breathing may cause inadequate feeding and eventually lead to poor hydration. Further, tachypnoe and fever increases fluid loss, potentially worsening the dehydration, so adequate hydration is fundamental [18, 26, 28]. Oral feeding may be sustained and breastfeeding should be encouraged [30]. Enteral feeding by gastric tube, as boluses or continuously, should be started if the infant will not suck [29] as it can improve the nutritional status of infants and can be a direct route for breast milk administration [1]. However, it can interfere with breathing in compromised infants and intravenous fluids (IV) are preferred in these cases to reduce the risk of aspiration [28].

The current guidelines recommend that the amount of fluids should not exceed 100% of the usual daily requirement to avoid fluid overload [18, 29]. Monitoring of body weight, urine and serum osmolarity and electrolytes may therefore be useful in these cases [26]. Inhaled normal saline (0.9%) can be administered to

increase clearing of mucous [30], although it is not suggested in current guidelines and reviews [26, 34, 39].

Antivirals
The only antiviral agent ever licensed by the FDA for the therapy of severe RSV infections is ribavirin, a synthetic nucleoside analog with broad in vitro virustatic activity. Unfortunately, by the time the infection manifests clinically in vivo, most of the viral load has already been cleared, and the disease process is driven primarily by inflammatory mechanisms largely independent from viral replication. After some initial encouraging data from industry sponsored studies, a series of randomized trials were unable to demonstrate any short- or long-term improvement in the clinical course of bronchiolitis, leading to a rapid decline and virtual disappearance of ribavirin use in this setting. Therefore, inhaled ribavirin is no longer recommended for routine treatment of RSV infection, although it may be considered in select immunocompromised individuals, who can continue to shed virus for several months because replication is not limited by host defenses.

Currently, there is no known role for antiviral therapy in bronchiolitis and therefore no indication for ribavirin, either nebulized or intravenous [3]. Continuous positive airway pressure (CPAP) may improve respiratory failure and help avoid intubation of patients in the Intensive Care Unit. In cases where nasal CPAP is not sufficient, proper mechanical ventilation can be applied [19]. Children with severe bronchiolitis (especially those with bronchopulmonary dysplasia), who do not improve despite mechanical ventilation, can benefit from extracorporeal membrane oxygenation [22].

AAP not recommends using chest physiotherapy for infants and children with a diagnosis of bronchiolitis [34]. Gentle nasal suction to keep the air passages clear could be beneficial in infants with copious secretion [7].

Bronchodilators.
Albuterol does not provide consistent benefit in the treatment of RSV infection and should not be administered to infants and children diagnosed as having bronchiolitis. A brief trial with objective evaluation of the response may be warranted, but this therapy should be discontinued if no improvement occurs because of the significant adverse effects, including tachycardia, tremor, hypokalemia, and hyperglycemia. These adverse effects can be amplified and become life-threatening in patients with underlying lung or heart disease, also due to the interaction with other commonly used therapies (eg, diuretics). Other inhaled selective b-agonists, such as levalbuterol, have no demonstrable advantage over albuterol in humans despite preliminary data in rodent models that suggest potential benefits.[32].

Inhalation with adrenaline may reduce mucosal swelling, which has led to frequent use in infants with bronchiolitis. However, a clinically important, significant effect has been documented for neither adrenaline nor beta-2-agonists. Studies on short-term effects show conflicting results. A recent Cochrane review concludes that inhaled (racemic) adrenaline does not improve important clinical outcomes such as length of hospital stay or the use of supportive care in moderate to severe bronchiolitis inpatients [14]. This is supported by a recent large Norwegian randomised controlled trial (RCT) of 404 infants [36]. In this study, treatment "as needed" rather than on a fixed schedule resulted in less inhalations, shorter hospital stay, less use of supplemental oxygen and less ventilatory support. The effect was predominantly seen in children <3 months (25 hours reduced hospital stay), which also tended to have a negative effect of adrenaline compared to saline, supporting a conservative approach particularly in this age group. Adrenaline is therefore not recommended as a standard treatment in infants with bronchiolitis, but a trial might be performed in children >3 months, with critical evaluation of effect with respect to continuation of administration. Beta-2-agonists are not recommended for infants with bronchiolitis [12]

Corticosteroids.
Neither systemic nor inhaled corticosteroids have consistent benefit in the treatment of acute RSV disease or in the prevention of post-RSV wheezing. [17, 33]

In particular, a systematic review of 13 trials of corticosteroid therapy in 1,198 children with viral wheezing ages 0 to 30 months concluded that this therapy lacks any significant clinical benefit compared with placebo and is not indicated for this patient group. The findings of this meta-analysis have been complemented by a number of more recent individual studies that have reached more or less the same conclusions.[32].

Another area of concern derives from safety considerations. In fact, viral bronchiolitis typically occurs during the first year after birth and coincides with a critical phase of rapid lung growth. The safety of corticosteroids during this developmental window is virtually unknown, and corticosteroids are not approved by the Food and Drug Administration (FDA) for use in the treatment of bronchiolitis or asthma in the first year after birth. Therefore, on the basis of current and extensive scientific evidence, corticosteroids are not recommended for routine use in the treatment of acute bronchiolitis. It has been argued that virus-induced wheezing in infants and young children could be the early manifestation of persistent asthma and therefore warrant the use of corticosteroids for the secondary prevention and control of asthma. However, in general young children without an atopic phenotype who wheeze in response to viral infections show a poor response to corticosteroids, and even children who will ultimately develop chronic asthma are usually unresponsive to this therapy when they develop virus-induced wheezing during their first years after birth.

Antimicrobials
Antibiotics should be used in patients with bronchiolitis only when specific evidence of coexistent bacterial infection is present. Such coinfections are uncommon, so antibiotic therapy may be justified in some children with bronchiolitis who require intubation and mechanical ventilation for respiratory failure [Shawn]. Although, latest research shows that Clarithromycin prevents human respiratory syncytial virus-induced airway epithelial responses by modulating activation of interferon regulatory factor-3 and significant reduction in RSV-mediated IL-8, CCL5, IFN-β and -λ production [43].

Oxygen
Oxygen should be administered in hypoxic infants with bronchiolitis, and administered via nasal cannulae or a face mask [26]. However, there is no consensus on what level of oxygen saturation (SpO2) oxygen support should be aiming at, and no randomized controlled trials have compared alternative oxygen supplementation regimes. In the UK, oxygen is commonly given to achieve a SpO2 of 92-95%, while the AAP recommends a limit of SpO2 of 90% in otherwise healthy children [6, 34]. The AAP

guidelines also recommend a reduced level of monitoring as the infants improve [34].

Nutrition
Oral feeding may be sustained in milder cases, if needed by small volume frequent feed, and breastfeeding should be encouraged. Through GT feeding, infants may achieve a better nutritional status and nitrogen balance, which may be beneficial for recovery, and may be a route for giving expressed breast milk [29]. Feeding by GT may be given as boluses, or continuously in case of major respiratory distress [26]. Currently there is not sufficient evidence for or against the use of GT feeding in infants with bronchiolitis and in a recent large study from Australia no differences in major outcomes were found between the two methods [28]. However, feeding by GT has been increasingly adopted, and used as routine in Norway, New Zeeland and Australia [2].

Inhaled normal saline (0.9%) is commonly used for children with bronchiolitis to increase clearing of mucous, and is included as placebo in many studies evaluating the effect of bronchodilators or hypertonic saline. However, we are not aware of any randomised study comparing normal saline with no treatment, and normal saline is not suggested in current guidelines and reviews [26, 34, 39]. Consequently, no recommendations can be given.

Inhaled hypertonic saline
Because of the paucity of therapeutic options available, recent literature has focused on novel therapies, such as hypertonic saline, for the management of bronchiolitis. Since the pathology of bronchiolitis involves airway inflammation and mucus plugging, improving mucus clearance should be beneficial in resolving bronchiolitis.

Hypertonic saline shifts the flow of water into the mucus layer by osmosis, reducing submucosal edema, reducing viscosity of mucus, improving mucus clearance, and rehydrating the air surface liquid.[23]. The updated AAP guidelines support the use of hypertonic saline nebulization for infants and children hospitalized for bronchiolitis, except in the emergency department (ED). This recommendation was made based on evidence from randomized controlled trials with inconsistent findings in the ED setting. For this article, we have reviewed the current literature and the rationale behind the AAP recommendations for hypertonic saline in the management of bronchiolitis. [34].

Hypertonic saline was shown to be more effective than normal saline (NS) in improving bronchiolitis clinical scores in some studies [24,44].

In the ED setting, both saline preparations, hypertonic or normal, were effective in reducing bronchiolitis scores [15,42]. The determination by the AAP that hypertonic saline is not effective in this setting is intriguing in light of the effectiveness of both forms of saline (NS and hypertonic saline) in these trials.

In some studies noted that LOS for patients who received hypertonic saline was shorter than for those given NS [24,44], although according to other authors there was no difference between saline preparations in terms of LOS. [11, 38]. This may reflect a benefit from any saline intervention, whether hypertonic or NS, since no comparison was made to patients who were not placed on a saline preparation. A comparison to patients who were not enrolled in these studies, carried out during the same bronchiolitis season, may be helpful in delineating the role of any saline preparation in the management of addition, LOS is a difficult outcome to correlate with the efficacy of an intervention as a result of its dependence on many factors according to institutional or caregiver situations. It would be helpful to study LOS using this method in more trials. The AAP guidelines stipulate that a LOS that is expected to last for 72 hours or longer may justify the use of hypertonic saline, a determination that may be clinically challenging to make.

Prevention
Currently, passive protection against RSV is achieved successfully through injection of the humanized monoclonal anti-RSV antibody palivizumab. Palivizumab was licensed by the US Food and Drug Administration in June 1998. There are 3 clear statements of the AAP about prevention of RSV bronchiolitis: clinicians should not administer palivizumab to otherwise healthy infants with a gestational age of 29 weeks, 0 days or greater; clinicians should administer palivizumab during the first year of life to infants with hemodynamically significant heart disease or chronic lung disease of prematurity defined as preterm infants 21% oxygen for at least the first 28 days of life; clinicians should administer a maximum 5 monthly doses (15 mg/kg/ dose) of palivizumab during the RSV season to infants who qualify for palivizumab in the first year of life [34].

Hand hygiene
Secretions from infected patients can be found on beds, crib railings, tabletops, and toys. RSV, as well as many other viruses, can survive better on hard surfaces than on porous surfaces or hands. It can remain infectious on counter tops for ≥6 hours, on gowns or paper tissues for 20 to 30 minutes, and on skin for up to 20 minutes. It has been shown that RSV can be carried and spread to others on the hands of caregivers, so all people should disinfect hands before and after direct contact with patients, after contact with inanimate objects in the direct vicinity of the patient, and after removing gloves [34].

Conclusion.
Bronchiolitis is the most common reason for hospitalization during infancy, being a burden for the child and family, and bearing huge costs for the healthcare systems. Acute bronchiolitis is characterized by viral upper respiratory prodromes followed by increased respiratory effort, wheezing and diffuse bilateral crackles; the most common etiologic agent is RSV. The diagnosis of bronchiolitis is mostly clinical and usually does not require investigation. The main principles for treatment include minimal handling, maintenance of oxygen saturation, fluid balance and nutrition. Other therapeutic options are inhalations normal saline or hypertonic saline, but the evidences for their use are sparse. CPAP and heated humidified high-flow nasal cannulae are commonly used in those with respiratory failure, but more high-quality studies are needed to prove their efficacy. Very few children may be in need of mechanical ventilation.

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SUMMARY

ACUTE VIRAL BRONCHIOLITIS IN INFANTS (REVIEW)

[1]Chkhaidze I., [2]Zirakishvili D.

[1]Tbilisi State Medical University; [2]M. Iashvili Central Children Hospital, Tbilisi, Georgia

Bronchiolitis is a common condition in children less than 2 years of age and is a leading cause of infant hospitalization. Acute bronchiolitis is characterized by acute wheezing in infants or children and is associated with signs or symptoms of respiratory infection; the most common etiologic agent is respiratory syncytial virus. There is a lack of consensus regarding the clinical definition of acute viral bronchiolitis in children and hence the management varies across the globe. Usually it does not require investigation, treatment is merely supportive and a conservative approach seems adequate in the majority of children, especially for the youngest ones. Managing bronchiolitis, both in the outpatient and inpatient setting remains a challenge to the treating pediatrician. Several recent evidence-based reviews have suggested that bronchodilators or corticosteroids lack efficacy in bronchiolitis and should not be routinely used. The cornerstones of the management of viral bronchiolitis are the administration of oxygen and appropriate fluid therapy, and overall a “minimal handling approach” is recommended. Inhaled adrenaline is commonly used in some countries, but the evidences are sparse. Recently, inhalation with hypertonic saline has been suggested as an optional treatment. When medical treatment fails to stabilize the infants, non-invasive and invasive ventilation may be necessary to prevent respiratory failure. The key to reducing the morbidity and mortality in children with RSV bronchiolitis is through prevention of infection through immunoprophylaxis especially in high-risk children. This review focuses on the epidemiological, clinical, radiographic, and pathologic characteristics, as well as the recent advances in management of acute bronchiolitis.

Keywords: bronchiolitis, infants, respiratory syncytial virus infection, inhalation therapy, corticosteroids.

РЕЗЮМЕ

ОСТРЫЙ ВИРУСНЫЙ БРОНХИОЛИТ У ДЕТЕЙ РАННЕГО ВОЗРАСТА (ОБЗОР)

[1]Чхаидзе И.Г., [2]Зиракишвили Д.А.

[1]Тбилисский государственный медицинский уноверситет, [2]Центральная детская больница им. М. Иашвили, Тбилиси, Грузия

Целью обзора являлся анализ текущей и ретроспективной научной медицинской литературы по вопросу распространения, патогенеза, патофиизологии, клинической манифестации и лечения острого вирусного бронхиолита. Бронхиолит является распространенным заболеванием детей младше 2 лет и ведущей причиной детской госпитализации. Острый бронхиолит характеризуется свистящим дыханием у младенцев или детей и ассоциируется с признаками или симптомами респираторной инфекции. Наиболее распространенным этиологическим агентом является респираторно-синцитиальный вирус. По сей день не существует консенсуса касательно клинического определения острого вирусного бронхиолита у детей и, следовательно, ведение больных в разных странах отличается. Бронхиолит, обычно, не требует дополнительного диагностического исследования: лечение, в основном, поддерживающее, и в амбулаторных и стационарных условиях является проблемой для педиатра. В нескольких, основанных на новейших фактических данных, обзорах указывается, что применение бронходилататоров или кортикостероидов при лечении детей с бронхиолитом неэффективно и не должно использоваться рутинно. Краеугольным методом в ведении вирусного бронхиолита являются кислород и соответствующая инфузионная терапия, а в целом рекомендуется «подход минимального вмешательства». В некоторых странах используется ингаляционный адреналин, однако эффективность применения этого метода недостаточно обоснована. В качестве дополнительного лечения предложены ингаляции с гипертоническим раствором. В случаях, когда в результате лечения состояние младенцев не стабилизируется, для предотвращения дыхательной недостаточности целесообразно применение инвазивной или неинвазивной вентиляции. Способом снижения показателей заболеваемости и смертности детей с респираторно-синцитиальным вирусным бронхиолитом является иммунопрофилактика, особенно у детей с высоким риском. В данном обзоре представлены эпидемиологические, клинические и патологические характеристики, а также последние достижения в лечении острого бронхиолита.

რეზიუმე

მწვავე ვირუსული ბრონქიოლიტი ადრეული ასაკის ბავშვებში (მიმოხილვა)

[1]ი. ჩხაიძე, [2]დ. ზირაქიშვილი

[1]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, [2]მ. იაშვილის სახ. ბავშვთა ცენტრალური საავადმყოფო, თბილისი, საქართველო

კვლევის მიზანს წარმოადგენდა მიმდინარე და რეტროსპექტული სამეცნიერო სამედიცინო ლიტერატურის მიმოხილვა მწვავე ვირუსული ბრონქიოლიტის გავრცელების, პათოგენეზის, პათოფიზიოლოგიის, მისი კლინიკურ მანიფესტაციისა და მკურანლობის საკითხებზე.

ბრონქიოლიტი 2 წლამდე ასაკის ბავშვებში გავრცელებულ კლინიკურ მდგომარეობას და ჰოსპიტალიზაციის ერთ-ერთ ხშირ მიზეზს წარმოადგენს. მწვავე ბრონქიოლიტს ახასიათებს მსტვინავი სუნთქვა და რესპირაციული სისტემის დაზიანების სხვა ნიშნები. მისი ყველაზე გავრცელებული გამომწვევია რესპირაციულ-სინციტიური ვირუსი. მწვავე ვირუსული ბრონქიოლიტის კლინიკურ განმარტებასთან დაკავშირებით კონსესუნსი არ არსებობს და, შესაბამისად, ბრონქიოლიტის მართვაც სხვადასხვა ქვეყანაში განსხვავებულია. ბრონქიოლიტის დიაგნოსტიკისათვის დამატებითი კვლევები,როგორც წესი,აუცილებელი არ არის,მისი მკურნალობა,ძირითადად,დამხმარე თერაპიაა, რაც სრულიად საკმარისია პაციენტთა უმრავლესობისთვის, თუმცა, ბრონქიოლიტის ყველა შემთხვევის მართვა როგორც ამბულატორიულ,ისე სტაციონარულ დონეზე ჯერ კიდევ გამოწვევად რჩება პედიატრებისთვის. ბოლო წლებში ჩატარებული მტკიცებულებებზე დაფუძნებული რამდენიმე კვლევა მიუთითებს, რომ ბრონქოდილატატორები და კორტიკოსტეროიდები არ უნდა იყოს გამოყენებული რუტინულად ბრონქიოლიტის მართვისთვის. ბრონქიოლიტის მკურნალობის ქვაკუთხედია ჟანგბადის და სითხეების დამატებითი მიწოდება. ზოგადად, რეკომენდებულია “მინიმალური ჩარევის” მიდგომა. რამდენიმე ქვეყანაში გამოიყენება საინჰალაციო ადრენალინი, თუმცა, მისი ეფექტურობის დამადასტურებელი მტკიცებულებები მცირეა. ბოლო პერიოდში მოწოდებულია ჰიპერტონული ხსნარით ინჰალაცია. როდესაც მკურნალობის შედეგად მდგომარეობის სტრაბილიზირება ვერ მიიღწევა, სუნთქვის უკმარისობის განვითარების თავიდან აცილების მიზნით, შესაძლოა საჭიროა გახდეს ფილტვების ინვაზიური ან არაინვაზიური ვენტილაცია. რესპირაციულ-სინციტიური ვირუსით გამოწვეული მწვავე ბრონქიოლიტის ავადობის და ლეტალობის შემცირების საშუალებას წარმოადგენს იმუნოპროფილაქტიკა, განსაკუთრებით - მაღალი რისკის ჯგუფის ბავშვებში. მიმოხილვა ფოკუსირებულია მწვავე ბრონქიოლიტის ეპიდემიოლოგიურ, კლინიკურ და პათოგენეზურ თავისებურებებზე, ასევე, განიხილავს ბრონქიოლიტის მართვის უახლეს რეკომენდაციებს.

IMPACT OF INTERNET GAMBLING ON MENTAL AND PSYCHOLOGICAL HEALTH OF CHILDREN OF VARIOUS AGES

Khundadze M., Geladze N., Kapanadze N.

Tbilisi State Medical University, Department of Child Neurology, Georgia

Internet gambling is an urge to gamble continuously despite negative consequences or a desire to stop. The problem with internet gambling is often defined by harm experienced by the gambler or others, rather than by the gambler's behavior. If the gambler meets certain criteria, the severe dependence on internet gambling is diagnosed as clinical pathological gambling.

Pathological gambling is a common disorder that is associated with both social and family costs [4].

Clinicians apply DSM-5 provisional criteria for Internet gambling disorders as mild, moderate and severe. This classification is based on time-spent gaming and how much this compromises overall functioning [5,6].

The clinicians can diagnose individuals with Internet gambling if they indicate at least four of the following symptoms in a 12-month period:
1. Need to gamble with increased amounts of money in order to achieve the desired excitement.
2. Is restless or irritable when attempting to cut down or stop gambling.
3 Made repeated unsuccessful efforts to control, cut back or stop gambling.
4. Is often preoccupied with gambling.
5. Often gambles when feels distressed (e.g helpless, guilty, anxious, depressed).
6. Was jeopardized or lost a significant relationship, education or career opportunity because of gambling.

Children and teenagers tend to use Internet gambling as a medium to socialize. Although pathological Internet gambling, spending ever-increasing amounts of time in online activities can cause such problems as social withdrawal, self-neglect, poor diet and various family problems. The consequences of Internet gambling are dramatic. They often become apparent after months of Internet gaming and eventually engulf all aspects of the child's life [1,8].

Above all the European Parliament should now have an opinion about the number of hours that young children are spending in front of the screen and in particular the age at which they start. The European goal should be to reduce children's daily dose to fewer hours per day by raising awareness of parents [9].

Eighty percent of adult brain size growth occurs during a child's first 3 years when they are most vulnerable to the effects of screen media. There should be an early years buffer zone whereby this stage of child development is "cordoned off" from premature exposure to screen media. Parents should delay/minimize screen watching until age 3. Parents should have no screens in children's bedrooms. Ideal screen time limits are 3-7 years: 0.5-1 hour per day; 7-12 years: 1 hour per day. 12-15 years: 1.5 hours per day; 16 years and more: 2 hours per day [10].

Brain imaging studies showed that internet gaming affectes brain regions responsible for reward, impulse control and sensory-motor coordination. Brain activation studies revealed as well that video-game playing involves changes in reward and loss of control and that gaming pictures activates regions similarly to those activated by cue-exposure to drugs. Structural studies indicated alterations in the volume of the ventral striatum possible as result of changes in reward. Furthermore, videogame addicted individuals associated with dopamine release similar in magnitude to those of drugs of abuse with faulty inhibitory control and reward mechanisms. Finally, treatment studies using functional MRI showed reduction in craving for videogames and reduced associated brain activity.

Early childhood television exposure is severely associated with academic, psychosocial and physical well being by middle childhood. The researchers concluded: the study expected the impact of early TV viewing to disappear after seven and a half years of childhood. However, the findings indicate that severe negative outcomes remain after the years.

Precisely, they found that "every additional hour of TV exposure per day among toddlers correspond to a future decrease in classroom engagement and success at math, increased victimization by classmates, a more sedentary lifestyle, higher consumption of junk food and ultimately higher body mass index [3]. Between ages of two and four even incremental exposure to television delayed development.

Thus the aim of this study was to assess the impact of internet gambling on children's mental and phycological health and find correlation between the age, duration of internet use and type of comorbidity associated with internet gambling.

Material and methods. The study assessed 50 patients with internet gambling (35 boys, 15 girls) from 2013 -2016 years. The age range was 3-15 years. 15 patients were from 3-7 y of age, 20 patients from 7-12 y of age and 15 patients from 12-15 y of age. The duration of internet gambling was assessed according to ideal screen time limits scale. All patients underwent detailed neurological and neuropsychological examination and assessment of IQ by Raven's scale. The study also assessed the patients' anamnesis. Among them 10 patients were preterm (born at 32-34 gestational age), 7 were born with perinatal hypoxia, 2 with asphyxia.

In case of 4 patients the study found various degree of psychomotor delay. Among them the most patients' mothers were employed with 80%, 3-6 years old children went to kindergarten with 40%, and others were under supervision of nurses with 20%. Screen dependency in children related with computer or mobile device, and with TV shows with 85% and 15%, respectively. The study excluded all patients with mental retardation and language impairment. The main problem occurring in these children were insomnia, language delay, stuttering, behavioral disturbances, aggressive behavior phobias. These complaints correlated with age of patients.

Results and their discussion. According to our results the group of patients from 3-7 years of age exhibited sleep disturbances such as insomnia (10 cases) and language impairment (5 cases), mainly presented with stuttering (Fig. 1).

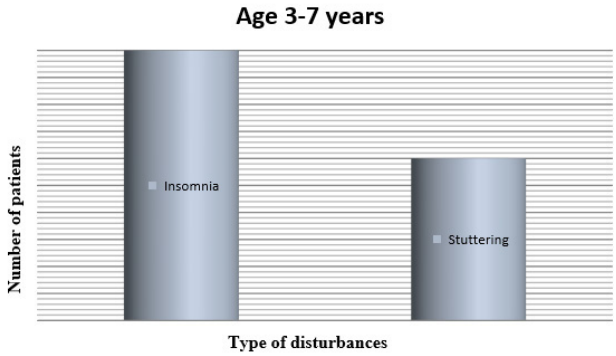

Fig. 1. The consequences of Internet gambling in children 3-7 years of age

The complaints occurring in children from 7-12 years of age are: tics-3; insomnia-3, phobias-3, emotional disturbances-4, daily fatigues-5, attention-deficit-7. Some patients reported multiple disorders (Fig. 2).

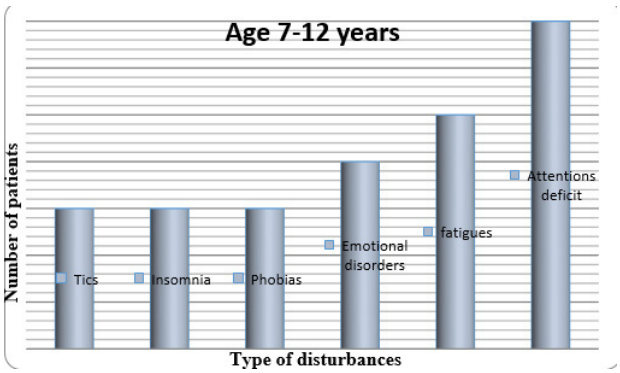

Fig. 2. Consequences of internet gambling in children 7-12 years of age

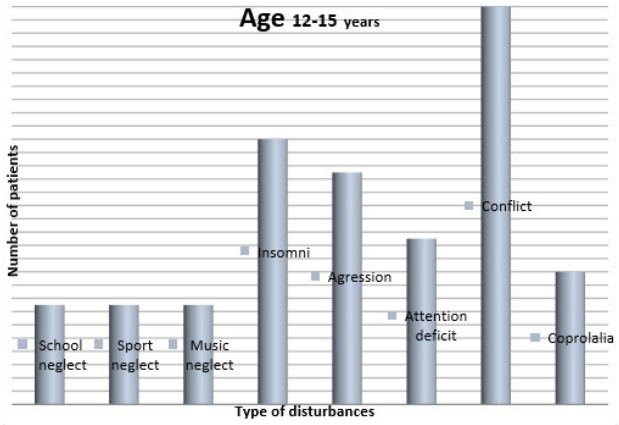

Fig. 3. Consequences of internet gambling in children 12-15 y of age

The group of children aged 12-15 years mainly revealed the following: poor academic performance (school neglect) -3, refuse to

play sport games (sport neglect)-3, refuse to play music (music neglect)-3, insomnia- 8, aggressive behavior - 7, attention deficit-5, conflict with parents-12, coprlolalia (4 cases). Here, as well, some patients reported multiple disorders (Fig. 3).

We assessed 50 patients with internet gambling (35 boys, 15 girls). The core problem common for all patients were internet overuse for computer games, mobile device and other gadgets. The main problem occurring in these children were insomnia, language delay, stuttering, behavioral disturbances, aggressive behavior phobias. These complaints were ranged with age of patients. The group of patients from 3-7 years of age exhibited sleep disturbances and language impairment, mainly presented with stuttering. The complaints occurring in children from 7-12 y of age are: tics, insomnia, phobias, emotional disturbances, daily fatigue, and attention-deficit. The group of children aged 12-15 years mainly revealed poor academic performance, refuse to play sport games, refuse to play music, insomnia, aggressive behavior, attention deficit, conflict with parents, coprolalia.

As study presented children with internet gambling reportedly become physically aggressive when parents try to remove them from the computer. In case if parents change environment children become less aggressive and they abandoned internet overuse. Therefore the internet gambling is called playing abuse. Those children live in their own "virtual" space far from reality. Late night use of the Internet can cause sleep deprivation and fatigue, which can adversely affect work performance and can result in reversed sleep pattern and job loss [7]. Internet gambling is also commonly associated with depression, anger problems and anxiety disorders.

In the long term, internet gambling can cause serious health problems. Repetitive strain injury and back ache are common complaints. There were reports from Korea and China that internet gambling users collapsing and dying following several days of uninterrupted online video game playing [2]. A sedentary life-style can increase risk of deep vein thrombosis and pulmonary embolus, eventually leading to obesity and associated complications. Treatment of internet gambling is mainly psychological. There is no standardized treatment for internet gambling. Treatment is based on family therapy, social skills training and addiction counseling. During treatment programmes, patients abstain from using computers; however, because they are so readily accessible, relapse rates are thought to be high. Some clinics also provide educational resources. These include: educational outreach programmes for schools, hospitals and universities; on-site workshops; accredited online home study courses; and an e-booklet guide to assessment and treatment of internet gambling. There is no formal training for psychiatrists yet in its assessment and treatment. Main priority is given to family therapy, as well as Young's behavioral strategies is effective as a treatment plan. Young's behavioral strategies include: Practicing the opposite – identifying the patients pattern of Internet use and doing neutral activities during that time; External stoppers – use of external prompts, for example, an alarm clock to remind them when it is time to stop. Setting clear goals-reminder cards – negative consequence of Internet use are written down on a reminder card and carried at all times. Personal inventory – make a list of hobbies [11].

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SUMMARY

IMPACT OF INTERNET GAMBLING ON MENTAL AND PSYCHOLOGICAL HEALTH OF CHILDREN OF VARIOUS AGES

Khundadze M., Geladze N., Kapanadze N.

Tbilisi State Medical University, Department of Child Neurology, Georgia

The aim of the study was to assess the impact of internet gambling on children's mental and physical health and find correlation between the age, duration of internet use and type of comorbidity associated with internet gambling. The study assessed 50 patients with internet gambling (35 boys, 15 girls) from 2013-2016 y. The age range was 3-15 years. 15 patients were from 3-7 y of age, 20 patients from 7-12 y and 15 - from 12-15 y of age. The core problem common for all patients were internet overuse by computer games, mobile device and other gadgets. The main problem occurring in these children were insomnia, language delay, stuttering, behavioral disturbances, aggressive behavior phobias. These complaints were correlated with age of patients. The group of patients from 3-7 years of age exhibited sleep disturbances and language impairment, mainly presented with stuttering. The complaints occurring in children from 7-12 y of age are: tics, insomnia, phobias, emotional disturbances, daily fatigue, and attention-deficit. The group of children aged 12-15 years mainly revealed poor academic performance, refuse to play sport games, refuse to play music, insomnia, aggressive behavior, attention deficit, conflict with parents, coprolalia. Thus internet overuse affects physical and psychological aspects of child development which has to be managed by parental and psychologist's joint effort.

Keywords: Internet gambling, insomnia, tics, stuttering, phobias, attention deficit.

РЕЗЮМЕ

ВЛИЯНИЕ ИНТЕРНЕТ-ЗАВИСИМОСТИ НА МЕНТАЛЬНУЮ И ПСИХОЛОГИЧЕСКУЮ АКТИВНОСТЬ ДЕТЕЙ РАЗЛИЧНОГО ВОЗРАСТА

Хундадзе М.С., Геладзе Н.М., Капанадзе Н.Б

Тбилисский государственный медицинский университет, департамент детской неврологии, Грузия

Целью исследования явилось изучение влияния интернет-зависимости на ментальную и психологическую активность детей в возрасте от 3 до 15 лет. Обследовано 50 детей: от 3 до 7 лет - 15 пациентов, от 7 до12 лет – 20 и от 12 до 15 лет – 15. Всех пациентов объединяло длительное нахождение за компьютером, мобильным телефоном или другими экранными играми. Исследовался неврологический и психологический статус детей. Согласно полученным данным, основные проблемы, связанные с детской интернет-зависимостью выражались в нарушении сна, речи (логоневроз) и поведения – фобии и агрессия. Причем, эти симптомы в различных возрастных группах проявлялись по-разному: в группе детей от 3 до7 лет наиболее частыми были нарушение сна и речи; от 7 до 12 лет – тики, нарушение сна и внимания, фобии, эмоциональное расстройство, утомляемость; от 12 до 15 лет – низкая академическая успеваемость, отказ от других развлечений (спортивная активность, занятие музыкой), нарушение сна и речи, дефицит внимания и агрессия по отношению к членам семьи, особенно в случае отказа или ограничения общения с экраном.

Таким образом, чрезмерное увлечение компьютером и другими экранными играми вызывают нарушения у детей, коррекция которых возможна только при совместном усилии психологов, педагогов и родителей.

რეზიუმე

ინტერნეტ-დამოკიდებულების გავლენა სხვადასხვა ასაკის ბავშვთა მენტალურ და ფსიქოლოგიურ სტატუსზე

მ. ხუნდაძე, ნ. გელაძე, ნ. კაპანაძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, ბავშვთა ნევროლოგიის დეპარტამენტი, საქართველო

კვლევის მიზანს წარმოადგენდა ინტერნეტ-დამოკიდებულების შეფასება ბავშვის მენტალურ და ფსიქიკურ აქტივობაზე. შესწავლილია 3-15 წლამდე 50 ბავშვი, 35 ვაჟი, 15 გოგონა; 15 პაციენტი იყო 3-7 წლის ასაკის, 20 პაციენტი - 7-12, 15 პაციენტი - 12-15 წლის ასაკის. გამოკვლეულია ნევროლოგიური და ფსიქოლოგიური სტატუსი. ყველა პაციენტს აერთიანებდა საათობით გატაცება კომპიუტერული თამაშებით, მობილურით და სხვა ეკრანული თამაშებით. კვლევის შედეგების მიხედვით, ძირითადი პრობლემები, რომელიც გამოვლინდა ინტერნეტ-დამოკიდებულების დროს იყო ინსომნია, მეტყველების და ქცევითი დარღვევები, ფობია, აგრესია. საყურადღებოა, რომ ასაკის მიხედვით ეს სიმპტომები სხვადასხვაგვარად ნაწილდებოდა: 3-7 წლის ასაკში უფრო ხშირი იყო ძილისა და მეტყველების დარღვევა, 7-12 წლის ასაკში - ტიკური ჰიპერკინეზი, ძილის დარღვევა, ყურადღების დეფიციტი, შიში, ემოციური ლაბილობა და დაღლილობა, ხოლო 7-15 წლის ასაკში კი პირველ პლანზე იყო შრომის უნარის დაქვეითება, სწავლასა და სპორტულ აქტივობაზე უარის თქმა, ძილისა და მეტყველების დარღვევა, ყურადღების დეფიციტი, აგრესია მშობლების მიმართ, განსაკუთრებით, ეკრანთან ურთიერთობის აკრძალვის ან შეზღუდვის შემთხვევაში. ამრიგად, ბავშვების ინტერნეტით გადაჭარბებული გატაცება იწვევს დარღვევებს, რომელთა კორექცია შესაძლებელია მხოლოდ მშობლების, პედაგოგებისა და ფსიქოლოგების ერთობლივი ძალისხმევით.

THE ROLE OF PRIMARY HEALTH CARE IN ASSESSING AND PREVENTING HEALTH RISK FACTORS OF ADOLESCENTS IN GEORGIA

Mirzikashvili N., Baramidze L.

Tbilisi State Medical University, Faculty of Public Health, Georgia

Adolescents that are 1.2 billion population aged 10 to 19 are the most healthy population group in the world. However, the research shows that there is still significant death, illness and diseases rate among this group. The main risk factors prove to be alcohol and/or tobacco use, lack of physical activity, unprotected sex and/or exposure to violence. These can significantly influence not only their current health condition, but more often their health in the later periods of their life According to WHO: "promoting healthy practices during adolescence and taking steps to better protect young people from health risks are critical for the prevention of health problems in adulthood, and for countries' future health and social infrastructure". [15]

Adolescence is a period during which important health behaviors are set and it is critical to ensure that adolescents adopt healthy behaviors. 70% of preventable adult deaths are linked to risk behaviors that start in adolescence. [12] Therefore the health of future adult population will depend, to large extent, on whether or not adolescent avoid alcohol consumption, avoid tobacco smoking and take up healthy diets with appropriate physical activity.

[11] The survival, health and well-being of adolescents as well as women, and children are essential to achieving the Sustainable Development Goals.

According to National Statistics Office of Georgia there is 426 100 adolescents in Georgia 10-19 years old in 2016. In the recent decade there is a significant decline of the share of the adolescent population in the overall population in Georgia. [8] There is no routine collection of the data on adolescents apart from specific international and local studies, which focus on different aspects and does not provide overall picture of the adolescents' health.

The goal of this study was to evaluate health risk factors, specifically tobacco use and alcohol consumption among adolescents and primary health care role in health promotions activities.

Material and methods: The quantitative survey was conducted among 1000 adolescents interviewed across Georgia using a standard questionnaire. Questionnaires were administered in the schools, universities and in the streets between March-May 2014 and September- October 2014 in the vast majority of cases. The target group was adolescents aged 11-19 years. The survey sampling methodology was multi-stage probability sampling using the following stages: cluster sampling by selected region; simple random sampling. Response rate was more than 80%.

All information was analyzed in SPSS v21. The study was approved by the medical ethics committee of National Center for Disease Control and Public Health of Georgia. All participating in-school young people provided informed consent.

Results and their discussion. To the question "how many of your friends or acquaintances smoke cigarette?" 6.3% (n=50) of respondents answered that all of the friends and acquaintances do smoke cigarette, 30.7%(n=245) indicated the majority, 34% (n=271) indicated the minority, and only 13.2% (n=105) indicated that none of their friends or acquaintances smoke cigarette.

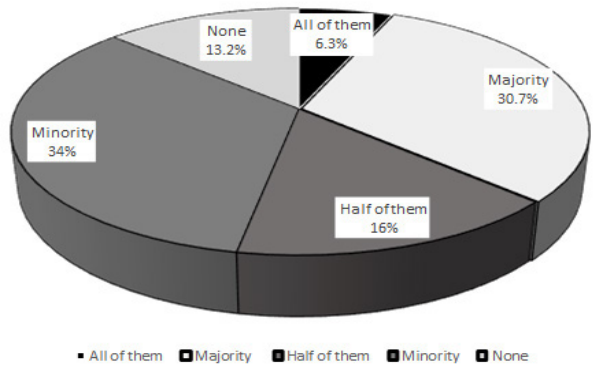

Fig. 1. How many of your friends or acquaintances smoke cigarette?

The study shows statistically significant relation between the age group and cigarette smoking among friends and acquaintances. In the higher age group of adolescents, typically aged 17-19 there is a higher rate of smoker friends and acquaintances ($\chi2$= 223.184a; df=8; P<0.05).

According to the survey one third (32.1% n=256) of respondents have tried cigarette at least once, 64.3% (n=513) of respondents have never tried. There is a clear distinction between age subgroups: only 21.2% (n=31) of adolescents between 10-13 years tired cigarette at least once, while total 39.1% (n=99) of the 17-19 years old young people have tried it. The rate of the smoker adolescents increases with the age. ($\chi2$=26.519a; df=4; P<0.05). The study also shows the relation of cigarette smoking and gender and it is proved statistically, that male respondents used to be more likely to smoke than females. ($\chi2$=15.318a; df=2; P<0.05).

As regards to alcohol consumption, the majority of interviewed adolescents (90.5% n=698) stated that they tried alcohol at least once. The 2.5% (n=19) of respondents drink alcohol without limit and the 2.7% (n=21) - drinks frequently.

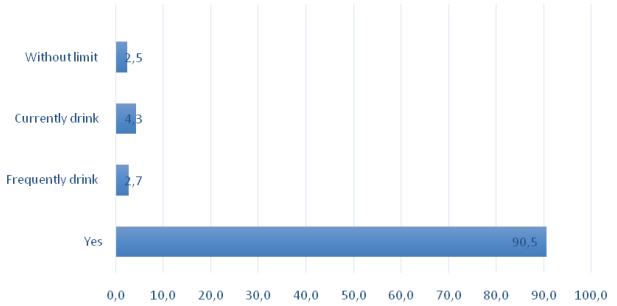

Fig. 2. Did you try alcohol?

The research reveals that this no statistically significant relation between alcohol consumption and place of residency in rural and urban areas ($\chi2$=2.976a; df=6; P=0.812). The research shows the similar situation regarding the cigarette smoking - ($\chi2$=3.122a; df=4; P=0.538). The attitude of adolescents towards alcohol is interesting: 0.8% (n=1) of 10-13 years old respondents indicate that they currently drink, while the 3.6% (n=14) among 14-16 years old respondents and the 7.1% (n=18) of 17-19 years old respondents indicate the same. There interrelation between age sub-group and alcohol consumption was statistically proved ($\chi2$=29.855a ; df=6; P<0.05).

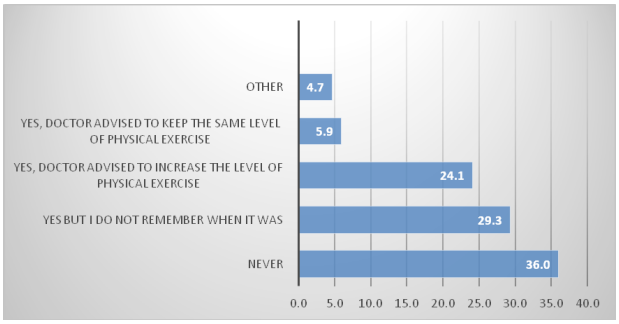

Fig. 3. Did you get any information about physical exercise?

It is ultimately important that the primary health care doctors and other health care professionals provide information and recommendations to young people about healthy life style, particularly about physical activity and healthy eating, risk factors of tobacco and alcohol consumption. To the question "Did you get any information about physical exercise? 36% (n=285) of interviewed young people declared that they have never received information from the doctor about the need of physical exercise, the 29.3% (n=232) do not remember specific cases, but they are informed about the need of physical exercise. The 24.1% (n=191) of respondents declared that doctors advised to increase the level

of physical exercise. The 5.9% (n=47) respondents indicate that doctors advised to keep the same level of physical exercise. Only 29.3% (n=232) of respondents do regular morning exercise on the daily basis. With the increase of age the adolescents are less involved in physical activities.

To the question: "If you ever had conversation with a family doctor about reproductive health and prevention of sexually transmitted infections (such as contraception, HIV/AIDS, STIs, etc.)?" The77.3% (n=611) of respondents indicated negative answer.

As regards to the advices for healthy eating habits, around one third (41.3% n=331) of respondents indicate that they have never received advice on this subject from health care professionals.

As mentioned above, adolescents are generally considered a healthier group of population, although many problems in the adulthood are rooted in inadequate treatment of problems in the period of adolescence. Teenagers are acknowledged to be at high risk of health damaging behavior including smoking, drug and alcohol use. These behaviors may result in immediate health problems such as injuries or sexually transmitted diseases, as well as increasing the risk of choric diseases such as heart diseases and cancer in later life. [14] From the public health perspective adolescence is a very important period to focus in order to educate young people and promote healthy life style. Therefore the primary health care professionals do have ultimately significant role in this process.

Non communicable diseases are in the leading position among the cases of death in Georgia as well as abroad. Chronic diseases are among the most prevalent and costly health conditions. Chronic diseases have high financial burdens on health care system and financial burdens are likely to increase in the future, because of expected increases in prescription drug costs as well as chronic disease prevalence worldwide [1]. Therefore one of the top priorities of the national healthcare policy in 2014-2020 of Georgian Government is to improve prevention and control of non-communicable diseases "including legislative and program initiative regarding main risk factors and threats to public health; the facilitation of a systematic integration of screening programmes organized at a primary health care level; actions towards raising the awareness of the population (especially in teens and the young generation); and development of standard protocols at a primary health care level and their introduction in routine practices of patient management" [2].

The results of the study are in line with international surveys that were conducted recently in Georgia. The European School Survey Project on Alcohol and Other Drugs (ESPAD) is an International Survey Project implemented in more than 35 countries. Georgia joined the Project in 2015 and became the ESPAD member Country. According to the ESPAD data lifetime-prevalence rate of cigarette smoking in Georgian students is 43%. Overall experience of smoking seems less prevalent among girls (30%) than boys (54%). 18% of students have reported that they have used cigarettes during the last 30 days.

According to ESPAD research the 21% of students had tried cigarettes at the age of 13 or younger. In Georgia prevalence of last month smoking among boys (26%) is almost three times higher than among girls (9%). Regularly smokes 12% (19% boys and 4% girls) of students. 4% of students reported that they have started to smoking on daily bases at the age of 13 or earlier. 60% of students declared that it is fairly easy or very easy to get of cigarettes if they want to do so [7].

The Global Youth Tobacco Survey was conducted in Georgia 2014. The 12.3% overall, among which 16.5% of boys and 7.8% of girls, currently used some kind of tobacco products. The 10.0% overall, among which 13.9% of boys, and 5.7% of girls currently smoked tobacco. The 7.0% overall, among which 9.9% of boys, and 3.8% of girls currently smoked cigarettes [16]. In 2014 it was conducted another survey "Attitude of Georgian citizens towards smoking and tobacco control policy" and 18-29 young people were interviewed. 30% of respondents say that they currently smoke tobacco. It should be mentioned that most smokers begin smoking during their teens. A person who smokes cigarettes in adolescence is more likely to progress to daily smoking and become addicted than someone who experiments with cigarettes in adulthood. Dependence on alcohol and tobacco also is correlated: people who are dependent on alcohol are three times more likely than those in the general population to be smokers, and people who are dependent on tobacco are four times more likely than the general population to be dependent on alcohol [6].

The research shows that many *adolescents start* to drink at very young *ages* and many of them experience negative consequences. Underage drinking is a leading public health problem in many countries. As children move from adolescence to young adulthood, they encounter dramatic physical, emotional, and lifestyle changes. Developmental transitions, such as puberty and increasing independence, have been associated with alcohol use. So in a sense, just being an adolescent may be a key risk factor not only for starting to drink but also for drinking dangerously [10].

Nowadays in Georgia the tobacco and alcohol products are easily accessible. According to the ESPAD-2015 in Georgia there are 85% of students (86% of boys and 83% of girls) have reported that they have drunk alcohol at least once during their lifetime. Most of those who have tried alcohol at least once have used alcohol for 40 or more occasions – 22%; boys (31%) had almost three times higher consumption levels than girls (12%). Wine is the most common early alcoholic beverage and 64% of students reported that they had drunk at least one glass of wine at the age of 13 or younger. 43% of students have reported alcohol use during the 30 days immediately prior to the survey [7].

According to the National Youth Survey 21.6 per cent of 15- to 29-year-old people in Georgia claim that they are regular smokers, and the majority of this group is men. A total 39.6 per cent of men surveyed stated that they smoke on a regular basis, while only 4.1 per cent of women stated that they smoke regularly. Among young people aged 15-29 in Georgia, the average age at which they start to smoke is 17.Young people in Georgia smoke an average of 18 cigarettes a day. The proportion who said they had drunk alcoholic beverages over the past 12 months was 63.4 per cent, while 66.8 per cent drank alcoholic beverages once a month or less [13].

The Government of *Georgia* has approved Tobacco Control State Strategy *(Decree #196; 30 July, 2013*) and Action Plan. The following activities have been implemented within the State Tobacco Control Action Plan: (1) increase of tobacco excise tax (September 1, 2013, January 1 2015) and introduction of ad valorem component (July 1, 2015); (2) Approval of State Health

Promotion Program "Civil Movement for Healthy Georgia"; (3) Training of PHC doctors in smoking cessation brief intervention; (4) PSA campaign; [4] In addition to abovementioned, there is a health promotion state program implemented by the National Center for Disease Control and Public Health. The purpose of health promotion program is to positively influence the health behavior of individuals and communities as well as the living and working conditions that influence their health [3].

Nevertheless, it can be concluded that at this stage the *government* attempts could not achieve significant reduction of adolescent smokers and alcohol consumption. The investment in the primary health care should be emphasized to facilitate reduction of the number of teenage smokers and level of alcohol consumption among adolescents.

The National Center for Disease Control and Public Health elaborated "Alcohol Abuse Reduction Strategy 2015". The Strategy describes epidemiological situation in Georgia regarding alcohol consumption, including teenagers and provides recommendations that are in line with those of the Council of Europe, WHO and other international organization. The National Strategy is focused on the main interventions: policy, legislative, increasing public awareness, limiting access to alcohol, alcohol price regulation, etc. [9]. In spite of Government efforts the situation remains grave. There is a need of multi-sectoral integrated approach and increased coordination between different government agencies and international and national programs.

In line with the WHO recommendations, The Ministry of Labour, Health and Social Affairs of Georgia adopted the guideline on "The *key principle* of the child health screening and surveillance" in 2009. Guideline is a comprehensive set of recommendations that provides a framework and content of preventive health services for pediatricians and family medicine doctors.

According to the Guideline adolescents are encouraged to visit pediatricians/family medicine doctors annually between 13-16 years. During such visits doctor should gather clinical information, full examination, developmental assessment, special questionnaire for parents to evaluate child development. These visits should also include the consultation about tobacco, alcohol and drug addiction and explanations on their potential health risks. [5]

Primary health care doctors can play a key part in teaching young people about alcohol and drug use by talking honestly and openly about the effects that alcohol, tobacco and drugs can have on their health, schoolwork, and relationships. Annual visits offer the opportunity to reinforce health promotion messages for both adolescents and their parents, identify adolescents who have initiated health risk behaviors or who are at early stages of physical or emotional disorders, provide immunizations, and develop relationships with the adolescents that will foster an open disclosure of future health information.

Despite the Guidelines, the study reveals that adolescents in Georgia do not receive sufficient information on health risk factors, as recommended by local and international guidelines. The role of primary health care is very limited in this process. According to survey results primary health care professionals do rarely talk with young people about healthy life style, health promotion issues, that's why the rate of teenagers who smoke cigarette and drink alcohol is high compare with European countries.

Conclusion. The survey indicates that more than one third of respondents smoke tobacco and more than 90% tried alcohol at least once. These results prove the outcomes of other international surveys' conducted recently in Georgia.

The increased government efforts should be acknowledges, although the insufficient implementation of the international and national guidelines should also be mentioned. There is a strong need for strengthening government efforts in primary health care particularly with preventive health care and public awareness measures. It is essential that health promotion objectives are integrated into primary health care strategies. Multi-sectoral and integrated approach involving different government agencies is needed to improve the adolescent health and thus to strengthen and contribute to healthy population in the country over the years to come.

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SUMMARY

THE ROLE OF PRIMARY HEALTH CARE IN ASSESSING AND PREVENTING HEALTH RISK FACTORS OF ADOLESCENTS IN GEORGIA

Mirzikashvili N., Baramidze L.

Tbilisi State Medical University, Faculty of Public Health, Georgia

The goal of this study was to evaluate health risk factors, specifically tobacco use and alcohol consumption among adolescents and primary health care role in health promotions activities.

The quantitative survey was conducted among 11-19 years old adolescents. Overall, 1000 young people were interviewed across Georgia using a standard questionnaire in 2014. The survey sampling methodology was multi-stage probability sampling. All information was analyzed in SPSS 21 version. According to survey results 32.1% (n=256) respondents consume tobacco; 90.5% (n=698) tried alcohol at least once. The 2.5% (n=19) of respondents drink alcohol without limit and the 2.7% (n=21) - drinks frequently.

According to survey results, primary health care professionals do rarely talk with young people about healthy life style. It is very essential to implement health promotion topics at primary health care level. There is a need to adopt effective measures, including launching an information campaign focusing on adolescents' awareness that tobacco use and alcohol consumption are harmful to health. There is a need of multi-sectoral integrated approach and increased coordination between different government agencies and international and national programs to improve the adolescent health.

Keywords: health risk factors, tobacco use, alcohol consumption.

РЕЗЮМЕ

ПРЕВЕНЦИЯ РИСК-ФАКТОРОВ ЗДОРОВЬЯ СРЕДИ ПОДРОСТКОВ ГРУЗИИ

Мирзикашвили Н.Г., Барамидзе Л.Г.

Тбилисский государственный медицинский университет, департамент общественного здравоохранения, Грузия

Цель исследования – изучение потребления алкоголя и табачных изделий подростками в Грузии и разработка превентивных мероприятий.

В 2014 г. проведено исследование среди проживающих в Грузии 1000 подростков в возрасте от 11-19 лет. Выбор респондентов осуществлен методом многоступенчатой вероятности.

Полученные данные обработаны с использованием программы SPSS v21. В результате проведенных исследований выявлено, что из 1000 подростков 256 (32.1%) употребляют табачные изделия хотя бы раз, 64.3% (n=513) никогда не курили. Что касается потребления алкоголя, из 1000 подростков 698 (90,5%) хотя бы раз употребляли алкогольные напитки; 19 (2,5%) респондентов постоянно потребляют, 21 (2.7%) – часто.

Делается вывод о необходимости многосекторального интеграционного подхода и совершенствования координации между различными правительственными учреждениями национальными и международными программами с целью повышения уровня осведомленности подростков о вреде для здоровья курения и потребления спиртных напитков. Обращается внимание на необходимость контроля за выполнения принятых законов о контроле потребления табака и алкоголя. На основании вышеизложенного разработаны рекомендации по профилактике вредных привычек серди молодежи.

რეზიუმე

ჯანმრთელობის რისკ-ფაქტორების პრევენცია საქართველოს მოზარდახალგაზრდებში

ნ. მირზიკაშვილი, ლ. ბარამიძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საზოგადოებრივი ჯანდაცვის დეპარატმენტი, საქართველო

კვლევის მიზანს წარმოადგენს საქართველოში მოზარდთა ჯანმრთელობის რისკ- ფაქტორების შესწავლა, კერძოდ ალოკოჰოლის და თამბაქოს მოხმარება მოზარდ პოპულაციაში და კვლევის შედეგებზე დაყრდნობით რეკომენდაციების შემუშავება.

2014 წელს ჩატარდა რაოდენობრივი კვლევა 11-19 წლის 1000 მოზარდს შორის მთელი საქართველოს მაშტაბით. რესპოდენტების შერჩევა განხორციელდა მრავალსაფეხურიანი ალბათური შერჩევის მეთოდიოთ. მიღებული მონაცემები დამუშავდა SPSS 21 ვერსიაში.

ჩატარებული კვლევის შედეგების თანახმად,ახალგაზრდების 32.1% (n=256) მოიხმარს თამბაქოს და 90.5% (n=698) ერთხელ მაინც გასინჯული აქვს ალკოჰოლი. ხაზგასასმელია რომ, აღნიშნული კვლევის შედეგები თანხვედრაშია ბოლო დროს ჩატარებული საერთაშორისო კვლევის შედეგებთან. კვლევის შედეგებიდან გამოდინარე შემუშავდა რეკომენდაციები, რომელიც მოიცავს ახალგაზრდებში ცნობიერების ამაღლებას რისკ-ფაქტორების მავნე ზემოქმედების შესახებ,პირველადი ჯანდაცვის დონეზე ოჯახის ექიმების აქტიურ მუშაობას ახალგაზრდებთან ჯანმრთელობის ხელშეწყობის საკითხებზე და თამბაქოს და ალკოჰოლის კონტროლის კანონმდებლობის აღსრულებას ტექნიკური და საკანონმდებლო ბაზის განვითარების მეშვებობით.

NEW METHOD OF TREATMENT OF PYOINFLAMMATORY SOFT TISSUE COMPLICATIONS IN PATIENTS WITH DIABETES MELLITUS

Karatieieva S., Plesh I., Yurkiv O., Semenenko S., Kozlovskaya I.

Higher State Educational Institution of Ukraine "Bukovinian State Medical University:, Chernivtsi, Ukraine

Diabetes mellitus (DM) is a chronic, progressive disease characterized by hyperglycemia induced by impaired insulin secretion, action or both. Regardless of the type of diabetes, it puts patient at high risk of tissue, organ and vessel damage. Unfortunately the mechanisms of these damages are still not clear [1,2,5,10]. Hyperglycemia induced pyoinflammatory processes of soft tissues occur in 40% of patients with diabetes and mortality rate remains high – 10-15%. Cellular and humoral immunity impairments lead to rapid spread of pathogens, nevertheless local signs of inflammation is not present for a long period. Because of this certain peculiarity of the disorder it becomes hard to diagnose and begin treatment of the disease at an early stage [3,4,8].

The leading factors in formation and progression of pyoinflammatory complications of soft tissues in patients with diabetes mellitus include: blood clots, vessel wall damage, changes in blood hemorheological properties, impairment of lipid peroxidation (LPO), antioxidant protection (AOP) and the oxidative modification of proteins (OMP) [6,7,9]. It is important to search for new methods for restoring the compensatory-adaptive processes, able to improve the course of morphogenetic processes in diabetic patients with pyoinflammatory complications of soft tissues.

Therefore the objective of our study is to evaluate the efficacy of intravenous application of ozone therapy as a treatment option for pyoinflammatory complications in patients with diabetes.

Material and methods. In total, 124 patients presenting with pyoinflamatory complications of soft tissue and concomitant diabetes mellitus were observed. Patients were divided into two groups according the treatment method. The study group consisted of 53 (42,7%) patients who received an intravenous ozone therapy application together with conservstive and surgery treatment (antibiotics, infusion therapy, antiplatelet agents, antispasmodics, vitamins, insulin and other). The control group consisted of 71 (57,2%) patients, who were treated only by conventional methods.

All patients from the study group received intravenous ozone saline into the ulnar vein through catheter in complex with conservative and surgical treatment. Treatment period was 6-15 days. Patients from control group received only conservative and surgical treatment.

Pyoinflammatory markers were evaluated 3 times during the study period: at the beginning, during and after termination of treatment. The list of markers and the way of their evaluation are given below.

The oxidative modification of proteins (OMP) and the products of lipid peroxidation (LPO) in plasma was determined by reaction of 2,4-dinitrophenylhydrazine with the formation of hydrazones of characteristic absorption spectrum. The OMP rate was estimated by the number of formed aldehyde and ketone groups. LPO was determined by reaction with thiobarbituric acid. The method is based on the reaction between malondialdehyde (MDA) and thiobarbituric acid, which at high temperature and acidic pH value proceeds with the formation of colored trimetine complex containing one molecule of malondialdehyde and two molecules of thiobarbituric acid. The maximum absorption of the complex is at 532 nm. MDA content was calculated on the basis of the molar extinction coefficient ($1,56x10^5 M^{-1}см^{-1}$). Ceruloplasmin (CP) was determined by the method, based on the oxidation of p-phenylenediamine involving ceruloplasmin. Enzymic reaction was stopped by adding sodium fluoride. The concentration of ceruloplasmin, determined by a modified Revin method, was judged upon by optical density value of the formed products. To calculate the results, the obtained optical density value was multiplied by conversion factor and in such way ceruloplasmin concentration rate (in mg/L of serum) was found. It constitutes 205,4±13,5 mg/liter of serum.

Determination of leukocyte index of intoxication (LII) was evaluated by Y.Y. Khalf-Khalif formula (1941): LII = (4Mn + 3Yn + 2Bn + Sn)(Pl + 1) / (L + Mn)(e + 1), where: LII- leukocyte index of intoxication; Mn – myelocytes number; Yn – young neutrophils number; Bn – band neutrophils number; Sn – segmented neutrophils number; Pl – plasma cells number; L – lymphocytes; Mn – monocytes number; e – eosinophils number. According to the author the normal LII value was 1,0±0,5.

Results and their discussion. In total, 124 patients with pyoinflammatory complications of soft tissues and diabetes were observed. During the treatment period patients underwent following surgical procedures: 33 (26,6%) patients underwent primary debridement; disarticulation of the toes was performed in 37 (29,8%) patients: in 11 (8,9%) cases – a big toe, in 10 (8,1%) cases – the 2nd toe, in 5 (4,0%) cases – a middle toe, in 4 (3,2%) cases – the 4th toe, in 7 (5,6%) cases – a little toe; opening and draining of abscesses of soft tissues occurred in 30 (24,2%) patients.

The study did not reveal any significant differences in neither treatment period between study and control groups according the changes in the activity of AOP factor – ceruloplasmin, LPO products – malonic aldehyde and OMP (Table 1).

Table 1. LPO, OMP and AOP rates in diabetic patients with pyoinflammatory complications (M±m)

Rates	Main group n=53			Control group n=71			
	before treatment	during treatment	after treatment	before treatment	during treatment	after treatment	p
Ceruloplasmin (E/g of plasma)	5,2±0,10	5,1±0,30	5,1±0,10	5,3±0,30	5,5±0,7	5,5±0,50	>0,05
Malonic aldehyde (mmol/l)	0,23±0,06	0,24±0,05	0,20±0,05	0,22±0,03	0,23±0,05	0,19±0,06	>0,05
OMP rate (ΔE/ml of plasma)	2,2±0,05	2,2±0,04	2,0±0,06	1,5±0,05	1,4±0,03	1,6±0,04	>0,05

These changes can be considered as favorable biochemical attributes for the application of this treatment in diabetic patients with inflammatory complications.

We evaluated the dynamic of toxicity markers - leukocyte index of intoxication (LII), hematological toxicity index (HTI) and sorption capacity of red blood cells (SCE) in both study groups.

Study showed that baseline values of LII did not differ between the groups (p>0.05). At the beginning of the treatment mean LII in study group patients was 3.6±0.3 (Figure 1). In the same group mean LII was 2.9±0.2 on the 7th day, and 1.9±0.1 on the 16th day of treatment (r≤0.01). At the beginning of the treatment mean LII in control group was 3.6±0.2, 3.7±0.2 on the 7th day and 2.7±0.1 on the 16th day of treatment (r≤0.01).

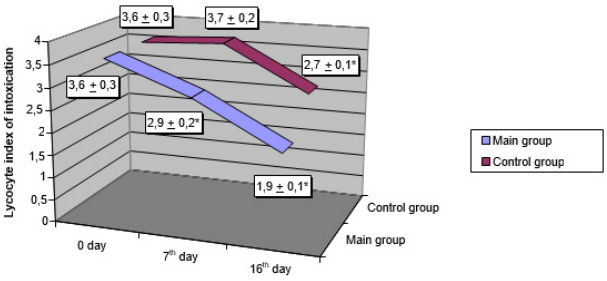

Fig. 1. LII dynamics in diabetic patients with pyoinflammatory complications of soft tissues

HTI dynamics in patients with pyoinflammatory complications and diabetes mellitus are shown in figure 2. Baseline levels of HTI did not differ between the groups (p>0.05). Mean baseline levels of HTI in the study group was 8.6±0.4 and significantly decreased on 7th and 16th days after treatment (mean value was 4.8±0.4 and 3.5±0.4, respectively; p≤0.01). The trend of mean HTI in the control group was 7.9±0.4 at baseline, slightly increased on 7th day after surgery (reaching 9.0±0.4) and decreased to 5.6±0.3 on 16th day (p≤0.001).

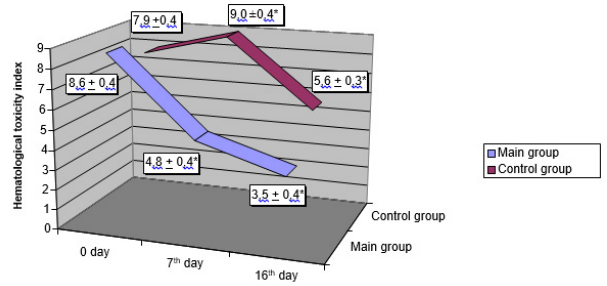

Fig. 2. HTI dynamics in patients with puyoinflammatory complications of soft tissues and diabetes mellitus

Normal values of HTI in healthy individuals is 0,620±0,068. Increasing level of HTI indicates the presence of pathological process in the body that causes development of intoxication syndrome, while decreasing levels indicate the reduction of endogenous intoxication. This index normilizes later than LII, hence it is more specific value of endogenous intoxication.

SCE dynamics in patients with pyoinflammatory complications and diabetes mellitus are shown in figure 3. In healthy individuals red blood cells absorb up to 37.1±1.43% of dye from 0,025% methylene blue solution. Mean baseline levels of SCE in study group reached 47.3±0.8%. In our study, baseline levels of SCE did not differ between the groups (p>0.05).On the 7th day and 16th days after treatment SCE decreased to 43.1±0.7% and 39.1±1.0%, respectively. Mean baseline level of SCE in the control group was 46.9±0.7%; As like LII and HTI, SCE also showed a small increase on 7th day and decreased on 16th day after surgery (mean values were 47.4±0.6% and 42.1±0.6%, respectively).

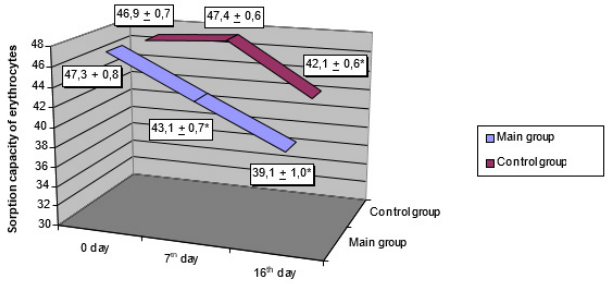

Fig. 3. SCE dynamics in patients with pyoinflammatory complications of soft tissues and diabetes mellitus

Conclusion. Our study demonstrated that implementation of ozone therapy in patients with pyoinflammatory complications and diabetes mellitus is not accompanied by negative injury responses at the level of hemostasis parameters and blood biochemical characteristics. The use of intravenous ozone therapy in complex treatment of patients with diabetes and purulent inflammation of soft tissues positively effects on the postoperative wound healing process. Therefor, ozone therapy can be used in addition to conventional therapy in patients with pyoinflammation complications of soft tissue and diabetes mellitus.

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SUMMARY

NEW METHOD OF TREATMENT OF PYOINFLAMMATORY SOFT TISSUE COMPLICATIONS IN PATIENTS WITH DIABETES MELLITUS

Karatieieva S., Plesh I., Yurkiv O., Semenenko S., Kozlovskaya I.

Higher State Educational Institution of Ukraine "Bukovinian State Medical University:, Chernivtsi, Ukraine

Our study evaluated the levels of peroxide oxidation of lipids, oxidative modification of proteins, antioxidant protection and dynamic changes in markers of toxicity in patients with diabetes mellitus and purulent-inflammatory complications. In total, 124 patients were enrolled in the study and were divided into two groups according the treatment methods. Study group consisted of 53 patients, who received intravenously ozonized saline in addition to conservative treatment. The control group consisted of 71 patients who received only conventional therapy. The study period was 6-15 days. The results showed that the use of ozone therapy is not accompanied by negative injury responses at the level of hemostasis parameters and blood biochemical characteristics. Furthermore, ozone therapy may have a favorable effect on treatment outcome in patients with purulent-inflammatory complications and daibetes mellitus.

Keywords: diabetes, pyoinflammatory complications, ozone therapy, intoxication markers.

РЕЗЮМЕ

НОВЫЙ МЕТОД ЛЕЧЕНИЯ ГНОЙНО-ВОСПАЛИТЕЛЬНЫХ ОСЛОЖНЕНИЙ МЯГКИХ ТКАНЕЙ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ

Каратеева С.Ю., Плеш И.А., Юркив О.И., Семененко С.Б., Козловская И.М.

Высшее государственное учебное заведение Украины «Буковинский государственный медицинский университет», Черновцы, Украина

Изучена динамика изменений показателей перекисного окисления липидов, окислительной модификации белков, антиоксидантной защиты и маркеров интоксикации у больных сахарным диабетом с гнойно-воспалительными осложнениями. В исследовании приняли участия 124 пациента. Пациенты с учетом метода лечения были разделены на две группы. Основную группу составили 53 пациента, которым помимо консервативного и хирургического лечения проводили внутривенное введение озонированного физиологического раствора через катетер в локтевую вену, курс лечения 6-15 дней. Контрольная группа включала 71 пациента, которые получали только традиционное лечение. Результаты исследования показали, что применение озонотерапии не сопровождается развитием реакций повреждения на уровне параметров гемостаза и биохимических показателей крови. Авторы статьи, опираясь на полученные в результате исследования данные рекомендуют применение озонотерапии в комплексном лечении больных СД с гнойно-воспалительными осложнениями.

რეზიუმე

რბილი ქსოვილების ჩირქოვან-ანთებითი გართულებების მკურნალობის ახალი მეთოდი პაციენტებში შაქრიანი დიაბეტით

ს. კარატეევა, ი. პლეში, ო. იურკოვი, ს. სემენენკო, ი. კოზლოვსკაია

უკრაინის უმაღლესი სახელმწიფო სასწავლო დაწესებულება "ბუკოვინის სახელმწიფო სამედიცინო ინუვერსიტეტი", ჩარნოვცი, უკრაინა

კვლევის მიზანს წარმოადგენდა რბილი ქსოვილების ჩირქოვან-ანთებითი გართულებების ოზონოთერაპიით მკურნალობის ეფექტურობის შეფასება შაქრის დიაბეტით ავადმყოფებში.

შესწავლილია ლიპიდებზე ზეჟანგის ზემოქმედების, ცილების მჟავითი მოდიფიკაციის და ანტიოქსიდანტური დაცვითი მაჩვენებლების და ინტოქსიკაციის მარკერები შაქრიანი დიაბეტით ავადმყოფებში ჩირქოვან-ანთებითი გართულებებით. კვლევაში მონაწილეობდა 124 პაციენტი. პაციენტები მკურნალობის მეთოდის გათვალისწინებით გაყოფილი იყო ორ ჯგუფად: ძირითადი ჯგუფი შეადგინა 53 პაციენტმა,რომლებსაც კონსერვატულ და ქირურგიულ მკურნალობასთან ერთად უტარდებოდა ოზონოთერაპია, ოზონირებული ფიზიოლოგიური ხსნარის ვენაში კათეტერის მეშვეობით შეყვანით. საკონტროლო ჯგუფი შედგებოდა 71 პაციენტისგან, რომლებსაც ჩაუტარდა მხოლოდ ტრადიციული მკურნალობა.

მკურნალობის შედეგად გამოვლინდა,რომ ოზონოთერაპიის გამოყენება არ იწვევს დაზიანებით რეაქციებს ჰემოსტაზის და სისხლის ბიოქიმიური პარამეტრების დონეზე. მიღებულ შედეგებზე დაყრდნობით ავტორებს გამოტანილი აქვთ დასკვნა, შაქრიანი დაიბეტით და თანმხლები ჩირქოვან-ანთებითი გართულებებით პაციენტებში ოზონოთერაპიის გამოყენების მიზანშეწონილობის შესახებ.

ВЛИЯНИЕ ОДНО- И МНОГОСОСУДИСТЫХ ПОРАЖЕНИЙ КОРОНАРНЫХ АРТЕРИЙ НА ТЕЧЕНИЕ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА У БОЛЬНЫХ С СОПУТСТВУЮЩИМ САХАРНЫМ ДИАБЕТОМ 2 ТИПА

Сыпало А.О., Кравчун П.Г., Кадыкова О.И.

Харьковский национальный медицинский университет, кафедра внутренней медицины №2 и клинической иммунологии и аллергологии, Украина

На сегодняшний день сахарный диабет (СД) можно сравнить с эпидемией. Численность больных СД ежегодно растет в геометрической прогрессии и по данным Международной диабетической федерации (International Diabetes Federation, IDF) к 2030 г. составит 552 млн. [7]. Пациенты с СД 2 типа составляют группу весьма высокого кардиоваскулярного риска. Ведущее место среди сердечно-сосудистой патологии в этой группе пациентов принадлежит ишемической болезни сердца (ИБС), в основе которой лежит атеросклеротическое поражение коронарных сосудов. Для лиц с СД 2 го типа характерно более раннее развитие атеросклеротического поражения коронарных артерий (КА), быстрое прогрессирование процесса, мультисегментарность поражения преимущественно дистально расположенных артерий среднего и малого калибра [2].

Сочетание ИБС и СД 2 типа характеризуется многососудистым диффузным атеросклеротическим поражением коронарного русла с привлечением дистальных отделов, сложной морфологией стенозов, слабой выраженностью коллатерального кровотока, малым диаметром артерий (менее 3 мм), частым поражением ствола левой коронарной артерии, высокой частотой рестенозирования вследствие избыточного неоинтимального ответа и нарушений эндотелиальной функции при СД 2 типа [5].

Высокая распространенность атеросклеротических изменений множественного характера у больных диабетом, прежде всего, связана с влиянием гипергликемии на развитие атерогенеза в сосудистой стенке, реализуются из-за повреждения эндотелия, контролирующего рост гладкомышечных клеток, фибринолиз, тромбообразование, пролиферацию и взрывное усиление окислительного стресса с тригерной ролью цитокинов [1].

Хроническая гипергликемия является одним из основных факторов, приводящих к поражению сосудистой стенки при СД. Она увеличивает гликозилирование и окисление белков, вовлеченных в обмен липидов, систему свертывания крови и сосудистого гемостаза. Под влиянием гипергликемии нарушается продукция матрикса эндотелиальными клетками, что приводит к утолщению базальной мембраны. Глюкозотоксическое действие вызывает уменьшение эндотелийзависимого расслабления сосудов, рост вазоконстрикции, стимуляцию гиперплазии гладкомышечных клеток и развитие атеросклероза.

Инсулинорезистентность (ИР) является независимым фактором риска атеросклеротического поражения сосудов и в большинстве случаев играет основную роль в патогенезе. Исследования японских ученых у больных с ангиографически подтвержденным атеросклерозом обнаружили существование тесной взаимосвязи между степенью резистентности к инсулину и выраженностью коронарного атеросклероза. ИР является прогностическим фактором степени выраженности кальцификации КА и, очевидно, связана с повышенным риском сердечно-сосудистых заболеваний у пациентов с СД в той же степени, как и у пациентов без диабета [9].

Целью исследования явилось определение влияния одно- и многососудистых поражений коронарных артерий на течение ишемической болезни сердца у больных с сопутствующим сахарным диабетом 2 типа.

Материал и методы. Проведено комплексное обследование 75 больных ИБС и СД 2 типа, находящихся на лечении в кардиологическом отделении Коммунального учреждения здравоохранения «Харьковской городской клинической больницы №27», которая является базовым лечебным учреждением кафедры внутренней медицины №2 и клинической иммунологии и аллергологии Харьковского национального медицинского университета Министерства здравоохранения Украины. В зависимости от количества сосудистых поражений коронарных артерий, по данным компьютерной томографии (КТ) все больные ИБС и СД 2 типа были разделены на две группы. Первую группу составили 27 больных ИБС и СД 2 типа с однососудистым поражением коронарных артерий; вторую группу - 48 больных ИБС и СД 2 типа с многососудистыми поражениями коронарных артерий. Всем больным проведена мультидетекторная (64-срезовая) КТ-ангиография коронарных артерий по договору между ООО «Гемо Медика Харьков» Европейским радиологическим центром с Харьковским национальным медицинским университетом.

Всем больным проводили общеклинические и инструментальные обследования, при поступлении в стационар проводили трехкратное измерение артериального давления по методу С.М. Короткова с использованием стандартного тонометра с манжетой соответствующего диаметра (резиновая часть не менее 2/3 длины и не менее 3/4 окружности плеча) в области передней локтевой ямки на одной и той же руке с интервалом 5-10 минут в положении пациента сидя. Уровень систолического артериального давления (САД) определяли по I фазе, а уровень диастолического артериального давления (ДАД) по V фазе тонов Короткова. За конечное (регистрируемое) принимали среднее значение измерений.

Использовали индекс инсулинорезистентности HOMA (Homeostasis model assessment), который рассчитывали по формуле: инсулин (мЕд/мл)×глюкоза натощак (ммоль/л)/22,5. Этот критерий был предложен на основании определения уровня верхнего квартиля распределения данных в исследовании NHANES III. При индексе HOMA> 2,77 пациентов считали инсулинорезистентными.

Для характеристики массы тела использовали индекс массы тела (ИМТ), который рассчитывался как отношение массы тела (кг) к росту ($м^2$). Диагноз ожирения ставили при величине ИМТ> 30,0 $кг/м^2$, при ИМТ 25,0-29,9 $кг/м^2$ состояние расценивалось как избыточная масса тела.

Определение содержания гликозилированного гемоглобина в цельной крови проводили фотометрическим методом по реакции с тиобарбитуровой кислотой с использованием коммерческой тест-системы фирмы «Реагент» (Украина) в соответствии с прилагаемой инструкцией.

Уровень глюкозы определяли глюкозооксидантным методом в капиллярной крови, забранной натощак. Нормальным считался уровень глюкозы 3,3-5,5 ммоль/л.

Концентрацию инсулина определяли иммуноферментным методом с использованием коммерческой тест-системы «INSULIN ELISA KIT» («DRG», Германия).

Содержание сортилина в сыворотке крови больных определяли иммуноферментным методом с использованием набора реактивов «Human SORT 1 ELISA Kit» (США). Исследования проводились в биохимическом отделе центральной научно-исследовательской лаборатории Харьковского национального медицинского университета МОЗ Украины.

Определение показателей липидного обмена, а именно уровня общего холестерина (ОХС) липопротеидов высокой плотности (ЛПВП), уровня триглицеридов (ТГ) проводили по стандартной биохимической методике.

Расчет коэффициента атерогенности (КАГ) проводили по формуле Климова А.М.
КАГ=(ОХС-ЛПВП)/ЛПВП;
уровень липопротеидов очень низкой плотности (ЛПОНП)=ТГ/2,2×0,45, ммоль/л;
уровень липопротеидов низкой плотности (ЛПНП)=ОХС-(ЛПОНП+ЛПВП), ммоль/л.

ЭХО КГ исследование проводили по стандартной методике (Х.Фейгенбаум, 1999) - указать лит. источник на ультразвуковом аппарате RADMIR (Ultima PRO 30, Харьков, Украина). В М-режиме определяли следующие параметры левого желудочка (ЛЖ): конечный диастолический размер (КДР, см), конечный систолический размер (КСР) (см), толщину задней стенки левого желудочка (ТЗСЛЖ, см), толщину межжелудочковой перегородки (ТМЖП, см). Конечный диастолический и систолический объемы (КДО и КСО, см^3) ЛЖ рассчитывали по методу Simpson (1991) - указать лит. источник, после чего вычисляли фракцию выброса (ФВ) ЛЖ (%). Массу миокарда ЛЖ (ММЛЖ) вычисляли по формуле R. Devereux и соавт. (1986): - указать лит. источник

1,04х[(ТМЖП+ТЗСЛЖ+КДР)3] – [КДР]3 – 13,6

Также определяли размер левого предсердия (ЛП, см и аорты, см). Диастолическая функция ЛЖ исследовалась путем регистрации доплеровского трансмитрального диастолического потока. Определяли максимальные скорости раннего (Е, см/с) и позднего (А, см/с) наполнения ЛЖ, их соотношение (Е/А, от), время изоволюметрического расслабления ЛЖ (iVRT, мс). Структуру диастолического наполнения ЛЖ классифицировали согласно традиционным критериям (М.Н. Алехин, В.П. Седов, 1996) - указать лит. источник. Псевдонормальный тип трансмитрального диастолического потока идентифицировали с помощью пробы Вальсальвы.

Полученные результаты представлены в виде среднего значения ± стандартное отклонение от среднего значения (M±SD). Статистическую обработку данных осуществляли с помощью пакета Statistica, версия 6,0. Оценку различий между группами при распределении, близком к нормальному, проводили с помощью критерия Пирсона. Статистически достоверными считали различия при $p<0,05$.

Результаты и их обсуждение. В ходе исследования достоверных различий между возрастом, уровнем систолического артериального давления (САД), частотой сердечных сокращений (ЧСС) и пульсом у больных обеих групп с ИБС и СД 2 типа с одно- и многососудистым поражением не обнаружено ($p>0,05$). Так, средний возраст у больных первой группы составил 70,60±11,10 лет, второй - 69,08±9,07 лет, уровень САД в первой группе составил - 142,00±17,89 мм рт.ст., второй - 150,21±22,86 мм рт.ст., ЧСС в первой подгруппе - 88,00±25,98 уд/мин., во второй группе - 88,54±13,56 уд / мин., пульс у больных первой подгруппы составил 88,54±13,56 уд/мин., а у больных второй подгруппы - 77,88±11,99 уд/мин ($p>0,05$, таблица.)

Изучение показателей углеводного обмена, в частности, определение гликозилированного гемоглобина, глюкозы натощак, ИМТ достоверных различий не выявило ($p>0,05$). У больных ИБС и СД 2 типа с односсудистым поражением КА ИМТ составил 31,96±4,23 кг/м^2, уровень гликозилированного гемоглобина - 10,70±1,42 мкмоль фруктозы/гНb, уровень глюкозы натощак - 5,8±1,61 ммоль/л. В группе больных ИБС и СД 2 типа с многососудистым поражением КА эти показатели существенно не отличались: ИМТ=29,95±4,66 кг/м^2, уровень гликозилированного гемоглобина = 10,86±1,84 мкмоль фруктозы/гНb, уровень глюкозы натощак - 6,99±2,38 ммоль/л, $p>0,05$.

Изучение индекса HOMA определено достоверное его повышение у больных ИБС и СД 2 типа с многососудистым поражением КА - 5,43±2,72 в сравнении с показателем больных ИБС и СД 2 типа с односсудистым поражением КА 3,72±1,03 ($p<0,05$). ИР приводит к более выразительному и множественному поражению КА. Подтверждение этого факта представлено в работе японских ученых во главе с Schauer I.E. [9], в которой выявлено наличие тесной взаимосвязи между степенью резистентности к инсулину и степенью выраженности коронарного атеросклероза. Доказано, что при СД 2 типа ИР существенно влияет на атерогенез посредством индукции вазоконстрикции, воспаления и тромбоза. Согласно полученным данным ИР является прогностическим фактором степени выраженности кальцификации КА, и количества сосудистых поражений у больных ИБС и СД 2 типа. Также, согласно данным Л.В. Квитковой и соавт. [6], многососудистое поражение коронарного русла имеет прямую связь с индексом HOMA ($r=0,304$, $p=0,0001$) и встречается чаще у больных с IP на фоне СД 2 типа и ИБС (86%, $p <0,001$).

В проведенном исследовании заслуживает внимания достоверное повышение уровня сортилина 233,47±47,85 нг/л и инсулина 17,59±5,53 мклЕ/мл у больных второй группы, по сравнению с больными первой группы, в которой уровень сортилина составил 174,16±46,03 нг/л и инсулина - 14,59±2,32 мклЕ/мл ($p<0,05$). Повышение уровня сортилина у больных ИБС и СД 2 типа с многососудистым

Таблица. Влияние одно и многососудистых поражений КА на течение ишемической болезни сердца у больных с сопутствующим СД 2 типа (M±SD)

Показатели	ИБС и СД 2 типа с однососудистым поражением КА (n=27)	ИБС и СД 2 типа с многососудистым поражением КА (n=48)
Возраст, лет	70,60±11,10	69,08±9,07
САД, мм.рт.ст	142,00±17,89	150,21±22,86
ЧСС, уд/мин	88,00±25,98	88,54±13,56
Пульс, уд/мин	88,54±13,56	77,88±11,99
HOMA, ЕД	3,72±1,03	5,43±2,72*
ИМТ, кг/м^2	31,96±4,23	29,95±4,66
Гликозилированный гемоглобин,(мкмоль фруктозы /г Hb)	10,70±1,42	10,86±1,84
Глюкоза, (ммоль/л)	5,8±1,61	6,99±2,38
Сортилин, (нг/л)	174,16±46,03	233,47±47,85*
Инсулин, мклЕ/мл	14,59±2,32	17,59±5,53*
ОХС, (ммоль/л)	4,71±1,34	5,18±1,67
ХС ЛПВП, (ммоль/л)	1,15±0,22	1,21±0,17
ТГ, (ммоль/л)	1,83±1,28	2,78±0,69*
ХС ЛПНП, (ммоль/л)	2,53±1,07	3,18±1,55
ХСЛПОНП, (ммоль/л)	0,82±0,57	1,29±0,31*
КАГ, (ОД)	3,42±1,31	3,37±1,53
КДО, (мл)	79,00±21,18	115,00±31,29*
КСО, (мл)	41,02±18,79	53,25±21,16
КДР, (см)	4,89±1,36	7,87±0,54*
КСР, (см)	3,61±1,19	5,49±0,53*
ФВ, (%)	56,81±8,07	53,83±7,49
ТЗСЛЖ, (см)	1,3±0,04	1,3±0,04
ТМЖП, (см)	1,2±0,05	1,21±0,04
Е	0,52±0,11	0,57±0,13
А	0,60±0,07	0,65±0,14
Е/А	0,80±0,12	0,84±0,27
ЛП, (см)	3,49±0,76	4,07±0,41
Аорта, (см)	3,28±0,30	3,37±0,33

** - p<0,05 при сравнении обех подгрупп*

поражением коронарных артерий может свидетельствовать о значительной роли данного маркера в выраженности атеросклеротического процесса в КА за счет участия сортилина в процессах тромбообразования в КА. Так, в исследовании Ogawa K. и соавт [8] плазменный уровень сортилина достоверно коррелирует с количеством тромбоцитов у больных ИБС и СД 2 типа. Повышение уровня сортилина связано с активацией тромбоцитов, которые вовлекаются в патологический процесс путем повышенного тромбообразования и поражения сосудистой стенки КА и, по всей вероятности, является значительным фактором риска для атеротромбоза у больных ИБС и СД 2 типа.

Повышение уровня инсулина у больных с многососудистыми поражениями КА связано с тем, что инсулин осуществляет прямое атерогенное действие на стенки сосудов, вызывая пролиферацию и миграцию гладкомышечных клеток, пролиферацию фибробластов, активацию свертывающей системы крови, снижение активности фибринолиза. Подтверждение этому находим в работе Журавлевой Л.В. [3]. Таким образом гиперинсулинемия вносит весомый вклад в развитие и прогрессирование атеросклероза, способствуя склонности к тромбообразованию и поражению большего количества КА у больных ИБС и СД 2 типа.

В ходе исследования у больных ИБС и СД 2 типа с одно и многососудистыми поражениями КА оценивали показатели липидного обмена. У больных первой и второй групп среди таких показателей липидного обмена как ОХС, ХС ЛПВП, ХС ЛПНП и КАГ достоверных различий не обнаружено (p>0,05), кроме таких показателей, как ТГ и ХС ЛПОНП (p>0,05). У больных с многососудистыми поражениями КА уровень ТГ составил 2,78±0,69 ммоль/л против 1,83±1,28 ммоль/л у больных с однососудистым поражением КА, уровень ХС ЛПОНП у больных второй группы - 1,29±0,31 ммоль/л в отличие от больных первой группы - 0,82±0,57 ммоль/л (p>0,05). Значительное повышение уровня ТГ и ХС ЛПОНП играет значимую роль в прогрессировании коронарного атеросклероза с поражением большего количества КА. Изменения липидного обмена с повышением уровня ТГ и ХС ЛПОНП у больных с многососудистыми поражениями КА доказано и в работе Журавлевой Л.В. и соавт. [4].

При сопоставлении показателей кардиогемодинамики в группах, где сравнивали больных ИБС и СД 2 типа с одно- и многососудистыми поражениями КА существенных различий не обнаружено (p>0,05), кроме таких показателей, как КДО, КДР, КСР (p<0,05). КДО у больных с многососудистыми поражениями составил 115,00±31,29 мл, против 79,00±21,18 мл у больных с однососудстым поражением КА, КДР во второй группе составил 7,87±0,54 см, против 4, 89±1,36 см первой группы, КСР во второй группе - 5,49±0,53см, против 3,61±1,19 см у больных первой группы (p<0,05). Полученные результаты могут свидетельствовать об отрицательном влиянии многососудистых поражений КА на ремоделирование

миокарда левого желудочка за счет увеличения размеров и полости левого желудочка у больных ИБС и СД 2 типа. По параметрам КСО, ФВ, ТЗСЛЖ, ТМЖП, Е, А, Е / А, размера ЛП и аорты возможных изменений не выявлено.

Выводы.

1. Анализ показателей углеводного обмена выявил увеличение индекса HOMA на 25,40% и уровня инсулина на 17,05% у больных с многососудистыми поражениями КА при ишемической болезни сердца и сахарном диабете 2 типа в сравнении с больными с односсудистым поражением коронарных артерий.
2. Сочетанное течение ИБС и СД 2 типа с многососудистым поражением коронарных артерий было связано с гиперсортилинемией (233,47±47,85нг/л).
3. Значительное повышение уровня ТГ и ХС ЛПОНП играет значительную роль в прогрессировании коронарного атеросклероза с поражением большего количества КА у больных ИБС и СД 2 типа.
4. У больных ИБС и СД 2 типа с многососудистыми поражениями КА ремоделирование миокарда левого желудочка происходило за счет увеличения размеров и полостей левого желудочка.

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SUMMARY

THE INFLUENCE OF MONO- AND MULTIVASCULAR LESIONS OF CORONARY ARTERIES ON THE COURSE OF CORONARY HEART DISEASE IN PATIENTS WITH DIABETES MELLITUS TYPE 2

Sypalo A., Kravchun P., Kadykova O.

Kharkiv National Medical University, Department of Internal Medicine №2 and Clinical Immunology and Allergology, Ukraine

The article assesses the influence of mono- and multivascular lesions of coronary arteries on the course of coronary heart disease at patients with diabetes mellitus type 2.

For this purpose, a comprehensive survey of 75 patients with coronary heart disease and diabetes mellitus type 2 was arranged. Depending on the number of vascular lesions of the coronary arteries, according to the data of coronary arteries computer tomography, all patients were divided into two subgroups. The first subgroup included 27 patients with coronary heart disease and diabetes mellitus type 2 with monovascular lesions of coronary arteries. To the second subgroup were included 48 patients with coronary heart disease and diabetes mellitus type 2 with multivascular lesions of coronary arteries.

During the analysis of carbohydrate metabolism in cases of coronary heart disease and diabetes mellitus type 2 the HOMA index increase by 25.40% and insulin level increase by 17.05% were revealed at patients with multivascular lesions of coronary arteries in comparison with patients with monovascular lesions of coronary arteries, respectively. The combination of coronary heart disease and diabetes mellitus type 2 with multivascular lesions of coronary arteries was associated with an increase of sortilin level (233,47±47,85 ng/l). A significant increase in triglycerides, lipoprotein cholesterol of very low density influences greatly on the progression of coronary atherosclerosis with lesions of greater number of coronary arteries at patients surveyed. At patients with coronary heart disease and diabetes mellitus type 2 with multivascular lesions of coronary arteries the left ventricle myocardial re-modeling occurred through the increase of left ventricle's size and cavity.

Keywords: coronary heart disease, diabetes mellitus type 2, lesions of coronary arteries, sortilin, insulin resistance.

РЕЗЮМЕ

ВЛИЯНИЕ ОДНО- И МНОГОСОСУДИСТЫХ ПОРАЖЕНИЙ КОРОНАРНЫХ АРТЕРИЙ НА ТЕЧЕНИЕ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА У БОЛЬНЫХ С СОПУТСТВУЮЩИМ САХАРНЫМ ДИАБЕТОМ 2 ТИПА

Сыпало А.О., Кравчун П.Г., Кадыкова О.И.

Харьковский национальный медицинский университет, кафедра внутренней медицины №2 и клинической иммунологии и аллергологии, Украина

Целью исследования явилась оценка влияния одно- и многососудистых поражений коронарных артерий на течение ишемической болезни сердца у больных с сопутствующим сахарным диабетом 2 типа.

С этой целью проведено комплексное обследование 75 больных ишемической болезнью сердца и сахарным диабетом 2 типа. В зависимости от количества сосудистых поражений коронарных артерий по данным компьютерной томографии коронарных артерий все больные были разделены на 2 группы: первую группу составили 27 больных ишемической болезнью сердца и сахарным диабетом 2 типа с однососудистым поражением коронарных артерий; в вторую – 48 больных ишемической болезнью сердца и сахарным диабетом 2 типа с многососудистыми поражениями коронарных артерий.

Анализ показателей углеводного обмена выявил увеличение индекса HOMA на 25,40% и уровня инсулина на 17,05% у больных с многососудистыми поражениями коронарных артерий при ишемической болезни сердца и сахарном диабете 2 типа в сравнении с больными с однососудистым поражением коронарных артерий. Сочетанное течение ишемической болезни сердца и сахарного диабета 2 типа с многососудистыми поражениями коронарных артерий было связано с гиперсортилинемией (233,47±47,85 нг/л). Значительное повышение уровня триглицеридов, холестерина липопротеидов очень низкой плотности играет значительную роль в прогрессировании коронарного атеросклероза с поражением большего количества коронарных артерий у обследованных больных. У больных ишемической болезнью сердца и сахарным диабетом 2 типа с многососудистыми поражениями коронарных артерий ремоделирование миокарда левого желудочка происходило за счет увеличения размеров и полости левого желудочка.

რეზიუმე

მონო- და მულტისისხლძარღვოვანი კორონარული არტერიების დაზიანების ზემოქმედება გულის იშემიური დაავადების მანიფესტაციაზე თანმხლები დიაბეტი ტიპი 2-ით პაციენტებში

ა. სიპალო, პ. კრავჩუნი, ო. კადიკოვა

ხარკოვის ეროვნული სამედიცინო უნივერსიტეტის შინაგანი მედიცინის №2
და კლინიკური იმუნოლოგიის და ალერგოლოგიის კათედრა, უკრაინა

გამოკვლევაში შეფასდა მონო- და მულტისისხლძარღვოვანი კორონარული არტერიების დაზიანების გავლენა გულის იშემიური დაავადების მანიფესტაციაზე თანმხლები დიაბეტი ტიპი 2-ით პაციენტებში.

ამ მიზნით ჩატარდა 75 პაციენტის კომპლექსური გამოკვლევა გულის იშემიური დაავადებით და დიაბეტით ტიპი 2-ით. კორონარული არტერიების დაზიანების ტიპიდან გამომდინარე, რომელიც დადგინდა კომპიუტერული ტომოგრაფიით, პაციენტები დაიყო 2 გუფად: პირველი ჯგუფი შეადგინა 27 პაციენტმა გულის იშემიური დაავადებით, თანმხლები დიაბეტი ტიპი 2-ით მონოსისხლძარღვოვანი დაზიანებით, მეორე ჯგუფი კი - 48 პაციენტმა გულის იშემიური დაავადებით, თანმხლები დიაბეტი ტიპი 2-ით და მულტისისხლძარღვოვანი დაზიანებით.

ნახშირწყლოვანი ცვლის პარამეტრების ანალიზმა აჩვენა HOMA ინდექსის 25.40%-ით და ინსულინის დონის 17.05%-ით ზრდა პაციენტებში მულტისისხლძარღვოვანი კორონარული არტერიების დაზიანებით, გულის იშემიური დაავადებით და დიაბეტი ტიპი 2-ით, შედარებით პაციენტებთან მონოსისხლძარღვოვანი კორონარული არტერიების დაზიანებით, გულის იშემიური დაავადებით და დიაბეტი ტიპი 2-ით. გულის იშემიური დაავადების და ტიპი 2 დიაბეტის მულტისისხლძარღვოვანი დაზიანებით კომბინირებული მანიფესტაცია დაკავშირებულია ჰიპერსორტილინემიასთან (233,47±47,85 ნგ/ლ).

ტრიგლიცერიდების, ქოლესტერინის და დაბალი სიმკვრივის ლიპოპროტეიდების დონის ზრდა მნიშვნელოვან როლს თამაშობს კორონარული ათეროსკლეროზის პროგრესირებასა და მულტისისხლძარღვოვანი კორონარული არტერიების დაზიანებაში. პაციენტებში გულის იშემიური დაავადებით, თანმხლები დიაბეტი ტიპი 2-ით და მულტისისხლძარღვოვანი დაზიანებით მიოკარდიუმის რემოდელირება ხდებოდა მარცხენა პარკუჭის ზომებისა და ღრუს მატების ხარჯზე.

СОВРЕМЕННЫЕ МЕТОДЫ ДИАГНОСТИКИ СУБКЛИНИЧЕСКИХ ПРОЯВЛЕНИЙ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ

[1]**Азаракш А.Х.,** [1,2]**Иванов Г.Г.,** [2,3]**Буланова Н.А.,** [3]**Стажадзе Л.Л.,** [2]**Николаева М.В.,** [2]**Востриков В.А.**

[1]Российский университет дружбы народов, медицинский институт, кафедра госпитальной терапии, Москва; [2]ФГАОУ ВО Первый Московский государственный медицинский университет им. И.М. Сеченова Минздрава России, отдел кардиологии НИЦ; [3]ФГБУ ДПО «Центральная государственная медицинская академия» Управления делами Президента РФ, кафедра скорой медицинской помощи, неотложной и экстремальной медицины, Москва, Россия

Хроническая сердечная недостаточность (ХСН) остается одной из актуальных проблем кардиологии. В течение последних 30 лет в лечении ХСН достигнуты определенные успехи, их внедрение в клиническую практику улучшило выживаемость больных и снизило частоту госпитализаций, однако смертность среди этой категории пациентов все еще остается высокой, а прогноз – неблагоприятным [12,13,16].

Согласно данным Российских эпидемиологических исследований [10], распространенность ХСН в общей популяции составила 7%, при этом клинически выраженная ХСН составляет 4,5%. Диагностика ранних, доклинических проявлений ХСН, наблюдаемых соответственно у 2,5% от всех больных, крайне важна для раннего выявления этой категории больных и своевременного начала лечения.

Некоторые вопросы градации ХСН являются спорными [1,4]. С целью определения степени выраженности ХСН в клинике наиболее часто используется классификация Нью-Йоркской кардиологической ассоциации (NYHA). По данным В.С. Моисеева и соавт. [6], ХСН функциональный класс (ФК) 0 (по NYHA) определяется при пороге дистанции 6-минутной ходьбы > 551 метра, ХСН ФК I – 426-550 метров и ХСН ФК II – 301-425 метров, ХСН ФК III – при прохождении 151-300 метров и ХСН ФК IV - менее 150 метров.

К инструментальным методам, используемым для верификации ХСН, относятся определение уровня мозгового натрийуретического пептида (МНУП), ультразвуковое исследование сердца, рентгенография органов грудной клетки, анализ максимального потребления кислорода. Опубликованы данные о возможности применения протонной масс-спектрометрии выдыхаемого воздуха, в связи с тем, что концентрация ацетона в конденсате выдыхаемого воздуха у больных ХСН повышена и прямо коррелирует с уровнем МНУП [5].

В последние годы для улучшения диагностики ХСН используется метод мультичастотной биоимпедансометрии с целью оценки водного баланса и его перераспределения по регионам [2,3,7,8,11,14,15]. Большинство опубликованных исследований посвящено оценке водного баланса у больных ХСН ФК III-IV, т.е. при уже имеющихся нарушениях гидратации [9]. Объективной оценке состояния больных ХСН ФК I-II уделяется пристальное внимание (с выделением 0 фазы процесса) [1,6], для этого необходимы методы и показатели, обладающие хорошей чувствительностью и воспроизводимостью.

Единого мнения о том, насколько метод биоимпедансометрии может соответствовать этим требованиям, в доступной литературе нами не найдено, поэтому целью настоящего исследования явился анализ диагностических возможностей метода биоимпедансометрии в диагностике начальных проявлений хронической сердечной недостаточности.

Материал и методы. Исследовано 427 лиц. Больные были распределены в две основные группы: контрольная группа - 92 условно здоровых лица в возрасте от 20 до 60 лет и основная группа - 335 больных с сердечно-сосудистыми заболеваниями в возрасте от 36 до 80 лет.

Пациенты основной группы госпитализированы в кардиологическое отделение, выраженность проявлений ХСН при поступлении определялась как ХСН ФК I-II по NYHA. Основная группа включала 55% мужчин (n=184), 41% пациентов этой группы курили, 59% обследованных основной группы страдали артериальной гипертонией, 46% – ишемической болезнью сердца, 36,4% – фибрилляцией предсердий, 55% – ХСН, 16% – сахарным диабетом 2 типа, заболеваниями желудочно-кишечного тракта – 12%, заболеваниями легких – 17%.

По истечении года, посредством опроса пациентов по телефону, анализировали следующие конечные точки исследования: случаи смерти, повторные госпитализации по поводу декомпенсации ХСН, внезапную сердечную смерность.

Критерием включения пациентов в исследование была ведущая патология сердечно-сосудистой системы при госпитализации: стабильные формы ишемической болезни сердца, обострение артериальной гипертонии, пароксизмальная форма фибрилляции предсердий (на момент поступления ритм был синусовым). Критерии исключения: наличие инкурабельной патологии, тяжелые формы хронической обструктивной болезни легких, ожирение III степени, сахарный диабет в стадии декомпенсации, гипертиреоз, гипотиреоз, анемия, артериальная гипертония, противопоказания к выполнению тестов с физической нагрузкой.

Дизайн исследования. I этап: физикальный осмотр, эхокардиография, биохимическое и реографическое обследования. Тяжесть ХСН при поступлении в стационар оценивали путем определения ФК ХСН по NYHA.

II этап: на 5 сутки госпитализации повторно выполняли физикальный осмотр и реографическое обследование, проводили 6-минутный тест ходьбы для оценки физической толерантности и объективизации функционального статуса больных ХСН. По результатам теста 6-минутной ходьбы на 5 сутки после поступления больные основной группы были разделены на подгруппы с ХСН ФК 0, ХСН ФК I, ХСН ФК II по NYHA.

Эхокардиография выполнялась дважды - в первый и пятый дни госпитализации на аппарате VIVID-7 “GeneralElectric” (США) по стандартному протоколу.

Для биоимпедансометрии использован прибор «АВС-01 Медасс» с программным обеспечением АВС01-0441 и

ABC01-038 для анализа баланса водных секторов организма и оценки фазового угла (ФУ), отражающего состояние клеточных мембран. Измерения проводились в положении лежа на спине с руками, отведенными от туловища. Индекс гидратации легких (ИГЛ) рассчитывался по формуле:
ИГЛ = $R_5/R_{50,}$ где R_5 — активное сопротивление на частоте зондирующего тока 5 кГц, R_{50} — активное сопротивление на частоте зондирующего тока 50 кГц. Нормы определялись отдельно для мужчин и женщин. Также оценивали значения биоимпеданса торса и ног на низких частотах и высоких частотах с расчетом водного баланса и ФУ, показатели общей воды организма (ОВО), клеточной (КЖ) и внеклеточной жидкости (ВКЖ).

Уровень МНУП в плазме крови определялся при поступлении больных в кардиологический стационар на аппарате «RocheCARDIACproBNP+ «N-terminalproBNP» Cobash 232» от Roche с использованием реактивов REF 05533643190 «RocheCARDIACproBNP+ test 1 codechip» (Германия).

В каждой группе проводился анализ стандартных показателей ЭКГ: фиксировались нарушения сердечного ритма и признаки гипертрофии левого желудочка.

Статистическая обработка результатов проведена с помощью пакета статистических программ MicrosoftExcel 2007 и пакета STATITICA v 6.0. Результаты исследования представлены как средние арифметические значения ± стандартное отклонение (M±δ). Для оценки значимости различий между данными исследования в разных группах больных использован t-критерий Стьюдента с коэффициентом Уатта и без него. Различия считались достоверными при $p<0,05$. Для оценки достоверности различий качественных показателей применены критерии Пирсона и Фишера. Время выживания больных с сердечно-сосудистыми заболеваниями оценивали с помощью кривых Каплана-Майера.

Результаты и их обсуждение. В группе больных без клинических признаков ХСН ФК I-II по NYHA при поступлении начальные проявления гипергидратации выявлены у 4% больных, на 5 сутки - у 16%.

Распределение больных основной группы на подгруппы проводилось на 5 сутки после поступления. По результатам теста 6-минутной ходьбы больные распределились следующим образом: подгруппа 1 - пациенты с ХСН ФК 0 (n=96), подгруппа 2 - пациенты с ХСН ФК I (n=107), подгруппа 3 - больные с ХСН ФК II (n=87). Часть пациентов была отнесена к ХСН ФК III-IV (n=45), в связи с чем в дальнейшем исследовании не участвовала.

Данные каждой из подгрупп рассматривались в трех диапазонах значений индекса массы тела (ИМТ): <25 кг/м^2, от 25 до 30 кг/м^2, >30кг/м^2.

Динамика показателей водного баланса у больных ХСН ФК 0. Показатели биоимпедансометрии ОВО и ВКЖ выявили гипергидратацию у больных ХСН ФК 0 относительно контрольной группы (таблица 1).

Средние значения ОВО от первого ко второму этапу имели тенденцию к снижению ($p<0,05$). При оценке в трех диапазонах ИМТ достоверные различия выявлены только между первой и третьей подгруппами ($p<0,05$).

С увеличением ИМТ выявлена тенденция к снижению ФУ (снижение ФУ составило 1,3±0,2 градуса). Выявлены статистически значимые различия значений ФУ у обследованных больных по сравнению с контрольной группой на всех этапах исследования и во всех исследуемых подгруппах ($p<0,05$).

Динамика показателей водного баланса у больных ХСН ФК I. Как следует из таблицы 2, средние значения показателя ОВО у больных с ИМТ более 30 кг/м^{2}снижаются от первого ко второму этапу исследования, на фоне лечения. Значения всех показателей водного баланса - ОВО, ВКЖ и КЖ и на первом, и на втором этапах оказались выше у больных ХСН относительно контрольной группы.

Максимальные различия всех показателей водного баланса выявлены для пациентов с ИМТ более 30 кг/м^2 средние значения у больных ХСН ФК I значимо превышают значения

Таблица 1. Показатели биоимпедансометрии у больных с ХСН ФК 0

ИМТ, кг/м^2	Группа, этап/ показатель		Показатели биоимпедансометрии, л		
			ОВО	ВКЖ	КЖ
<25	ХСН ФК 0 (n=30)	I	35,9±1,7	20,4±1,5*	24,0±2,7*
		II	35,0±0,8*	21,1±2,1	24,1±1,9*
	Контроль (n=36)		31,6±3,9	11,3±0,8	20,7±2,1
25-30	ХСН ФК 0 (n=28)	I	36,2±1,5*	21,7±2,4*	24,5±1,6
		II	35,0±2,2*	20,0±2,2*	23,2±2,7
	Контроль (n=24)		32,0±1,9	13,7±3,1	21,5±2,0
<30	ХСН ФК 0 (n=38)	I	37,6±3,4	23,1±3,3*	25,9±4,6
		II	36,4±2,5#	22,3±1,0	25,4±1,2
	Контроль (n=32)		33,6±3,9	15,3±1,2	22,5±3,7

*примечание: *- различия средних значений показателя относительно контрольной группы статистически значимы($p<0,05$); #- различия средних значений показателя относительно этапа I статистически значимы ($p<0,05$), ИМТ – индекс массы тела, ХСН ФК – функциональный класс хронической сердечной недостаточности, I, II – этапы исследования, ОВО – общая вода организма, КЖ – клеточная жидкость, ВКЖ – внеклеточная жидкость*

Таблица 2. Показатели биоимпедансометрии у больных с ХСН ФК I

ИМТ кг/м²	Группа, этап/ показатель		Показатели биоимпедансометрии, л		
			ОВО	ВКЖ	КЖ
<25	ХСН ФК I (n=37)	I	38,7±1,8*	22,4±2,4	26,0±3,3
		II	35,2±2,2*†	20,1±1,9	24,1±1,5*
	Контроль (n=36)		31,6±3,9	11,3±0,8	20,7±2,1
25-30	ХСН ФК I (n=34)	I	39,2±1,8*	23,7±1,5*	27,5±1,8*
		II	37,8±2,1†	21,0±2,2	25,2±1,6*
	Контроль (n=24)		32,0±1,9	13,7±3,1	21,5±2,0
>30	ХСН ФК I (n=36)	I	41,6±2,7*	25,1±1,6*	28,9±3,0*
		II	38,9±4,6*	24,3±1,9*	27,4±2,4*
	Контроль (n=32)		33,6±3,9	15,3±1,2	22,5±3,7

*примечание: *- различия средних значений показателя относительно контрольной группы статистически значимы (p<0,05); †- различия средних значений показателя относительно этапа I статистически значимы (p<0,05)*

контрольных пациентов как при поступлении в стационар, так и в процессе лечения, на пятые сутки. Необходимо отметить, что для пациентов с ХСН ФК 0, рассматриваемых ранее, такой закономерности не обнаружено.

Значения ФУ у пациентов группы ХСН ФК I статистически значимо превышали данные, полученные в контрольной группе. Это различие наблюдалось для пациентов с ИМТ менее 25 кг/м²: 5,1° на первом этапе, 5,2° на втором этапе и 6,5° для пациентов контрольной группы (p<0,05). Различия сохранялись для пациентов с ИМТ 25-30кг/м²: 4,8°, 5,2° и 6,4°,соответственно (p<0,05) и пациентов с ИМТ >30 кг/м² : 4,6°, 4,6° и 6,0°, соответственно (p<0,05).

Необходимо подчеркнуть, что выявленные у пациентов с ХСН ФК I в возрасте старше 60 лет и ИМТ более 30к г/м² увеличение ОВО и снижение ФУ в сравнении с пациентами с ХСН ФК 0 и контрольной группы являются маркерами начальных проявлений ХСН.

Динамика показателей водного баланса у больных* ХСН *ФК II. Средние значения показателей водных секторов организма и ФУ у пациентов с ХСН ФК II в зависимости от ИМТ представлены в таблице 3. У больных ХСН ФК II содержание воды во всех секторах организма значимо выше, чем в контрольной группе (p<0,05). На фоне проводимого лечения отмечается снижение значений ОВО и КЖ у пациентов с ИМТ более 30 кг/м² (p<0,05), от первого ко второму этапу.

В отличие от рассмотренных ранее пациентов с ХСН ФК I максимальные различия показателей водного баланса выявлены у пациентов с ИМТ менее 25 кг/м² и более 30кг/м² -средние значения у больных ХСН ФК II превышают контрольные значения при поступлении и на пятые сутки лечения.

Необходимо подчеркнуть выявленные различия в степени гипергидратации больных ХСН ФК II и ХСН ФК I относительно контрольной группы - степень гипергидратации больных ХСН ФК II выше в сравнении с пациентами с ХСН ФК I. Нарушения гемодинамики в большей степени у больных ХСН ФК II подтверждается у них более высокими значениями показателей водного баланса и низкими значениями ФУ в сравнении с больными ХСН ФК I.

Диагностическая ценность МНУП, ФУ, фракции выброса и импеданса ног на низких частотах для выявления начальных проявлений ХСН ФК I-II (на 5 сутки). Проведено сравнение прогностической ценности различных методов диагностики ХСН (таблица 4). В ходе анализа наиболее высокая чувствительность выявлена для МНУП — 82%, в то время как специфичность составила 88%. Наименьшие

Таблица 3. Показатели биоимпедансометрии у больных ХСН ФК II

ИМТ кг/м²	Группа, этап/ показатель		Показатели биоимпедансометрии, л		
			ОВО	ВКЖ	КЖ
<25	ХСН ФК II (n=27)	I	43,2±1,1*	26,1±0,6*	28,7±2,5*
		II	42,3±0,8*	23,4±1,2*†	24,5±1,2*†
	Контроль (n=36)		31,6±3,9	11,3±0,8	20,7±2,1
25-30	ХСН ФК II (n=30)	I	46,6±1,3*	24,7±1,8	29,9±3,1
		II	44,0±2,9*	24,4±0,9	28,1±2,7*
	Контроль (n=24)		32,0±1,9	13,7±3,1	21,5±2,0
>30	ХСН ФК II (n=30)	I	47,3±3,0*	25,9±2,7*	33,7±1,4
		II	46,8±2,4*†	25,7±1,5*	32,0±3,5*†
	Контроль (n=32)		33,6±3,9	15,3±1,2	22,5±3,7

*примечание: * - различия средних значений показателя относительно контрольной группы статистически значимы (p<0,05); † - различия средних значений показателя относительно этапа I статистически значимы (p<0,05)*

Таблица 4. Диагностическая ценность ФВЛЖ, МНУП, ФУ и импеданса ног (Z) на НЧ и ВЧ для выявления начальных проявлений ХСН ФК I-II на 5 сутки госпитализации

Показатели	Методы					
	Тест 6-минутной ходьбы, м	ФВЛЖ, %	МНУП, Пг/мл	ФУ, град	Z Ног на НЧ, Ом	Z ног на ВЧ, Ом
	≤ 298	≤ 45	≥ 125	≤ 5,1	≤ 146	≤ 124
Чувствительность, %	67	71	82	77	69	68
Специфичность, %	72	86	88	83	74	97
ПЦПР, %	81	72	91	91	77	94
ПЦОР, %	65	89	66	56	53	83
ОПЦ, %	57	68	65	60	58	86

Таблица 5. Прогностическая ценность ФВЛЖ, МНУП, ФУ и импеданса ног (Z) на НЧ у пациентов с ХСН ФК I-II

Показатели	Методы				
	Тест 6-минутной ходьбы, м	ФВЛЖ, %	МНУП, пг/мл	ФУ, град	Z ног на НЧ, Ом
	≤ 298	≤ 40	≥ 315	≤ 4,2	≤ 176
Чувствительность, %	63	73	75	77	68
Специфичность, %	69	64	82	81	60
ПЦПР, %	61	57	69	67	52
ПЦОР, %	78	59	54	55	58
ОПЦ, %	66	58	61	53	57

значения чувствительности и специфичности оказались у теста 6-минутной ходьбы и импеданса ног на низких частотах — чувствительность 67% и 69%, специфичность 72% и 74%, соответственно. При этом у импеданса ног на высоких частотах наблюдалась чувствительность 68% и специфичность 97%. Предсказательная ценность положительного результата оказалась высокой у показателей ФУ (91%) и МНУП (91%), в то время как наименьшее значение предсказательной ценности положительного результата показано для фракции выброса левого желудочка (72%). Для каждого показателя рассчитаны также предсказательная ценность отрицательного результата и общая предсказательная ценность, результаты которых представлены в таблице 4.

Прогностическая ценность биоимпедансной спектроскопии, МНУП для отдаленного прогноза в группе начальных проявлений ХСН (ХСН ФК I-II). Анализ чувствительности и специфичности ФУ, биоимпеданса ног, фракции выброса левого желудочка и МНУП для отдаленного прогноза выявил результаты, представленные в таблице 5. При сравнении прогностической ценности указанных методов наиболее высокие показатели чувствительности и специфичности имел тест 6-минутной ходьбы - 63% и 69%, соответственно. Наименьшие значения чувствительности и специфичности наблюдались у биоимпеданса ног на низких частотах, для данного метода они составили 68% и 60%, соответственно. Предсказательная ценность положительного результата была наиболее высокой у МНУП (69%) и ФУ (67%), а наименьшее значение данного показателя выявлено для фракции выброса левого желудочка (57%).

Кривые выживаемости Каплана-Майера. За период наблюдения число смертельных исходов среди исследуемых больных составило 15: 6 больных ХСН ФК I и 9 больных ХСН ФК II. Из них 2 пациентов с ХСН ФК I и 5 пациентов с ХСН ФК II умерло в течение одного месяца после выписки из стационара. Причиной летальных исходов стали острая декомпенсация ХСН или внезапная сердечная смерть.

По результатам первого месяца наблюдения в группе пациентов с ХСН ФК I риск смерти оказался достоверно ниже в сравнении с пациентами группы с ХСН ФК II (ОР=0,18; 95% ДИ [0,04-0,77], p=0,02). При этом по данным годичного наблюдения статистически значимых различий в летальности не выявлено (ОР = 0,88, 95% ДИ 0,4311-1,6754, p=0,21).

Таким образом, исследование показало, что метод биоимпедансной спектроскопии может применяться для выявления начальных проявлений ХСН у больных ХСН ФК I-II. Этот неинвазивный метод позволяет выявить скрытую ХСН по показателям биоимпеданса торса, ног и ФУ, проанализировать характер и степень нарушений водного баланса организма. Оценка динамики показателей водного баланса может применяться и на фоне проводимой комплексной терапии. В качестве критерия оценки вероятности развития неблагоприятных отдаленных исходов у больных сердечно-сосудистыми заболеваниями может применяться пороговое значение показателя ФУ ≤4,2°, обладающее 77% чувствительностью и 81% специфичностью.

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SUMMARY

CONTEMPORARY APPROACH TO DIAGNOSIS OF SUBCLINICAL HEART FAILURE

[1]**Azaraksh A.,** [2,1]**Ivanov G.,** [2,3] **Bulanova N.,** [3]**Stazhadze L.,** [2]**Nikolaeva M.,** [2] **Vostrikov V.**

[1]Russian Peoples' Friendship University, Medical Institute, Department of Hospital Therapy, Moscow; [2]Department of Cardiology, Sechenov First Moscow State Medical University; [3]Central State Medical Aacademy of Department of Presidential Affairs of the Russian Federation, Department of Emergency Medical Care, Urgent and Emergency Medicine, Moscow, Russian Federation

Treatment of congestive heart failure (CHF) remains one of the challenging problems in cardiology. In recent years, the method of multifrequency bio-impendancemetry is used in patients with CHF for the assessment of water imbalance and determination of its severity.

The aim of the study was to determine the diagnostic capabilities of bio-impendancemetry in evaluation of the early manifestations of CHF.

The study included 92 healthy individuals, and 335 patients who were hospitalized in the cardiology department with NYHA I-II functional class (FC) of chronic CHF. The echocardiography, rheography and biochemical examination were performed for determination of FC of CHF. Procedures were repeated at day 5 of hospitalization, 6-minute walk test was performed to assess physical tolerance and objectification of the functional status of patients with CHF. 45 patients had signs of CHF FC III-IV, therefore, they were excluded from the study. Analysis of endpoints was conducted by telephone survey in 1 year after discharge from the hospital.

The results of the comparison of the predictive value of different methods for diagnosing CHF showed maximum sensitivity for brain natriuretic peptide (BNP) which was 82%, specificity was 88%. The 6-minute walk test showed the lowest values of sensitivity and specificity (sensitivity 67%, specificity 72%) as well as leg impedance at low frequencies (LF) (sensitivity 69%, specificity 74%). The values for the leg impedance at high frequencies (HF) were as follows: sensitivity 68%, specificity 97%. High predictive value of a positive result (PPV) was shown in phase angle (91%) and BNP (91%). Left ventricle ejection fraction(LVEF) measurements had the lowest PPV (72%).

Keywords: bioelectrical impedance analysis, chronic heart failure, the 6-minute walk test, echocardiography, latent heart failure, phase angle, total body water, extracellular fluid, intracellular fluid.

РЕЗЮМЕ

СОВРЕМЕННЫЕ МЕТОДЫ ДИАГНОСТИКИ СУБКЛИНИЧЕСКИХ ПРОЯВЛЕНИЙ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ

[1]**Азаракш А.Х.,** [1,2]**Иванов Г.Г.,** [2,3]**Буланова Н.А.,**
[3]**Стажадзе Л.Л.,** [2]**Николаева М.В.,** [2]**Востриков В.А.**

[1]Российский университет дружбы народов, медицинский, институт, кафедра госпитальной терапии, Москва; [2]ФГАОУ ВО Первый Московский государственный медицинский университет им. И.М. Сеченова Минздрава России, отдел кардиологии НИЦ; [3]ФГБУ ДПО «Центральная государственная медицинская академия» Управления делами Президента РФ, кафедра скорой медицинской помощи, неотложной и экстремальной медицины, Москва, Россия

Лечение хронической сердечной недостаточности (ХСН) по сей день остается одной из актуальных проблем кардиологии. В последние годы для улучшения диагностики ХСН у больных с клинически выраженными нарушениями гидратации используется метод мультичастотной биоимпедансометрии для оценки и перераспределения водного баланса.

Целью исследования явился анализ диагностических возможностей метода биоимпедансометрии в оценке начальных проявлений хронической сердечной недостаточности.

Обследовано 335 больных, госпитализированных в отделение кардиологии, у которых при поступлении выявлена ХСН I-II функционального класса по NYHA, а также 92 условно здоровых лица. На I этапе выполняли физикальный осмотр, ЭХО-КГ, биохимическое и реографическое обследование, определяли функциональный класс ХСН. На II этапе на 5 сутки госпитализации повторно выполняли процедуры I этапа и проводили 6-минутный тест ходьбы для оценки физической толерантности и объективизации функционального статуса больных ХСН. По результатам теста у 45 больных выявлена ХСН функционального класса III-IV, поэтому они были исключены из исследования. Анализ конечных точек наблюдения проводили по данным телефонного опроса спустя один год.

Результаты сравнения прогностической ценности методов диагностики ХСН показали максимальную чувствительность для мозгового натрийуретического пептида - 82%, специфичность составила 88%. Наименьшие показатели определены для теста 6-минутной ходьбы (чувствительность - 67%, специфичность - 72%) и импеданса ног на низких частотах (чувствительность - 69%, специфичность - 74%). Для импеданса ног на высоких частотах чувствительность составила 68%, специфичность - 97%. Высокой прогностической ценностью положительного результата характеризовались фазовый угол (91%) и уровень мозгового натрийуретического пептида (91%), наименьшей - фракция выброса левого желудочка (72%).

Таким образом, для выявления начальных проявлений ХСН одним из наиболее оптимальных методов неинвазивной диагностики является метод биоимпедансной спектроскопии. Для оценки вероятности наступления неблагоприятных отдаленных исходов у больных сердечно-сосудистыми заболеваниями может быть использован показатель фазового угла с пороговым значением ≤4,2°, чувствительностью 77% и специфичностью 81%.

რეზიუმე

ბიოიმპედანსომეტრიული მეთოდის გამოყენება გულის ქრონიკული უკმარისობის მქონე ავადმყოფების მიმართ კარდიოლოგიურ სტაციონარში დიაგნოსტირების მიზნით

[1]ა. აზარკაში, [2,1]გ. ივანოვი, [2,3]ნ. ბულანოვა, [3]ლ. სტაჟაძე, [2]მ. ნიკოლაევა, [2]ვ. ვოსტრიკოვა

[1]რუსეთის ხალხთა მეგობრობის სახელობის უნივერსიტეტი, სამედიცინო ინსტიტუტი, საგოსპიტალოზაციო თერაპიის კათედრა, მოსკოვი; [2]მოსკოვის ი.მ. სეჩენოვის სახ. პირველი სახელმწიფო სამედიცინო უნივერსიტეტი, კარდიოლოგიის სამეცნიერო-კვლევითი ცენტრი; [3]რუსეთის ფედერაციის პრეზიდენტის საქმეთა სამმართველოს დამატებითი პროფესიული განათლების ფედერალური სახელმწიფო საბიუჯეტო დაწესებულება "ცენტრალური სახელმწიფო სამედიცინო აკადემია", გადაუდებელი და ექსტრემალური მედიცინის სასწრაფო სამედიცინო დახმარების კათედრა, მოსკოვი, რუსეთის ფედერაცია

გულის ქრონიკული უკმარისობის (გქუ) მკურნალობა კარდიოლოგიის ერთ-ერთი აქტუალური პრობლემაა. გქუ-ს დიგნოსტიკის გაუმჯობესობის მიზნით, ჰიდრატაციის დარღვევის კლინიკური გამოვლინებით პაციენტებში, წყლის ბალანსის შეფასების და გადანაწილების მიზნით, გამოიყენება ე.წ. მრავალსიხშირული ბიოიმპედანსომეტრია.

გამოკვლევის მიზანს წარმოადგენს ბიოიმპედანსომეტრიული მეთოდის დიაგნოსტიკური შესაძლებლობების ანალიზი გულის ქრონიკული უკმარისობის საწყისი გამოვლინებების პერიოდის შეფასებაში.

გამოკვლეულია 335 ავადმყოფი, განთავსებული კარდიოლოგიის განყოფილებაში NYHA-ს კლასიფიკაციის შესაბამისად გქუ-ს I-II ფუნქციონალური კლასებით (ფკ). გამოკვლევა ჩაუტარდათ 92 პირობით ჯანმრთელ პირს. I ეტაპზე განხორციელდა ავადმყოფთა გასინჯვა და მეთვალყურეობა, ექოკარდიოგრამის გადაღება, ბიოქიმიური და რეოგრაფიული გამოკვლევები და განისაზღვრა გქუ-ს ფუნქციონალური კლასები. II ეტაპზე, ავადმყოფთა განთავსების მე-5 დღეს, ხელახლა ხორციელდებოდა I ეტაპის პროცედურები და შესრულებული იყო 6-წუთიანი გასეირნების ტესტი, მათი ფიზიკური ტოლერანტობის შეაფასების და გქუ-ით ავადმყოფების ობიექტური ფუნქციონალური სტატუსის დადგენის მიზნით. მოცემული ტესტის შედეგების შესაბამისად, 45 ავადმყოფს დაუდგინდა გქუ-ს ფკ III-IV და ამის გამო, ისინი გდმოყვანილი იყვნენ გამოკვლევის პროცესიდან. ავადმყოფებზე დაკვირვების საბოლოო პუნქტების ანალიზი ჩატარებული იქნა სატელეფონო გამოკითხვის საშუალებით 1 წლის შემდეგ.

ჩატარებული კვლევის შედეგებზე დაყრდნობით და გქუ-ს დიაგნოსტიკური მეთოდების პროგნოსტიკული ღირებულების მონაცემების შედარების შედეგად გამოვლინდა თავის ტვინის ნატრიურეტული პეპტიდის (თტნუპ) უმაღლესი მგრძობელობა - 82%, სპეციფიკა - 88%. ყველაზე დაბალი მაჩვენებლები დადგინდა 6-წუთიანი სიარულის ტესტის და ფეხების იმპედანსის მიმართებით

დაბალ სიხშირეებზე - 67% და 69%, სპეციფიკამ, შესაბამისად, შეადგინა 72% და 74%. ფეხების იმპედანსის მიმართებით მაღალსიხშირეებზე აღინიშნებოდა 68% მგრძნობიარობა და 97% სპეციფიკურობა. დადებითი შედეგის მაღალი საწინასწარმეტყველო ღირებულება აღმოაჩნდა საფაზო კუთხეს (91%) და თტნუპ-ს (91%). ყველაზე დაბალი კი - მარცხენა პარკუჭის განდევნის ფრაქციას (72%). ამგვარად, გქუ-ს პირველადი გამოვლინებების დასადგენად ერთ-ერთ ყველაზე ოპტიმალურ და არაინვაზიურ დიაგნოსტიკურ მეთოდს წარმოადგენს ბიოიმპედანსური სპექტროსკოპია. პაციენტებში გულის სისხლძარღვთა დაავადებით არასასურველი და გრძელვადიანი შედეგების შესაფასებლად შეიძლება გამოყენებული იყოს ფაზური კუთხის მაჩვენებლის ზღვრული მნიშვნელობით ≤4,2°, მგრძობელობით - 77% და სპეციფიკურობით - 81%.

UNUSUAL MANIFESTATION OF NEUROBORELIOSIS (CASE REPORT)

Beridze M., Khizanishvili N., Mdivani M., Samushia O., Gogokhia N.

Tbilisi State Medical University, Neurological Department of the First University Clinic, Georgia

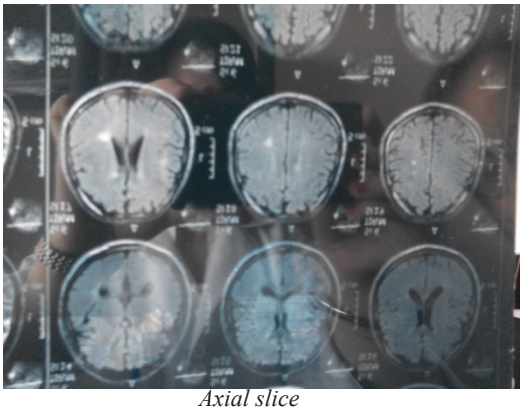
As known, Multiple Sclerosis (MS) is the chronic inflammatory, autoimmune disease with multiple causative factors, which can impact the clinical expression and conduction of MS. Immunologic, genetic, environmental, viral causes and even the dietary patters are all considered to play a role in MS development. Therefore, the etiology of MS is likely to involve multiple, interacting factors that ultimately lead to the chronic, progressive neurologic disease [1-4]. MS mostly impacts the patients at the age of 20 to 40 years and nearly 80-85% of cases comprise relapse remitting (RRMS) course of the disease. Approximately 40% of patients with RRMS can develop a secondary progressive course marked by a gradual progression of symptoms with or without occasional relapses and minor remissions. Alternatively, a primary progressive form of MS may develop from the onset of disease with progressive worsening of symptoms and with possible minor remissions [5]. There is a consensus for diagnostics of MS according to the McDonald Criteria [6], but sometimes despite of adherence to these criteria exceptional cases appear that have to be discussed thoroughly to avoid the future misdiagnosis. Description of such cases will help for further understanding of the mechanisms and the other possible causes of MS.

Material amd methods. *Case report.* We investigated a 44 year-old male patient diagnosed in 2013 as Multiple Sclerosis (MS), who within two years developed the typical clinical signs of Parkinsonism. In November of 2012 the patient first applied to the oculist and afterwards to the neurologist complaining for sudden decrease of the vision in the right eye. Before symptoms onset the patient worked hard, got a severe exhaustion and suffered the serious emotional stress. Patient found to be the road worker mending the roads in various climate conditions. Two months before the appearance of the first symptoms he also suffered the pain in joints and in the heart. Patient applied to the family doctor and was prescribed the treatment with oral steroids (gradually decreasing 48mg methylprednisolone) and vitamins group B for 14 days. After 1 month the vision was practically restored. In June of 2015 the patient applied to the neurological department of the First University Clinic of Tbilisi State Medical University complaining difficulties in walking and feeling to be constrained in joints. Upon admission, the vital signs were within normal ranges. An extensive neurological examination was performed, which revealed horizontal nystagmus, amimic face, oligobradikinesia, extrapyramidal rigidity in all limbs. The muscle, tendon, bone reflexes found to be slightly, symmetrically increased. The resting tremor was revealed in fingers, dynamic coordination tests were normal. Strength and motion was preserved in all limbs, abdominal skin reflexes were slightly, symmetrically decreased. Palmo-mental axial reflex was present at both sides. Romberg test was positive, primitive sensation was preserved; vibration sense was slightly diminished in the low extremities. Babisnki sign was negative in both lower extremities. Urination pattern was not changed. Brain contrast MRI (1.5 Tesla) was performed and 5 ml Cerebrospinal Fluid (CSF) was taken by lumbar puncture to research oligoclonal bands. The blood was researched by ELISA method to detect IgM and IgG against Chlamydia pneumonie, Mycoplasma pneumonie, Borrelia burgdorferi, Herpes simplex 1/2, Cytomegalovirus.

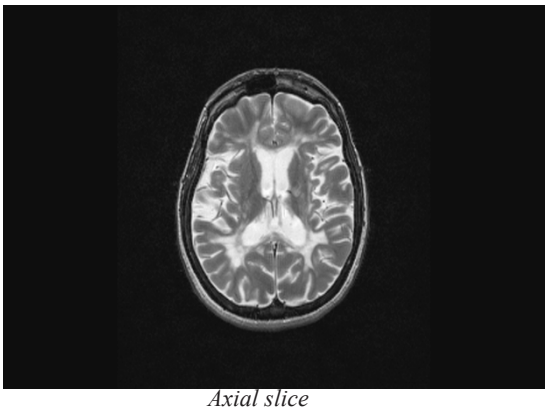
Results and their discussion. The brain MRI showed multiple gadolinium enhanced demyelization lesions in periventricular and subcortical white matter (Figs 1,2,3). CSF oligoclonal bands were positive without dysfunction of blood-brain barrier. Particularly, CSF-Serum ratio of IgG was 4.6 kA, Albumine CSF/Serum ratio -6.2 kA, Tibbling CSF ratio-0.75 kA, Local IgG synthesis (Reiber)-1.3 kA, Range Albumin CSF-Serum ratio-7.0 kA.

The blood IgM, IgG detected as negative against Chlamydia pneumonie, Mycoplasma pneumonie, Herpes simplex 1/2, Cytomegalovirus. The blood IgG was strongly positive against Borrelia Burgdorferi, confirmed by following Western blot test. CSF conventional PCR (target ospA gene) showed positive results against Borrelia Burgdorferi. Patient was stabilized by puls-therapy with 1gr/intravenous Solumedrol (5 days) along with Rocephin treatment (2 gr /iv) for 21 days **f**ollowed by long term therapy with Antiparkin (Carbidopa 250 mg, Levodopa 25 mg).

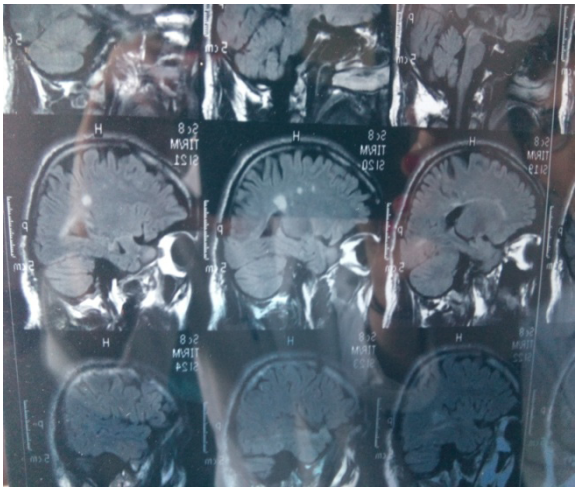
Despite the extensive basic and clinical investigations many aspects of MS etiology and pathogenesis still remain unclear. The



Axial slice



Axial slice



Sagittal Slice

Fig. Brain subcortical and periventricular demyelination regions

epidemiology of MS suggests that infections might have a role in clinical course of MS. Several intracellular bacteria and viruses are well-recognized as causes of demyelization and inflammation [1]. There is also suggestion that more than one infectious trigger can interact synergistically and result in autoimmune response [2]. It is also proposed that environmental exposure to "slow-acting viruses", which can stay inside the organism for months and years can cause the illness supported by unfavorable conditions like susceptibility, stress, exhauster, cold and etc. Infectious theory of MS might be supported by the case of Faroe Islands when four successive epidemics of MS occurred in 1943. The disease was introduced by British troops who occupied the islands and remained localized within the Faroe for half a century. What was introduced must have been an infection, called the primary MS affection (PMSA) that was spread to successive cohorts of Faroese [3]. Taking in account all above mentioned, and envisaging the non-standard clinical expression of MS in presented case, we decided to check the possibility of neuroinfection and to perform the blood serology testing for several possible triggers. The positive result was revealed for Borrelia Burgdorferi that was followed by western blot test and later- by blood PCR test targeting the ospA gene. Apparently, Borrelia burgdorferi was presented in the blood of our patient. Several authors suggest that Lyme's disease can imitate number of syndromes including MS, Parkinson's, ALS , Fibromialgia and even Alzheimer's disease [7-9]. At their opinion the Lewy body inclusions as well as amyloidal plaques might represent the spirochetes' cystic forms in brain tissue. It should be considered that Borrelia spirochete is the intracellular causative agent that can take the cystic form and dwell in neuronal cells for years. Borrelia infection exhibits molecular mimicry with human nervous tissue and can evoke antimyelin T-cells against myelin basic protein. As known, Lyme disease's symptoms can mimic those of MS, such as blurred vision caused by optic neuritis, dysesthesias and weakness in extremities, coordination disturbance, confusion, cognitive dysfunction, and fatigue [10,11]. It can also follow a relapse-remittance course, the results of an MRI and cerebrospinal fluid findings look similar among the people with either condition. It has been discovered that Borrelia burgdorferi exhibits molecular mimicry with human nervous tissue and can evoke antimyelin T-cells against myelin basic protein. This was proved by demonstration of the antibodies to the myelin basic protein in CSF of patients with Lyme disease [12-14]. In our case, we had the possibility to research only CSF for olygoclons and to make the brain contrast MRI. The strange fact that the patient with Parkinson's syndrome found to have the positive oligoclonal bands in CSF and also had the optic neuritis in anamnesis made us to suspect some other pathology than MS and Parkinson's disease [15,16]. For this reason we prescribed the serology testing for number of infections and found positive results for Borrelia Burgdorferi. Envisaging the different treatment approaches in these diseases, misdiagnosis in clinical practice can lead to the grave results and the higher disability rate in suspicious patients.

Conclusion: MS and even Parkinsonism in suspicious cases should be differentiated from chronic neuroboreliosis.

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SUMMARY

UNUSUAL MANIFESTATION OF NEUROBORELIOSIS (CASE REPORT)

Beridze M., Khizanishvili N., Mdivani M., Samushia O., Gogokhia N.

Tbilisi State Medical University, Neurological Department of the First University Clinic, Georgia

The paper reported the verified case of neuroboreliosis with unusual clinical presentation of Parkinsonism. Study aimed at establishing the significance of a precise differential diagnosis with substantial analysis of the symptoms of several diseases to avoid the false diagnosis and to conduct the opportune and adequate therapeutic management.

We described the case of the diagnosed neuroboreliosis with clinical expression of Multiple Sclerosis (MS) and Parkinsonism.

A 44 years old man was diagnosed as MS according to the McDonald's Criteria, who within two years developed typical clinical signs of Parkinsonism. Patient investigated neurologically, Brain contrast MRI (1.5 Tesla) was performed; Cerebrospinal fluid was researched for oligoclonal bands. Blood IgM and IgG were researched against Chlamidia pneumonie, Micoplasma pneumonie, Borrelia Burgdorferi, Herpes simplex 1/2, Cytomegalovirus by ELISA method.

Clinically the patient expressed amimic face, oligobradikinesia, extrapiramidal rigidity in all limbs, resting tremor in upper limb fingers, horizontal nystagmus. Brain MRI showed multiple gadolinium enhanced demyelization lesions in periventricular and subcortical white matter. CSF oligoclonal bands were positive without dysfunction of blood-brain barrier. Blood IgM, IgG detected to be negative against Chlamidia pneumonie, Micoplasma pneumonie, cytomegalovirus, Herpes simplex ½, while the blood IgG was strongly positive against Borrelia burgdorferi, confirmed by followed Western blot test. Patient was stabilized by puls-therapy with 1 gr/intravenous Solumedrol (5 days) along with Rocephin treatment (2 gr /iv) for 21 days followed by long term treatment with Antiparkin (Carbidopa 250 mg, Levodopa 25 mg).

MS and even Parkinsonism in suspicious cases should thoroughly be investigated for differentiation from chronic Neuroboreliosis.

Keywords: Multiple Sclerosis, autoimmune reaction, oligoclonal bands, parkinsonism, neuroinfection, neuriboreliosis.

РЕЗЮМЕ

НЕОБЫЧНОЕ ПРОЯВЛЕНИЕ НЕЙРОБОРЕЛИОЗА (СЛУЧАЙ ИЗ ПРАКТИКИ)

Беридзе М.З., Хизанишвили Н.А., Мдивани М.Т., Самушия О.Ш., Гогохия Н.А.

Тбилисский государственный медицинский университет, Первая университетская клиника, неврологический департамент, Грузия

В статье приводится случай диагностированного нейроборелиоза с клиническим проявлением паркинсонизма. Целью исследования явилось определение значимости скрупулезного дифференциального диагноза на фоне тщательного анализа специфической симптоматики того или иного заболевания с целью избежания неправильного диагностирования и для своевременного и адекватного лечения.

Описывается случай диагностированного нейроборелиоза с клиническим проявлением рассеянного склероза и паркинсонизма у мужчины 44 лет с рассеянным склерозом, который был диагностирован согласно критериев Мак-Дональда. Пациент был обследован неврологически. Проведена магнитно-резонансная томография (МРТ-1.5 Тесла) головного мозга. Методом ELISA исследованы цереброспинальная жидкость на наличие олигоклонных включений, иммуноглобулины

крови IgM и IgG - на хламдий, микоплазмы, борелия, простого герпеса 1/2, цитомегаловируса. Клиническое обследование выявило амимичное лицо, олигобрадикинезию, экстрапирамидную ригидность во всех конечностях, тремор покоя в пальцах рук, горизонтальный нистагм. МРТ головного мозга выявила множественные очаги демиелинизации, включающие гадолиниум перивентрикулярно и в подкорковом белом веществе. В ликворе установлено наличие олигоклонных включений без повреждений гемато-энцефального барьера. Негативными оказались иммуноглобулины крови против хламдий, микоплазмы, простого герпеса 1/2, цитомегаловируса. Иммуноглобулин IgG был резко положительный в отношении возбудителя борелия, что подтвердилось тестом блотирования. Состояние пациента стабилизировалось после проведения пульстерапии солумедролом 1 гр/ив (5 дней) на фоне лечения роцефином (2 гр/ив) в течение 21 дня с последующим длительным лечением антипаркином (карбидопа 250 мг, леводопа 25 мг).

В результате проведенного исследования авторы рекомендуют в сомнительных случаях рассеянного склероза и пракинсонизма провести дифференциальную диагностику с целью исключения или подтверждения нейроборелиоза.

რეზიუმე

ნეირობორელიოზის იშვიათი კლინიკური გამოვლინება (კლინიკური შემთხვევა)

მ. ბერიძე, ნ. ხიზანიშვილი, მ. მდივანი, ო. სამუშია, ნ. გოგოხია

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, პირველი საუნივერსიტეტო კლინიკა, ნევროლოგიური დეპარტამენტი, საქართველო

ნაშრომში მოყვანილია ვერიფიცირებული ნეირობორელიოზის შემთხვევა პარკინსონის იშვიათი კლინიკური გამოვლინებით. შრომის მიზანია ამა თუ იმ დაავადებათა იშვიათი სიმპტომატიკის საფუძვლიანი ანალიზისა და სკრუპულოზური დიფერენციული დიაგნოსტიკის მნიშვნელობის განსაზღვრა მცდარი დიაგნოზის თავიდან აცილებისა და დროული, ადეკვატური მკურნალობის მენეჯმენტში.

აღწერილია ნეირობორელიოზის დიაგნოსტირებული შემთხვევა გაფანტული სკლეროზის და პარკინსონიზმის კლინიკური გამოვლინებით.

44 წლის მამაკაცს, რომელსაც მაკ-დონალდის კრიტერიუმებით დაუდგინა გაფანტული სკლეროზი, დაავადების დაწყებიდან ორ წელიწადში განუვითარდა პარკინსონიზმის ტიპური კლინიკური ნიშნები: ა ამიმიური სახე, ოლიგობრადიკინეზია, კუნთების ტონუსის მატება ექსტრაპირამიდული ტიპით, მტევნის თითებში მოსვენების ტრემორი, ჰორიზონტალური ნისტაგმი. პაციენტს ჩაუტარდა თავის ტვინის კონტრასტული მაგნიტურ-რეზონანსული ტომოგრაფია (მრტ -1.5 ტესლა). ცერებროსპინური სითხე გამოკვლეული იყო ოლიგოკლონურ ჩანართებზე. სისხლის იმუნოგლობულინები IgM და IgG გამოკვლეული იყო ქლამიდიის, მიკოპლაზმის, ბორელიის, მარტივი ჰერპესის 1.2, ციტომეგალოვირუსის გამომწვევების მიმართ ELISA მეთოდით.

კლინიკური სიმპტომატიკა წარმოდგენილია ამიოსტატიკური სინდრომით, თავის ტვინის მრტ-ზე გამოვლინდა მრავლობითი გადოლინიუმ-გაფართოებადი დემიელინიზაციის კერები პერივენტრიკულურად და ქერქ-ქვეშა თეთრ ნივთიერებაში. ლიქვორში დადგინდა ოლიგოკლონური ჩანართების არსებობა ჰემატოენცეფალური ბარიერის დისფუნქციის გარეშე. სისხლში იმუნოგლობულინები (IgM, IgG) უარყოფითი აღმოჩნდა ქლამიდიას, მიკოპლაზმას, მარტივი ჰერპესის 1/2, ციტომეგალოვირუსის მიმართ და მკვეთრად დადებითი - ბორელიას გამომწვევზე (IgG), რაც შემდგომ დადასტურდა ბლოტირების ტესტით. პაციენტს ჩაუტარდა მკურნალობა სოლუმედროლით (1 გრ/ი.ვ.) 5 დღის განმავლობაში, როცეფინის ფონზე (დღიური დოზა 2 გრ ინტრავენურად) 21 დღის მანძილზე, რაც გაგრძელდა ხანგრძლივი ტაბლეტირებული მკურნალობით ანტიპარკინით (კარბიდოპა 250 მგ, ლევოდოპა 25 მგ). პაციენტის მდგომარეობა მკვეთრად გაუმჯობესდა.

ჩატარებული კვლევის შედეგებზე დაყრდნობით ავტორებს გამოტანილი იქვთ დასკვნა გაფანტული სკლეროზის და პარკინსონიზმის საეჭვო შემთხვევაში ჩატარებულ იქნას დიფერენციული დიაგნოსტიკა ნეირობორელიოზის გამორიცხვის ან დადასტურების მიზნით.

PLANT AEROALLERGENS IN TWO MAJOR CITIES OF GEORGIA – TBILISI AND KUTAISI

[1]Abramidze T., [1]Gotua M., [2]Chikhelidze N., [1]Cheishvili T., [1]Gamkrelidze A.

[1]Center for Allergy and Immunology Research, Tbilisi; [2]Institute of Botany, Ilia State University, Tbilisi, Georgia

Pollen allergy (hay fever/pollinosis) is caused by a hypersensitivity reaction mainly of the respiratory tract and eye conjunctivae to pollen grains. It includes allergic rhinitis, allergic conjunctivitis, allergic bronchial asthma, and less frequently, urticaria [8]. Seasonal allergies are often characterized by the recurrence of symptoms, which show periods of improvement and relapse [9]. The allergic manifestations are more prevalent during the plant pollination season; hence, accurate descriptions of its start and end periods are important for both patients and clinicians alike [10,11,14]. Pollen grains, a causative agent of asthma and rhinitis, are among the commonest allergens in atopic patients. Pollen allergy is now a public health problem due to its elevated prevalence and associated costs in terms of impaired work fitness, sick leave, and cost of healthcare [5,6].

The number of people allergic to plant aeroallergens has substantially increased in big cities and industrial areas [15]. The percentage of sufferers is considerable, especially among the younger population: a recently published study demonstrates that between 10% and 20% of adolescents aged 13-14 years suffer from severe allergic rhinitis [3]. According to the last phase of ISAAC study, which was conducted in Georgia in 2012, the prevalence of asthma and allergies markedly increased among 6- to 7-year-old children and 13- to 14-year-old adolescents, especially for the symptoms of rhino-conjunctivitis [1,2].

The monitoring of aerobiological parameters is of paramount importance for the characterization of allergenic risks. The patients sensitized to pollens should read their regional pollen bulletins to keep themselves properly up-to-date on allergic disease prevention and treatment. In the last decades aerobiological studies have been developed rapidly in most part of Europe. In our country, the monitoring of pollen and fungi spores concentrations was started in 2012. Running a Burkard Volumetric Spore Samplers and producing the pollen and spore counts have been done in two cities - Tbilisi and Kutaisi, which was selected in accordance with epidemiology ISAAC study centers.

The aims of presented study were as follows: to profile the plant aeroallergens in two major cities of Georgia, to compare the character of pollination curves, to determine the dates of beginning of pollen seasons and their duration in particular cities.

Material and methods. *Study area.* Tbilisi is a capital of Georgia, with climate transitional from humid subtropical to relatively mild continental. The city experiences very warm summers and moderately cold winters. Like other regions of Georgia, Tbilisi receives significant rainfall throughout the year with no distinct dry period. The city's climate is influenced both by dry (Central Asian/Siberian) air masses from the east and oceanic (Atlantic/Black Sea) air masses from the west. Because the city is bounded on most sides by mountain ranges, the close proximity to large bodies of water (Black and Caspian Seas) and the fact that the Greater Caucasus Mountains Range (further to the north) blocks the intrusion of cold air masses from Russia, Tbilisi has a relatively mild microclimate compared to other cities that possess a similar climate along the same latitudes. The average annual temperature in Tbilisi is 13.3^{0}C. January is the coldest month with an average temperature of 2.3^{0}C. July is the hottest month with an average temperature of 24.9^{0}C.

Kutaisi, the legislative capital, has a humid subtropical climate with a well-defined on-shore/monsoonal flow (characteristic of the Colchis Plain) during the autumn and winter months. The summers are generally hot and relatively dry while the winters are wet and cool. Average annual temperature in the city is 14.5 degrees Celsius. January is the coldest month with an average temperature of 5.3 degrees Celsius while July is the hottest month with an average temperature of 23.2 degrees Celsius. Average annual precipitation is around 1,530 mm. Rain may fall in every season of the year. The city often experiences heavy, wet snowfall (snowfall of 30 cm or more per single snowstorm is not uncommon) in the winter, but the snow cover usually does not last for more than a week. Kutaisi experiences powerful easterly winds in the summer, which descend from the nearby mountains.

Plant Aeroallergens/Pollen Monitoring. The airborne pollen monitoring was performed with a Burkard Seven Day Volumetric Spore-trap (Burkard Manufacturing Co Ltd, UK) during the seasons of 2016, following the recommendations of European Aerobiology Society [7]. The measuring sites/stations described in the Table 1.

A strip of silicone-coated Melinex tape was exposed to the air for trapping the plant aeroallergens, and was changed once a week. The exposed tape was cut into 48 mm segments representing 24 h periods. These segments were mounted on microscopic slides using Mowiol mixed with a stain (basic fuchsin) to enable visualization under a high resolution light microscope at 400× magnification.

Pollens concentration was calculated and expressed as the number of pollen grains per cubic meter of air (p/m^3). According to the EAN (European Aeroallergen Network) definition season threshold was standard: season begins at 5%, ends at 95% of total sum. Principle Particle Period (ppp) showed start and end of time period, which contains 90 % present of the yearly particle count.

Results and their discussion. The numerical results of the plant aeroallergens pollen season characteristics were summarized in Table.2. The main tree pollen types for both centers were: *Alnus, Betula, Carpinus, Castanae, Corylus, Cupressaceae, Fagus, Fraxinus, Juglans, Morus, Pinus, Platanus, Quercus, Salix, Tilia,* and *Ulmus.* Comparison analysis had shown that the pollination season of the most trees began earlier in Kutaisi. As an example, the beginning of pollination was about 10-15 days earlier for *Corylus (*January 12th in Kutaisi vs January 21st in Tbilisi*) and Alnus (*January 15th in Kutaisi vs February 2nd in Tbilisi). The difference in pollen count of particular taxa was observed as well. It was much higher in Kutaisi for *Corylus* (632.6 total number p/m^3 vs. 365.4), *Alnus* (2907.6 total number p/m^3 vs. 1044.5) and *Cupressaceae* (21257.6 total number p/m^3 vs. 10432.0) and significantly higher in Tbilisi for*, Platanus* (3423.7 total number p/m^3 vs. 202.3) and *Pinus* (1064.0 total number p/m^3 vs 206.6). The highest account of tree pollen about 4471.6 *Cupressaceae* grains

Table 1. The measuring sites/stations description

The station's name and location	Latitude	Longitude	Sampling height above ground level (m)	Sampling height above sea level (m)	Flow rate of the pollen trap and frequency of control
Tbilisi (Botanic Institute Building of the Ilia State University of Georgia)	41.68605	44.80986	about 15 m	380-600 m	10 l/min. Weekly check
Kutaisi (Z. Tskhakaia Interventional Medicine Clinic of West Georgia)	42.269836	42.676221	about 20 m	80-120 m	10 l/min. Weekly check

Table 2. Summary results of airborne pollen seasons in 2016

Particle	Tbilisi				Kutaisi			
	peak value (p/m^3)	total	ppp start (date)	ppp end (date)	peak value (p/m^3)	total	ppp start (date)	ppp end (date)
Abies	4.2	45.9	4/7/2016	4/29/2016	-	-	-	-
Acer	42.9	328.9	3/11/2016	4/8/2016	-	-	-	-
Aesculus	3.2	13.1	5/7/2016	5/23/2016	-	-	-	-
Alnus	402.3	1044.5	2/7/2016	2/18/2016	678.9	2907.6	1/15/2016	2/14/2016
Ambrosia	72.1	1055.4	8/11/2016	9/20/2016	86	643.4	8/20/2016	9/17/2016
Artemiasia	142.6	1759.4	8/18/2016	10/28/2016	7	37.6	7/19/2016	9/27/2016
Betula	1.1	2.1	4/26/2016	5/24/2016	1.6	4.7	5/10/2016	5/28/2016
Cannabaceae	136.7	656.8	5/10/2016	5/23/2016	-	-	-	-
Carpinus	24.4	267.7	3/25/2016	4/27/2016	4.7	37	3/18/2016	5/2/2016
Castanae	17	81.3	6/12/2016	8/1/2016	45.5	319.6	6/4/2016	6/28/2016
Cedrus	1.1	4.2	10/14/2016	10/31/2016	-	-	-	-
Chenopodium	44.6	1070.3	7/14/2016	9/13/2016	9.5	114.5	7/18/2016	9/23/2016
Compositae	4.4	50.6	5/23/2016	10/27/2016	-	-	-	-
Corylus	85.9	365.4	1/21/2016	3/1/2016	58.3	632.6	1/12/2016	2/28/2016
Cruciferae	9.5	269.6	4/5/2016	7/2/2016	7.2	80.1	4/3/2016	6/3/2016
Cupressaceae	1303.1	10432	2/15/2016	3/26/2016	4471.6	21257.6	2/8/2016	2/25/2016
Fabaceae	2.7	27.4	6/26/2016	8/27/2016	-	-	-	-
Fagus	14.3	159.5	4/2/2016	5/14/2016	18	75.6	4/2/2016	5/23/2016
Fraxinus	121.3	464.2	2/18/2016	4/5/2016	53.5	274.3	2/10/2016	3/27/2016
Juglans	16.4	81.3	4/5/2016	5/8/2016	6.4	48.3	3/25/2016	4/16/2016
Morus	304.2	1164.4	4/2/2016	4/13/2016	21.2	137.3	3/19/2016	4/25/2016
Picea	3.7	27.2	5/8/2016	6/14/2016	-	-	-	-
Pinus	195	1064	4/13/2016	5/28/2016	35	206.6	3/25/2016	6/7/2016
Plantago	3.7	15.6	5/18/2016	7/26/2016	1.1	3.2	6/2/2016	6/8/2016
Platanus	714.4	3423.7	3/26/2016	4/13/2016	47.2	202.3	3/27/2016	5/10/2016
Gramineae	61.5	743.2	5/7/2016	9/19/2016	53	285.9	4/13/2016	9/11/2016
Populus	1.1	2.1	4/11/2016	4/21/2016	-	-	-	-
Quercus	37.1	346.8	4/8/2016	5/17/2016	22.8	149.7	3/6/2016	5/3/2016
Rosacea	0.5	0.5	3/17/2016	3/17/2016	-	-	-	-
Rumex	3.7	13.2	5/8/2016	7/17/2016	-	-	-	-
Salix	2.7	5.9	2/6/2016	3/15/2016	9.5	68.2	2/20/2016	3/25/2016
Tilia	3.2	14.8	6/5/2016	7/21/2016	1.6	19	5/13/2016	6/18/2016
Ulmus	672.6	3045.8	2/25/2016	3/5/2016	32.3	217.6	2/7/2016	3/2/2016
Urticacea	7.4	90.4	7/23/2016	10/2/2016	1.1	4.1	8/9/2016	8/24/2016

in m^3 per 24 h was observed in Kutaisi at the middle of February (date 2016-02-20). Main grass pollen was *Gramineae:* the pollination started a little bit earlier in Kutaisi, but the pollen count was generally higher in Tbilisi. The features of pollen seasonal distribution and amount were revealed also for the weeds (mainly *Ambrosia* and *Artemiasia).* Pollen season was started earlier, especially for Artemisia in Kutaisi. The total amount of pollen grains was higher for both weed plant aeroallergens in Tbilisi (*Ambrosia* – 1055.4 vs 643.4 and *Artemisia* 1759.4 vs 37.6).

Some plant aeroallergens were not revealed during the observation period (2016) in Kutaisi center, particularly – *Abies, Acer,*

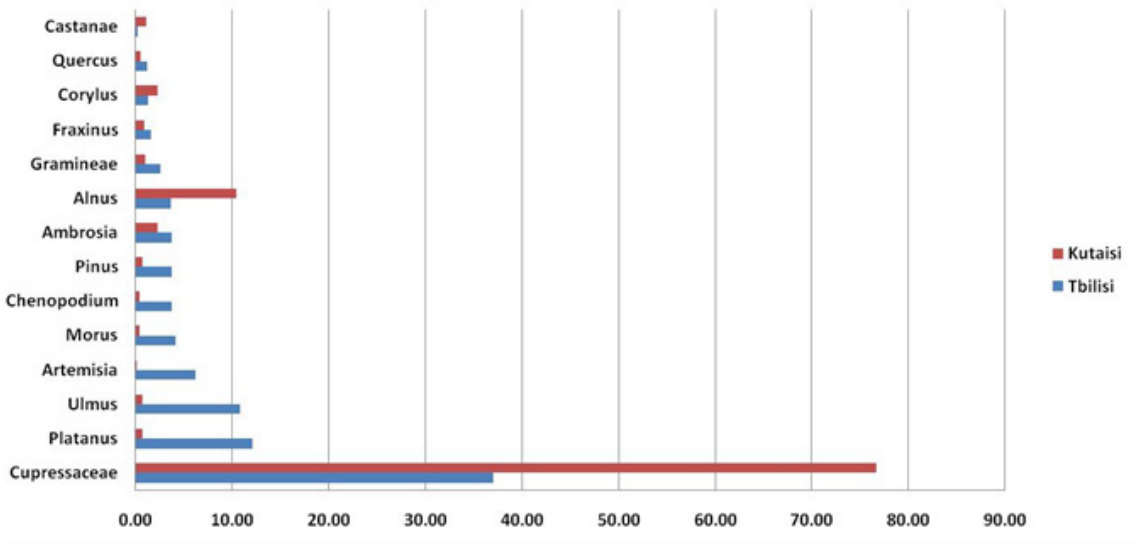

Fig. Percentages of pollen of some plant taxa in the pollen spectrum of Tbilisi and Kutaisi

Aesculus, Cannabaceae, Cedrus, Fabaceae, Picea, Populus, Rosacea and *Rumex.*

In both centers the major pollen producers were trees, namely Cupressaceae (37.1%), Platanus (12.2%) and Ulmus (10.8%) for Tbilisi and Cupressaceae (76.7%) and Alnus (10.5%) for Kutaisi.

The monthly airborne pollen concentrations in Tbilisi for different plant taxa were very high in February – May 2016, when 80% of annual total pollen concentration was recorded. For Kutaisi monitoring site 94 % of annual total pollen concentration was recorded at the period of January-April 2016.

The results of investigation show that plant aeroallergens distribution was different in two studied cities. The concentration of pollen grains in the air over a city is determined by the individual rhythm of plant pollination, meteorological condition, and composition of local flora, geographical location and kind of urban structure (loose or compact housing, areas with many gardens or with scarce vegetation, industrial areas, agricultural areas or forests) [15].

The major pollen type for both cities is *Cupressaceae* (37.1% for Tbilisi and 76.7% for Kutaisi of annual total pollen concentration), which associated with *Cupressus* or *Juniperus* spp. from ornamentals in the city's trees and parks. Cypress releases an enormous amount of anemophilous pollen and it has been recognized to be responsible for a large part of total annual amount of most allergenic tree pollen in several Mediterranean areas. In the city of Cordoba, southern Spain, Cupressaceae pollen represents at least 30% of the total pollen count during the winter season, whereas in Italy and Albania it reaches 20-40% of annual pollen rain [6]. Our results are comparable to Mediterranean pollen data.

Platanus pollen appears to be one of the most common taxon in the air of Tbilisi during March. This is a very common and widespread urban tree; airborne pollen concentrations and therefore the severity of the allergy symptoms depend on the abundance of these trees as ornamentals [4]. Much less *Platanus* pollen was recorded in Kutaisi; this genus accounted only 0.73% of total pollen and peak value was 47.2 grains/m^3.

Significant pollen contributor for Tbilisi was Ulmus, which was widely planted as an ornamental in urban settings, with peak of pollination period at the end of February. The elm family contributed little pollen to the air in Kutaisi (less than 1% of the total pollen recorded). The importance of *Ulmaceae* pollen in asthma, allergic rhinitis and other allergy conditions has been demonstrated by numerous studies from around the world [6].

Alnus pollen produced by alder trees is a very strong allergen, similar to that produced by hazel. Clinical symptoms can appeared at the pollen concentration as low as 50 grains in m^3 per 24 h. In Kutaisi the peak value (678.9 grains/m^3) for *Alnus* pollen was fixed at February.

The concentration of grass and weeds pollen was expected to provoke hay fever in summer time. The long *Gramineae* pollination season in Georgia (Tbilisi – 157 days and Kutaisi – 129 days) could be interpreted as in all European countries. One of the causes of this phenomenon could be the fact that grass pollen, which can be identified only at the family level, is originated from many species of wildgrasses, with different, overlapping flowering time, lasting for several months [12].

Ambrosia artemisiifolia L. (common or short ragweed) has been considered to be an invasive and alien plant by the European and Mediterranean Plant Protection Organization since 2004. It is an important weed in agriculture and source of highly allergenic pollen. The plant has now become naturalized in Europe and frequently forms part of the flora. The prevalence of sensitization to Ambrosia pollen allergens is increasing in Europe and reflects the expansion of Ambrosia populations [13]. The Ambrosia pollen count is higher and pollination season is longer in Tbilisi, eastern part of Georgia, where according to the local data this invasive plant widely spread. The same result was obtained for other weed – *Artemisia*, which is also typical for eastern Georgia's flora, especially Tbilisi area.

The differences (beginning of season, peak day, length of season, quantity of grains in m^3 per 24 h) noted in pollen count between two major cities of Georgia may be due to a different composition of local flora and the influence of weather. Future research in order to end up with comprehensive description of peculiarities of pollen distribution in different regions of Georgia as well as weather influence on pollen release should be done.

Conclusion. The study of the plant aeroallergens behavior reveals the aerobiological differences that exist between two studied cities: Plant aeroallergen concentration in the atmosphere of Tbilisi (capital of Georgia, eastern part of the country) was reported to be highest for *Cupressaceae, Platanus, Ulmus* and *Artemisia*; Pollen concentration in the atmosphere of Kutaisi (legislative capital, western part of country) was reported to be the highest for *Cupressaceae* and *Alnus*; The differences in the time of the beginning of pollination were notable and start about 10-15 days earlier in the western part of the country (Kutaisi site); The differences in the pollen count of particular taxa were also significant, particularly, much higher in Kutaisi for *Corylus*, *Alnus* and *Cupressaceae* and significantly higher in Tbilisi for *Platanus* and *Pinus.*

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SUMMARY

PLANT AEROALLERGENS IN TWO MAJOR CITIES OF GEORGIA – TBILISI AND KUTAISI

[1]Abramidze T., [1]Gotua M., [2]Chikhelidze N., [1]Cheishvili T., [1]Gamkrelidze A.

[1]Center for Allergy and Immunology Research, Tbilisi; [2]Institute of Botany, Ilia State University, Tbilisi, Georgia

Pollen allergy is caused by a hypersensitivity reaction mainly of the respiratory tract and eye conjunctivae to pollen grains. The number of people allergic to plant aeroallergens has substantially increased in big cities and industrial areas. The monitoring of aerobiological parameters is of paramount importance for the characterization of allergenic risks. The aims of presented study were as follows: to profile the plant aeroallergens in two major cities of Georgia, to compare the character of pollination curves, to determine the dates of beginning of pollen seasons and their duration in particular cities. Two Burkard 7-day samplers were located in cities: Tbilisi, with climate transitional from humid subtropical to relatively mild continental and Kutaisi, with humid subtropical with a well-defined on-shore/monsoonal flow. Pollen counts were expressed as a daily mean value in number of pollen grains/spores per m^3 of air. Data was obtained in 2016 year. The main tree pollen types for both centers were: *Alnus* (Alder), *Betula* (Birch), *Carpinus* (Hornbeam), *Castanae* (Chestnut), *Corylus* (Hazel), *Cupressaceae* (Cypress), *Fagus* (Beech), *Fraxinus* (Ash), *Juglans* (Walnut), *Morus* (Mulberry), *Pinus* (Pine), *Platanus* (Plane Tree), *Quercus* (Oak), *Salix* (Willow), *Tilia* (Lime), and *Ulmus* (Elm Tree). Comparison analysis had shown that the pollination season of the most trees began earlier in Kutaisi. As an example, the beginning of pollination was about 10-15 days earlier for *Corylus* and *Alnus*. The difference in pollen count of particular taxa was observed as well. It was much higher in Kutaisi for *Corylus*, *Alnus* and *Cupressaceae* and significantly higher in Tbilisi for *Platanus* and *Pinus*. Main grass pollen was *Gramineae*

(Grasses)*:* the pollination started a little bit earlier in Kutaisi, but the pollen count was generally higher in Tbilisi. The features of pollen seasonal distribution and amount were revealed also for the weeds (mainly *Ambrosia* (Ragweed) and *Artemiasia* (Mugwort)).

The differences noted in pollen count between two major cities of Georgia may be due to a different composition of local flora and the influence of weather.

Keywords: plant aeroallergens, pollen season.

РЕЗЮМЕ

РАСТИТЕЛЬНЫЕ АЭРОАЛЛЕРГЕНЫ В ДВУХ ОСНОВНЫХ ГОРОДАХ ГРУЗИИ – ТБИЛИСИ И КУТАИСИ

[1]Абрамидзе Т.Г., [1]Готуа М.А., [2]Чихелидзе Н.З., [1]Чеишвили Т.Г., [1]Гамкрелидзе А.Г.

[1]Центр исследований аллергии и иммунологии, Тбилиси; [2]Государственный университет Ильи, Институт ботаники, Тбилиси, Грузия

Аллергия к пыльце растений вызвана в основном реакцией гиперчувствительности респираторного тракта и конъюнктивы глаза к пыльцевым зернам. Количество людей, аллергичных к растительным аэроаллергенам, неуклонно растет в больших городах и индустриальных зонах. Мониторинг аэробиологических параметров необходим для определения рисков аллергии. В ходе исследования поставлены следующие задачи: определение растительных аэроаллергенов в двух основных городах Грузии, сравнение характера полинации, определение начала сезона пыльцы и его продолжительность в исследуемых городах.

Два аппарата (Burkard 7-day sampler) были локализованы в городах: Тбилиси с переходным климатом между субтропическим и умеренно континентальным и Кутаиси с влажным субтропическим и ветренным климатом. Концентрация пыльцы выражалась дневным значением количества пыльцы в кубическом метре воздуха. Наблюдения проводились в течение 2016 года.

Для обоих центров основными типами пыльцы деревьев являлись: *Alnus* (Ольха)*, Betula* (Береза)*, Carpinus* (Граб)*, Castanae* (Каштан)*, Corylus* (Лещина)*, Cupressaceae* (Кипарис)*, Fagus* (Бук)*, Fraxinus* (Ясень)*, Juglans* (Орех)*, Morus* (Тутовое дерево)*, Pinus* (Сосна)*, Platanus* (Платан)*, Quercus* (Дуб)*, Salix* (Ива)*, Tilia* (Липа) и *Ulmus* (Вяз). Сравнительный анализ выявил, что сезон полинации для большинства деревьев начинается раньше в Кутаиси. Примером является *Corylus* и *Alnus*, цветение которых начинается на 10-15 дней раньше. Наблюдается также различие в количестве пыльцы. В Кутаиси больше пыльцы *Corylus*, *Alnus* и *Cupressaceae,* в Тбилиси - *Platanus* и *Pinus*. Пыльца травянистых растений в основном представлена *Gramineae* (Травы): сезон полинации наступает раньше в Кутаиси, однако количество пыльцы больше в Тбилиси. Особенности распространения и количества пыльцы выявлены также для сорняков - *Ambrosia* (Амброзия) и *Artemiasia* (Полынь).

Различия, наблюдаемые в показателях мониторинга пыльцы в двух основных городах Грузии, возможно, связаны с особенностями местной флоры и влиянием погодных условий.

რეზიუმე

მცენარეული აეროალერგენები საქართველოს ორ ძირითად ქალაქში – თბილისსა და ქუთაისში

[1]თ. აბრამიძე, [1]მ. გოთუა, [2]ნ. ჩიხელიძე, [1]თ. ჭეიშვილი, [1]ა. გამყრელიძე

[1]ალერგიისა და იმუნოლოგიის კვლევითი ცენტრი, თბილისი; [2]ილიას სახელმწიფო უნივერსიტეტი,ბოტანიკის ინსტიტუტი, თბილისი, საქართველო

მცენარეული მტვრის მიმართ ალერგია, ძირითადად, გამოწვეულია რესპირაციული ტრაქტისა და თვალის კონიუნქტივის ჰიპერმგრძობელობის რეაქციით მცენარეული მტვრის მარცვლის მიმართ. დიდ ქალაქებსა და ინდუსტრიულ ზონებში განუხრელად იზრდება მცენარეული აეროალერგენების მიმართ ალერგიული პირების რიცხვი. აერობიოლოგიური პარამეტრების მონიტორინგი მეტად მნიშვნელოვანია ალერგიის რისკების შესაფასებლად. აღნიშნული კვლევის მიზნებია: მცენარეული აეროალერგენების განსაზღვრა საქართველოს ორ ძირითად ქალაქში, პოლინაციის მრუდეების ერთმანეთთან შედარება, პოლინაციის სეზონის დაწყებისა და ხანგრძლივობის განსაზღვრა.

მცენარეული მარცვლის შემაგროვებელი ორი აპარატი (Burkard 7-day sampler) განთავსებული იყო თბილისში - სუბტროპიკული და ზომიერად კონტინენტური გარდამავალი კლიმატით და ქუთაისში - ნოტიო-სუბტროპიკული ქარიანი კლიმატით. მცენარეული მარცვლის კონცენტრაცია განისაზღვრა მარცვლების რაოდენობით ჰაერის ერთ კუბურ მეტრში. მონაცემების დაგროვება ხდებოდა 2016 წლის განმავლობაში.

ორივე ცენტრისთვის ხეების მცენარეული მარცვლის ძირითად ტიპებს წარმოადგენდნენ: *Alnus* (მურყანი)*, Betula* (არყის ხე)*, Carpinus* (რცხილა)*, Castanae* (წაბლი)*, Corylus* (თხილი)*, Cupressaceae* (კვიპაროსი)*, Fagus* (წიფელი)*, Fraxinus* (იფანი)*, Juglans* (კაკლის ხე)*, Morus* (თუთის ხე)*, Pinus* (ფიჭვი)*, Platanus* (ჭადარი)*, Quercus* (მუხა)*, Salix* (ტირიფი)*, Tilia* (ცაცხვი) და *Ulmus* (თელა). შედარებითმა ანალიზმა გამოავლინა, რომ პოლინაციის სეზონი ხეების უმეტესობისთვის უფრო ადრე იწყება ქუთაისში. მაგალითად, *Corylus* და *Alnus* პოლინაცია, თბილისთან შედარებით, 10-15 დღით ადრე იწყება. განსხვავებულია, აგრეთვე, მცენარეული მტვრის მარცვლის რაოდენობაც: მაჩვენებელი მაღალია ქუთაისში *Corylus*, *Alnus* და *Cupressaceae* ხეებისთვის, ხოლო თბილისში - *Platanus* და *Pinus*-სთვის. ბალახებს შორის, ძირითადად, გავრცელებულია *Gramineae* (ბალახები); პოლინაციის სეზონი შედარებით ადრე იწყება ქუთაისში, მტვრის მარცვლის რაოდენობა კი მეტია თბილისში. თავისებურებები გამოვლინდა, აგრეთვე, სარეველების, უპირატესად *Ambrosia* (ამბროზია) და *Artemiasia* (ავშანი) მტვრის გავრცელებასა და რაოდენობაში.

საქართველოს ორ ძირითად ქალაქს შორის მცენარეული მტვრის მარცვლების მაჩვენებლების სხვაობა შესაძლოა განპირობებული იყოს ადგილობრივი ფლორის თავისებურებებით და ამინდის გავლენით.

COMPARATIVE STUDY OF FIB-4 INDEX AND TRANSIENT ELASTOGRAPHY AMONG PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION IN GEORGIA

[1,2,3]Dolmazashvili E., [1,2]Karchava M., [1,2]Abutidze A., [1,2,3]Sharvadze L., [1,2,3]Tsertsvadze T.

[1]Hepatology Clinic "HEPA", Tbilisi; [2]Infectious Diseases, AIDs & Clinical Immunology Research Center, Tbilisi; [3]Iv. Javakhishvili Tbilisi State University, Georgia

Hepatitis C virus (HCV) infection is a major global health problem that affects 130-150 million people worldwide. Chronic hepatitis C is associated with significant morbidity and mortality, which results mainly from the progression of liver disease towards cirrhosis and hepatocellular carcinoma [18].

Novel drugs known as direct-acting antivirals (DAAs) with or without pegylated interferon and ribavirin revolutionized HCV treatment by dramatically increasing sustained virological response rates, and providing shortened and simplified regimens while minimizing treatment-related side effects.

Even in the DAA era, prognosis and management of chronic HCV infection greatly depend on the degree and progression of liver fibrosis (LF) [10,12].

Several approaches have been developed for evaluating severity of LF. Liver biopsy (LB) is traditionally considered as the reference standard for fibrosis staging [3]. However, this method has several limitations [2]. Firstly, the sample obtained during the procedure represents small part of the liver (1/50000) and therefore, sampling error can occur [2]; in addition, it has also been shown that 1/3rd of LBs had a difference of at least one stage of fibrosis when samples taken from the left and right lobes laparascopically [7].Secondly, histological examination is prone to intra and interobserver variation, which may occur even when widely validated systems are used to score liver damage [17]. Thirdly, the procedure requires specially trained personnel and is not accessible for all clinics. Finally, LB is an invasive procedure with the risk of different complications: the rate of serious bleeding requiring blood transfusion is reported to occur in 1.7%, pain occurs in 87% of cases and persists in 20% beyond the day of the procedure; inadvertent biopsy of other organs is rare. The risk of death is estimated to be 0.01-0.1% of cases [17]. Despite these serious adverse effects, these are uncommon and LB is generally considered to be a safe procedure when guided by imaging and performed by experienced hands. However, there is low patient acceptability for this procedure. Altogether these limitations have led to the development of non-invasive methods for assessment of LF. These methods rely on two distinct approaches: a "biological" approach based on the quantification of biomarkers in serum samples and a "physical" approach based on the measurement of liver stiffness (LS) for which transient elastography (TE) has been the pioneer technique used [3]. Direct serum biomarkers (laminin, type IV collagen, collagenases, metalloproteases etc.) reflect the deposition or removal of extracellular matrix in the liver, while indirect markers (platelet count, prothrombin index, ratio of aspartate to alanine aminotransferase (AST/ALT), etc.) can be measured in routine blood specimens and indicate alterations in hepatic function.

As for the imaging methods: TE, ultrasound-based techniques and 3-D magnetic resonance (MR) elastography are use [1].

Taking into account the importance of accurate diagnosis for clinical implications, prognosis and treatment decisions, it is critically important to evaluate degree of fibrosis/cirrhosis by two different strategies. Therefore, many algorithms were proposed including TE and serum biomarkers or several serum biomarkers [13; 4] in patients with viral hepatitis.

The objective of our study was to retrospectively evaluate LF severity among HCV infected patients and analyze the concordance between two methods: liver stiffness measurement (LSM) using TE and a simple blood test called FIB-4 index (FIB-4), which combines standard biochemical values of platelets, AST, ALT and patient's age.

Material and methods. We conducted a retrospective study among 750 patients with chronic HCV mono-infection at Georgian - French Joint Hepatology Clinic "HEPA" from March 2015 to February 2016. The mean age of the study population was 51 years; 595 (79.3%) were male and 155 (20.7%) were female.

We have studied the utility of TE and FIB-4 for LF evaluation. Clinical data were obtained from the patient's medical records.

Patients with confirmed HCV infection, valid Fibroscan measurements and biological samples results within one-week time frame were included in the study. Patients with hepatitis B virus infection, autoimmune hepatitis, cholestatic liver disease, alcoholic and nonalcoholic steatohepatitis, hemochromatosis, Wilsons Disease, those receiving hepatotoxic drugs and patients under the age of 18 were excluded from the study. The study protocol was approved by the Institutional Review Board of the clinic "HEPA".

Diagnosis of HCV infection was based on detection of HCV antibodies (Anti HCV) in serum by Enzyme-Linked Immuno Sorbent Assay (ELISA) using ORTO HCV 3.0 test and subsequent HCV RNA test by COBAS TaqMan HCV Test v2 (Roche, Basel, Switzerland) with the quantification limit of 25 Iu/ml.

LF was staged using TE (Fibroscan 502, Echosens, Paris, France), which measures the velocity of a low frequency (50Hz) elastic shear wave propagating through the liver. The velocity is directly related to tissue stiffness. The results are expressed in kilopascals (kpa) and range from 1.5 to 75 kpa with normal values around 5 kpa. TE was performed according to the manufacturer's instructions using M or XL probe on a patient lying supine, with the right arm elevated to facilitate access to the right liver lobe; XL probe was used for patients with Body Mass Index >28kg/m^2. Two officially trained operators were responsible for carrying out the LSM. TE result was regarded as valid, if the following criteria were fulfilled: (1) at least ten valid shots; (2) a success rate above 60%; (3) an interquartile range, reflecting the variability of measurements less than 30% of the median LS value.

LSM ≤7.0 kpa was considered as fibrosis stage F0-F1 by Metavir, 7.1-8.5 kpa – fibrosis stage F1-F2, 8.6-9.5 kpa – F2, 9.6-12.5 kpa

– F3, 12.6-14.5 kpa – F3-F4 and LSM >14.5 kpa – fibrosis stage F4 by Metavir, respectively.

The FIB-4 score was calculated using specific web based algorithm:
Patient's age X AST (IU/L)/platelet count (expressed as platelets $X10^9$/L) X ALT ^{½} (IU/L) [9].
LF was ranked using standard cut-off values [8,9].
Class 1 – FIB-4 index < 1.45, which is interpreted as absence of significant fibrosis;
Class 2 – FIB-4 index between 1.45 – 3.25 as inconclusive result and
Class 3 – FIB-4 index > 3.25 as significant fibrosis of F3-F4 by Metavir, respectively.

Definitions:
Concordance between results of FIB-4 and TE was defined if the study subjects had FIB-4 index <1.45 and LSM ≤9.5 kpa (low grade fibrosis concordant group) or FIB-4 index >3.25 and LSM >9.5 kpa (high grade fibrosis concordant group).

Discordance between results of FIB-4 and TE was defined if the study subjects had FIB-4 index <1.45 and LSM >9.5 kpa or FIB-4 index >3.25 and LSM ≤9.5 kpa.

Additional analyses of prothrombin index, albumin concentration, presence of splenomegaly on abdominal ultrasound and esophageal varices on upper gastrointestinal endoscopy were performed among selected patients.

Ultrasound examinations were performed within 1 week of the LSM; spleen size was assessed by the longitudinal size as this variable has been demonstrated to correlate with the actual spleen volume and was considered normal up to 13 centimeters.
Upper gastrointestinal endoscopy was performed within 3-month timeframe of LSM. The cut-off values of 35 g/L for albumin concentration and 80% for prothrombin index were chosen.

Categorical variables are described as number (%). To compare categorical variables, the chi-square or Fisher's exact test were used. These tests were 2-sided. The P values <0.05 was considered statistically significant. Analysis was performed with SAS version 9.3 software (SAS Institute, Inc., Cary, NC, USA).

Results and their discussion. *Transient elastography*
Of total 750 patients analyzed, 335 (44.7%) had LSM more than 9.5 kpa. There was no statistically significant difference by gender regarding the fibrosis score (45.2% vs. 42.6%, p=0.62). Patients above 40 had significantly higher probability of high grade LF (48.6% vs. 17.2%, p<0.0001).

FIB-4 test
Of total 750 patients, 418 (55.7%) had FIB-4 < 1.45, while FIB-4 >3.25 was found in 162 (21.6%) cases. Remaining 170 (22.7%) patients had inconclusive FIB-4 index (1.45-3.25).

Concordant results obtained by TE and FIB-4 were observed in 534 (71.2%) cases. Among them 372 (49.6%) subjects represented low grade fibrosis concordant group, while 162 (21.6%) - high grade fibrosis concordant group (Table 1).

Discordant results (FIB-4 <1.45 and LSM >9.5 kpa) were observed among 46 (6.1%) patients (Table 1). Discrepancy showing high FIB-4 index (>3.25) and low LSM (≤ 9.5 kpa) were not observed in our cohort.

Among those remaining 170 patients representing 22.7% of total study population with inconclusive FIB-4 score, 43 had low grade fibrosis (LSM ≤ 9.5 kpa) and 127 had significant fibrosis (LSM >9.5 kpa) (Table 1).

The FIB-4 < 1.45 and > 3.25 was concordant with TE results in 89% and 100%, respectively. From 418 patients having FIB-4 below 1.45, LSM >9.5 kpa was found in 11% (N=46, mean LSM=18.2 kpa) (Table 2).

Table 1. Comparison of FIB-4 and LSM scores

FIB-4 INDEX AND LSM		TOTAL (750)
Concordant results	< 1.45	372 (49.6%)
	≤ 9.5 kpa	
	>3.25	162 (21.6%)
	>9.5 kpa	
Inconclusive results	1.45-3.25	43 (5.7%)
	≤ 9.5 kpa	
	1.45-3.25	127 (16.9%)
	>9.5 kpa	
Discordant results	< 1.45	46 (6.1%)
	>9.5 kpa	

Table 2. Comparison of FIB-4 Index and Transient Elastography (Metavir)

FIB-4 Index	F0-F1-F2	F3-F4
< 1.45 (n=418)	89% (n=372)	11% (n=46)
1.45 – 3.25 (n=170)	25.3% (n=43)	74.7% (n=127)
>3.25 (n=162)		100% (n=162)
Total (n=750)	55.3% (n=415)	44.7 % (n=335)

Table 3. Distribution of indirect markers of significant fibrosis among discordant and low grade fibrosis concordant groups

Variables	High LSM (n=46)	Low LSM (n=372)	P
Albumin < 35g/L,n (%)	4 (8.7)	2 (0.54)	0.0016
Prothrombin Activity < 80%, n (%)	9 (19.6)	3 (0.8)	0.0001
Esophageal varices, n (%)	7 (15.2)	1 (0.27)	0.0001
Splenomegaly, n (%)	24 (52.2)	34 (9.1)	0.0001

Distribution of indirect markers of significant fibrosis among discordant and low grade fibrosis concordant groups

Additional parameters (prothrombin index, albumin concentration, presence of splenomegaly on abdominal ultrasound and esophageal varices on endoscopy) of significant fibrosis were evaluated and compared between two patient groups in order to assess the reliability of each test used. Low albumin concentration (<35 g/l), low prothrombin index (<80%), occurrence of esophageal varices and splenomegaly were significantly correlated with TE results (P=0.0016, P=0.0001, P=0.0001, P=0.0001 respectively) (Table 3).

Use of reliable tools for estimating LF stage in HCV-infected patients is essential for clinical evaluation as well as for follow-up of patients with the risk of developing LF [5].

LB is considered as gold standard for the staging of hepatic fibrosis; however, it is an invasive procedure with important limitations [7].

Therefore, several non-invasive tests are developed and widely used as markers for LF among patients with HCV infection [16]

LSM using Fibroscan is a reliable, painless and accurate non-invasive tool for diagnosing fibrosis stage. TE is the most widely used and studied validated technique [16]. It can be used for screening to exclude liver cirrhosis for all patients with HCV infection [16]. It can reduce the need for LBs in the majority of chronic hepatitis C patients. Advantages of TE also include a short procedure time (< 5 minutes), immediate results and the ability to test at the bedside or in an outpatient clinic [3]. However, applicability of TE is limited due to obesity, ascites and operator experience and false positive results can be obtained in case of high grade inflammation, narrow intercostal spaces, right heart failure, or other causes of congestive liver and excessive alcohol intake.

The FIB-4 is also a non-invasive method for the evaluation of LF, based on simple variables such as age, AST, ALT and platelet count. Calculations of the results are simple and available immediately; another advantage of this method is that there are no additional costs, as the FIB-4 parameters are included in the standard blood test [11].

We have conducted a retrospective evaluation of FIB-4 and TE among HCV positive patients undergoing HCV care. To our knowledge, it was first attempt to compare FIB-4 and TE among Georgian HCV infected patients.

The FIB-4 index <1.45 showed a negative predictive value of 89% to exclude severe fibrosis while the FIB-4 of more than 3.25 had a positive predictive value of 100% to confirm the existence of significant fibrosis (F3-F4 by Metavir).

Our results show concordance of TE and FIB-4 for fibrosis staging among 2/3 of HCV infected study population. Among remaining patients, FIB-4 test showed inability to make correct identification of fibrosis severity. Namely, majority of remaining patients had inconclusive FIB-4 result, while some patients showed discordant results of high LSM and low FIB-4 score. It should be taken into account that around 75% of these patients with inconclusive FIB-4 results have significant fibrosis (F3-F4) by TE.

We still consider LSM to be more precise, as it has been shown to accurately diagnose patients with advanced LF and is considered as gold standard for non-invasive assessment of LS which correlates with LF [16]. In addition, supplemental testing results among our study patients strengthened reliability of TE results, showing concordance between TE and prothrombin index, albumin concentration, presence of splenomegaly on abdominal ultrasound and esophageal varices on endoscopy. We suggest that low FIB- 4 score in this group of patients was due to the young age and normal platelet count.

Our results are different from those reported by Zhang X et. al. Authors compared several non-invasive methods including TE and FIB-4 and found that they are similarly reliable for diagnosis of advanced LF. The difference between these two studies could be due to the characteristics of the study population and infection with HBV virus. Similar to our results the author also concluded that combination of these two methods does not significantly improve the diagnostic accuracy of TE [14].

Our findings were consistent with data from Kwok R et al. [6]. This study showed comparison of TE with FIB-4, as well as with other non-invasive tests such as Aspartate/Platelet Ratio Index (APRI), Aspartate/Alanine aminotransferase Ratio (AAR), Age/Platelet Index (API) and Fibrosis Index (FI).

Authors showed superiority of TE for every stage of fibrosis when compared with FIB-4, APRI, API, AAR and FI in patients with chronic hepatitis B virus infection. In terms of diagnostic accuracy TE was followed by FIB-4 and APRI.

Study by Zykus R et al. [15] comparing TE with serum based markers such as FIB-4 and APRI showed that TE has the best specificity and sensitivity to predict the histological stage of fibrosis especially in higher stages. Authors suggested that adding FIB-4 test to TE improves diagnostic accuracy for predicting $F \geq 2$ and $F \geq 1$.

Our study demonstrates importance of using FIB-4 index as screening test for LF evaluation among resource limited settings, where TE is not available. As FIB-4 test is easily available, inexpensive, and reproducible, it could rapidly replace expensive and/or invasive methods to assess LF in some scenarios. However, our results stress the importance of adding TE to FIB-4 as confirmatory test in order to improve diagnostic accuracy. Nevertheless, unlike study results reported by Zykus R et al, our data suggest that diagnostic accuracy of TE is not improved by adding FIB-4.

Our study is subject to some limitations. First, considering the nature of retrospective study, the patients' clinical conditions

may be underestimated and certain social-demographic status was not routinely recorded. Secondly, more non-invasive indices/ scores should be included to test which formula can improve the diagnostic value of TE. And finally, the main limitation of our study was the absence of LB data, which remains gold standard for fibrosis evaluation. However, TE still is considered as reliable replacement of LB for LF evaluation [1].

Conclusion. Our findings showed a good correlation between TE and FIB-4 for assessment of the severity of LF. However, our study demonstrated superiority of TE. LSM correlated better with indirect markers of significant fibrosis. Despite relatively good accuracy, a significant number of patients could not be assessed by FIB-4 test due to inconclusive results; Nevertheless, FIB-4 test is feasible for routine use in resource limited settings and can be included in diagnostic algorithms of large-scale public health programs.

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SUMMARY

COMPARATIVE STUDY OF FIB-4 INDEX AND TRANSIENT ELASTOGRAPHY AMONG PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION IN GEORGIA

[1,2,3]Dolmazashvili E., [1,2]Karchava M., [1,2]Abutidze A., [1,2,3]Sharvadze L., [1,2,3]Tsertsvadze T.

[1]Hepatology Clinic "HEPA", Tbilisi; [2]Infectious Diseases, AIDs & Clinical Immunology Research Center, Tbilisi; [3]Iv. Javakhishvili Tbilisi State University, Georgia

Liver biopsy remains the reference standard for fibrosis staging. However, it has several limitations, which have led to the development of non-invasive methods.

We evaluated liver fibrosis severity among HCV infected patients by comparing transient elastography (TE) and FIB-4 index.

Retrospective study was conducted. Clinical data for 750 patients were obtained. The mean age of the study population was 51 years; 595 (79.3%) were male and 155 (20.7%) were female.

TE and tests on biological samples were performed within one-week timeframe. Additional analyses of prothrombin index, albumin concentration, splenomegaly on abdominal ultrasound and esophageal varices on upper gastrointestinal endoscopy were performed among selected patients.

Comparable results were observed among 534 patients (71.2%). FIB-4<1.45 had a negative predictive value of 89% to exclude significant fibrosis and FIB-4>3.25 had a positive predictive value of 100 % to confirm the existence of significant fibrosis.

Inconclusive FIB-4 score was obtained in 170 (22.7%) patients. Of them 127 (74.7%) had significant fibrosis (F3-F4) by TE.

Discordant results (FIB-4 <1.45 and Liver Stiffness Measurement (LSM) >9.5 kpa) were observed in 46 (6.1%) of patients. Low prothrombin index, low albumin concentration, splenomegaly and esophageal varices were significantly (p<0.001) correlated with TE results. Discrepancy showing high FIB-4 score and low LSM was not observed in our cohort.

There was a good correlation between TE and FIB-4 score. FIB-4 could rapidly replace expensive methods to assess liver fibrosis severity in some scenarios. However, our study demonstrated superiority of TE. LSM correlated better with indirect markers of significant fibrosis.

Keywords: hepatitis C, Liver fibrosis, Non-invasive diagnosis, Fibroscan.

РЕЗЮМЕ

СРАВНИТЕЛЬНОЕ ИЗУЧЕНИЕ FIB-4 ИНДЕКСА И ЭЛАСТОГРАФИИ ПЕЧЕНИ У ПАЦИЕНТОВ С ХРОНИЧЕСКИМ ГЕПАТИТОМ С В ГРУЗИИ

[1,2,3]Долмазашвили Э.Р., [1,2]Карчава М.К., [1,2]Абутидзе А.Т., [1,2,3]Шарвадзе Л.Г., [1,2,3]Церцвадзе Т.Н.

[1]Гепатологическая клиника "ГЕПА", Тбилиси; [2]Научно-практический центр инфекционных заболеваний, СПИДа и клинической иммунологии, Тбилиси; [3]Тбилисский государственный университет им. Ив. Джавахишвили, Грузия

Биопсия печени остается эталонным стандартом для оценки стадии фиброза. Тем не менее, метод имеет ряд ограничений, которые привели к развитию неинвазивных методов. Проведена оценка стадии фиброза печени с помощью эластографии и FIB-4 индекса.

Изучены клинические данные 750 пациентов, из них 595 (79,3%) мужчин и 155 (20,7%) женщин, средний возраст обследованных пациентов составил 51 год.

В течение одной недели проводились эластография печени и лабораторные исследования, а также дополнительные анализы протромбинового индекса, альбумина, УЗИ брюшной полости и эндоскопия на выявление спленомегалии и варикоза вен пищевода.

Сопоставимые результаты наблюдались у 534 (71,2%) пациентов. При исключении выраженного фиброза печени, результат FIB-4 <1,45 имел 89% отрицательную прогностическую ценность, а при подтверждении результата FIB-4 >3,25 - 100% положительную прогностическую ценность.

Неопределенный FIB-4 выявлен у 170 (22,7%) пациентов. Из них 127 (74,7%) имели выраженный фиброз (F3-F4), выявленный при помощи эластографии. Дискордантные результаты (FIB-4 <1,45 и LSM> 9,5 кпа) наблюдались у 46 (6,1%) пациентов. Гипопротромбинемия, гипоальбуминемия, спленомегалия и варикозное расширение вен пищевода достоверно (p<0,001) коррелировали с результатами эластографии. Дискордантные результаты с высоким индексом FIB-4 и низким LSM в исследуемой когорте не наблюдались.

Результаты проведенного исследования позволяют заключить, что FIB-4 индекс значительно коррелирует с эластографией печени. В некоторых случаях FIB-4 может быстро заменить дорогостоящие методы для оценки фиброза печени. Тем не менее, данное исследование показало, что преимущественным оценочным методом является эластография печени, которая значимо коррелирует с косвенными маркерами значительного фиброза.

რეზიუმე

FIB-4 ინდექსის და ღვიძლის ელასტოგრაფიის შედარებითი შესწავლა ქრონიკული HCV ინფექციით პაციენტებში საქართველოში

[1,2,3]ე. დოლმაზაშვილი, [1,2]მ. ქარჩავა, [1,2]ა. აბუთიძე, [1,2,3]ლ. შარვაძე, [1,2,3]თ. ცერცვაძე

[1]ჰეპატოლოგიური კლინიკა „ჰეპა", თბილისი; [2]ინფექციური პათოლოგიის, შიდსის და კლინიკური იმუნოლოგიის ს/პ ცენტრი, თბილისი; [3]ი. ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი, საქართველო

კვლევის მიზანს წარმოადგენდა ღვიძლის ფიბროზის სტადიის შეფასება ორი მეთოდის - ღვიძლის ელასტოგრაფიის და FIB-4 ინდექსის გამოყენებით C ჰეპატიტის ვირუსით ინფიცირებულ პირებში.

ჩატარდა რესტროსპექტული კვლევა, დამუშავდა 750 პაციენტის კლინიკური მონაცემები, მათ შორის - 595 (79,3%) მამაკაცი და 155 (20,7%) – ქალი, საშუალო ასაკი – 51 წელი. ღვიძლის ელასტოგრაფია და ლაბორატორიული გამოკვლევები შესრულებული იყო ერთკვირიანი ინტერვალით. 46 (6,1%) პაციენტში დამატებით შეფასდა პროთრომბინის ინდექსი, ალბუმინის კონცენტრაცია, სპლენომეგალია - მუცლის ღრუს ექოსკოპიით და საყლაპავი მილის ვენების ვარიკოზი - ეზოფაგოგასტროდუოდენოსკოპიით.

კონკორდანტული შედეგები მიღებული იქნა 534 (71.2%) პაციენტში. FIB-4<1.45 და FIB-4>3.25 შედეგს ჰქონდა, შესაბამისად,89% უარყოფითი და 100% დადებითი პროგნოზული ღირებულება ღვიძლის შორსწასული ფიბროზის გამოსარიცხად ან დასადასტურებლად. დაუზუსტებელი FIB-4 ქულა გამოვლინდა 170 (22.7%) პაციენტში,მათგან 127-ს (74.7%) ღვიძლის ელასტოგრაფიით დაუდგინდა ღვიძლის შორსწასული ფიბროზი (F3-F4).

დისკორდანტული შედეგები (FIB-4<1.45; ღვიძლის სიხისტე >9.5 კპა) მიღებულია 46 (6.1%) პაციენტში. პროთრომბინის დაბალი ინდექსი, ალბუმინის დაბალი კონცენტრაცია,სპლენომეგალიის და საყლაპავი მილის ვენების ვარიკოზის მაჩვენებლები მნიშვნელოვნად კორელირებს (p<0.001) ღვიძლის ელასტოგრაფიის შედეგებთან. დისკორდანტული შედეგები მაღალი FIB-4 ინდექსით და ღვიძლის სიხისტის დაბალი მაჩვენებლით საკვლევ კოჰორტაში არ დაფიქსირებულა.

FIB-4 ინდექსსა და ღვიძლის ელასტოგრაფიას შორის ვლინდება მნიშვნელოვანი კორელაცია. შემთხვევების

ნაწილში შესაძლებელია FIB-4 ინდექსით ჩანაცვლდეს ძვირადღირებული მეთოდები და მარტივად შეფასდეს ღვიძლის ფიბროზის სიმძიმე, თუმცა, კვლევამ აჩვენა ღვიძლის ელასტოგრაფიის უპირატესობა. ღვიძლის სიხისტის მაჩვენებელი მტკიცედ კორელირებს ღვიძლის შორსწასული ფიბროზის არაპირდაპირ მარკერებთან.

COMBINED ANTIVIRAL TREATMENT OF HEPATITIS C VIRUS INFECTION WITH PEGYLATED INTERFERON (PEG-IFN) α-2A (PEGFERON) AND RIBAVIRIN (COPEGUS) IN INMATES

Vashakidze E., Imnadze T.

Tbilisi State Medical University, Department of Infectious Diseases;
Ministry of Corrections and Probation, Department of Prison Health Services, Georgia

Hepatitis C virus (HCV) is the most common parenteral viral infection persisting in approximately 3% of the world population. According to the World Health Organization (WHO), approximately170-300 million individuals worldwide are infected with HCV. A full recovery was fixed in 15-20% of patients with acute course of hepatitis C. In 80-85% of cases infectious process appeared to proceed to chronic, therefore, chronic hepatitis is considered as a major form of HCV infection. Nowadays, hepatitis C virus has become the most common cause of liver cirrhosis - 40%, hepatocellular carcinoma - 60% and liver transplantation - 30%, worldwide [1-3]. In Georgia, where the rate of HCV infection among the population is higher in comparison with the population of Eastern European countries (>10%), ways of virus spread are not sufficiently blocked; C hepatitis is considered as one of the most pressing problem of healthcare system. The issue is particularly relevant to the prisoners. In comparison with general population data a number of infectious diseases including HIV, B and C hepatitis, as well as tuberculosis are more common in prisoners. High prevalence rates of HCV infection was caused by behavior of the prisoners and socio-economic problems, as well as high spread rate of mentioned diseases among prison population [4,5]. Hepatitis C is the most common infectious disease in penal institutions (correction facilities). Prevalence of HCV is 3-4 times higher in prison populations than in the general population in different countries. According to the meta-analysis a direct correlation between HCV- infection and injection-drug using in male inmates has been detected [6,7]. Since 2014, due to the problem urgency, Georgia has started the hepatitis C program for prevention, testing and treatment of Hepatitis C in the prison system, implying detection of HCV rate in prisoners, their complete clinical laboratory and instrumental examinations, and application of modern antiviral therapy to prevent disease spread.

The aim of the study was to assess the clinical effectiveness of combined antiviral therapy with pegylated interferon (Pegferon) and Ribavirin (Copegus)) in prisoners with Hepatitis C virus.

Material and methods. The obtained data were analyzed according to patient's sex, age, HCV genotype and hepatic injury – degree of fibrosis (scarring). In total, 210 patients with chronic C hepatitis have been observed. Patients involvement criteria: adult age (>18 years), the patients of both sexes with antiHCV in blood detected by ELISA-3 test and diagnosis of active hepatitis C confirmed searching for HCV RNA by PCR test. Exclusion criteria: infection with other hepatotropic virus - HDV, HBV, HIV, severe concomitant diseases, pregnancy as well as cirrhosis in its advanced stage.

The patients were divided into 3 groups according to HCV genotype:
Group I: - 70 patients infected with genotype 1a/1b;
Group II: - 70 patients infected with genotype 2a/2b;
Group III: - 70 patients infected with genotype 3a.

Each group was divided into 2 subgroups:
a) Patients with low degree of fibrosis (F_1-F_2);
b) Patients with high degree of fibrosis (F_3-F_4).

Table. reflects initial biochemical evidence for study group

Biochemical evidence	I genotype average arithemtical evidence standard deviation.	II genotype average arithemtical evidence standard deviation	III genotype average arithemtical evidence standard deviation	P value
ALT	62,96±53.92	68.77±56.61	60.94±52.66	
AST	77.57±53.64	81.80±50.85	78.87±53.64	
GGT	108.59±77.16	115.54±74.39	102.33±73.26	
T.BIL	20.78±6.221	21.46±5.96	21.07±5.18	<0.001
Albumini	40.33±10.49	41.09±11.32	40.87±9.65	
Pt	67.86±7.94	68.57±8.52	64.41±5.71	
Fe	143.47±77.37	138.83±75.38	166.94±75.52	

We used the ANOVA test for the analysis of received data. We considered a P value of <0.001 statistically significant.

Results and their discussion. All the patients underwent combined antiviral therapy with Pegylated Interferon (PEG-IFN) α -2a,180 mcg/week and Ribavirin 100 mg/day if weight <75 kg and 1200 mg if body weight >75 kg. Treatment duration is 24 weeks in patients with genotypes 2-3 and 48 weeks in patients with genotype 1a/1b, respectively.

During treatment, the side effects were being monitored, so that conventionally they were divided as follows: detailed analysis of patient's history and detection of risk-factors for antiviral chemotherapy side effects incidentally; outline individual treatment plan for effective and successful management of side effects and involvement of the specialists of other fields, if necessary; introduction of therapy side effects to the patient and their management; patient monitoring and management of side effects.

General adverse/side effects - asthenia, fatigue, fatigue, weakness, headache. Flu-like symptoms - chills, fever, dizziness, sweating, arthralgia, myalgia. Respiratory and cardiovascular symptoms - cough, dyspnea, chest tightness, shortbreathing. Gastrointestinal symptoms -anorexia, diarrhea, nausea, vomiting, taste changes, burning tongue and weight loss. Neuro - psychiatric symptoms - anxiety, headache, lack of concentration, weakness, insomnia, depression, fear.

Dermatologic symptoms - alopecia, itching, local, injection site reaction, rash, dry skin. Hematological changes - hemoglobin concentration, leukopenia, neotropenia, thrombocytopenia.

In case of most common flu-like symptoms (pain of different localization) – localization, rate and intensity of pain have been detected (other etiologies were excluded).

One of the most common symptoms was weakness – revealed at some stages of treatment in 100% of cases; worsened treatment process; difficult to manage; no relieve pain at rest; capable and well on exercise. The other causes of weakness such as anemia, depression, thyroid dysfunction, increased blood sugar were excluded.

Mental changes, associated with HCV therapy, like depression and/or other mental disorders were common in patients with intravenous drug abuse.

The most severe mental side effect of suicide attempt was observed in 1 patient where the treatment was stopped.

Hematological side effects (anemia, leukopenia, neotropenia, thrombocytopenia) were revealed in 3 cases - group I (4.3%), 4 cases – group II (5.7%) and group III (4.3%), respectively. Assessment of the severity of hematologic side effects, reduction of Interferon and Ribavirin doses and further monitoring is of great importance.

Management of hematologic disorders performed using Recormon (epoetin beta produced by genetic engineering, recombinant human natural erythropoietin); and Neupogen (filgrastim-granulocyte colony-stimulating factor); TSH, ALT, glucose monitoring and management was conducted (once a month before and after treatment and then every 12 weeks during the treatment, consultation of endocrinologist if recommended); Depression Screening - basically and routinely at every visit - antidepressant therapy and consultation of psychiatrist.

Clinical laboratory examinations were conducted: at a minimum of weeks 4 after initiation of treatment - RVR – rapid virological response, at 12 weeks - EVR – early virological response, at 24 weeks with genotypes 2-3 and 48 weeks with genotype 1a/1b - EOT – end of treatment, respectively.

In 24 weeks after the end of treatment - the patients achieving sustained virologic response (SVR) can be discharged as cured.

In the group I (1a /1b–F_3–F_4) due to severe side effects treatment was stopped in 3 cases at up to 12 weeks.

Among them in 2 cases hemorrhagic complications (thrombocytopenia, leukopenia) were developed, in 1 case – sharp deterioration in psychological status.

In 10 cases – conducting a full course of treatment became possible through the management of adverse effects: 1) anemia – with Recormon (epoetin beta produced by genetic engineering, recombinant human natural erythropoietin); 2) leukopenia - Neupogen (filgrastim-granulocyte colony-stimulating factor); 3) thrombocytopenia–Eltrombopag (Revolade), respectively.

Group II (2a /2b–F_3–F_4) –in 2 cases (activation of concomitant tuberculosis).
Group III (3a–F_3–F_4) – in 2 cases - 1 (thrombocytopenia); 1 (caused by major depression).

Group I - subgroups I and II (1a/1b F_1-F_2 F_3-F_4) RVR - rapid virological response was negative in 100 %.

Biochemical data in the subgroups I and II (group I) were reduced in comparison with the previous data, excluding GGT, albumin, glucose and TSH, which vary considerably compared to the norm.

In the subgroups I and II of group I (1a/1b F_1-F_2 F_3-F_4) EVR - early virological response - was negative in 69 (99.0%) patients; in 1 case (1 patient 1.0%) (F_3-F_4) –virus was detected in blood using PCR method and consequently, the treatment was stopped (3 cases – treatment was stopped due to experienced severe adverse effects).

At this stage of treatment in the patients EVR biochemical data was improved in comparison with the date obtained on the 4th week, with exception of albumin andGGT.

In the subgroups I and II of group I (1a/1b F_1-F_2 F_3-F_4) EOT- end of treatment response – negative in 66 patients – 94%.

To theend ofthe treatment the biochemical data wereimproved more compared to the data obtained on the 12th weekexcludingGGT.

In the subgroups I and II of group I (1a/1b F1-F2 F3-F4) SVR - sustained virologic response was in 64 patients (91%), in 2 cases (3%) – (F3-F4), the virus can be detected by PCR-test in 6 months after treatment.

Consequently, 64 of 70 patients in the group I were treated successfully (91%) - sustained virologic response; 4 patients (6%)

were excluded from the study on the 12th week; in 2 of the cases relapse had occurred.

In the subgroups I - II of Group II (2a/2b F_1-F_2 F_3-F_4), RVR -rapid virological response was negative in 100%.

Biochemical data in the patients of subgroups I and II (group II) were reduced in comparison with the previous data excluding GGT and TSH, which vary considerably compared to the norm.

In the subgroups I and II of group II (2a/2b F_1-F_2 F_3-F_4) EVR_early virological response - was negative in 69 patients (99%); in 1 case (1 patient 1.0%) (F_3-F_4) – virus was detected in blood by PCR-test and consequently, the treatment was stopped. In 3 cases – treatment was stopped due to experienced severe adverse effects.

At this stage of treatment in the patients EVR biochemical data were improved in comparison with the date obtained on the 4th week, with exception of GGT.

In the subgroups I - II of the Group II (2a/2b F_1-F_2 F_3-F_4), EOT-end of treatment response was in patients 67 (96%).

To the end of the treatment the biochemical data were improved more compared to the data obtained on the 12th week.

In the subgroups I - II of the Group II (2a/2b F_1-F_2 F_3-F_4),SVR - sustained virologic response was in 64 (91%) patients and in 3 cases (4%) – (F_3-F_4), the virus can be detected by PCR-test in 6 months after treatment.

Consequently, 64 of 70 patients in the group II were treated successfully (91%) - sustained virologic response; 3 (4%) patients were excluded from the study on the 12th week; though, in 3 of the cases relapse developed.

In the subgroups I - II of the GroupIII (3a F_1-F_2 and F_3-F_4), RVR - rapid virological response was negative in 100%.

Biochemical data in the patients of the subgroups I – II (Group III) were reduced in comparison with the previous ones, excluding GGT, albumin and TSH, which vary considerably compared to the norm.

In the subgroups I - II of the GroupIII (3a F_1-F_2 and F_3-F_4), EVR early virological response - was negative in 66 (94%) patients; in 2 (3%) cases the virus was detected in blood by PCR-test and consequently, the treatment was stopped. In 2 (3%) cases – treatment was stopped due to experienced severe adverse effects.

At this stage of treatment EVR biochemical data were improved in comparison with the date obtained on the 4th week, with exception of GGT.

In the subgroups I - II of the Group III (3a F_1-F_2 and F_3-F_4), EOT-end of treatment response was negative in 66 (94%) patients.

To the end of treatment the biochemical data were improved more compared to the data obtained on the 12th week excluding GGT.

In subgroups I - II of the Group III (3a F1-F2 and F3-F4), SVR – sustained virologic response was in 65 (93%) patients.

In 1 patient (F_2) the virus was detected by PCR-test in 6 months after the end of treatment treatment.

Consequently, 65 of 70 patients in the group III were treated successfully (93%) - sustained virologic response; 4 (6%) patients were excluded on the 12th week; in 1 of the cases relapse had occurred.

Thus, in patients with genotype I (1a/1b F_1-F_2 F_3-F_4) RVR – rapid virological response was negative in 100%, EVR – early virological response was negative in 99%, EOT – end of treatment results was negative in 94% while SVR- sustained virologic response was achieved in 91%.

In patients infected with HCV genotype II (2a/2b F_1-F_2 F_3-F_4) RVR – rapid virological response was negative in 100%, EVR – early virological response was negative in 99%, EOT – end of treatment results was negative in 96% while SVR- sustained virologic response was achieved in 91%.

In patients infected with HCV genotype III (3a F1-F2 da F3-F4) RVR – rapid virological response was negative in 100%, EVR – early virological response was negative in 94%, EOT – end of treatment results was negative in 94% while SVR- sustained virologic response was achieved in 93%.

Consequently, among the patients infected with HCV genotype 1 - successful recovery was achieved in 64, with genotypes II- 64, and in patients with genotype III – 65, respectively.

It should be noted that, HCV infection is widespread in penal institutions but the Hepatitis C prevention, care, and treatment program is not applied in many countries. According to our observations the final results of antiviral therapy, side effects occurred during treatment and their management, do not differ significantly from the effects achieved using antiviral therapy in other populations. Despite the differences in psychological conditions, which is common for this type of institutions, the program is having beneficial effects and the obtained results justify expedience of continuation as it will not only improve quality of life in prisoners but also reduce medical costs related to disease progression and prevent further dissemination of hepatitis C as inside of penal institutions/prisons as well as throughout the country.

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SUMMARY

COMBINED ANTIVIRAL TREATMENT OF HEPATITIS C VIRUS INFECTION WITH PEGYLATED INTERFERON (PEG-IFN) α-2A (PEGFERON) AND RIBAVIRIN (COPEGUS) IN INMATES

Vashakidze E., Imnadze T.

Tbilisi State Medical University, Department of Infectious Diseases; Ministry of Corrections and Probation, Department of Prison Health Services, Georgia

The aim of the study was to assess the impact of combined antiviral therapy in prisoners with HCV. In total, 210 patients with chronic C hepatitis have been observed. The patients were divided into 3 groups according to HCV genotype: Group I: - 70 patients infected with genotype 1a/1b; Group II: - 70 patients infected with genotype 2a/2b; Group III: - 70 patients infected with genotype 3a. As for the patients with genotype I: RVR – rapid virological response was negative in 100%; EVR – early virological response was negative in 99%; EOT – end of treatment results was negative in 94% and SVR- sustained virologic response was negative in 91%. In patients with genotype II: RVR – rapid virological response was negative in 100%, EVR – early virological response was negative in 99%, EOT – end of treatment results was negative in 96% and SVR-sustained virologic response was negative in 91%. In patients with genotype III: RVR – rapid virological response was negative in 100%, EVR – early virological response was negative in 94%, EOT – end of treatment results was negative in 94% and SVR- sustained virologic response was negative in 93%. According to our observations, side effects and their management, do not differ significantly from the antiviral therapy in other populations. Despite the differences in psychological conditions, which is common for this type of institutions, the program is having beneficial effects and the obtained results justify expedience of continuation as it will not only improve quality of life in prisoners but also reduce medical costs related to disease progression and prevent further dissemination of hepatitis C as inside of penal institutions/prisons as well as throughout the country.

Keywords: HCV, hepatitis C, prisoners.

РЕЗЮМЕ

КОМБИНИРОВАННАЯ АНТИВИРУСНАЯ ТЕРАПИЯ HCV- ИНФИЦИРОВАННЫХ ЗАКЛЮЧЕННЫХ ПЕГИЛИРОВАННЫМ ИНТЕРФЕРОНОМ α-2a (ПЕГФЕРОН) И РИБАВИРИНОМ (КОПЕГУС)

Вашакидзе Э.Т., Имнадзе Т.М.

Тбилисский государственный медицинский университет, департамент инфекционных заболеваний, Грузия; Министерство по исполнению назаканий и пробации, Грузия

Целью исследования явилось определение эффективности комбинированного антивирусного лечения заключенных с хроническим гепатитом С (HCV). Исследовано 210 пациентов, которые в соответствии с генотипом HCV были разделены на три группы: I группу составили 70 пациентов, инфицированных генотипом 1a/1b; II группу – 70 пациентов, инфицированных генотипом 2a/2b; III группу – 70 пациентов, инфицированных генотипом 3a. Среди пациентов I группы быстрый вирусный ответ был отрицательным в 100% случаев; ранний вирусный ответ был отрицательным в 99% случаев; ответ в конце лечения был отрицательным в 94% случаев; стойкий вирусный ответ был отрицательным в 91% случаев. Среди пациентов II группы быстрый вирусный ответ был отрицательным в 100%; ранний вирусный ответ был отрицательным в 99%; ответ в конце лечения был отрицательным в 96%; стоикий вирусный ответ был отрицательным в 91% случаев. Среди пациентов III группы быстрый вирусный ответ был отрицательным в 100% случаев; ранний вирусный ответ был отрицательным в 94%; ответ в конце лечения был отрицательным в 94%; стойкий вирусный ответ был отрицательным в 93% случаев. Делается вывод, что гепатит С распространенное инфекционное заболевание среди заключенных. Несмотря на отличающиеся психологические условия в учреждениях принудительного заключения, результаты антивирусного лечения заключенных, инфицированных хроническим гепатитом С, не отличаются от результатов антивирусного лечения пациентов с хроническим гепатитом С. Программа успешно проводится и полученные результаты свидетельствуют в пользу ее продолжения.

რეზიუმე

HCV-ინფიცირებული პატიმრების კომბინირებული ანტივირუსული მკურნალობა პეგილირებული ინტერფერონით α–2a (პეგფერონი) და რიბავირინით (კოპეგუსი)

ე. ვაშაკიძე, თ. იმნაძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, ინფექციურ სნეულებათა დეპარტამენტი; საქართველოს სასჯელაღსრულებისა და პრობაციის სამინისტრო, სამედიცინო დეპარტამენტი, თბილისი, საქართველო

შრომის მიზანს წარმოადგენდა HCV-ინფიცირებული პაციენტების (პატიმრების) ანტივირუსული თერაპიის ეფექტურობის დადგენა და გვერდითი ეფექტების მართვა.

გამოკვლეულია 210 პაციენტი. პაციენტები HCV-გენოტიპის მიხედვით დაიყო სამ ჯგუფად: I ჯგუფი – 70 პაციენტი, ინფიცირებული გენოტიპით 1a/1b; II ჯგუფი – 70 პაციენტი, ინფიცირებული გენოტიპით 2a/2b; III ჯგუფი – 70 პაციენტი, ინფიცირებული გენოტიპით 3a.

I ჯგუფის პაციენტებში სწრაფი ვირუსული პასუხი უარყოფითი იყო 100%-ში, ადრეული ვირუსული პასუხი უარყოფითი იყო 99%-ში, მკურნალობის ბოლოს უარყოფითი იყო 94%-ში, მყარი ვირუსული პასუხი უარყოფითი იყო 91%-ში.

II ჯგუფის პაციენტებში სწრაფი ვირუსული პასუხი უარყოფითი იყო 100%-ში, ადრეული ვირუსული პასუხი უარყოფითი იყო 99%-ში, მკურნალობის ბოლოს პასუხი უარყოფითი იყო 96%-ში, მყარი ვირუსული პასუხი უარყოფითი იყო 91%-ში.

III ჯგუფის პაციენტებში სწრაფი ვირუსული პასუხი უარყოფითი იყო 100%-ში, ადრეული ვირუსული პასუხი უარყოფითი იყო 94%-ში, მკურნალობის ბოლოს პასუხი უარყოფითი იყო 94%-ში, მყარი ვირუსული პასუხი უარყოფითი იყო 93%-ში.

დადგენილია, რომ HCV ინფექცია ფართოდაა გავრცელებული სასჯელაღსრულების დაწესებულებებში. ჩატარებული ანტივირუსული მკურნალობის საბოლოო შედეგები, მკურნალობის მსვლელობაში განვითარებული გვერდითი მოვლენები და მათი მართვა მიუხედავად განსხვავებული ფსიქოლოგიური პირობებისა, რომლებსაც ადგილი აქვს ამ ტიპის დაწესებულებებში, მნიშვნელოვნად არ განსხვავდება თავისუფლებაში მყოფი ამავე დაავადებით პაციენტების მკურნალობის ანტივირუსული მკურნალობის შედეგებისაგან. პროგრამა წარმატებით მიმდინარეობს; მიღებული შედეგები მიუთითებს მისი გაგრძელების მიზანშეწონილობაზე.

АНАЛИЗ ГЕНОВ ОДНОУГЛЕРОДНОГО МЕТАБОЛИЗМА И КОМПЛЕКСА ЭПИДЕРМАЛЬНОЙ ДИФФЕРЕНЦИРОВКИ У БОЛЬНЫХ ИХТИОЗОМ ПРОСТЫМ

[1]Федота А.М., [2]Рощенюк Л.В., [3]Садовниченко Ю.А., [4]Меренкова И.Н., [5]Гонтарь Ю.В., [2]Воронцов В.М.

[1]Харьковский национальный университет им. В.Н. Каразина, кафедра акушерства и гинекологии; [2]КУЗ «Областной клинический кожно-венерологический диспансер №1», Харьков; [3]Харьковский национальный медицинский университет, кафедра медицинской биологии; [4]КУЗ «Харьковский городской родильный дом №1»; [5]ООО «Медицинский центр ИГР», Киев, Украина

Ихтиоз является наиболее распространенным моногенным генодерматозом, клиническими проявлениями которого являются гиперкератоз и/или чрезмерное шелушение кожи различной степени тяжести в результате нарушения процессов ороговения эпидермиса [8,10,48]. Распространенность ихтиоза в Харьковской области составляет 1:2557 [17]. В настоящее время описано более 30 клинических форм заболевания, однако 80-95% случаев приходится на ихтиоз простой [10].

Ихтиоз простой (Q 80.1.0, OMIM 146700) имеет аутосомно-доминантный тип наследования с неполной пенетрантностью и обусловлен мутациями в гене эпидермального белка филаггрина (*FLG*, OMIM 135940) [54]. Обнаружено более 40 мутаций в этом гене, среди них R501X, 2282del4, 3321delA, Q2417X, E2422X, суммарная частота которых в европейских популяциях составляет 7-10%, в азиатских — 3,0% [24,53,54]. Эти мутации вызывают снижение концентрации белка профилаггрина в зернистом слое эпидермиса, почти полное исчезновение этого слоя и истончение шиповатого слоя, уменьшение содержания гигроскопичных аминокислот натурального увлажняющего фактора (NMF) и повышение трансэпидермальной потери воды [28, 54]. Мутации в гене *FLG* также могут повышать риск развития атопии, пищевой аллергии, заболеваний желудочно-кишечного тракта, рака кожи, сахарного диабета, некоторых вирусных заболеваний [25,26,31,42,44,46,54,60]. На роль гена-модификатора, усиливающего фенотипическое проявление мутаций гена *FLG* у гетерозигот, предложен один из генов одноуглеродного метаболизма *MTHFR* [17].

Ген *MTHFR* (OMIM 607093) кодирует фермент метилентетрагидрофолатредуктазу. Дефицит или снижение активности этого фермента способствует гипометилированию ДНК, которое приводит к нарушению расхождения хромосом и клеточного цикла вплоть до гибели клеток, а также к гипергомоцистеинемии, что является фактором риска развития нарушений с широким спектром клинических симптомов. Из более чем 20 описанных вариантов однонуклеотидных полиморфизмов гена *MTHFR* наиболее изученной является транзиция C677T. Для этого полиморфного варианта установлена связь с развитием такого генодерматоза, как псориаз [17,57], доказаны ассоциации с сердечно-сосудистыми и неврологическими заболеваниями, предраковыми и раковыми состояниями различных органов [37,40], акушерской патологией — невынашиванием беременности и ее осложнениями, тромбофилией, гестозом [23,27,40,62].

Поскольку в литературе представлены данные о ряде аллергических заболеваний, в частности, атопическом дерматите и экземе, в развитии которых полиморфизм генов как одноуглеродного метаболизма, так и комплекса эпидермальной дифференцировки играет существенную роль [33,55], можно ожидать совместного плейотропного эффекта указанных генов, а также развития и других заболеваний.

При некоторых формах ихтиоза могут наблюдаться гинекологические нарушения, в том числе цервикальная интраэпителиальная неоплазия и рак шейки матки [22]. Однако в мировой литературе не хватает сведений об ассоциации мутаций в гене *FLG* с обоими заболеваниями [54]. Анализ ассоциации ихтиоза и мутаций в гене *FLG* с раком шейки матки становится сложен, так как развитие скрининговых программ по раку шейки матки, особенно в странах Европы, существенно снизило долю этого вида рака в структуре онкологической заболеваемости. Так, в Великобритании за 15 лет заболеваемость раком шейки матки снизилась на 42%, а в Швеции, Швейцарии, Словении снижается на 15-30% каждые пять лет [13].

Сложная генетическая природа этих и других тяжелых гинекологических заболеваний — эндометриоза, миомы матки и новообразований репродуктивной системы — является основанием для развития всесторонних исследований этих патологий.

Эндометриоз встречается у 15-50% женщин репродуктивного возраста [4,12,32]. Каждая из существующих теорий

эндометриоза — эмбриональная, трансплантационная, метапластическая и другие, объясняет происхождение отдельных форм заболевания [4]. Согласно генетической теории, эндометриоз является мультифакториальным заболеванием, в основе развития которого лежит взаимодействие факторов среды и ряда генов, которые также взаимодействуют между собой. К генной сети эндометриоза в настоящее время относят гены системы детоксикации ксенобиотиков — *CYP1A1*, *CYP2E1*, *CYP17A1*, *CYP19A1*, *EPHX1, GSTM1*, *GSTT1* и *NAT2*, иммунного ответа — *IL4*, *IL4R*, *IL6*, *TGFB1*, *TNFA*, эндокринных функций — *ERα*, *ERβ* и *PR*, межклеточных взаимодействий *HLA-DQB1, HLA-DRB1* и проонкогены *TP53*, *RASK* [3].

Распространенность миомы (фибромы, фибромиомы) матки у женщин может достигать 77%, начиная с 40-50 лет, что обусловлено мультифакториальной природой патологии и хромосомными аномалиями [19].

Рак эндометрия является одной из наиболее распространенных онкопатологий органов малого таза у женщин, развивается в возрасте 50-70 лет. Для этого вида рака установлена ассоциация с рядом генов, например *PTEN*, *CTNNB1*, *PIK3CA*, *ARID1A* [32,47].

Распространенность и тяжесть течения указанных заболеваний обусловливает актуальность поиска кандидатных генов путем анализа ассоциаций этих патологий с другими, для которых определены генные сети. Исходя из вышеизложенного, целью исследования было оценка эффекта аллельного полиморфизма генов *FLG* и *MTHFR* и их ассоциаций у больных простым ихтиозом с гинекологическими заболеваниями.

Материал и методы. Сбор и анализ клинико-генеалогической информации проводились методом единичной регистрации пробанда на базе ОККВД №1 и кожно-венерологических диспансеров Харьковской области. Диагноз и форма дерматоза установлены на основе анализа клинико-генеалогических данных и результатов лабораторных исследований в соответствии с МКБ-10: ихтиоз простой (Q 80.1.0). Проанализирована информация о 38 семьях, к которым принадлежали 18 женщин и 20 мужчин в возрасте от 26 до 76 лет, больных ихтиозом простым. В качестве показателя репродуктивной способности больных ихтиозом определяли среднее количество детей в семье. Проверка данных на соответствие закону нормального распределения выполнена по методам Шапиро-Уилка и Колмогорова-Смирнова [20]. Исследование связи между признаками проводилось с помощью корреляционного анализа по Пирсону и Спирмену. Проверка статистических гипотез об ассоциации изученных аллелей и генотипов и оценка рядов распределения проведена с помощью критерия $\chi 2$ [1].

Результаты и их обсуждение. Анализ географического распределения частот мутантных аллелей гена *FLG* и соответствующих генотипов среди населения стран Европы по литературным данным показал, что частота аллелей R501X и 2282del4, а также гетерозигот по гену *FLG* в целом снижалась с севера на юг (таблица 1) в северном полушарии, от Шотландии до Италии (таблица 1). Следует отметить, что в некоторых странах исследовались только две вышеупомянутые мутации.

Установлена статистически значимая прямая связь частот мутантных аллелей и гетерозиготных генотипов по гену *FLG* с географической широтой. Коэффициенты корреляции представлены в таблице 2.

По мнению J.P. Thyssen с соавт. [52,54], рост частоты мутаций в гене *FLG* от экватора до Северного полюса имеет адаптивное значение, поскольку оно повышает проницаемость кожи для ультрафиолетового излучения, что может способствовать повышению уровня витамина D в плазме крови, особенно в странах с низкой интенсивностью инсоляции.

В связи с тем, что мутации в гене филаггрина обусловливают развитие ихтиоза простого, описанного как аутосомно-доминантный дерматоз с неполной пенетрантностью, мы сравнили полученные нами ранее данные с данными других авторов. По результатам наших исследований [17], пенетрантность гомозигот по мутации 2282del4 в гене *FLG*, также, как и дигетерозигот по мутациям R501X и 2282del4, составила 100%. Для гетерозигот по мутации R501X характерна полная пенетрантность 100%, а для гетерозигот по мутации 2282del4 – неполная (84,2%). В исследованиях ирландских, шотландских и американских семей европейского происхождения с ихтиозом, проведенных C.N.A. Palmer с соавт. [44] и F.J.D. Smith с соавт. [51], установлена также полная пенетрантность гомозигот по

Таблица 1. Показатели частоты аллелей и генотипов по гену FLG среди населения стран Европы

Страна	Геогр. широта	R501X			2282del4			Сумма частот мутаций	Источник
		Частота			Частота				
		генотипа		аллеля	генотипа		аллеля		
		Aa	AA	A	Aa	AA	A		
Великобритания (Шотландия)	55°52′–57°09′	5,32	0,20	2,86	5,47	0,00	2,73	5,59	[56]
Дания	55°41′	3,36	0,09	1,77	4,59	0,12	2,41	4,18	[53]
Великобритания (Англия)	54°55′	5,98	0,00	2,99	4,83	0,00	2,41	7,39	[25]
Ирландия	53°20′	6,35	0,00	3,17	2,15	0,00	1,08	4,25	[44]
Польша	51°47′	1,96	0,00	0,98	4,41	0,00	2,21	3,19	[39]
ФРГ	47°59′–52°31′	4,13	0,00	2,07	4,82	0,00	2,41	4,82	[42]
Франция	48°50′	3,03	0,00	1,52	1,01	0,00	0,51	2,03	[43]
Австрия	47°16′	2,82	0,00	1,41	2,26	0,00	1,13	2,54	[31]
Хорватия	45°48′	0,24	0,00	0,12	2,36	0,00	1,18	1,30	[46]
Италия	41°54′	0,00	0,00	0,00	1,00	0,00	0,50	4,8	[26]

Таблица 2. Показатели связи между параметрами географической широты, частотами аллелей и генотипов по генам FLG и MTHFR

Показатели	Коэффициент корреляции, r	Уровень значимости, p
Широта – частота аллеля 2282del4	0,755	0,012
Широта – частота генотипа N/2282del4	0,733	0,016
Широта – частота аллеля R501X	0,770	0,009
Широта – частота генотипа N/R501X	0,770	0,009
Широта – сумма частот аллелей *FLG*	0,539	0,108
Широта – частота аллеля T	-0,648	0,043
Широта – частота генотипа CT	-0,721	0,019
Широта – частота генотипа TT	-0,345	0,328
Частота генотипа N/2282del4 – частота генотипа CT	-0,903	0,0003
Частота генотипа N/2282del4 – частота генотипа TT	-0,212	0,556
Частота аллеля 2282del4 – частота генотипа CT	-0,926	0,00012
Частота аллеля 2282del4 – частота генотипа TT	-0,288	0,419
Частота генотипа N/2282del4 – частота аллеля T	-0,673	0,033
Частота аллеля 2282del4 – частота аллеля *T*	-0,755	0,012
Частота генотипа N/R501X – частота генотипа CT	-0,552	0,098
Частота генотипа N/R501X – частота генотипа TT	0,067	0,855
Частота генотипа N/R501X – частота аллеля T	-0,224	0,533
Частота аллеля R501X – частота генотипа CT	-0,552	0,098
Частота аллеля R501X – частота генотипа TT	0,067	0,855
Частота аллеля R501X – частота аллеля T	-0,224	0,533
Сумма частот мутантных аллелей *FLG* – частота генотипа CT	-0,552	0,098
Сумма частот мутантных аллелей *FLG* – частота генотипа TT	0,442	0,200
Сумма частот мутантных аллелей *FLG* – частота аллеля T	-0,091	0,803

Таблица 3. Показатели частоты аллелей и генотипов по полиморфному варианту C677T гена MTHFR среди населения стран Европы

Страна	Геогр. широта	Частота генотипа			Частота аллеля		Источник
		CC	CT	TT	C	T	
Великобритания (Шотландия)	55°57′ – 57°09′	48,72	41,40	9,87	69,43	30,57	[61]
Дания	55°41′	50,28	41,42	8,30	70,99	29,01	[38]
Великобритания (Англия)	54°55′	46,19	42,73	11,07	67,56	32,44	[45]
Ирландия	53°20′	46,41	43,61	9,99	68,21	31,79	[23]
Польша	52°20′	49,47	42,76	7,77	70,85	29,15	[49]
ФРГ	49°24′ – 53°04′	48,65	40,78	10,57	69,04	30,96	[37]
Франция	48°50′ – 49°29′	37,59	52,63	9,77	63,91	36,09	[23]
Австрия	48°13′	42,98	43,53	13,50	64,74	35,26	[29]
Хорватия	45°48′	46,05	44,74	9,21	68,42	31,58	[41]
Италия	41°54′	29,03	54,84	16,13	56,45	43,55	[23]

мутации 2282del4 в гене *FLG* и компаундов. Пенетрантность гетерозигот по мутации 2282del4, согласно данным литературы, варьирует в пределах от 80% [44] до 100% [51], тогда как пенетрантость гетерозигот по транзиции R501X в наших исследованиях выше, чем в других и составляет 100% [30,44,51]. Таким образом, данные, полученные нами для восточноукраинской популяции, существенно не отличаются от общеевропейских показателей.

Неполная пенетрантность и вариабельная экспрессивность делеции 2282del4 в гене *FLG* может быть обусловлена наличием или отсутствием в генотипе определенных генов-модификаторов, влияющих на фенотипическое проявление мутантного аллеля. На роль гена-модификатора мутаций в гене *FLG* нами был предложен ген *MTHFR*. Генотип CT по полиморфному варианту C677T приводит к снижению активности метилентетрагидрофолатредуктазы и гипергомоцистеинемии [11,29,58]. Избыток гомоцистеина в организме корректируется путем его превращения в метионин или цистеин, который входит в состав α-кератинов - основных белков ногтей, кожи и волос. Очевидно, гетерозиготность по этому однонуклеотидному полиморфизму гена *MTHFR* является общим или неспецифическим предиктором для многих дерматозов, обусловленных нарушениями кератинизации, в том числе ихтиоза.

Анализ распределения частот аллелей и генотипов по полиморфному варианту C677T гена *MTHFR* показал, что от экватора на север частота аллеля *T* снижается (таблица 3), и демонстрирует статистически значимую обратную связь с географической широтой (таблица 2).

Установлено, что в районе экватора у местного населения генотип TT отсутствует, а в странах Средиземноморья и Ближнего Востока его частота достигает 30% [23]. Снижение интенсивности ультрафиолетового излучения по градиенту

широты обуславливает ослабление фотодеструкции фолатов [35]. Действие отбора против аллеля *T* в этих регионах также ослабевает ввиду того, что природные источники фолатов традиционно представляют пищевую культуру их населения. По данным ряда авторов, коррекция нарушений фолатного обмена, обусловленных аллельным полиморфизмом гена *MTHFR*, с помощью витаминов и фолатов существенно снижает риск врожденных пороков развития и расщелины губы и неба, репродуктивных нарушений и потерь [21,36,59].

Частота гетерозигот CT по полиморфному варианту C677T гена *MTHFR* снижается в том же направлении и демонстрирует статистически значимую обратную связь с показателями географической широты (r=-0,721) (таблица 2).

Исследование ассоциации между частотами гетерозигот N/2282del4 по гену *FLG* и CT по гену *MTHFR* в Европе показало существование значимой обратной связи между этими показателями (таблица 2). Распределение частот указанных генотипов имеет противоположную широтную зональность: частота гетерозигот по гену *FLG* растет в направлении от экватора к полюсу, а по гену *MTHFR*, наоборот, уменьшается. Вероятно, наличие мутаций в гене *FLG* усиливает действие отбора против гетерозигот по гену *MTHFR*, поскольку нарушает целостность кожи, повышает ее проницаемость для ультрафиолета и способствует фотодеструкции фолатов.

Установленная связь позволяет прогнозировать развитие у пациентов-гетерозигот по обоим генам N/2282del4 и CT ряда заболеваний различных систем органов. В свете сохранения здоровья нации наибольшее внимание привлекают репродуктивные нарушения, онкологические заболевания, дерматозы и их ассоциации. Поэтому нами был проведен анализ показателей репродукции у пробандов с ихтиозом и их родственников.

У женщин (n=18, 47,4%) и мужчин (n=20, 52,6%) репродуктивного и пострепродуктивного возраста (26-76 лет) с ихтиозом простым из 38 семей средний возраст на момент исследования составил 47,8±3,1 (31-70) и 52,4±3,1 (26-76) лет, соответственно.

Среди 58 детей в семьях больных ихтиозом соотношение лиц мужского и женского пола составило 25:33 (1:1,32, p=0,294), 1:1 среди потомства больных ихтиозом женщин 15:16 (1:1,07, p=0,857) и мужчин 9:18 (1:2, p=0,083).

У больных ихтиозом в Харьковской области в течение четырех десятилетий (1968-2007 гг.) среднее количество детей в семьях составило 1,5±0,1 (0-4 ребенка): у женщин — 1,7±0,2 (0-4) ребенка, у мужчин — 1,4±0,1 (0-2) детей. Динамика этого показателя репродукции у больных соответствовала таковой в Украине и в Харьковской области (рис.) [2,7,18], значимой разницы между показателями не обнаружено (p=0,954).

Средний возраст деторождения у женщин с ихтиозом составил 24,1±1,2 года, что свидетельствует о возможности реализовать свой репродуктивный потенциал только в молодом возрасте, до начала развития гинекологических заболеваний, которые вызывают бесплодие. В то же время средний возраст манифестации эндометриоза у женщин в Украине — 38,5±8,2 года [9], распространенность миомы достигает максимума у 40-летних женщин [15], а пик заболеваемости раком шейки матки приходится на возрастную категорию 35-59 лет [6], рака эндометрия — на 40,6-60,5 лет [5].

Среди шести всесторонне обследованных женщин репродуктивного возраста с ихтиозом простым, с генотипами N/2282del4 и CT, 33,3% (n=2) имели гинекологические заболевания, в том числе фиброму матки, эндометриоз и рак эндометрия, которые были диагностированы в возрасте 27-29 лет. По Харьковской области в 2015 г. заболеваемость эндометриозом составила 292,81 на 100000 женщин, что составляет 1:341 (0,29%) [14], а заболеваемость раком эндометрия - 35,4 на 100 тыс. женского населения или 1:2825 (0,35%) [16]. Таким образом, распространенность гинекологической патологии у женщин с ихтиозом статистически значимо выше, чем среди женского населения Харьковской области (p<0,05).

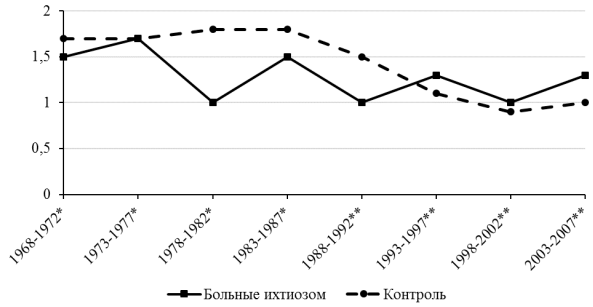

Рис. Распределение количества детей, родившихся в 1968-2007 гг. у женщин с простым ихтиозом в Харьковской области
*примечания: *статистические данные за 1968-1987 гг. представлены по Украине; **статистические данные за 1988-2007 гг. — по Харьковской области*

Известно, что эндометриоз обусловлен проникновением клеток эндометрия в другие ткани и органы, в эндометриальных клетках которых происходят процессы как в нормальном эндометрии [32]. В связи с тем, что ген *FLG* экспрессируется и в клетках эндометрия, его мутации способствуют нарушению плотности эпителия и повышению его проницаемости для возбудителей инфекционных заболеваний, например, папилломавируса человека, вызывающего рак шейки матки, самой матки, влагалища, полового члена, шеи и головы [50]. Изменения, происходящие в эпителии при наличии мутаций гена *FLG* и аномального филаггрина, позволяют предположить возможный вклад последних в генез эндометриоза.
Анализ эффекта полиморфного варианта C677T гена *MTHFR* у больных ихтиозом показал, что для гетерозигот *CT* вероятность развития ихтиоза почти в 4 раза (OR=3,71, 95% CI 1,62-8,46, p<0,05) выше, чем в среднем в популяции. Для носителей мутаций в гене *FLG* гетерозиготность CT по полиморфизму C677T увеличивает вероятность развития клинических проявлений ихтиоза почти в 7 раз (OR=6,5, 95% CI 1,09-38,63, p<0,05), по сравнению с носителями мутаций R501X и 2282del4 без ихтиоза [17].

Таким образом, наличие у больных ихтиозом простым определенных комбинаций аллелей и генотипов по генам *FLG* и *MTHFR* позволяет прогнозировать развитие гинекологических и онкологических заболеваний у этих пациентов, предложить концепции профилактики заболеваний репродуктивной сферы и онкопатологии и сформировать современные синтетические концепции этиологии и патогенеза исследованных заболеваний.

Заключение. Обнаружена прямая корреляция между географической широтой и частотами мутантных аллелей гена

FLG, а также между географической широтой и частотой гетерозиготных носителей этих мутаций. Частоты аллеля *T* и генотипа CT по полиморфному варианту C677T гена *MTHFR* демонстрируют обратную связь с показателями географической широты. Противоположную широтную зональность имеют распределения частот аллеля 2282del4 и генотипа CT, генотипов N/2282del4 и CT, аллелей 2282del4 и T, генотипа N/2282del4 и аллеля T. Установленные связи позволили прогнозировать развитие гинекологических патологий у женщин с простым ихтиозом. В Харьковской области у пациенток с простым ихтиозом распространенность эндометриоза и рака эндометрия составила 33,3%, тогда как средний показатель среди женского населения региона — 0,29-0,35%. Количество детей у женщин с простым ихтиозом не отличалось от регионального показателя.

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SUMMARY

ANALYSIS OF ONE-CARBON METABOLISM GENES AND EPIDERMAL DIFFERENTIATION COMPLEX IN PATIENTS WITH ICHTHYOSIS VULGARIS

[1]Fedota O., [2]Roshchenyuk L., [1,3]Sadovnychenko I., [4]Merenkova I., [5]Gontar I., [2]Vorontsov V.

[1]V.N. Karazin Kharkiv National University, Department of Obstetrics and Gynecology; [2]Communal Enterprise of Health Care «Regional Clinical Dispensary for Skin and Venereal Diseases», Kharkiv; [3]Kharkiv National Medical University, Department of Medical Biology; [4]Communal Enterprise of Health Care «Kharkiv Municipal Maternity Hospital No. 1»; [5]LLC «Medical Center IGR», Kyiv, Ukraine

The aim of the study was to evaluate the effects of allelic polymorphism of the *FLG* and *MTHFR* genes and their associations in gynecological patients with ichthyosis vulgaris. Gynecological disorders are observed in presence of some forms of ichtyosis. From the prospective of improving nation's healthcare, the greatest attention is drawn to reproductive disorders. Based on this, the research was also tasked with studying of the genetic nature of gynecological diseases, as well as the influence of geographical latitude on the frequencies of mutagenic alleles of the *FLG* gene and heterogeneous carriers of these mutations. The collection of clinical-gynecological history was carried out by the method of single registration

of the proband on the basis of the Regional Clinical Dermatological and Venereological Health Center No. 1 and the Dermatovenerological Health Centers of the Kharkiv Region. The diagnosis and form of dermatosis is established on the basis of the analysis of clinical and gynecological data and the results of laboratory tests in accordance with ICD-10: ichthyosis vulgaris (Q 80.1.0, OMIM 146700). The data on 18 women and 20 men from 3 families, aged 26 to 76 years old, suffering from ichthyosis, were analyzed. As a result of the study, a direct correlation was determined between the latitude and frequencies of mutant alleles of the *FLG* gene, as well as between the geographical latitude and frequency of heterozygous carriers of these mutations. The frequencies of the T allele and the CT genotype according to polymorphic variant C677T of the *MTHFR* gene demonstrate feedback with the latitude indicators. The frequency distributions of the 2282del4 allele and the CT genotype, the N/2282del4 and CT genotypes, the 2282del4 and T alleles, the N/2282del4 genotype and the T allele have opposite latitudinal zonation. The established connections made it possible to predict the development of gynecological pathologies in women with ichthyosis vulgaris. The prevalence of endometriosis and endometrial cancer in women with ichthyosis vulgaris in the Kharkiv region was 33.3%, while the average for the female population in the region was 0.29-0.35%. The number of children born to women with ichthyosis vulgaris did not differ from the regional index.

Keywords: ichthyosis vulgaris, filaggrin, 5,10-methylenetetrahydrofolate reductase, geographic distribution, gynecological disorders.

РЕЗЮМЕ

АНАЛИЗ ГЕНОВ ОДНОУГЛЕРОДНОГО МЕТАБОЛИЗМА И КОМПЛЕКСА ЭПИДЕРМАЛЬНОЙ ДИФФЕРЕНЦИРОВКИ У БОЛЬНЫХ ИХТИОЗОМ ПРОСТЫМ

[1]Федота А.М., [2]Рощенюк Л.В., [3]Садовниченко Ю.А., [4]Меренкова И.Н., [5]Гонтарь Ю.В., [2]Воронцов В.М.

[1]Харьковский национальный университет им. В.Н. Каразина, кафедра акушерства и гинекологии; [2]КУЗ «Областной клинический кожно-венерологический диспансер №1», Харьков; [3]Харьковский национальный медицинский университет, кафедра медицинской биологии; [4]КУЗ «Харьковский городской родильный дом №1»; [5]ООО «Медицинский центр ИГР», Киев, Украина

Целью исследования явилась оценка эффектов аллельного полиморфизма генов *FLG* и *MTHFR* и их ассоциаций с гинекологическими заболеваниями у больных простым ихтиозом. При некоторых формах ихтиоза наблюдаются гинекологические нарушения. В свете сохранения здоровья нации наибольшее внимание привлекают репродуктивные нарушения. Исходя их этого задачу исследования составляет также изучение генетической природы гинекологических заболеваний, а также влияния географичекой широты на частоты мутагенных аллелей гена *FLG* и гетерогенных носителей этих мутаций. Сбор и анамнез клинико-гинекологической информации проведен методом единичной регистрации пробандов на базе Областного клинического кожно-венерологического диспансера №1 и Кожно-венерологических диспансеров Харьковской области. Диагноз и форма дерматоза установлены на основе анализа клинико-гинекологических данных и результатов лабораторных исследований в соответствии с МКБ-10: ихтиоз простой (Q 80.1.0, OMIM 146700). Проанализирована информация о 38 семьях, к которым принадлежали 18 женщин и 20 мужчин в возрасте от 26 до 76 лет, больных ихтиозом простым. В результате проведенного исследования обнаружена прямая корреляция между географической широтой и частотами мутантных аллелей гена *FLG*, а также между географической широтой и частотой гетерозиготных носителей этих мутаций. Частоты аллеля T и генотипа CT по полиморфному варианту C677T гена *MTHFR* демонстрируют обратную связь с показателями географической широты. Противоположную широтную зональность имеют распределения частот аллеля 2282del4 и генотипа CT, генотипов N/2282del4 и CT, аллелей 2282del4 и T, генотипа N/2282del4 и аллеля T. Установленные связи позволили прогнозировать развитие гинекологических патологий у женщин с простым ихтиозом. В Харьковской области у пациенток с простым ихтиозом распространенность эндометриоза и рака эндометрия составила 33,3%, тогда как средний региональный показатель среди женской популяции - 0,29-0,35%. Количество детей у женщин с простым ихтиозом не отличалось от регионального показателя.

რეზიუმე

ერთნახშირბადიანი გენების მეტაბოლიზმის და ეპიდერმული დიფერენცირების კომპლექსის ანალიზი მარტივი იხტიოზით ავადმყოფებში

[1]ა. ფედოტა, [2]ლ. როშჩენიუკი, [3]ი. სადოვნიჩენკო, [4]ი. მერენკოვა, [5]ი. გონტარი, [2]ვ. ვორონცოვი

[1]ხარკოვის ვ.მ.კარაზინის სახელობის ეროვნული უნივერსიტეტი, მეანობისა და გინეკოლოგიის კათედრა; [2]საოლქო კლინიკური დერმატოვენეროლოგიური დისპანსერი №1, ხარკოვი; [3]ხარკოვის ეროვნული სამედიცინო უნივერსიტეტი,სამედიცინო ბიოლოგიის კათედრა; [4]ხარკოვის საქალაქო სამშობიარო სახლი №1; [5]კიევის სამედიცინო ცენტრი, უკრაინა

კვლევის მიზანს შეადგენდა *FLG* და *MTHFR* გენების ალელური პოლიმორფიზმის ეფექტების და გინეკოლოგიურ დაავადებებთან მათი ასოციაციის შეფასება მარტივი იხტიოზით ავადმყოფებში. იხტიოზის ზოგიერთი ფორმის დროს აღინიშნება გინეკოლოგიური დარღვევები. ერის ჯანმრთელობის შენარჩუნების თვალსაზრისით, რეპროდუქციული დარღვევების შესწავლა უდიდეს მნიშვნელობას იძენს. აქედან გამომდინარე,კვლევის ამოცანას შეადგენდა გინეკოლოგიური დაავადებების გენეტიკური მხარის და გეოგრაფიული განედის გავლენის შესწავლა *FLG* და *MTHFR* გენების ალელური მუტაგენების სიხშირეებსა და ამ მუტაციების ჰეტეროგენულ მტარებლებზე. კლინიკურ-გინეკოლოგიური ანამნეზი და ინფორმაცია შეგროვილია პრობანდების ერთხელობრივი რეგისტრაციის მეთოდით ხარკოვის ოლქის კლინიკური დერმატოვენეროლოგიური №1 დისპანსერისა და დერმატოვენეროლოგიური დისპანსერების ბაზებზე. დერმატოზის დიაგნოზი და ფორმა დადგენილია კლინიკურ-გინეკოლოგიური მონაცემების და ლაბორატორიული კვლევების შედეგების ანალიზის საფუძველზე - მარტივი იხტიოზი (Q 80.1.0, OMIM 146700). გაანალიზებულია 38 ოჯახის მონაცემები, რომელსაც მიეკუთვნებოდა მარტივი იხტიოზით დაავადებული 26-76 წლის ასაკის 18 ქალი და 20 მამაკაცი.

ჩატარებული კვლევის შედეგად დადგენილია პირდაპირი კორელაცია გეოგრაფიულ განედსა და *FLG* გენის მუტაციური ალელების სახშირეებს,ასევე,გეოგრაფიულ განედსა და ამ მუტაციების ჰეტეროზიგოტულ მტარებლებს შორის. T ალელის და T გენოტიპის სიხშირეები

MTHFR გენის C677T პოლიმორფული ვარიანტის მიხედვით გეოგრაფიულ განედის მაჩვენებლებთან უკუკავშირს ავლენს. საწინააღმდეგო განედური ზონალობა აქვს 2282del4 ალელისა და CT გენოტიპის, გენოტიპების N/2282del4 და CT, ალელების 2282del4 და T, N/2282del4 გენოტიპი ა და T ალელის სიხშირეების განაწილებას. დადგენილი კავშირები იძლევა გინეკოლოგიური პათოლოგიების განვითარების პროგნოზირების საშუალებას მარტივი იხტიოზით დაავადებულ ქალებში. ხარკოვის ოლქში მარტივი იხტიოზით დაავადებულ პაციენტ ქალებს შორის ენდომეტრიოზისა და ენდომეტრიუმის კიბოს გავრცელებამ შეადგინა 33.3%,მაშინ,როდესაც საშუალო რეგიონული მაჩვენებელი ქალთა პოპულაციაში 0,29-0,35%-ია. შვილების რაოდენობა მარტივი იხტიოზით დაავადებულ ქალებში რეგიონული მაჩვენებლისაგან არ განსხვავდებოდა.

THE EFFECTS OF NON-FUNCTIONAL OVERREACHING AND OVERTRAINING ON AUTONOMIC NERVOUS SYSTEM FUNCTION IN HIGHLY TRAINED GEORGIAN ATHLETES

Kajaia T., Maskhulia L., Chelidze K., Akhalkatsi V., Kakhabrishvili Z.

Tbilisi State Medical University, Georgia

The modern sports training program commonly comprises a component of repetitive overloading to initiate structural and functional changes in an attempt to achieve favorable adaptation to the workouts and enhance athlete's sports performance. Intensified training can result in a decline in performance. However, when appropriate periods of recovery are provided, a "supercompensation" effect may occur with the athlete exhibiting an enhanced performance compared to baseline levels and "functional overreaching" (FO) can be achieved. In this situation, the physiological responses will compensate for the training-related stress [4,19]. When this intensified training continues, the athletes can evolve into a state of extreme overreaching or "non-functional overreaching" (NFO). As it is possible to recover from short-term or 'functional' overreaching within a period of 2 weeks, the recovery from the NFO state may lead to a stagnation or decrease in performance which will not resume for several weeks or months. However, if overreaching is extreme and prolonged excessive training takes place concurrent with an additional stressor and insufficient recovery, overtraining syndrome (OTS) may result [15]. The OTS is characterized by chronic maladaptations and a sports-specific decrease in performance together with disturbances in mood state and persistent fatigue [5, 10]. Athletes who suffer from OTS may need months or even years to completely recover, leading frequently to cessation of a sports career [11,14,17]. Many researchers consider overreaching and overtraining as a continuum [7,15], others suggest that NFO precedes OTS [13,16,22]. This is in line with findings on the ''sympathetic versus parasympathetic OTS'' regarding different resting cortisol levels and exercise-induced changes in free plasma catecholamines, and recent neuroendocrine findings using a double-exercise test [9,15]. Early detection of NFO is very important in terms of prevention of overtraining, as well as for interruption of NFO/OTS progression.

Besides other physiological, biochemical, immunological, psychological and performance markers [5], heart rate (HR) and its modulations are intensively investigated as a practical and reliable sign of overtraining. Advancements in technology made it easy to assess the beat-to-beat variation in resting pulse rates, i.e. heart rate variability (HRV) [6,12,15,18]. Heart rate fluctuation may be considered an output variable of a feedback network that is continuously monitored and regulated by the autonomic nervous system (ANS). HRV analysis is used as a measure of cardiac autonomic balance (sympathetic vs. parasympathetic), with an increase in HRV indicating an increase in vagal tone relative to sympathetic activity. Autonomic nervous system, also as well as endocrine system, plays an important role from the point of view of physiologic reactions and adaptation to the physical training, and influences recovery phase [2,3,10]. In overtraining the ANS can show an excessive shift in the balance, either in the direction of parasympathethetic or sympathetic [1].

Aim of the study was to compare the autonomic nervous system functioning, as measured by HRV, in athletes with non-functional overreaching and overtraining and athletes without NFO/OTS.

Material and methods. On the initial stage of the study conducted in the Clinical Center of Sports Medicine and Rehabilitation of Tbilisi State Medical University physical condition and health state of 348 high level athletes (aged 22±4,7y.o.) were examined and 43 subjects with NFO/OTS were revealed, among them 37(10,6%) athletes with non-functional overreaching and 6 (1,7%) athletes with overtraining of different severity and duration (Table 1) [9].

Diagnosis of OTS was based on the checklist provided by the consensus statement of the European College of Sports Science

Table 1. Distribution of non-functional overreaching and overtraining in sports disciplines

Sport Discipline	Athletes with NFO, n (%)	Athletes with OTS, n (%)
Cycling, n=6	0	
Basketball, n=32	2 (6,25)	
Boxing, n=15	1 (6,7)	
Rugby, n=38	2 (5,3)	
Football, n=114	9 (7,9)	2 (1,8)
Weightlifting, n=10	1 (10,0)	
Water-polo, n= 29	3 (10,3)	
Wrestling, n=104	19 (18,3)	4 (3,8)

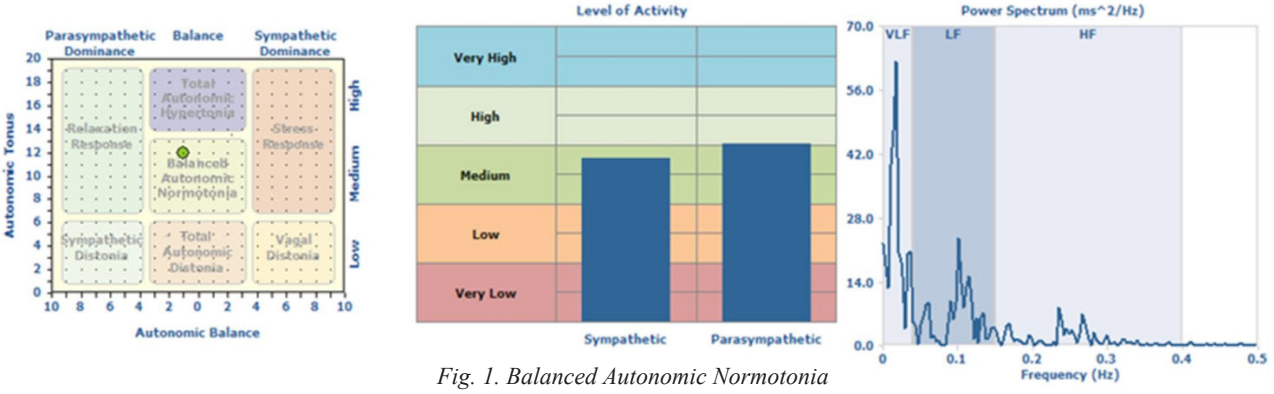

Fig. 1. Balanced Autonomic Normotonia

(ECSS) and the American College of Sports Medicine (ACSM) [8,15]. The flowchart as presented in the ACSM-ECSS consensus statement could help to establish the exclusion diagnosis for the detection of OTS. When previous training load was high enough, the occurrence of persistent problems in performance creates a suspicion for OTS. The flowchart starts with the key symptoms: decrease in performance; duration of symptoms; then other major diseases that are related to underperformance are ruled out; then performance changes are defined and then possible confounding conditions (psychological signs and symptoms, social factors, recent or multiple time zone travel, etc.) and diseases are checked; then training errors (increased volume, intensity, high number of competitions, etc.) are considered and exercise test is performed. In this study prevalence of NFO and OTS was seen in sporting disciplines with mixed high intensity workload, among them 27 (62,8%) NFO and 4 (9,3%) OTS, particularly, majority of NFO/OTS was revealed in wrestling: NFO-19 (44,2%) and OTS- 4 (9,3%) [9].

On the following stage of the study, in 43 athletes with NFO/OTS, in 40 athletes of the same sporting disciplines but without NFO/OTS, as well as in 35 sedentary subjects of the same age and gender the autonomic nervous system function was evaluated with the Autonomic Balance Test, based on the HRV analysis of resting heart rate recordings of 5 minutes long.

The athletes and controls were instructed not to drink any alcohol or caffeine or to smoke in the preceding 24 hours. On the testing day the autonomic balance test was conducted after fasting for at least 2 hours. The recording was performed in a comfortable relaxed sitting position with limiting body movements. Heart rate variability was assessed according to the standards set forth by the Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology, based on the two methods of analysis of HRV data: time- and frequency-domain analysis [20, 21], using Heart Rhythm Scanner Professional Edition (Biocom Technologies). The following time-domain parameters were calculated: mean heart rate value (Mean HR), mean heartbeat interval value (Mean RR), standard deviation from the mean RR value (SDNN), root mean square of the standard deviation (RMS-SD), percentage of heartbeat intervals differing more than 50 ms from previous intervals (pNN50), and Tension Index (TI).

A power spectrum analysis was applied to a 5-min sequence of normal heartbeat intervals. The following frequency-domain parameters were calculated: Total Power (TP), Very Low Frequency (VLF, frequency range from 0,0033 to 0,04 Hz), Low Frequency (LF, frequency range from 0,04 to 0,15 Hz), High Frequency (HF, frequency range from 0,15 to 0,4 Hz) components, Low Frequency to High Frequency Ratio (LF/HF ratio), Normalized Low Frequency (LF norm, %), and Normalized High Frequency (HF norm, %).

The Heart Rhythm Scanner makes an assessment of the autonomic nervous system regulatory function condition based on two variables - Autonomic Balance (a ratio between levels of the sympathetic and parasympathetic activity) and Autonomic Tonus (a net level of the sympathetic and parasympathetic activity). The Autonomic Balance and Autonomic Tonus were calculated in points based on 80% of least deviated values of HRV parameters in the normative database. The Autonomic Balance ranged from -10 points (significant predominance of parasympathetic regulation) to +10 points (significant predominance of sympathetic regulation), and the Autonomic Tonus ranged from 0 points (significantly low) to +20 points (significantly high), (Fig. 1).

Based on the processing of above mentioned parameters, and according to the comparative analysis of Autonomic Balance and Autonomic Tonus, seven possible combinations of these two variables were established, showing autonomic nervous system regulatory function condition: Sympathetic Dystonia, Relaxation Response, Total Autonomic Dystonia, Balanced Autonomic Normotonia, Total Autonomic Hypertonia, Vagal Dystonia, Stress Response.

SPSS 12 software was used for statistical analysis. Obtained data were processed according Student's t-criterion, and data are presented as mean±SD. The level of statistical significance was set as p value <0,05.

Results and their discussion. In general, resting bradycardia, a decrease in HR during submaximal exercise, an increase in speed of heart rate recovery and increased vagal-related heart rate variability indices are all well accepted markers of improved aerobic fitness. In contrast, opposite changes in these HR measures are commonly interpreted as indicators of detraining, chronic fatigue, non-functional overreaching or overtraining. However, based on the limited and diverse literature available, those parameters may be proposed for monitoring training status, optimizing training programs and following accumulation of fatigue, but their role in overtraining detection and assessment is still to be elucidated [17]. This study evaluated HRV and distribution of autonomic power in athletes with non-functional overreaching and overtraining and subjects without NFO/OTS as well as sedentary controls. HRV indicators obtained by time domain analysis included Mean RR

Table 2.Time-domain parameters in athletes and controls

Parameter/Unit	Athletes without NFO/OTS	Athletes with NFO	Athletes with OTS	Control group
Age	24,7±6,1	24,3±4,7	23,7±5,2	23,8±3,6
Mean HR , bpm	67,5±10,8	73,6±6,4	74,1±5,7	74,8±4,2
Mean RR, ms	986±97*	923±76	836±54▪	875±34
SDNN, ms	77,2±6,8*	54,6±5,0	49,4±4,2	43,3±2,3
RMS-SD, ms	86,4±8,9*	62,4±5,7	31,3±3,4▪	50,1±2,5
pNN50, %	47,7±7,4*	28,3±3,8	19,5±1,9▪	30,0±2,6
TI, a.u.	67±4,5	89±3,7^	92±3,2^	78±2,7

**p<0,05 - Athletes without NFO/OTS compared to athletes with non-functional overreaching, to athletes with overtraining, and control group;*
▪p<0,05 - Athletes with OTS compared to athletes with NFO;
^p<0,05 - Athletes with NFO/OTS compared to athletes without NFO/OTS and control group

Table 3. Frequency-domain parameters in athletes and controls

Parameter, unit	Athletes without NFO/OTS	Athletes with NFO	Athletes with OTS	Control group
TP, ms²/ Hz	1797±274	1968±314	1471±121	974±87
LF, ms²/ Hz	585±107	956±124^	779±96^	301±65
HF, ms²/ Hz	658±187*	398±93	312±61	229±46
LF/HF, a.u.	1,3±0,61	3,0±0,54^	2,7±0,28^	1,8±0,69
LF norm, %	51±3,0	65±2,8	63±1,8	59±0,9
HF norm, %	49±3,0	35±2,8	37±1,8	41±0,9

**p<0,05 - Athletes without NFO/OTS compared to athletes with non-functional overreaching, to athletes with overtraining, and control group;*
^p<0,05 - Athletes with NFO/OTS compared to athletes without NFO/OTS and control group

and SDNN which reflect net effect of the autonomic regulation on cardiovascular function, both vagal, as well as sympathetic influences, whereas RMS-SD and pNN50 reflect the vagal influence on HRV. In our study Mean RR, SDNN, RMS-SD and pNN50 HRV indicators were significantly lower for the athletes with non-functional overreaching and overtraining, as well as for the sedentary controls, than for the athletes without NFO/OTS (p<0,05). This reflects lower heart rate variability and significant lower vagal influence in athletes with NFO/OTS and controls, than in highly trained athletes without NFO/OTS. Furthemore, Mean RR RMS-SD and pNN50 HRV indicators were significantly lower for the athletes with overtraining (p<0,05), than for the athletes with non-functional overreaching, showing more advanced changes in autonomic regulation, probably dysregulation, in athletes with OTS than in subjects with NFO. Tension index reflecting functional strain of the autonomic regulatory mechanisms was significantly greater in athletes with OTS and NFO (p<0,05) than in athletes without NFO/OTS and control group (Table 2).

HRV indicators obtained by frequency domain analysis included HF which reflects parasympathetic regulatory tone, LF which reflects sympathetic regulatory tone with some contribution of the parasympathetic tone, and LF/HF ratio which is determined by the balance between sympathetic and parasympathetic tone or fractional distribution of power of the ANS influence on the heart [1,20,21]. In this study mean HF values showed significant difference (p<0,05) between athletes without NFO/OTS and athletes with non-functional overreaching and overtraining, as well as sedentary controls, indicating significantly higher parasympathetic modulation of the heart in highly trained athletes without NFO/OTS (Table 3).

LF and the LF/HF ratio in our study were significantly higher (p<0,05) in athletes with non-functional overreaching and overtraining than in athletes without NFO/OTS and control group (Table 3). This indicates significant increased sympathetic cardiovascular control in athletes with non-functional overreaching and overtraining relative to the rest (Figs. 2, 3).

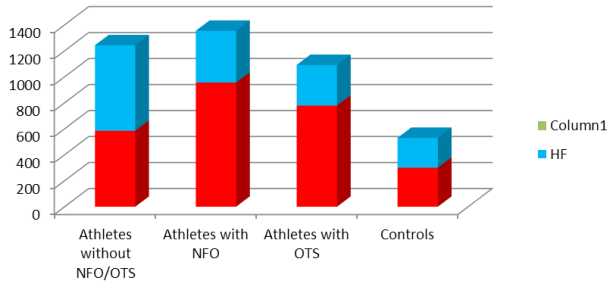

Fig. 2. Comparison of the LF and HF power distribution in athletes with NFO/OTS, athletes without NFO/OTS, and control group

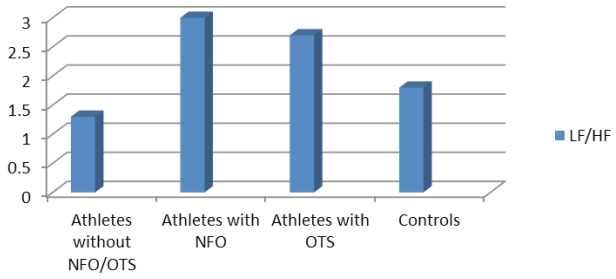

Fig. 3. Comparison of LF to HF ratio in athletes with NFO/OTS, athletes without NFO/OTS, and control group

Table 4. Distribution of types of Autonomis Tonus and Balance combinations among athletes and control group

Combination of autonomic tonus and balance	Athletes without NFO/OTS n=40, n (%)	Athletes with NFO n=37, n (%)	Athletes with OTS n=6, n (%)	Control group n=35, n (%)
Balanced Autonomic Normotonia	18 (45%)	20 (54%)	0	29 (83%)
Relaxation Response	9 (22,5%)	3 (8%)	0	5 (14%)
Total Autonomic Dystonia	0	1 (3%)	4 (67%)	0
Sympathetic Dystonia	0	0	0	0
Total Autonomic Hypertonia	12 (30%)	0	0	0
Vagal Dystonia	0	0	0	0

Such condition of autonomic nervous system is reflected in the distribution of types of Autonomic Tonus and Balance combinations among athletes and control group (Table 4, Fig. 3) where "Stress Response" was dominated in athletes with NFO and "Total Autonomic Dystonia" was prevalent in athletes with OTS. Interestingly, in our study neither "Sympathetic Dystonia", nor "Vagal Dystonia" was revealed (Table 4, Fig. 4).

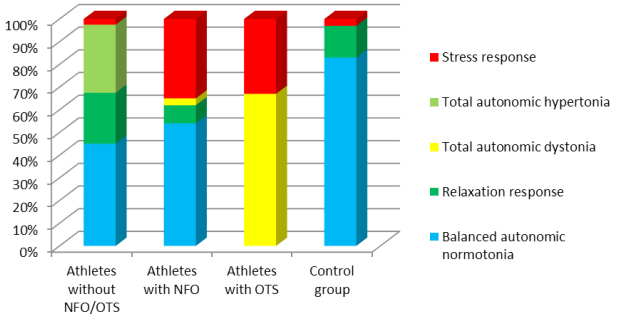

Fig. 4. Distribution of types of Autonomic Tonus and Balance combinations among athletes and control group

In athletes without NFO/OTS "Balanced Autonomic Normotonia"- a sign of optimum performance of the autonomic regulatory function was dominated (Fig. 1), and almost equally were seen "Relaxation Response"- a sign of achieving mentally/physically restful condition and good relaxation, and "Total Autonomic Hypertonia"- a sign of high level of performance of the autonomic regulatory function, which is typical for active healthy individuals, athletes and other trained people.

"Stress Response" in athletes with NFO, mostly wrestlers – 8(61,5%) (Table 5), as well as in some athletes with OTS, is typical sign of the sympathetic dominance, which may be a sign of physical or mental fatigue and chronic stress, causing a decreased regulatory function of the parasympathetic nervous system (Fig. 5), whereas "Total Autonomic Dystonia" in most of the athletes with OTS (67%) reflects more advanced stage of maladaptation associated with depressed regulatory function of the autonomic nervous system, both sympathetic, as well as parasympathetic influences (Fig. 6). Most of the "Total Autonomic Dystonia" in athletes with OTS was seen in wrestlers 3 (75%) (Table 5).

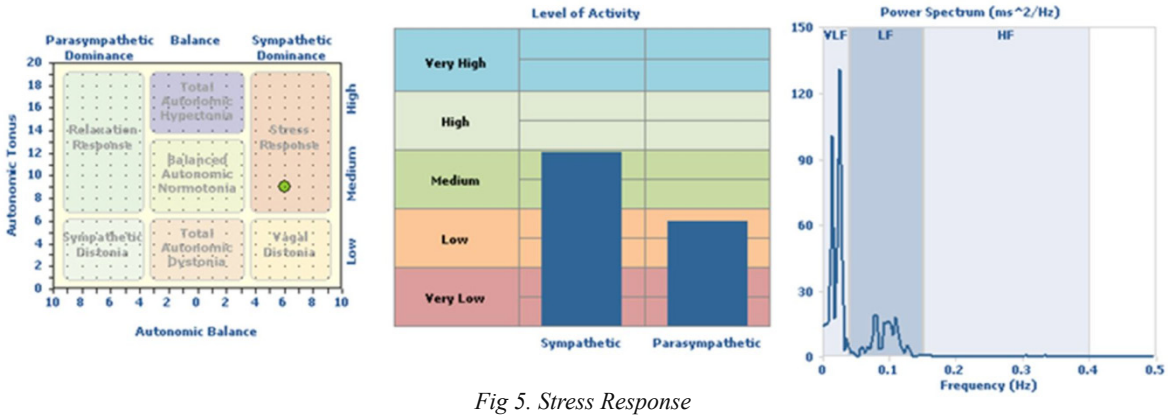

Fig 5. Stress Response

Table 5. Distribution of "Total Autonomic Dystonia" and "Stress Response" among athletes with NFO/OTS

Combination of autonomic tonus and balance	Total autonomic dystonia, n=5	Stress response, n=15
Athletes with NFO:		
Rugby	1	-
Football	-	5
Wrestling	-	8
Athletes with OTS:		
Football	1	1
Wrestling	3	1

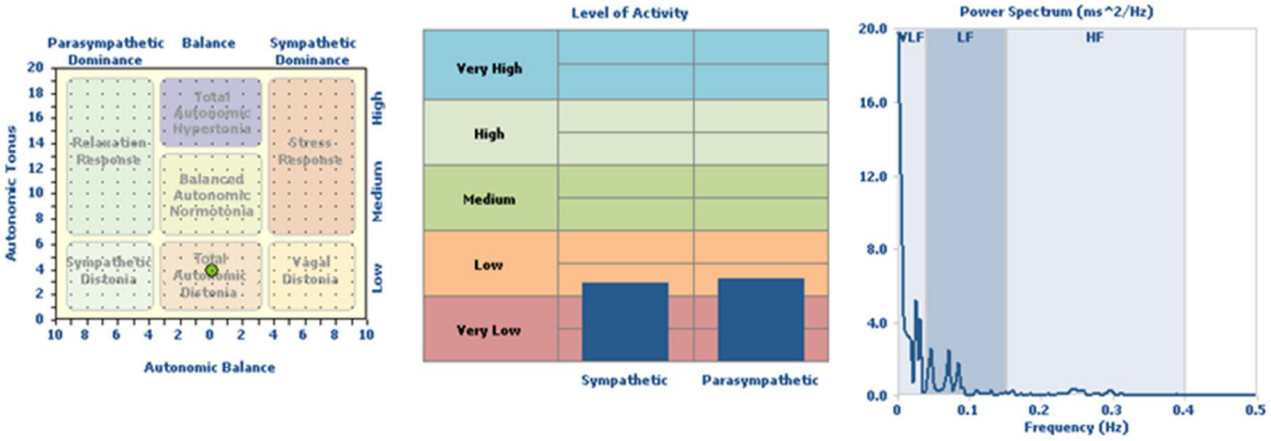

Fig. 6. Total Autonomic Dystonia

Thus, results of the study show progression of autonomic imbalance: higher level of sympathetic activity in athletes with NFO compared with athletes with OTS and depression of regulatory function of the autonomic nervous system in athletes with OTS. When considering progression of the OTS, researchers hypothesised that during the early stage of the overtraining, i.e. non-functional overreaching, the sympathetic system is continuously altered, whereas during advanced overtraining the activity of the sympathetic system is inhibited, resulting in a marked dominance of the parasympathetic system [18]. As it was mentioned above, in our study "Sympathetic Dystonia" - a sign of a decreased regulatory function of the sympathetic nervous system and marked dominance of the parasympathetic system was not found, which probably means better prognosis in case of studied athletes, but presence of "Stress Response" and particularly "Total Autonomic Dystonia" still is a subject for concern. In athletes with "Total Autonomic Dystonia" the level of functional activity of both, sympathetic and parasympathetic nervous system, is lower than normal (Picture 3), which could reflect inhibition of activities of both systems. We may hypothesize that further decrease in sympathetic tone with relative dominance of parasympathetic tone may lead to the extreme type of OTS – "parasympathetic OTS", for which it is required months or even years to completely recover, but frequently it is a cause of cessation of a sports career.

The main causes of overtraining syndrome, other than extreme and prolonged excessive training without sufficient recovery periods, are probably associated with too much accompanying psycho-emotional stress, such as too many competitions and too many non-training stress factors (e.g. social, educational, nutritional). In this study most frequently NFO and OTS were seen in wrestling, which needs further investigation and regular medical monitoring. Longitudinal studies on these groups are suggested.

The cardiac autonomic imbalance observed in overtrained athletes implies changes in HRV and therefore would consider that heart rate variability could provide valuable information in detection of overtraining in athletes. HRV can be a valuable adjacent tool for optimising athlete's training program as well as for timely diagnosis and prevention of progression of NFO/OTS.

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SUMMARY

THE EFFECTS OF NON-FUNCTIONAL OVERREACHING AND OVERTRAINING ON AUTONOMIC NERVOUS SYSTEM FUNCTION IN HIGHLY TRAINED ATHLETES

Kajaia T., Maskhulia L., Chelidze K., Akhalkatsi V., Kakhabrishvili Z.

Tbilisi State Medical University, Georgia

Aim of the study was to compare the ANS functioning, as measured by heart rate variability (HRV), in athletes with non-functional overreaching (NFO) and overtraining syndrome (OTS) and in athletes without NFO/OTS. In 43 athletes with NFO/OTS, 40 athletes without NFO/OTS, as well as in 35 sedentary subjects the ANS function was evaluated with the Autonomic Balance Test, based on the HRV analysis of resting heart rate recordings.

Results of the study show lower HRV and lower vagal influence along with increased sympathetic cardiovascular control in athletes with non-functional overreaching and particularly in athletes with overtraining, than in highly trained athletes without NFO/OTS. “Stress Response” in athletes with NFO, as well as in some athletes with OTS, showing sympathetic dominance, considered as a sign of physical or mental fatigue and chronic stress, whereas “Total Autonomic Dystonia” in most of the athletes with OTS (67%) reflects more advanced stage of maladaptation associated with depressed regulatory function of the ANS, both sympathetic, as well as vagal influences. Most frequently NFO and OTS were seen in wrestling, which needs further investigation and regular medical monitoring.

Thus, results of the study show progression of autonomic imbalance and depression of regulatory function of the autonomic nervous system in athletes with OTS. The cardiac autonomic imbalance observed in overtrained athletes implies changes in HRV and therefore would consider that heart rate variability may provide useful information in detection of overtraining in athletes and can be a valuable adjacent tool for optimising athlete’s training program as well as for timely diagnosis and prevention of progression of NFO/OTS.

Keywords: Non-functional overreaching, overtraining syndrome, autonomic nervous system, heart rate variability

РЕЗЮМЕ

ВЛИЯНИЕ НЕФУНКЦИОНАЛЬНОГО ПЕРЕНАПРЯЖЕНИЯ И ПЕРЕТРЕНИРОВКИ НА ФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ АВТОНОМНОЙ НЕРВНОЙ СИСТЕМЫ СПОРТСМЕНОВ ВЫСОКОЙ КВАЛИФИКАЦИИ

Каджаия Т.З., Масхулия Л.М., Челидзе К.Л., Ахалкаци В.И., Кахабришвили З.Г.

Тбилисский государственный медицинский университет, Грузия

Целью исследования явилась сравнительная оценка функционального состояния автономной нервной системы (АНС) спортсменов с нефункциональным перенапряжением (НФП) и синдромом перетренировки (СП), а также спортсменов без НФП/СП посредством измерения вариабельности сердечного ритма (ВСР). Оценка функционального состояния АНС проводилась посредством теста автономного баланса, на основе анализа ВСР в покое у 43 спортсменов с НФП/СП, 40 спортсменов без НФП/СП и 35 физически неактивных лиц в контрольной группе.

Исследование выявило снижение парасимпатической активности и повышенный симпатический кардиоваскулярный контроль в случае НФП/СП, особенно у спортсменов с перетренировкой в сравнении с спортсменами без НФП/СП. Характерная для симпатического доминирования «стресс-реакция» у спортсменов с НФП, также как и у некоторых спортсменов с перетренировкой, может быть показателем физической или умственной усталости и хронического стресса, тогда как «полная автономная дистония» у большинства (67%) спортсменов с СП является отражением нарушения адаптации более тяжелой степени, связанная с подавленной регуляторной функцией АНС, с точки зрения как симпатической, так и парасимпатической активности. Чаще всего НФП и СП наблюдались у борцов, что является предметом дальнейшего изучения и регулярного медицинского контроля.

Таким образом, результаты проведенного исследования выявили прогрессирование вегетативной неустойчивости и ослабление регуляторной функции АНС у спортсменов с СП. Следовательно, оценка вариабельности сердечного ритма может быть маркером выявления перетренировки у спортсменов и смежным инструментом в оптимизации программы тренировок, а также своевременной диагностики и превенции прогрессирования НФП/СП.

რეზიუმე

არაფუნქციური გადაძაბვისა და გადაწვრთნის გავლენა ავტონომიური ნერვული სისტემის ფუნქციურ მდგომარეობაზე მაღალი კვალიფიკაციის სპორტსმენებში

თ. ქაჯაია, ლ. მასხულია კ. ჭელიძე, ვ. ახალკაცი, ზ. კახაბრიშვილი

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

კვლევის მიზანს წარმოადგენდა ავტონომიური ნერვული სისტემის (ანს) ფუნქციური მდგომარეობის შედარებითი შეფასება არაფუნქციური გადაძაბვის (აფგ) და გადაწვრთნის სინდრომის (გწს) მქონე სპორტსმენებში და სპორტსმენებში აფგ/გწს-ის გარეშე. ავტონომიური ნერვული სისტემის ფუნქციური მდგომარეობა ფასდებოდა გულის რითმის ვარიაბელობის (გრვ) შესწავლით. 43 აფგ/გწს-ს მქონე სპორტსმენთან, 40 სპორტსმენთან აფგ/გწს-ს გარეშე და 35 იგივე სქესის ფიზიკურად არააქტიურ პირებში საკონტროლო ჯგუფში შეფასდა ანს-ის ფუნქცია მოსვენების მდგომარეობაში ავტონომიური ბალანსის სინჯის გამოყენებით, გულის რიტმის ვარიაბელობის ანალიზის საფუძველზე.

კვლევის შედეგად გამოვლინდა უფრო დაბალი პარასიმპათიკური გავლენა და მომატებული სიმპათიკური კარდიოვასკულური კონტროლი არაფუნქციური გადაძაბვის შემთხვევაში, განსაკუთრებით კი გადაწვრთნის მქონე სპორტსმენებში, ვიდრე მაღალი კვალიფიკაციის მქონე სპორტსმენებში აფგ/გწს-ს გარეშე.

სიმპათიკური დომინირებისთვის დამახასიათებელი "სტრესს-რეაქცია" აფგ-ს მქონე სპორტსმენებში, ისევე როგორც გწს-ს მქონე ზოგიერთ სპორტსმენთან, შეიძლება იყოს ფიზიკური ან მენტალური გადაღლის და ქრონიკული სტრესის მაჩვენებელი; "სრული ავტონომიური დისტონია" გწს-ს მქონე სპორტსმენთა უმეტესობაში (67%) ასახავს ადაპტაციის დარღვევის უფრო მძიმე ხარისხს, რომელიც ხასიათდება ანს-ის რეგულაციური ფუნქციის შესუსტებით როგორც სიმპათიკური, ისე პარასიმპათიკური აქტივობის თვალსაზრისით. უფრო ხშირად აფგ და გწს გამოვლინდა მოჭიდაველებში, რაც მომდევნო შესწავლას და რეგულარულ სამედიცინო მონიტორინგს მოითხოვს.

კვლევის შედეგებმა უჩვენა ავტონომიური დისბალანსის პროგრესირება და ავტონომიური ნერვული სისტემის რეგულაციური ფუნქციის შესუსტება გწს-ს მქონე სპორტსმენებში. მაშასადამე, გულის რიტმის ვარიაბილობის შეფასებით შესაძლებელია მნიშვნელოვანი ინფორმაციის მიღება გადაწვრთნის გამოსავლენად სპორტსმენებში, რაც ქმნის სპორტსმენთა საწვრთნელი პროგრამის ოპტიმიზების, ასევე, როგორც აფგ/გწს-ს დროული დიაგნოსტიკის და პროგრესირების პრევენციის შესაძლებლობას.

ИССЛЕДОВАНИЕ МИКРОФЛОРЫ КИШЕЧНИКА КРЫС ПОД ВОЗДЕЙСТВИЕМ ВНУТРЕННЕГО И ВНЕШНЕГО ОБЛУЧЕНИЯ

[1]Кайрханова Ы.О., [1]Чайжунусова Н.Ж., [1]Уразалин М.М., [2]Степаненко В.Ф., [3]Хоши М.

[1]Государственный медицинский университет г. Семей, Республика Казахстан; [2]Медицинский радиологический научный центр им. А.Ф. Цыба - филиал Федерального государственного бюджетного учреждения «Национальный медицинский исследовательский радиологический центр» Минздрава России, Обнинск, Россия; [3]Университет Хиросимы, Япония

Проведены многочисленные исследования по изучению состава и значения микрофлоры толстого кишечника [2,8,9,38]. Доказано, что в толстом кишечнике обитает от 300 до 500 видов различных микроорганизмов, 90% из них являются микробами мутуалистами (бифидо-, лактобактерии, бактероиды, пептострептококки), только малочисленная группа представлена условно патогенными микроорганизмами. Масса нормальной микрофлоры кишечника взрослого человека составляет более 2,5 кг, а её численность - 10^{14} [12,13].

Качественное и количественное соотношение микроорганизмов в органах и системах является чрезвычайно чувствительным индикатором состояния организма человека. Бактерии нормальной микрофлоры представляют собой эволюционно созданный «биологический барьер» макроорганизма, позволяющий ему существовать в биосфере [16,19,11]. Симбионтная микрофлора кишечника, в первую очередь бифидо- и лактобактерии, посредством антигенной стимуляции усиливает образование комплемента, лизоцима, иммуноглобулинов, индуцирует синтез интерферона, стимулирует лимфоидный аппарат кишечника, оказывая прямое влияние на дифференцировку Т- и В-лимфоцитов в пейеровых бляшках, индуцируя функциональную активность фагоцитов [14,18].

Однако при воздействии вредных экзо- и эндогенных факторов, этот мощный по составу и количеству микробиоценоз нарушается, в сторону увеличения неблагоприятной микрофлоры и способствует развитию дисбактериоза [10,17,20,32]. В результате чего микробные ассоциации не могут выполнять защитные и физиологические функции, осуществляющие в условиях нормоценоза. Одним из таких факторов, влияющих на микрофлору является ионизирующее излучение [21,22,30].

Проблема определения значимости облучения при поступлении в организм нейтрон-активированных радионуклидов, образовавшихся в почвенной пыли до настоящего времени является предметом дискуссий [26,28,29]. Согласно данным литературы [15,34], при атмосферных ядерных испытаниях, в результате нейтронной активации химических элементов, в составе почвы образуются бета- и гамма-излучающие радионуклиды. Одно из ведущих значений в этом процессе отводится короткоживущему ^{56}Mn ($T_{1/2}$=2,58 ч), который является одним из основных нейтронно- активированных бета-излучателей в течение первых часов после нейтронной активации частиц почвенной пыли [33,35,37].

Бактериологический анализ человека, а также экспериментальные исследования с использованием животных (мыши, крысы, свиньи, собаки) выявили множественные изменения специфической микрофлоры кишечника, демонстрируя чувствительность бактерий к общему и частичному облучению тела хозяина [30,31]. Изменения в бактериальной флоре способствуют нарушению сосудистой проницаемости слизистой оболочки и моторики кишечника [24,25]. По результатам исследований, проведенных в 1950-е и 1960-е годы, определены бактерии, присутствующие в фекалиях и являющиеся чувствительными к ионизирующему излучению. Облучение тонкого кишечника дозой 6,3 Гр у крыс приводит к 4-кратному уменьшению лактобактерий и 1000-кратному увеличению псевдомонад, достигая максимального уровня на 6-7 дни [36].

Облучение кишечника (19,4 Гр) или всего тела (13,6 Гр) у крыс вызывает избыточный бактериальный рост микроорганизмов в тонком кишечнике [27]. Таким образом, вышеприведенные данные указывают на изменения качественного и количественного состава микрофлоры в зависимости от вида и дозы облучения, времени и развития дисбактериоза.

Целью исследования явилось проведение сравнительной оценки качественного и количественного состава микрофлоры толстого кишечника крыс при воздействии внутреннего и внешнего облучения.

Материал и методы. Эксперимент проводили на 40 десятинедельных крысах-самцах линии Вистар, 200-230 г. Крысы приобретены в Казахском Научном центре карантинных и зоонозных заболеваний, Алматы, Казахстан. Крысы содержались со свободным доступом к основной диете и водопроводной воде.

Животные были разделены на четыре группы:
1. «Высокая» доза (0,90 Гр) - ^{56}Mn – 10 крыс (внутреннее облучение);
2. «Низкая» доза (0,69 Гр) - ^{56}Mn группа - 12 крыс (внутреннее облучение);
3. ^{60}Co группа (2 Гр) - 9 крыс (внешнее облучение);
4. Контрольная группа - 9 крыс.

Настоящее экспериментальное исследование проведено использованием нейтрон-активированного $^{56}MnO_2$ (внутреннее облучение) и внешнего облучения источником ^{60}Co (2 Гр).

Дозы внутреннего облучения (^{56}Mn) составили: в группе (1) - 0,14±0,03 Гр во всем теле и 1,90 ± 0.47 Гр в толстом кишечнике; в группе (2) - 0,091±0,026 Гр во всем теле и 0,69±0,17 Гр в толстом кишечнике. Доза внешнего облучения от ^{60}Co составила 2,0 Гр - группа (3)

Для дозиметрических исследований уровней внутреннего облучения использовали по три крысы из каждой ^{56}Mn группы. Органы и ткани извлекали спустя 3 часа после начала облучения – после умерщвления животных путем внутрибрюшинного введения кетамина.

Для бактериологических исследований (спустя 6 часов и на 3, 14 и 60 сутки после облучения) также использовали по три крысы из каждой группы (в группе ^{56}Mn (2) спустя 3 и 14 дней были использованы только две крысы).

Методика облучения с использованием нейтронно-активированного $^{56}MnO_2$ и последующая оценка дозы внутреннего облучения представлены в [15,34].

$^{56}MnO_2$ был получен путем нейтронной активации 100 мг порошка MnO_2 с использованием ядерного реактора Байкал-1 в Национальном ядерном центре, г.Курчатов, Казахстан. Флюенс тепловых нейтронов составлял 8×10^{14} н / см^2 и $1,6 \times 10^{15}$ н / см^2 (для двух вариантов облучения – с более высокой и более низкой актитвностью ^{56}Mn, соответственно). Спустя 6 мин. после окончания нейтронной активации осуществлялась экспозиция экспериментальных животных порошком ^{56}Mn. Активированный порошок - $^{56}MnO_2$, распыляли в специальных боксах, содержащий по шесть крыс в каждом. Один час спустя все крысы были перемещены в «чистые» боксы.

Измерения активности ^{56}Mn в органах и тканях животных проводили методом гамма-спектрометрии. Поглощенные доли энергии от внутреннего бета- и гамма- облучения органов, тканей и всего тела рассчитывали методом стохастического моделирования взаимодействия ионизирующего излучения с веществом (метод Монте-Карло, версия MCNP-4C) с использованием возрастозависимого математического фантома экспериментальной крысы [15,34].

Третья группа крыс подвергалась гамма-облучению ^{60}Co в дозе 2 Гр с мощностью 2,6 Гр/мин с использованием чешского радиотерапевтического устройства «Teragam K–2 unit» (UJP Praha, Praha-Zbraslav, Чехия). Для этого был разработан способ топометрическо-дозиметрической подготовки экспериментальных животных к облучению. Во время экспозиции животных помещали в специально сконструированные боксы из органического стекла с отдельными отсеками для каждой крысы. Облучение проводили с верхней (1Гр) и нижней (1Гр) поверхности бокса. Для измерения дозы от облучения ^{60}Co использовали радиофотолюминесцентный стеклянные дозиметры GD-302M (Chiyoda Technol Co., Токио, Япония). Четвертую группу составили интактные животные (контроль).

Все процедуры на животных согласованы и одобрены Комитетом по этике Государственного медицинского университета г. Семей, Казахстан (протокол №5 от 16.04.2014) в соответствии с требованиями Европейского парламента и Совета по Управлению и защите животных [23].

Содержимое толстого кишечника зибирали в стерильную емкость и отправляли на микробиологическии анализ, в бактериологическую лабораторию на базе Коммунального государственного казенного предприятия «Инфекционной больницы г. Семей» в течение двух часов. Бактериологическое исследование проводили по стандартной методике [4]. Образец взвешивали, гомогенизировали в 0,85% ратворе

хлорида натрия, получая исходное разведение 10^{-1}. Из исходного разведения готовили 9-десятикратных разведений в физиологическом растворе вплоть до разведения 10^{-10}. Засев из десятикратных разведений фекалий проводили сразу после их приготовления.

Посевы культивировали в течение 24-72 часов при температуре 37^0C.

Выделенные микроорганизмы идентифицировали по культуральным, морфологическим, тинкториальным и биохимическим свойствам. Подсчет каждой группы микроорганизмов в 1 грамме фекалий проводили по формуле:

$M=N*10^{n+1}$;
где M – число микроорганизмов в 1 грамме; N – количество колоний, выросших на поверхности пластинчатого агара и в глубине высокого столбика; n – степень разведения материала.

Окончательный результат количественного содержания бактерий в грамме фекалий выражали как lgKOE/г.

Полученные результаты анализировали с использованием непараметрической статистики по Манну-Уитни (программа SPSS 20) [6]. Посредством описательной статистики для каждого показателя определяли значение медианы, а также 25 и 75 квартильных диапазонов. Статистически значимыми считали различия между контрольной и опытной группами при значениях $p<0,05$.

Результаты и их обсуждение. Изучение характера микрофлоры толстого кишечника животных воздействием внутреннего и внешнего облучения выявило нарушения микрофлоры кишечного микробиоценоза. При этом изменяется количество и частота обнаружения представителей как облигатной, так и транзиторной флоры (таблица). Из таблицы явствует снижение численности анаэробов, молочнокислых бактерий: бифидобактерий, лактобактерий с одновременным повышением содержания условно патогенных бактерий (протей, цитробактер).

Количество бифидобактерий спустя 6 часов умеренно снижалось в обеих группах ^{6}Mn – до lg2,0 (2,0; 2,1) и lg2,0 (2,0; 2,15) в сравнении с контрольной - lg9,0 (8,92; 9,15) (p=0,037), а также с группой внешнего облучения ^{60}Co- 5,0 (4,65; 5,0) (p=0,034) на протяжении 14 суток. Количество лактобактерий в первой группе (высокая – 56 Mn) 6 часов и 3 дня спустя равнялось нулю, а спустя 14 дней обнаруживались в количестве lg2,0 (2,0; 2,15), в контрольной группе – в количестве lg4,3 (4,15; 4,38) (p=0,037).

Во второй группе (низкая-^{56}Mn) количество лактобактерий статистический значимо снизилось до lg2,0 (2,0; 2,15), и не изменялось до конца эксперимента (p=0,037), что полностью совпадает с литературными данными [27]. По количеству лактобактерий между второй (низкая-^{56}Mn) и третьей (^{60}Co) группой статистически значимых отличий не выявлено.

Эшерихий с нормальной ферментативной активностью 6 часов спустя в первой группе внутреннего облучения (^{56}Mn) не обнаруживалось, хотя через 3 дня их количество уже достигало lg5,0 (2,5; 5,23) (p=0,034), спустя 14 дней – равнялось нулю, а 2 месяца спустя - увеличилось до lg4,15 (4,0; 4,3).

Во второй группе (низкая-^{56}Mn) 6 часов спустя число эшерихий соответствовало норме, что, по всей вероятности, было вызвано низкой дозой (0,69 Гр). Однако трое суток спустя их количество резко уменьшилось - lg5,47 (5,38; 5,47), и на 14 сутки составило нуль. До уровня контрольной группы количество эшерихий достигло спустя 60 суток.

В группе ^{60}Co количество эшерихий с нормальной ферментативной активностью 6 часов спустя после воздействия умеренно понизилось - lg5,0 (5,0; 5,15) в сравнении с контрольной группой lg7,0 (7,0; 7,15) (p=0,043). На 3 сутки количество кишечной палочки нормализовалось, а к 14 – опять понизилось до lg2,0 (2,0; 2,5). Уровня контрольной группы количество эшерихий достигло 60 суток спустя.

Следует отметить, что в первой группе (^{56}Mn) из факультативной флоры выделялись гемолизирующие эшерихии в количестве lg7,0 (6,84; 7,15), которых в норме вообще нет и 3 дня спустя после воздействия ионизирующего излучения их колонии отсутствовали.

Известно, что гемолитические кишечные палочки (в норме они не присутствуют) способны вырабатывать токсины, и способствуют развитию кишечных и аллергических процессов.

У животных второй группы (низкая-^{56}Mn) спустя 14 дней регистрировались Proteus vulgaris в высоких разведениях lg5,3 (2,65; 5,57), а в группах 1 (^{56}Mn), 3 (^{60}Co) и 4 (контрольная) данные микроорганизмы не высевались. В этой же группе выявлялись Staphylococcus spp. в количестве lg3,47 (1,73; 3,58), однако статистически значимых отличий от других групп не выявлено.

Бактерии рода Citrobacter обнаруживались 6 часов спустя lg7,3 (3,65; 7,38) и через 14 дней lg5,3 (2,65; 5,6) в первой группе (высокая-^{56}Mn), а также 6 часов спустя lg7,3 (3,65; 7,38) и через 3 дня lg6,3 (3,15; 6,38) во второй группе (низкая-^{56}Mn). Однако спустя 2 месяца в микрофлоре толстого кишечника они не определялись.

Необходимо отметить, что появление в кишечнике повышенного количества условно-патогенной флоры, особенно аэробной, свидетельствует об ослаблении активности индигенного анаэробного компонента нормофлоры [1,3]. Известно, что в условиях пониженной резистентности макроорганизма определенные виды условно-патогенных микроорганизмов, достигшие популяционного уровня (10^5–10^6 КОЕ/мл), формируют ассоциации, объединенные в бактериальные биопленки, способные инициировать инфекционный процесс [4,7].

Значимым показателем дисбиотического состояния кишечника являются грибы рода Candida. Их обнаружили во всех экспериментальных группах, кроме контрольной. Так, в I группе (высокая-^{56}Mn) и 2 (^{56}Mn) 6 часов спустя выявлены грибы рода Candida в количестве lg4,0 (4,0; 4,15) и lg4,3 (4,2; 4,38), соответственно. Они регистрировались только 6 часов спустя, а на остальных сроках исследования отсутствовали. У облученных групп ^{60}Co грибы рода Candida обнаруживались на 14-е сутки - lg3,3 (3,15; 3,30).

Проведенные исследования свидетельствуют о выраженном влиянии нейтронно-активированного ^{56}Mn (внутреннее облучение) по сравнению с ^{60}Co (внешнее облучение) на состав

Таблица 1. Изменения просветной микрофлоры толстого кишечника Me (25; 75%), p.

Микро организмы	Высокая-^{56}Mn				Низкая-^{56}Mn				^{60}Co				Контроль			
	Через 6 часов	Через 3 суток	Через 14 суток	Через 60 суток	Через 6 часов	Через 3 суток	Через 14 суток	Через 60 суток			Через 14 суток	Через 60 суток	Через 6 часов	Через 3 суток	Через 14 суток	Через 60 суток
E.coli	0*#	5,0*# (2,5; 5,23)	0*#	4,15 (4,0; 4,3)	7,3 (3,65; 7,3)	5,47*# (5,38; 5,47)	7,3 (7,15; 7,3)	4,15 (4,0; 4,3)	5,0* (5,0; 5,15)	7,0 (7,0; 7,15)	2,0* (2,0; 2,5)	4,15 (4,0; 4,3)	7,0 (7,0; 7,15)	7,0 (7,0; 7,23)	7,0 (7,0; 7,15)	7,23 (7,0; 7,47)
E.coli гем+	7,0*# (6,84; 7,15)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pr.vulgaris	0	0	0	0	0	0	5,3 (2,65; 5,57)	0	0	0	0	0	0	0	0	0
Citrobacter	7,3 (3,65; 7,38)	0	5,3 (2,65; 5,6)	0	7,3 (3,65; 7,38)	6,3 (3,15; 6,38)	0	0	0	0	0	0	0	0	0	0
Bifidobacterium spp.	2,0*# (2,0; 2,1)	2,0*# (2,0; 2,15)	2,0*# (2,0; 3,15)	3,15 (2,0; 4,3)	2,0*# (2,0; 2,15)	5,47* (5,38; 5,47)	7,0* (7,0; 7,15)	7,38 (7,3; 7,47)	5,0* (4,65; 5,0)	4,3* (4,15; 4,38)	5,3* (5,15; 6,38)	7,23 (7,0; 7,47)	9,0 (8,92; 9,15)	8,47 (8,38; 8,73)	9,0 (8,5; 9,15)	8,73 (8,47; 9,0)
Lactobacillus spp.	0*#	0*#	2,0* (2,0; 2,15)	2,15 (2,0; 2,3)	2,0* (2,0; 2,15)	2,0* (2,0; 2,15)	2,4* (2,4; 2,7)	2,15 (2,0; 2,23)	2,0* (2,0; 2,15)	2,0* (2,0; 2,15)	4,0 (3,0; 4,15)	4,15 (4,0; 4,3)	4,3 (4,15; 4,38)	4,0 (4,0; 4,23)	4,0 (4,0; 4,23)	4,15 (4,0; 4,3)
Candida spp.	4,0* (4,0; 4,15)	0	0	0	4,3* (4,2; 4,38)	0	0	0	0	0	3,3* (3,15; 3,30)	0	0	0	0	0
Staphylococcus spp.	0	0	0	0	3,47 (1,73; 3,58)	0	0	0	0	0	0	0	0	0	0	0

*примечание. * – p<0,05 по отношению к данным в группе контроль, # – p<0,05 по отношению к данным в группе Co60*

пристеночной микрофлоры толстого кишечника. Кроме того, при дисбактериозах происходит резкое снижение количества анаэробной нормофлоры и увеличение числа условно-патогенных микроорганизмов.

Выводы

1. Воздействие внутреннего и внешнего ионизирующего излучения влияет на реактивность пристеночной микрофлоры кишечника животных.
2. Уровень дозы, полученной от распыления нейтронно-активированного порошка ^{56}Mn, был довольно низкий, а биологические эффекты - выраженными. Эти изменения оказались более тяжелыми и длительными, чем эффекты, связанные с гамма-облучением ^{60}Co.
3. Полученные в результате исследования данные указывают на потенциально высокие риски внутреннего облучения нейтрон-активированными радионуклидами, которые могли быть образованы вследствие атомных бомбардировок и/или атмосферных/наземных ядерных испытаний.

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SUMMARY

RESEARCH OF INTESTINAL MICROFLORA IN THE RATS FOLLOWING THE INTERNAL AND EXTERNAL IRRADIATION

[1]Kairkhanova Y., [1]Chaizhunusova N., [1]Urazalin M., [2]Stepanenko V., [3]Hoshi M.

[1]Semey State Medical University, Republic of Kazakhstan; [2]A. Tsyb Medical Radiological Research Center - National Medical Research Radiological Center, Ministry of Health of Russian Federation, Obninsk, Russia; [3]Hiroshima University, Hiroshima, Japan

The aim of the research was comparative investigation of the quantitative and qualitative composition of large intestinal microflora following internal (by dispersed powdered ^{56}Mn) and internal exposure of Wistar rats.

Ten weeks-old male Wistar rats were used. Rats were divided into four groups: L-^{56}Mn group with 12 rats, H-^{56}Mn with ten rats, ^{60}Co group with nine rats and control group with nine rats. L-^{56}Mn and H-^{56}Mn groups were exposed to two different doses of $^{56}MnO_2$ powder. ^{60}Co group received 2 Gy of external ^{60}Co γ-ray whole body irradiation. Totally 40 rats. Three rats from each group were sacrificed throw 6 hours and on days 3, 14, and 60 after the exposure. Animals were examined throw 6 hours and on days 3, 14 and 60 after exposure. Although the absorbed doses in large intestine were only 0.69 and 1.90 Gy in ^{56}Mn exposed groups, respectively, changes in large intestinal microflora were evident. After 6 hours and on day 3 after ^{56}Mn exposure amount of main representatives of large intestinal microflora (Bifidobacterium and lactobacilli) was decreased in the dose dependent manner. On the other hand, the amount of conditionally pathogenic bacteria was increased. These changes were persistent even on day 14. External ^{60}Co γ-irradiation at a dose of 2 Gy also changed the intestinal microflora, but these changes were not persistent and on day 14 after irradiation returned to the control level.

Our data suggest that internal exposure to dispersed powdered ^{56}Mn has a significant biological impact on the intestinal microflora for a prolonged period of time, when it is compared with the effects of external radiation.

Keywords: Manganese - 56, internal irradiation, external irradiation, intestinal microflora, rats.

РЕЗЮМЕ

ИССЛЕДОВАНИЕ МИКРОФЛОРЫ КИШЕЧНИКА КРЫС ПОД ВОЗДЕЙСТВИЕМ ВНУТРЕННЕГО И ВНЕШНЕГО ОБЛУЧЕНИЯ

[1]Кайрханова Ы.О., [1]Чайжунусова Н.Ж., [1]Уразалин М.М., [2]Степаненко В.Ф., [3]Хоши М.

[1]Государственный медицинский университет г. Семей, Республика Казахстан; [2]Медицинский радиологический научный центр им. А.Ф. Цыба - филиал Федерального государственного бюджетного учреждения «Национальный медицинский исследовательский радиологический центр» Минздрава России, Обнинск, Россия; [3]Университет Хиросимы, Япония

Целью исследования явилась оценка качественного и количественного состава микрофлоры толстого кишечника крыс при воздействии внутреннего и внешнего облучения.

Эксперимент проводили на 40 десятинедельных крысах-самцах линии Вистар. Крыс распределили на 4 группы: I группа – 10 крыс с более высокой дозой внутреннего облучения радионуклидом ^{56}Mn; II группа – 12 крыс с пониженной дозой внутреннего облучения радионуклидом ^{56}Mn; III группа – 9 крыс с внешним облучением ^{60}Co. Три крысы из каждой группы были декаптированы 6 часов спустя и на 3, 14 и 60 сутки после облучения. При поглощенных дозах внутреннего облучения толстого кишечника 0,69 Гр и 1,90 Гр у групп, подвергшихся воздействию ^{56}Mn, выявлено очевидное изменение микрофлоры толстого кишечника. 6 часов спустя и на 3 сутки после облучения ^{56}Mn показатели основных представителей микрофлоры толстого кишечника - бифидо- и лактобактерий понизились в зависимости от дозы, а количество условно патогенных бактерий увеличилось. Эти изменения сохранялись до 14 дня. Внешнее гамма-облучение ^{60}Co в дозе 2 Гр также изменило микрофлору кишечника, однако эти изменения не сохранялись и на 14 сутки после облучения возвращались к контрольному уровню.

Следует предположить, что внутреннее облучение ^{56}Mn, даже в условиях низких доз оказывает более существенное

биологическое воздействие на микрофлору кишечника в течение длительного периода времени в сравнении с внешним излучением.

რეზიუმე

შიდა და გარე დასხივების ქვეშ მყოფი ვირთაგვების ნაწლავების მიკროფლორა

[1]ი. კაირხანოვა, [1]ნ. ჩაიჯუნუსოვა, [1]მ. ურაზალინი, [2]ვ. სტეპანენკო, [3]მ. ხოში

[1]სემეის სახელმწიფო სამედიცინო უნივერსიტეტი,ყაზახეთი; [2]ა. ციბას სახ. სამედიცინო რადიოლოგიური სამეცნირო ცენტრი - რუსეთის ჯანდაცვის ფედერალური სახელმწიფო საბიუჯეტო დაწესებულება "ეროვნული სამედიცინო რადიოლოგიური სამეცნიერო ცენტრის" ფილიალი,ობნინსკი,რუსეთი; [3]ხიროსიმის უნივერსიტეტი, იაპონია

კვლევის მიზანს წარმოადგენდა ვირთაგვების მსხვილი ნაწლავის მიკროფლორის ხარისხობრივი და რაოდენობრივი შეფასება შიდა და გარე დასხივების პირობებში.

ექსპერიმენტი ჩატარდა 10 კვირის ასაკის ვისტარის ჯიშის 40 ვირთაგვაზე. ვირთაგვები დაიყო 4 ჯგუფად: I ჯგუფი – ვირთაგვები, რომლებიც შიდა დასხივებას რადიონუკლეიდით ^{56}Mn იღებდნენ საკმაოდ მაღალი დოზით; II ჯგუფი - 12 ვირთაგვა, ასევე, შიდა დასხივებით რადიონუკლეიდით ^{56}Mn შედარებით დაბალი დოზით; III ჯგუფის 9 ვირთაგვა იღებდა გარე დასხივებას ^{60}Co სხივებით. 3 ვირთაგვა თითოეული ჯგუფიდან დეკაპიტირებული იყო დასხივებიდან 6 საათის,3,14 და 60 დღე-ღამის შემდეგ. ^{56}Mn შიდა დასხივების შემდეგ 0,69 გრ და 1,90 გრ ოდენობით გამოვლინდა მსხვილი ნაწლავის მიკროფლორის შესამჩნევი ცვლილება. ^{56}Mn დასხივებდან 6 საათის და 3 დღე-ღამის შემდეგ მსხვილი ნაწლავის მიკროფლორის ძირითადი წარმომადგენლების - ბიფიდო- და ლაქტობაქტერიების მაჩვენებლები, დასხივების დოზისგან დამოკიდებულებით, დაქვეითდა, პირობითპათოგენური ბაქტერიების რაოდენობამ კი მოიმატა. ეს ცვლილებები შენარჩუნებული იყო 14 დღემდე. გარე გამა-დასხივებამ ^{60}Co 2 გრ ოდენობით, ასევე, შეცვალა ნაწლავების მიკროფლორა, იმ განსხვავებით, რომ ცვლილებები არ შენარჩუნდა და მე-14 დღეს დაუბრუნდა საწყის მაჩვენებლებს.

სავარაუდოდ, გარე დასხივებისგან განსხვავებით, ^{56}Mn-ით შიდა დასხივება დაბალი დოზის პირობებშიც კი საკმაოდ ხანგრძლივი დროის განმავლობაში ახდენს მნიშვნელოვან ბიოლოგიურ ზემოქმედებას ნაწლავის მოკროფლორაზე,

DEVELOPMENT OF THE GC-MS/MS METHOD FOR QUALITATIVE AND QUANTITATIVE DETERMINATION OF CLOZAPINE IN HUMAN BLOOD

[1]Sivsivadze K., [2]Jokhadze M., [2]Tushurashvili P., [1]Murtazashvili T., [1]Imnadze N.

[1]Tbilisi State Medical University, Department of Pharmaceutical and Toxicological Chemistry;
[2]Levan Samkharauli National Forensics Bureau, Tbilisi, Georgia

Clozapine is an atypical antipsychotic medication, sold under the different brand name. Pharmaceutical products, contains Clozapine are available in tablets of 25 mg, 50 mg and 100 mg for oral administration, in Georgia are registered under following brand names: Leponex, Clozapine, Zopin, Azaleptine. Clozapine is indicated for the treatment of severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment and for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state [8].

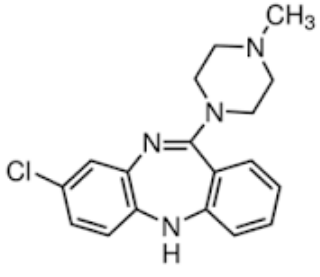

Fig. 1. Structural formula of Clozapine

Clozapine is a tricyclic dibenzodiazepine derivative, chemically is 8-Chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo[b,e] [1,4] diazepine, the structural formula is on Figure 1. The molecular formula is $C_{18}H_{19}ClN_4$, which corresponds to a molecular weight M_r 326.8, yellow, crystalline powder, practically insoluble in water, freely soluble in methylene chloride, soluble in ethanol (96 per cent), it dissolves in dilute acetic acid [3].

Mechanism of Action: the mechanism of action of clozapine is unknown. However, it has been proposed that the therapeutic efficacy of clozapine in schizophrenia is mediated through antagonism of the dopamine type 2 (D_2) and the serotonin type 2A ($5\text{-}HT_{2A}$) receptors. Clozapine tablets also act as an antagonist at adrenergic, cholinergic, histaminergic and other dopaminergic and serotonergic receptors.

Pharmacodynamics: Clozapine demonstrated binding affinity to the following receptors: histamine H1 (K_i 1.1 nM), adrenergic α_{1A} (K_i 1.6 nM), serotonin 5-HT_6 (K_i 4 nM), serotonin 5-HT_{2A} (K_i 5.4 nM), muscarinic M_1 (K_i6.2 nM), serotonin 5-HT_7 (K_i 6.3 nM), serotonin 5-HT_{2C} (K_i 9.4 nM), dopamine D_4 (K_i 24 nM), adrenergic α_{2A} (K_i 90 nM), serotonin 5-HT_3 (Ki 95 nM), serotonin 5-HT_{1A} (K_i 120 nM), dopamine D_2 (K_i 160 nM), dopamine D_1 (K_i 270 nM), dopamine D_5 (K_i 454 nM), and dopamine D_3 (K_i 555 nM). Clozapine causes little or no prolactin elevation. Clinical electroencephalogram (EEG) studies demonstrated that clozapine increases delta and theta activity and slows dominant alpha frequencies. Enhanced synchronization occurs.

Pharmacokinetics: Absorption - In humans, clozapine tablets (25 mg and 100 mg) are equally bioavailable relative to a clozapine solution. Following oral administration of clozapine tablets 100 mg twice daily, the average steady-state peak plasma concentration was 319 ng/mL (range: 102 to 771 ng/mL), occurring at the average of 2.5 hours (range: 1 to 6 hours) after dosing. The average minimum concentration at steady state was 122 ng/mL (range: 41 to 343 ng/mL), after 100 mg twice daily dosing. Food does not appear to affect the systemic bioavailability of clozapine tablets. Thus, clozapine tablets may be administered with or without food.

Distribution - Clozapine is approximately 97% bound to serum proteins. Metabolism and Excretion - Clozapine is almost completely metabolized prior to excretion, and only trace amounts of unchanged drug are detected in the urine and feces. CLZ is a substrate for many cytochrome P450 isozymes, in particular CYP1A2, CYP2D6, and CYP3A4. Approximately 50% of the administered dose is excreted in the urine and 30% in the feces. The demethylated, hydroxylated, and N-oxide derivatives are components in both urine and feces. Pharmacological testing has shown the desmethyl metabolite (norclozapine) to have only limited activity, while the hydroxylated and N-oxide derivatives were inactive. The mean elimination half-life of clozapine after a single 75 mg dose was 8 hours (range: 4 to12 hours), compared to a mean elimination half-life of 12 hours (range: 4 to 66 hours), after achieving steady state with 100 mg twice daily dosing. A comparison of single-dose and multiple-dose administration of clozapine demonstrated that the elimination half-life increased significantly after multiple dosing relative to that after single-dose administration, suggesting the possibility of concentration-dependent pharmacokinetics. However, at steady state, approximately dose-proportional changes with respect to AUC (area under the curve), peak, and minimum clozapine plasma concentrations were observed after administration of 37.5, 75, and 150 mg twice daily.

Indications and usage: Clozapine are indicated for the treatment of severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment. Because of the risks of severe neutropenia and of seizure associated with its use, clozapine tablets should be used only in patients who have failed to respond adequately to standard antipsychotic treatment. Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder. Suicidal behavior refers to actions by a patient that put him/herself at risk for death. The effectiveness of clozapine in reducing the risk of recurrent suicidal behavior was demonstrated over a two-year treatment period.

Dosage and administration: required laboratory testing prior to initiation and during therapy prior to initiating treatment with clozapine, a baseline the absolute neutrophil count (ANC), must be obtained. The baseline ANC must be at least 1500/μL for the general population, and at least 1000/μL for patients with documented Benign Ethnic Neutropenia (BEN). Dosing Information: The starting dose is 12.5 mg once daily or twice daily. The total daily dose can be increased in increments of 25 mg to 50 mg per day, if well-tolerated, to achieve a target dose of 300 mg to 450 mg per day (administered in divided doses) by the end of 2 weeks. Subsequently, the dose can be increased once weekly or twice weekly, in increments of up to 100 mg. The maximum dose is 900 mg per day. Over dosage Experience: the most commonly reported signs and symptoms associated with clozapine overdose are: sedation, delirium, coma, tachycardia, hypotension, respiratory depression or failure. Fatal overdoses have been reported with clozapine, generally at doses above 2500 mg. There have also been reports of patients recovering from overdoses well in excess of 4 g [7].

Toxicity - The most serious cardiac complications caused by clozapine, such as cardiomyopathy, myocarditis and pericarditis, are characterized by shortness of breath, heart palpitations/pains and thoracic pain. In most cases, electrocardiographic changes, pericardial effusion, and nonspecific signs of inflammation are observed. However, only a few cases of pericarditis and pericardial effusion induced by clozapine, even when used at low dosage, are reported in the literature. Was reported 65 cases of myocarditis, 52 cases of cardiomyopathy and only six cases of pericarditis occurring during clozapine treatment. The dose used is a poor predictor of clinical response, and there is little correlation between dose and plasma level, due to individual differences in metabolism, pharmacokinetic differences, gender, age, drug interactions and the smoking of tobacco products [1].

Caser reports toxicity: in literature review was discussed several cases, among them is the deaths of two patients with treatment-refractory schizophrenia treated with clozapine. A 29-year-old male had received gradually increasing doses of clozapine over two years due to ongoing treatment resistance. Plasma clozapine levels in the three months prior to his death ranged from 750 to 1200 μg/L. His final clozapine level taken 3 days before he died was 1180 μg/L. His post-mortem clozapine level was 2800 μg/L. In the second case, a 56-year-old female had been treated with clozapine for 6 years, including a consistent 500 mg daily dose for the 4 years preceding her death. Her CLZ levels varied between 290 and 1370 μg/L over her 6 years of CLZ treatment, although there were no levels greater than 1000 μg/L in the 2 years preceding her death. Her final clozapine level, taken 1 month before she died, was 770 μg/L. Her post-mortem clozapine level was in the range consistent with toxicity [9].

Although there is no simple relationship among clozapine levels, therapeutic efficacy, and toxicity, was compared 3 non-overlapping ranges and found: “medium” range (200 to 300 ng/mL) is a good initial target; low range (50 to 150 ng/mL) is not as effective as medium or high levels; high range (350 to 450 ng/mL) can be tried if clinical response is insufficient, although the high range was no more effective than the medium range. Over high levels (ie >1,000 ng/mL combined clozapine and norclozapine levels) have no proven benefit and increase seizure risk [4].

In this scenario, therapeutic drug monitoring (TDM) of psychotropic drugs is essential: it can help to enhance the therapeutic response, design optimal dosing regimens, avoid the build-up of excessively high and potentially toxic drug concentrations and

monitor patient's adherence to treatment. Also important clozapine determination for forensic purpose.

Over the last years, researchers have developed several methods to determine clozapine in biological fluids.

For quantification of clozapine and norclozapine in the sera of schizophrenic patients, treated with clozapine was developed ultra-performance liquid chromatography tandem mass spectrometry (UPLC-MS-MS) for simultaneous determination of clozapine and its major metabolite norclozapine in human serum. The compounds were extracted from serum by a single step protein precipitation and analyzed using a UPLC-triple-quadrupole detection (TQD) system. Separation of compounds was achieved on a BEH C18 (50 mm × 2.1 mm, 1.7 μm) analytical column using methanol and water (both containing 0.2% ammonium hydroxide) as the mobile phase at a flow rate of 0.40 mL/min. The compounds were ionized in the electrospray ionization ion source of the TQD and were detected in the multiple reaction monitoring (MRM) mode. The MRM transitions m/z 327 → 270 and m/z 313 → 192 for clozapine and norclozapine, respectively, were used for the quantification ions. Clozapine transition 327 → 192 and norclozapine transition 313 → 270 were used as confirmation ions. Method was applied for TDM [6].

Was described development of high-performance liquid chromatography coupled to tandem mass spectrometry (LC–MS-MS) to determine antipsychotics (olanzapine, quetiapine, clozapine and etc.) along with antidepressants, anticonvulsants and anxiolytics (diazepam and clonazepam) in plasma samples obtained from schizophrenic patients. The samples were prepared by protein precipitation. The target drugs were separated on an X Select SCH C18 column (100 mm × 2.1 mm × 2.5 μm) within 8.0 min by means of gradient elution. The drugs were then detected on a quadrupole tandem mass spectrometer equipped with an electrospray ionization source, operating in the multiple reactions monitoring mode and in the positive ionization mode [2].

An ultra-performance liquid chromatography–tandem mass spectrometry method was developed and validated for the quantification of 25 common pharmaceuticals in whole blood. The selected pharmaceuticals represent the most frequently detected drugs in forensic laboratory, among them was antipsychotic clozapine. Whole blood samples were extracted with butyl acetate after adjusting pH with 2M NaOH. The target analytes were separated on a 100 × 2.1 mm ACQUITY BEH 1.7 μm C18 column by a formic acid/acetonitrile gradient elution using a Waters ACQUITY Ultra-Performance Liquid Chromatography system. Quantification was performed on a Waters tandem quadrupole ACQUITY TQD using multiple reaction monitoring in positive mode. The analytes were eluted within 11 min. The limit of quantification (LOQ) ranged from 0.002 to 0.01 mg/kg depending on the analyte [5].

High quality exact analytical data are necessary in clinical and forensic toxicology, because unreliable data could lead to wrong or fatal treatment of the patient or to unjustified legal consequences for the defendant in court.

Therefore, sensitive and reliable analytical methods are required to for the detection and quantification of clozapine at these low concentration levels in biological matrices.

The aim of this study was to optimize workflow, minimize costs and develop a simple, fast, sensitive validated GC-MS/MS method for detection and quantification of clozapine in blood based on solid phase extraction.

Material and methods. Clozapine (CLZ) European Pharmacopoeia (EP) Reference Standard (CAS number 5786-21-0, catalogue number C2460000) was obtained from SIGMA-ALDRICH. Organic solvents of HPLC grade from Fluka and Merck (Germany). Methanol of analytical- reagent grades were purchased from Merck. Water passed through a Millipore system was used for sample dilution and in the mobile phases.

Blank human plasma was kindly supplied by Blood Institute, Georgia and kept on -20°C. All samples were negative for substances of abuse like THC, cocaine, methadone, amphetamines, methamphetamines, opiates, buprenorphine, benzodiazepines, barbiturates and tricyclic antidepressants with ELISA.

Preparation of stock and working standard solution
For preparing of the working standard solutions, stock standard solutions (200 $\mu g/mL^{-1}$ in methanol) were diluted in an appropriate volume of methanol. The calibration standards and quality control samples (QCs) were prepared by spiking the blank human blood samples with known concentrations of working standard solutions. The concentrations of the calibration standards range was 5, 50, 250, 750, 1000, 1500ng/mL for. Dilutions were used for preparing three levels of QCs, 50, 500, and 900 ng/mL in human blood. Stock standard solution QCs were stored at -20^0C. Working standard solutions were stored at $+5^0$C for one month. To prevent degradation of all samples including extracted standards were protected from light under the entire sample preparation by wrapping the samples in foil.

Prepare of the blood sample
The blood samples were weighted prior to analysis as a standard procedure in the laboratory. 20μL of QCs were added to 190 μL of human blood and was stored at -20 °C temperature.

Solid phase extraction
Was used The Gilson GX-271 ASPEC Solid phase extraction system with the cartridge Supelclean LC-18 SPE 500 mg.

Extraction procedure
Sample pretreatment - to 1mL of sample preparation add 4mL DI water and 2mL of 100mM phosphate buffer (pH 6.0).Mix/vortex on Stuart rotator and ultrasonic bath for homogenization. Centrifuge for 10 minutes at 5000 rpm and discard pellet. Received samples pH should be 6.0±0.5.Adjust pH accordingly with 100mM monobasic sodium phosphate.

Tube Conditioning - Rinse with 1 x 3mL Methanol and aspirate. Rinse with 1 x 3mL DI water and aspirate. Rinse with 1 x 1mL 100mM phosphate buffer (pH 6.0) and aspirate. To prevent packing bed from drying should be as pirated at ≤3 inches Hg.

Loading of the sample - Load at 1mL/minute.

Tube Wash - Rinse with 1 x 3mL DI water and as pirate. Rinse with 1 x 1mL 100mM acetic acid and aspirate. Rinse with 1 x 3mL Methanol and as pirate. Dry tube during 5 minutes at ≥ 10 inches Hg.

Elution - Elute 1 x 3mL with the mixture methylene chloride

(CH_2Cl_2) / Isopropyl alcohol (IPA) / Ammonium hydroxide (NH_4OH) with proportion 78:20:2. Collect eluate at 1-2mL/minute. Elution solvent should be prepared fresh daily. To 40mL of isopropanol, add 4 mL of concentrated ammonium hydroxide mix and add 156mL of methylene chloride and mix. Evaporate to dryness at <40°C.

Preparing for Analysis - evaporate reconstitute with 100µL ethyl acetate. Mix/vortex vigorously for 30 seconds and Inject 10 µL into chromatograph.

Apparatus GC-MS/MS Analysis
Analysis was carried out on a gas chromatograph Agilent 7000A Quadrupole GC-MS/MS (Agilent,USA) equipped with Gerstel automatic Sampler. GC run conditions - was used the capillary colum HP-5MS, 30m × 0.25mm I.D., coated with a 0.25µm film. Ionization was performed in the positive mode (EI+). Acquisition was made in total ion current (TIC) and multiple reactions monitoring (MRM) mode.

The GC conditions were as follows: the column temperature was programmed from 50°C to 305°C with an increase of 10°C/min; the injection port and the transfer line temperature were 310°C; helium was used as carrier gas at flow rate of 1.0mL/min; split ratio was 5:1. MS conditions - the mass analyzer operated by electron impact (70eV) in TIC and MRM. Quadrupole temperature 150°C. Quantitative analysis was carried out recording ions *m/z* 326 → 256, *m/z* 326 → 243 and *m/z* 326 → 192 for clozapine.

Results and their discussion. Received GC-MS chromatograms and mass spectrum are given on Figs. 2,3.

Method validation
Analytical validation of this method was based on current international EMA (European Medicines Agency) and FDA (Food and Drug Administration) guidelines.

Mass spectrometry: to obtain optimum sensitivity and selectivity, ESI technique operated in the positive ion mode was used for the GC-MS total ion current (TIC) and multiple reaction monitoring (MRM) analysis. For CLZ the most sensitive mass transition was monitored from ions *m/z* 326 → 256, *m/z* 326 → 243 and *m/z* 326 → 192.

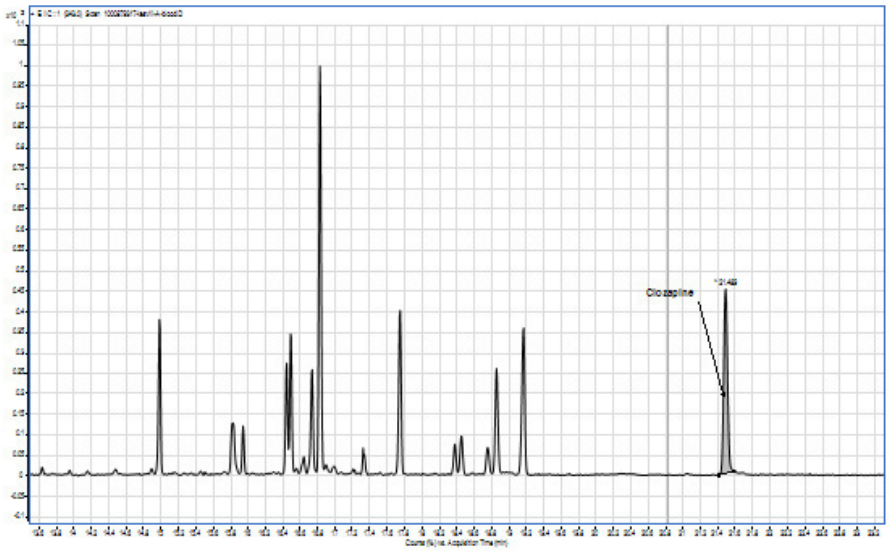

Fig. 2. GC-MS chromatogram of clozapine in blood sample

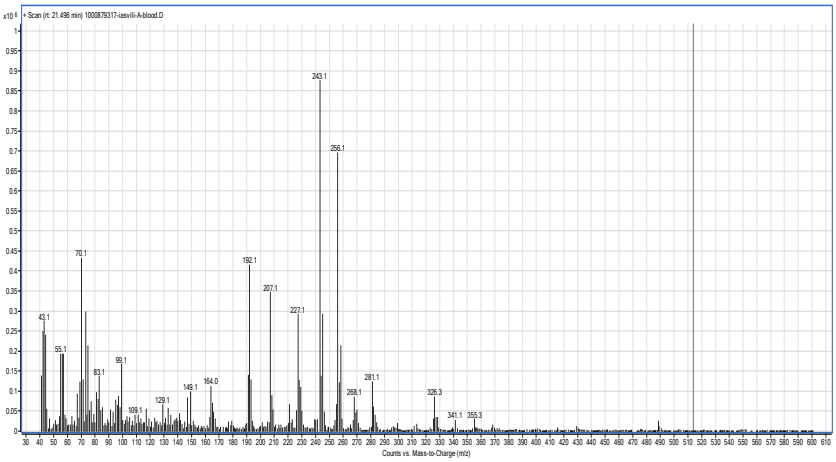

Fig. 3. Mass spectrum of clozapine in blood sample

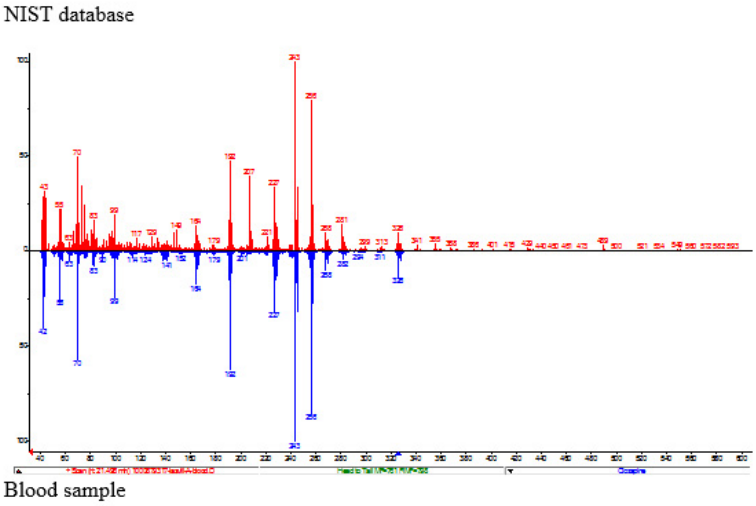

Fig. 4. Comparison of the mass spectrums of clozapine between database (NIST) and in blood sample

Table. Method validation parameters and results

Selectivity	Linearity (R^2)	Accuracy (bias %)		Precision (RSD %)		LOD	LLOQ	Recovery (%)	
		Low	High	Low	High			Low	High
No interference signals	0.9974	−17	−0.3	18	4	5.2ng/mL	8.3ng/mL	94	97

Selectivity was proven by analysis of six sources of blank human blood, processed with one zero sample (blank matrix with internal standard), verifying the absence of signal interferences.

Linearity was selected by analyzing 6 concentration levels, from 5 ng/mL to 1500ng/mL (5, 50, 250, 750, 1000, 1500 ng/mL) and each level was evaluated in triplicate according to a linear model. Based on the data it was concluded that the calibration curves used in this method were accurate for the determination of CLZ.

Accuracy and precision were estimated from the analysis of quality control (QC) samples at low (close to lower limit of quantification (LLOQ) and high concentration (1500 ng/mL), in six replicates for each level. The acceptance criterion for accuracy (statistical bias) was within ±15% of nominal value (±20% close to LLOQ), for precision was within ±15% relative standard deviation (RSD) (20% close to LLOQ).

The LOD (Limit of Detection) was determined by analysis of spiked samples with decreasing level of concentration of the analyte.

For LOD a value of signal-to-noise ratio equal to or greater than three was chosen. The LLOQ was determined by analysis of fortified samples with decreasing level of concentration of the analyte. For LLOQ a value of signal-to-noise ratio equal to or greater than ten was chosen. Recovery was calculated by analyzing extracted spiked samples at high and low concentration in relationship with the curve calibration, compared with the control samples.

Validation Results.
The method was validated by investigating the following parameters: selectivity, linearity, accuracy, precision, identification of LOD and LLOQ and recovery. The results are shown in Table.

Conclusion.
A simple, rapid, selective, sensitive analytical method was developed and validated for the determination of clozapine in human blood, using a solid-phase extraction and quantification by gas chromatography-mass spectrometry (GC-MS/MS).

From the results of the validation parameters given in this paper, we can conclude that the developed method can be useful for determination of clozapine: 1) for forensic investigations such as postmortem cases, violence cases and intoxication, 2) for TDM of schizophrenic patients, for the schizophrenia effective treatment, to improve therapeutic efficacy and minimize drug toxicity.

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SUMMARY

DEVELOPMENT OF THE GC-MS/MS METHOD FOR QUALITATIVE AND QUANTITATIVE DETERMINATION OF CLOZAPINE IN HUMAN BLOOD

[1]Sivsivadze K., [2]Jokhadze M., [2]Tushurashvili P., [1]Murtazashvili T., [1]Imnadze N.

[1]Tbilisi State Medical University, Department of Pharmaceutical and Toxicological Chemistry;
[2]Levan Samkharauli National Forensics Bureau, Tbilisi, Georgia

A simple, rapid, selective, sensitive gas chromatography-mass spectrometry (GC-MS/MS) method was developed and validated for the determination of clozapine in human blood. For isolation was used solid phase extraction. The calibration standards range was 5-1500ng/mL.

Analysis was carried out on a gas chromatograph Agilent 7000A Quadrupole GC-MS/MS. GC run conditions - capillary column HP-5MS, 30m × 0.25mm, coated with a 0.25μm film, column temperature from 50°C to 305°C with an increase of 10°C/min; the injection port and the transfer line temperature were 310°C; carrier gas - helium at flow rate of 1.0 mL/min; Ionization was performed in the positive mode (EI+). Acquisition was made in TIC and MRM mode, electron impact 70Ev. Quantitative analysis was carried out by recording ions *m/z* 326 → 256, *m/z* 326 → 243 and *m/z* 326 → 192 for clozapine.

The method was validated by investigating the following parameters: selectivity, linearity, accuracy, precision, identification of LOD and LLOQ and recovery.

Method, given in this paper can be useful for determination of clozapine in forensic investigations and for TDM of schizophrenic patients to improve therapeutic efficacy during clozapine treatment.

Keywords: GC-MS/MS, Solid Phase Extraction, Method validation.

РЕЗЮМЕ

РАЗРАБОТКА ГАЗОВОГО ХРОМАТО-МАСС-СПЕКТРОМЕТРИЧЕСКОГО (GC-MS/MS) МЕТОДА АНАЛИЗА ДЛЯ КАЧЕСТВЕННОГО И КОЛИЧЕСТВЕННОГО ОПРЕДЕЛЕНИЯ КЛОЗАПИНА В КРОВИ ЧЕЛОВЕКА

[1]Сивсивадзе К.Г., [2]Джохадзе М.С., [2]Тушурашвили П.Р., [1]Муртазашвили Т.Ж., [1]Имнадзе Н.Е.

[1]Тбилисский государственный медицинский университет, департамент фармацевтической и токсикологической химии;
[2]Национальное бюро судебной экспертизы им. Л. Самхараули, Тбилиси, Грузия

Разработан и валидирован быстрый, простой, селективный, чувствительный метод газовой хроматографии-масс-спектрометрии (GC-MS/MS) для определения клозапина в крови человека. Для изолирования использована твердофазная экстракция. Диапазон калибровочных стандартов составил 5-1500 нг/мл.

Анализ проводился газовым хроматографом Agilent 7000A Quadrupole GC-MS/MS. Рабочие условия: капиллярная колонка HP-5MS, 30м х 0,25мм, покрытая оболочкой 0,25 мкм, температура колонки 50^0C-305^0C, которая увеличивалась на 10^0C в минуту, температура инжектора и передатчика 310^0C, газовый носитель - гелий, скорость потока 1.0 мл/мин. Ионизация достигалась в положительным режиме (EI +). Сканирование протекало с полного ионного потока и с мониторингом многоразовых реакций (MRM), электронный удар 70эВ. Для клозапина количественный анализ проведен посредством регистрации ионов *m/z* 326 → 256, *m/z* 326 → 243 and *m/z* 32 → □ 192.

Метод валидирован по следующим параметрам: селективность, повторяемость, линейность, точность, правильность, предел количественного определения (LLOQ), предел обнаружения (LOD).

Метод, описанный в представленной статье, может быть использован для определения клозапина в крови человека для судебно-медицинских экспертиз и контроля терапевтической дозы у пациентов с шизофренией, лечившихся клозапином.

რეზიუმე

ადამიანის სისხლში კლოზაპინის თვისობრივი და რაოდენობრივი განსაზღვრის გაზურ ქრომატოგრაფიული – მასსპექტრომეტრული (GC-MS/MS) მეთოდის შემუშავება

[1]კ. სივსივაძე, [2]მ. ჯოხაძე, [2]პ. თუშურაშვილი,
[1]თ. მურთაზაშვილი, [1]ნ. იმნაძე

[1]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, ფარმაცევტული და ტოქსიკოლოგიური ქიმიის დეპარტამენტი; [2]ლევან სამხარაულის სახელობის სასამართლო ექსპერტიზის ეროვნული ბიურო,თბილისი,საქართველო

შემუშავებულია და ვალიდირებულია ადამიანის სისხლში კლოზაპინის განსაზღვრის მარტივი, სწრაფი, სელექციური,მგრძნობიარე გაზურ ქრომატოგრაფიული - მასსპექტრომეტრული (GC-MS/MS) მეთოდი. იზოლირებისათვის გამოყენებოდა მყარფაზური ექსტრაქცია. საკალიბრო სტანდარტების კონცენტრაცია მერყეობდა 5-1500 ნგ/მლ-ს შორის.

ანალიზი ჩატარდა გაზურ ქრომატოგრაფზე Agilent 7000A Quadrupole GC-MS/MS შემდეგი პირობებით: კაპილარული სვეტი HP-5MS, 30მ x 0.25მმ, რომელიც დაფარული იყო 0.25 მკმ გარსით, სვეტის ტემპერატურა - 50 - 305°C, რომელიც იზრდებოდა წუთში 10°C-ით, ინჟექტორის და გადამცემის ტემპერატურა - 310°C, ჰელიუმის ნაკადის სიჩქარე - 1.0 მლ/წთ. იონიზაცია მიიღწეოდა დადებითი რეჟიმით (EI+). სკანირება მიმდინარეობდა ჯამური იონური ნაკადით (TIC) და მრავალჯერადი რეაქციების მონიტორინგით (MRM), ელექტრონის იმპულსის 70 ევ. კლოზაპინის შემთხვევაში რაოდენობრივი ანალიზი ჩატარდა იონების აღრიცხვის გზით *m/z* 326 → 256, *m/z* 326 → 243, *m/z* 326 → 192.

მეთოდის ვალიდაცია მოხდა შემდეგ პარამეტრებზე: სელექციურობა, განმეორებადობა, სწორხაზოვნება, სიზუსტე, სისწორე, განსასაზღვრი მინუმუმი (LOD) და აღმოსაჩენი მინუმუმი (LLOQ).

სტატიაში შემუშავებული მეთოდის გამოყენება შესაძლებელია ადამიანის სისხლში კლოზაპინის განსაზღვრისათვის სასამართლო ექსპერტიზის დროს, ასევე, შიზოფრენიით დაავადებულ პაციენტებში თერაპიული დოზის კონტროლისათვის კლოზაპინით მკურნალობის დროს.

INFLUENCE OF OZONE THERAPY ON ORAL TISSUE IN MODELING OF CHRONIC RECURRENT APHTHOUS STOMATITIS

Kovach I., Kravchenko L., Khotimska Yu., *Nazaryan R., *Gargin V.

*State Establishment "Dnipropetrovsk Medical Academy", *Kharkiv National Medical University, Ukraine*

The diagnosis and management of the patient with recurrent oral ulceration requires a systematic approach based on the principles of taking an adequate history, clinical examination, investigations as appropriate, institution of management and, finally, review to allow for any necessary modifications of that management [12,16] and creation of new method of treatment. Chronic recurrent aphthous stomatitis (CRAS) belongs to the group of chronic, inflammatory, ulcerative diseases of the oral mucosa. Up to now, the etiopathogenesis of this condition remains unclear; it is, however, considered to be multifactorial [12,14,15].

For today, CRAS is one of the most common types of the inflammatory process in the oral mucosa, with a prevalence of 2% to 10% in Caucasian populations. To treat them properly, physicians should know their clinical appearance and course, conditioning factors, underlying causes, and differential diagnosis [1].

The underlying etiology is not clear, although a number of factors are known to predispose to the occurrence of oral aphthae, including genetic factors, food allergies, local trauma, endocrine disorders, stress, anxiety, smoking cessation, certain chemical products, microbial agents [4,16].

Till now many aspects of chronic recurrent aphthous stomatitis are unexplored and there is a necessity for further experimental investigation to clarify the pathogenesis of this disease for the creation of primary prevention and pathogenetically based treatment of patients with CRAS including their clinical manifestations in the oral cavity [5,9,14].

Various treatment options have been used for healing of the oral tissue in CRAS and other disorders. A range of mouthwash options are used because of the anti-inflammatory, anesthetic, analgesic, antipyretic, and antimicrobial properties. In addition, systemically administered pharmacological agents, such as pentoxifylline, thalidomide, and simvastatin, have been shown to correlate with the development and severity of all the complications reported [3]. Clinical trials have reported that these drugs reduce the frequency and severity of major complications. Despite these treatment options, there is still a need for other cost-effective modalities to prevent disorders of oral cavity [3].

Medical ozone is described as three atom molecules of oxygen known as O3 and ozone therapy has been proven safe to use in medical treatment because of antimicrobial, disinfectant, and healing properties [7]. In addition, small doses of ozone can ac-

tivate biochemical mechanisms and reactivate the antioxidant system. Diseases that can be treated with ozone are infected wounds, circulatory disorders, geriatric disorders, macular degeneration, viral diseases and other [8]. Although ozone treatment has substantial effects, there has been no study in literature about the influence of ozone on CRAS.

The aim of this study was to determine the effects of ozone on the morphofunctional peculiarities of the soft tissues in modeling chronic recurrent aphthous stomatitis.

Material and methods. We performed experimental investigation for study of the morpho-functional state of tissues of the oral mucosa in CRAS (Fig. 1a) with modeling as it had been suggested in the previously proposed and widely used scheme [6,9]; that allows to eliminate the influence of somatic pathology and social factors. Intraperitoneal injection of 1 ml ovalbumin and aluminum hydroxide were performed for modeling CRAS process in young animals (Dutch rabbits, males, aging three-month, weighting 2-2.4 kg) during first 3 days of the experiment. Twice lower dose of ovalbumin was instilled intranasally under local anesthesia five days later (Day 8) with repeated intranasal administration of ovalbumin through on the 16th, 17th, 20th and 21st day of the experiment. Doses of used medicine were determined according to animal body weight. Group of 8 animals with obtained mucosal changes was our comparison group. We formed group of 8 animals also which was treated by ozone therapy (Fig. 1 b,c) with the apparatus "Ozonimed" using (exposure of 40 seconds in each ulcer at the 9th power). The specimens of soft tissues of the oral cavity of were stained with hematoxylin and eosin (H&E) [2] after the routine proceeding. Microspecimens were performed in the Department of Pathological Anatomy of the Kharkov Medical Academy of Postgraduate Education (head of the department Irina Yakovtsova). Morphometric studies were performed.

Fig. 1. Modeling of chronic recurrent aphthous stomatitis with appearance of ulcerative defects covered whitish film on the oral mucosa of rabbit before treatment (a) preparation (b) and performing (c) ozone therapy after modeling CRAS

The procedure was done strictly in compliance with the Helsinki Declaration, European Convention for the protection of vertebrate animals (18.03.1986), European Economic Society Council Directive on the Protection of Vertebrate Animals (24.11.1986) after approval from the Regional Ethical Review Board at State Establishment "Dnipropetrovsk Medical Academy" protocol № 1 (18.01.2015).

Results and their discussion. Ulcerative defects of round or oval shape with 5 mm diameter with the imprinting surface and covered with whitish film have had been revealed on examination of the oral mucosa group of animals with modeling CRAS (Fig.1a) in comparison group and investigated group before ozone correction. Used ozone correction (Fig. 1b,c) was realized in reducing or disappearance of visible ulcerative changes. The histological examination of the obtained microspecimens shows that CRAS modeling is realised by a complex of pathological changes in the oral mucosa. Squamous epithelium is characterized by uneven thickness with necrotic, mainly erosive injuries (Fig. 2), but ulcers were detected also. Intraepithelial lymphocytes, eosinophils, signs of proliferation in the basal cellular layer, moderate development of papillomatous changes have been demonstrated in untreated animals. Inflammatory infiltration is expressed in the lamina propria of the oral cavity of animals before start of ozone therapy.

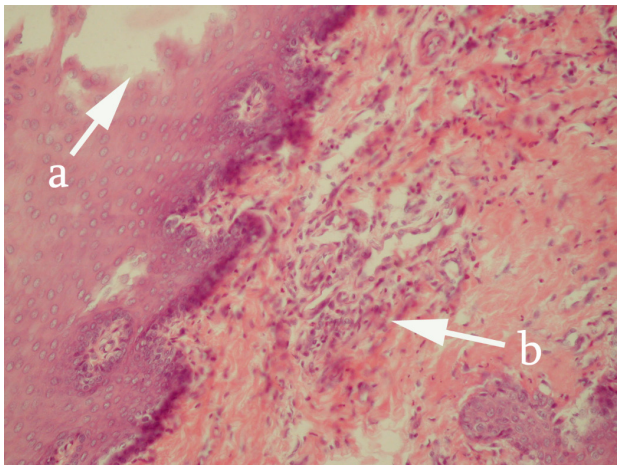

Fig. 2. Formation of erosive-ulcerative defect (a) with focal thinning of the squamous epithelium. The presence of perivascular inflammatory infiltrate (b) in the lamina propria. Group of animals without treatment. H&E stain. Objective 20

Simultaneously there are areas with infiltration by inflammatory both in the lamina propria and epithelium of the oral cavity (Fig. 3).

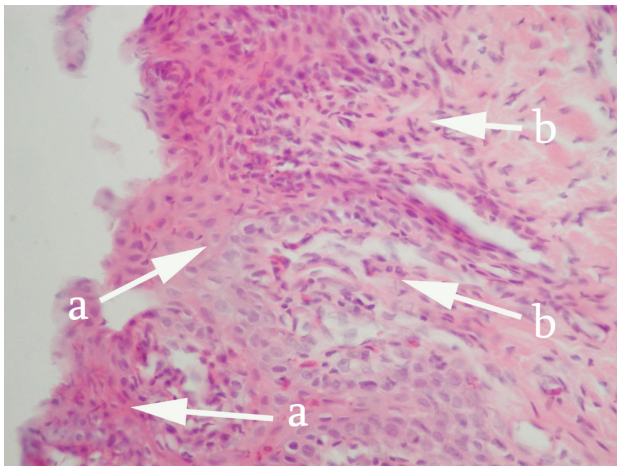

Fig. 3. Aarea with infiltration by inflammatory cells both in the epithelium (a) and lamina propria (b) of the oral cavity with formation of erosive-ulcerative defect. Group of animals without treatment. H&E stain. Objective 20

The examination of animals' oral cavity after ozone therapy revealed reducing of necrobiotic changes in the oral mucosa till

Table. Cellular consist (%) of gingival mucous membrane

	Comparison group (modeling CRAS)	Group of animals treated by ozone therapy
Histiocytes	4.62±0.21	32.21±2.42*
Young fibroblasts	17.02±1.20	13.47±1.42
Fibrocytes	19.91±1.42	27.42±1.43*
Lymphocytes	4.68±0.25	6.84±0.63
Plasma cells	4.83±0.24	4.31±0.67
Macrophages	4.72±0.38	6.02±0.42
Neutrophils	38.30±2.46	6.34±0.63*
Eosinophils	5.49±0.23	2.87±0.05*

** - changes are reliable, p<0,05*

disappearance of visible pathological changes. There are isolate mucosal erosions, with absence of ulcers or aphthous defects in majority of experimental animals; there are isolate no pronounced erosive changes in 2 rabbits from that group.

Histologically epithelium is uniform in thickness, but there are areas with pronounced thickening. Superficial cells are flat, near the spindle-shaped, the pycnosis phenomenon is not pronounced. The cytoplasm of the superficial epithelial cells is shown as a thin, eosinophilic, intensely stained border. As an approach to basal membrane cells are increased in volume by both the nucleus and the cytoplasm size.

The shape of the cells is changed from oval to elongate with simultaneously changing the orientation of the epithelial cells and the almost vertical position in the basal membrane. The nuclei of the basal epithelial cells are well defined, oval, uniform, hyperchromatic; cytoplasm is moderately basophilic. The location of the basal cell layer is regularly, without "jumping" the cells. Grouped intraepithelial lymph leukocyte elements were not detected. The basement membrane is uneven with uneven thick-

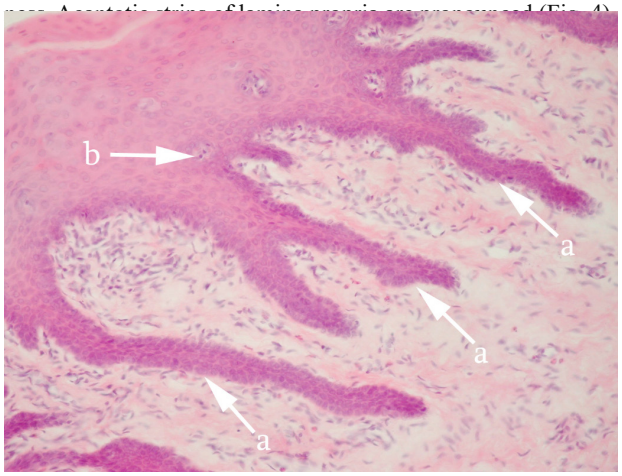

Fig.4. Well pronounced epithelialization in place of aphthous defect. Pronounced akantotic bands (a). Disappearance of necrobiotic processes in epithelium with isolate inflammatory cells (b). Restoration of the cellular layers of the epithelium. Moderately pronounced sclerosis of the papillary layer of the lamina propria. Superficial papillary layer of the lamina propria consists of loose connective tissue which is represented mainly elastic. H&E stain. Objective x20

Superficial papillary layer of the lamina propria consists of loose connective tissue which is represented mainly elastic fibers (Fig. 4). Reticular layer is located deeper and is represented by rough connective tissue fibers. Cellular consist of gingival mucous membrane is presented in the table 1. Cellular elements between connective tissue fibers (fibroblasts, histiocytes, lymphocytes, mast cells, macrophages) are isolated. Cells of connective tissue are presented by mature cells predominantly present in papillary and reticular layers. Lymphoid elements are dispersed evenly between the connective tissue fibers, without the formation of focal accumulations. Eosinophils are absent; signs of accumulation of inflammatory exudate have not been demonstrated.

Changes which obtained as result of our treatment could be recognized as positive changes [13,17] with healing of injured areas. Our results are combined with studies in literature indicating that ozone treatment reduces oxidative stress, improves wound healing, and increases tissue partial oxygen pressure [18]. Pathogenesis of periodontal inflammation might involve inhibition of cell death, through the apoptotic factors, due to the DNA damage by the product of catalysis [10,11] with highest levels activity found at sites of chronic inflammation. Small doses of ozone can activate biochemical mechanisms and reactivate the antioxidant system.

Changes in cellular component with reducing cells of inflammatory origin prove about positive process in ozone therapy, but connective tissue as fibroblasts, fibrocytes, histiocytes have an important role in wound healing and many studies in literature have examined the effect of different method of therapy on fibroblast cell growth mainly [3]. The results of this study demonstrated that ozone therapy as favorable influence for condition of connective tissue components. Histopathological examination has shown that ozone reduces inflammation and edema and is useful in wound healing in soft tissue.

The data of this study suggest that ozone therapy has positive effects in the treatment of CRAS. These results may be related to the duration and dose of ozone applications. Different duration or dose of ozone application may change the results.

Conclusion. Correction of tissual changes in chronic recurrent aphthous stomatitis could be obtained with ozone therapy that is realized morphologically in disappearance of necrobiotic processes, epithelialization of aphthous defect, growth of akantotic bands, pronounced reducing of inflammatory cells, restoration of the cellular layers of the epithelium, moderately pronounced sclerosis of the papillary layer of the lamina propria.

Conflict of Interest Statement. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUMMARY

INFLUENCE OF OZONE THERAPY ON ORAL TISSUE IN MODELING OF CHRONIC RECURRENT APHTHOUS STOMATITIS

Kovach I., Kravchenko L., Khotimska Yu., *Nazaryan R., *Gargin V.

*State Establishment "Dnipropetrovsk Medical Academy", *Kharkiv National Medical University, Ukraine*

Chronic recurrent aphthous stomatitis (CRAS) belongs to the group of chronic, inflammatory, ulcerative diseases of the oral mucosa. The aim of this study was to determine the effects of ozone on the morphofunctional peculiarities of the soft tissues in modeling chronic recurrent aphthous stomatitis.

We performed experimental investigation for study of the morpho-functional state of tissues of the oral mucosa in CRAS with using of previously proposed and widely used modeling scheme with ovalbumin and aluminum hydroxide. Two groups of animals were formed (Dutch rabbits, males, aging three-month, weighting 2-2.4 kg). Group of 8 animals with obtained mucosal changes was our comparison group. Other group of 8 animals with obtained mucosal changes was treated by ozone therapy. Histological investigation has been performed. Microscopical examination of tissue had shown that ozone therapy reduces inflammation and edema and is useful in wound healing in soft tissue as disappearance of necrobiotic processes, epithelialization of aphthous defect, growth of akantotic bands, pronounced reducing of inflammatory cells and changing of cellular ratio (with of neutrophils part from 38.30±2.46% to 6.34±0.63%, eosinophils from 5.49±0.23% to 2.87±0.05%), restoration of the cellular layers of the epithelium, moderately pronounced sclerosis of the papillary layer of the lamina propria. Described results allow to conclude that correction of tissual changes in chronic recurrent aphthous stomatitis could be obtained with ozone therapy using.

Keywords: chronic recurrent aphthous stomatitis, histology, experiment, ozone.

РЕЗЮМЕ

ВЛИЯНИЕ ОЗОНОТЕРАПИИ НА ТКАНЬ ПОЛОСТИ РТА ПРИ МОДЕЛИРОВАНИИ ХРОНИЧЕСКОГО РЕЦИДИВИРУЮЩЕГО АФТОЗНОГО СТОМАТИТА

[1]Ковач И.В., [1]Кравченко Л.И., [1]Хотимская Ю., [2]Назарян Р.С., [2]Гаргин В.В.

[1]Днепропетровская медицинская академия; [2]Харьковский национальный медицинский университет, Украина

Хронический рецидивирующий афтозный стоматит (ХРАС) относится к группе хронических, воспалительных, язвенных заболеваний слизистой оболочки полости рта.

Целью исследования явилось определение влияния озона на морфофункциональные особенности мягких тканей ротовой полости при моделировании хронического реци-

дивирующего афтозного стоматита. Проведено экспериментальное исследование для изучения морфофункционального состояния тканей слизистой оболочки полости рта при ХРАС на основе ранее предложенной и широко применяемой модели с использованием овальбумина и гидроксида алюминия. Сформированы две группы животных (голландские кроли, самцы, возраст три месяца, вес 2-2,4 кг). I группа из 8 животных с изменениями слизистой оболочки составила группу сравнения. II группа из 8 животных с изменениями слизистой оболочки ротовой полости получала озонотерапию. Проведено гистологическое исследование.

Микроскопическое исследование тканей показало, что озонотерапия уменьшает признаки воспаления, отека и способствует заживлению язвенных дефектов: наблюдается как исчезновение некробиотических процессов, эпителизация афтозных поражений, акантоз, выраженное уменьшение воспалительных клеток и изменение клеточного отношения - нейтрофилы с 38,30±2,46% до 6,34±0,63%, эозинофилы - с 5,49±0,23% до 2,87±0,05%, восстановление клеточных слоев эпителия, умеренно выраженный склероз сосочкового слоя собственной пластинки. Полученные результаты позволяют заключить, что озонотерапия способствует коррекции тканевых изменений при хроническом рецидивирующем афтозном стоматите.

რეზიუმე

პირის ღრუს ქსოვილზე ოზონოთერაპიის ზემოქმედება
ქრონიკული რეციდივირებული აფტოზური სტომატიტის დროს

[1]ი. კოვაჩი, [1]ლ. კრავჩენკო, [1]იუ. ხოტიმსკაია, [2]რ. ნაზარიანი, [2]ვ. გარგინი

[1]დნეპროპეტროვსკის სამედიცინო აკადემია; [2]ხარკოვის ნაციონალური სამედიცინო უნივერსიტეტი, უკტაინა

ქრონიკული რეციდივირებული აფტოზური სტომატიტი (ქრას) განეკუთვნება პირის ღრუს ლორწოვანი გარსის ქრონიკულ, ანთებით, წყლულოვან დაავადებათა რიცხვს. კვლევის მიზანს წარმოადგენდა პირის ღრუს რბილის ქსოვილების მორფოფუნქციურ თავისებურებებზე ოზონის ზეგავლენის განსაზღვრა ქრას მოდელირების პირობებში. ქრას დროს პირის ღრუს ლორწოვანი გარსის ქსოვილის მორფოფუნქციური მდგომარეობის შესწავლის მიზნით ჩატარებულია ექსპერიმენტული გამოკვლევა ადრე შემოთავაზებულ და ცნობილ მოდელზე ოვალბუმინის და ალუმინის ჰიდროქსიდის გამოყენებით 3 თვის მამრ ბაჭიებზე. ცხოველები დაყოფილი იყო ორ ჯგუფად: I (შედარების) ჯგუფი (8 ბაჭია) რებულობდა ქრას სააამკურანალო ტარდიციულ თერაპიას; II (ძირითადი) ასევე 8 ბაჭიისაგან შემდგარი ასევე პირის ღრუს ლორწოვანი გარსის ცვლილებებით დამატებით ღებულობდა ოზონოთერაპიას. შეამდეგ ჩატარდა ჰისტოლოგიური გამოკვლევა, რომელმად აჩვენა, რომ ოზონოთერაპია ამცირებს აბთების ნიშნებს, შეშუპებას და ხელს უწყობს წყლულოვანი დეფექტების შეხორცებას ხდება ნეკრობიოტიკური პროცედების ალაგება,აფტოზური დაზიანების ეპითელიზაცია,აკანტოზი, ანთებითი უჯრედების გამოხატული შემცირება, უჯრედული თანაფარდობის ცვლილება - ნეიტროფილების 38,30±2,46% დან 6,34±0,63% მდე, ეოზინოფილების 5,49±0,23% დან 2,87±0,05% მდე; ხორციელდება ეპითელიუმის უჯრედოვანი ფენების აღდენა.

EFFECT OF ARSENIC EXPOSURE ON BEHAVIOR OF RATS OF VARIOUS AGE GROUPS

[1]Bikashvili T., [1,2]Lordkipanidze T., [2]Gogichaishvili N., [1,2]Pochkhidze N.

[1]I. Beritashvili Center of Experimental Biomedicine, Tbilisi; [2]Ilia State University, Tbilisi, Georgia

Arsenic (As) is ranked first among toxicants posing a significant potential threat to human health based on known or suspected toxicity [11,15]. Currently, the permitted concentration of arsenic in water is 10μ g/L (10 ppb). However, people worldwide are exposed to excessive amounts of arsenic via drinking water.

Several regions (including Lukhuni region of Ambrolauri district and Madneuli area in Bolnisi region) known for their reach As deposits, are characterized by significant accumulation of As in ground water. From 8.9 mg/L to13.8 mg/L As content was found in Adjara and Ambrolauri regions (Rioni river). The catastrophic amounts of soluble As ranging from 83-184 mg/L were found in Lukhuniskali river in Lukhuni region known for realgar (arsenic sulfide) and auripigment mining. During the active mining periods in 1980s, the measurements of As in the regions of rivers Lukhunisckali and Korula revealed 45-170 mg/L of As content in the snow and 10-100 mg/L of As in grass samples [2]. Development of Lukhuni deposit has been ceased since 1985, however waste of the former As industry and the deserted underground excavations, from which mine waters flow into the main hydrographic unit of Lukhuni region, are powerful sources of As accumulation in Lukhunistskali river [21].

The epidemiological studies within the population of these regions revealed the increased susceptibility to acute respiratory disease, pathological pregnancy and premature birth. As compounds are known to induce significant health damage (gastrointestinal, hepatic, renal cardiovascular, reproductive effects, cancer and dia-

betes) as well as severe neurological problems such as peripheral neuropathy, retardation and intellectual impairment.

Some data suggest a potential adverse association between arsenic and children's behavior and indicate a need to further study the effects of arsenic and arsenic metabolites on neurobehavioral outcomes [17,19].

Recent animal studies suggest that neurons in the brain may be the major targets of arsenic neurotoxicity and show myelin damage, disappearance of axons, vacuolar degeneration, and loss of cell-cell junction [6,20]. Arsenic toxicity has different presentations and different mechanisms of damage that impact behavior; there is no simple explanation for arsenic toxicity.

Our main goal was to study the effect of As compounds on behavior changes in different age groups of rats. To perform our studies we decided 1) To study the effect of As on behavior of young rats and 2) To study the effect of As on behavior of adult animals.

Material and methods.

Animals: All experiments were performed using male 64 Wistar rats of two different age groups (young P21-23 and adult P60-65 at the initial day of experiments). Rats in control groups drank regular water, and rats in experimental groups got water containing As (Sodium arsenite (NaAsO2) was purchased from Sigma-Aldrich Cat. N S7400) at concentration 68 mg/L (35 ppm) for 3 months [14].

Rats were kept on regular light/dark cycles throughout the procedures with ad libitum access to food.

Care of animals during/after procedure(s) animals were transferred to the testing room and allowed to acclimatize to this room prior to testing. Animals were monitored while in the arena and returned to the home cage immediately after testing.

All experimental procedures were approved by Animal Studies Committee of Georgian I.Beritashvili Center of Experimental Biomedicine and are in accordance with guidelines of the EC Ethical Directives.

Behavioral tests:

Animals were subjected to following behavioral tests:

Open field test

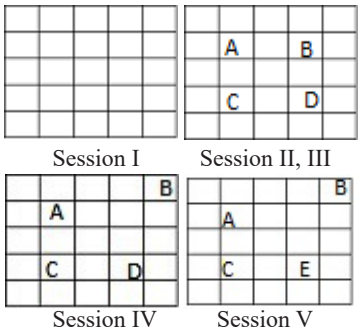
This test is used to evaluate the exploratory and anxiety behavior of rat.

Equipment: The Open Field is a circular arena with a diameter of 100 cm with walls 30 cm high. The floor is divided up into quarters with a central circle of 33cm diameter in the middle of the arena. Normal laboratory up lighting is required. Each animal is placed in the central circle and is observed for 5 min. The following events are recorded: ambulation - the number of grid lines crossed with all four paws; number of entry into the center of the open field; rearing – the number of times the animal stood on its hind limbs; hole reflex – looking into holes; grooming and defecation [4].

Open field 2 - Apparatus

An open-field square arena (65x65x75 cm) enclosed by walls made from wood and illuminated by a 60 W light bulb mounted 1 m above the area was used for the behavioral test. The floor of the arena was divided into 16 equal squares by white lines. The walls inside the arena were surrounded with a white cloth to a height of 1.5 m. The environment was uniform except for a one striped pattern poster (30 cm wide and 60 cm high) attached to the white cloth (the white cloth prevent the rat from looking out into the room and thereby, to maximize attention to the object of stimuli). An overhead camera and a video recorder were used to monitor and record the animal's behavior for subsequent analysis. The objects to be distinguished were made of glass, plastic, or metal and existed in duplicate. The weight of the objects ensured that they could not be moved by the rats. As far as could be ascertained, the objects had no natural significance for the rats and they had never been associated with areinforce.

Square open field-The novel object recognition memory



Session I: familiarization phase. Without objects.
Session II: training phase. Objects (A, B, C, D) acquisition.
Session III: habituation phase. Unchanged stimulus.
Session IV: testing phase. Object B was displaced to a new spatial location.
Session V: testing phase. Familiar object (D) was substituted with a novel object (E).

Intertrial interval 24 h. Duration of each trial 3 min.
Locomotor activity was measured by the number of grids crossed by each animal during the five sessions and the inter session score was analyzed.

To measure the habituation to the environment, habituation index was calculated according to the locomotor activity (HI loc.) and object exploration time (HI obj). Difference score was calculated by subtracting a number of grid crossings (HI loc) and object exploration time (HI obj) for each animal in session 3 from the session 2 respectively.

Preference score for displaced object was calculated as: the object displacement discrimination index (DID) = exploration time of the displaced objects / (mean exploration time of the non-displaced objects + exploration time of the displaced objects). Preference score for novel object was calculated as the object novelty discrimination index (DIN) = exploration time of the novel object / mean exploration time of the familiar objects + exploration time of the novel object [8].

Elevated Plus Maze (EPM)

The EPM is a widely used rodent behavioral test that is utilized to assess anxiety-related behavior. The EPM apparatus consists of four arms: two open, and two closed arms, the apparatus is elevated 50–70 cm from the floor. Each arm is 50 cm long and 5 cm wide, and the closed arms were shielded by 25 cm high side end walls. The four arms were linked at a central square (the junction). Briefly, rats are placed at the junction of the four arms of the maze, facing an open arm, and entries/duration in each arm are

recorded by a video-tracking system and observer simultaneously for 5 min. Other ethological parameters (i.e., rears, head dips and stretched-attend postures) can also be observed. An increase in open arm activity (duration and/or entries) reflects anti-anxiety behavior. In our laboratory, rats mice are exposed to the plus maze on one occasion; thus, results can be obtained in 5 min per rodent.

Spontaneous alternation behavior
Rats were trained in a four-arm plus shaped maze with floor and walls made of black Plexiglas. The arms of the maze (12.5 cm wide by 46 cm long by 7 cm high) extended radially from a central square platform 9 sides = cm); the floor of the maze was positioned 0.7 m above the floor. Each rat was placed at the center of the maze and allowed to transverse the maze freely for 10 min. The number and sequence of arms entered were recorded to determine alternation scores. An arm entry was defined as the entry was defined as the entry of all four paws into one arm. The sequence of arm entries was recorded with a video camera. An alternation was defined as entry into four different arms on overlapping quintuple sets. Five consecutive arms choices within the total set of arm choices make up a quintuple set, e.g. a quintuple set consisting of arms choices A, B, A, C, B was not considered an alternation. Using this procedure percentage alternation was calculated as follows: (Actual alternation/possible alternation) x 100; possible alternation sequences are equal to number of arm entries minus four.

Learning processin multi-branched maze
The process of learning is studied by means of multi-branched maze consisting from footbridges, mounted on props of 30 cm height. To move on an optimum trajectory animal is learning by a trial and error method. With the purpose of adaptation, all groups of animals for a few days are placed in a nest-box prior to the beginning of experiments. This nest-box is located at the exit platform of maze. At the beginning of the experiment an animal is placed on the start-platform and it has to find out the correct way to the nest-box. Process of learning proceeds without any food reinforcement and it can be described as follow: each passage of the crotch (when the animal has an opportunity of a choice of a direction) serves as a stimulus for further movement. Getting in a deadlock branch of the maze (error) and necessity of returning should be considered as a punishment for error and, probably, forces rat to avoid errors and to continue search of a correct way. Deliverance from nonethologic conditions (being on a maze platform) at the moment of hit in a nest-box is possible to consider as a reward and it serves as a motivation for maze learning. Each group of animals during 10 days was trained to pass a maze. The maze task was presented to each animal 5 times a day with at least 30 min intervals. The learning process is estimated by maze test performance (to reach the nest-box) within 5 min – by number of errors made during ambulation through the maze (enter into the blind-alley section) and by the time of maze passage [3]. For estimation of learning process, As was given to experimental animals for 3 month before the maze test. For evaluation of memory tests, animals were subjected to maze session after 2 months from the end of learning test.

Statistical analysis was performed using GraphPad Prism version 7.00 La Jolla California USA. Behavioral data from the different trial days were analyzed using repeated measures one-way ANOVA followed by post hoc Tukey's multiple comparison tests. Unpaired t-test with Welch's correction was used to determine a statistically significant difference between the two groups. $P<0.05$ were considered statistically significant. All data are presented as Mean ± SEM.

Results and their discussion. In order to detect how As effects body weight gain of various aged rats, animals were weigh every week, at the same time 10 a.m. The average body weight in young experimental groups was slightly attenuated (Fig. 1), but in adult animals this difference was statistically significant ($P<0.05$) (Fig. 2).

The average body weight of control rats during last three weeks of experimental trials (15 -17th weeks) was 347±8.25 g, whereas the average body weight of Arsenic exposed animals was 308±8.62 g.

These results suggest that arsenic might have more significant effect on body weight gain in adults rather than in young animals. It can be assumed that the loss of body weight caused by arsenic could be a result of reduction in the repair and synthetic activities of various cells. Body weight reduction found in rats treated with arsenic are in agreement with previous studies [12,13].

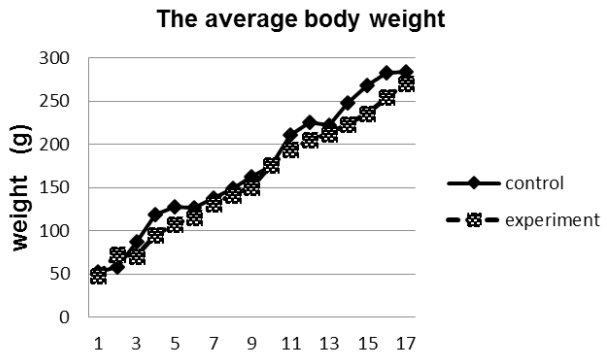


Fig. 1.The average body weight of young rats (1-17 weeks)

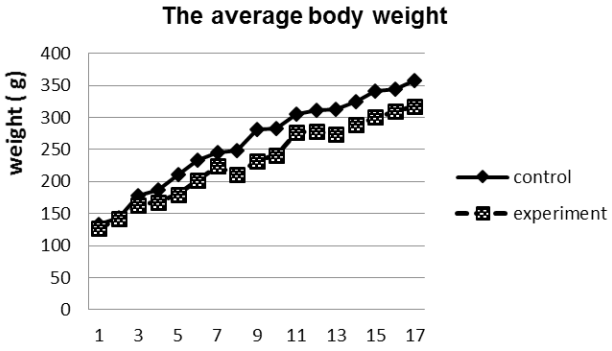


Fig. 2. The average body weight of adult rats (1-17 weeks)

The obtained results of open-field test showed that there is no significant difference between arsenic exposed and control animals' behavior in both age groups. However, it is notable that according to open-field test, statistically significant ($P<0.05$) increasing in grooming behavior was observed in both age groups of arsenic exposed rats. On the basis of existing literary data, grooming is considered as the typical behavioral form of rodents that serves to regulate emotional tension. The results obtained by our experiments indicate that arsenic exposure may result in rat's emotional instability despite the animals' age.

Table. Results of circular open field

	Young		Adult	
	Control	**As**	**Control**	**As**
Ambulation	21	20,29	36	27,5
Entry into the center	0,14	0,21	0,5	0,62
Rearing	11,14	7,14	7	7,75
Grooming	4,86	10,43*	8	13,88*
Hole reflex	3,57	2,71	3,5	4
Bolus	2,28	2,29	3,33	2,38

**** - statistically significant (p<0.05) was increasing grooming behavior in both age groups of arsenic exposed rats***

Results of elevated plus maze test:

No difference in the number of entries/duration in open and closed arms in control and arsenic exposed groups as in young so in adult animals has been revealed. Ratio of time spent in the open arms to time spent in closed arms in young control and arsenic exposed groups was 0.56 and 0.52, in adult control and arsenic exposed groups 0.35 and 0.39, correspondingly.

The elevated plus maze is a widely used behavioral assay for rodents and it has been validated to assess the anti-anxiety effects of pharmacological agents and steroid hormones, and to define brain regions and mechanisms underlying anxiety-related behavior. On the basis of existing literary data [6,7,16] arsenic exposure could be an enhancer the anxiety- or depression-like behavior in animal models; it depends on dose and duration of As exposure. Furthermore, there was notation that anxiety and depression may be a neuroendocrine continuum, in which anxiety occurs first during the life course and major depressive episodes occur later [6]. In this present study we could not find clearly expressed increasing emotional tension or depression-like behavioral changes.

Results of square open field-The novel object recognition memory

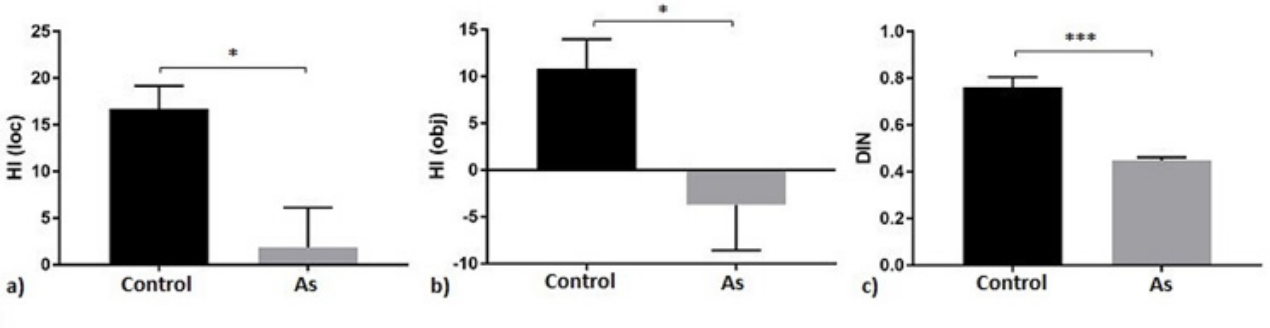


*Fig. 3. Effects of chronic Arsenic exposure on youn rat recognition memory in the Novel Object Recognition (NOR) test. Groups: Control, n=8; Arsenic (35 ppm) treatment, n=8. a) Habituation Index according to the locomotor activity (HI loc), indicating difference score between the training sessions III and II, t=3.023, df=9.628. P (two-tailed) = 0.0134, *p<0.05 control vs. treatment. b) Habituation Index according to the object exploration time (HI obj), indicating difference score between the training sessions III and II, t=2.524, df=10.27, P (two-tailed) = 0.0296, *p<0.05 control vs. treatment. c) Discriminative Index of object Novelty (DIN), indicating preference score between the exploration times of the novel object and mean exploration time of the familiar objects, t=7.001 df=7.187, P (two-tailed)=0.0002, ***p<0.001 control vs. treatment. Unpaired t-test with Welch's correction. All values indicate the Mean ± SEM*

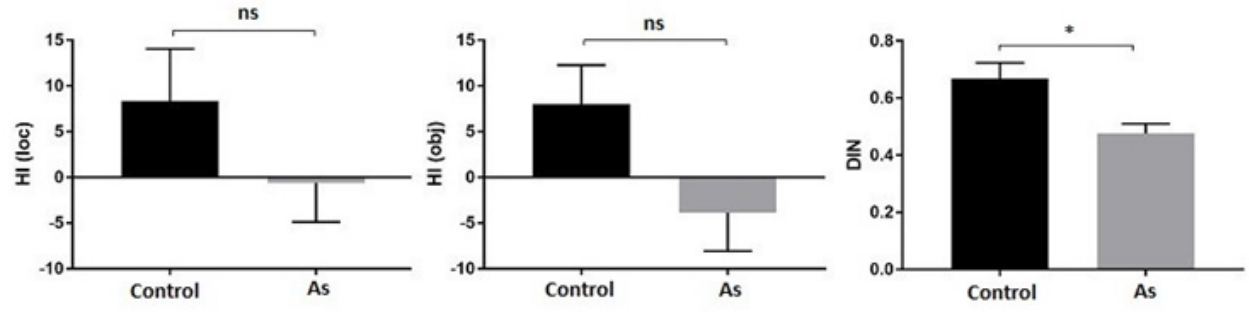


Fig.4. *Effects of chronic Arsenic exposure on adult rat recognition memory in the Novel Object Recognition (NOR) test. Groups: Control, n=8; Arsenic (35 ppm) treatment, n=8. a) Habituation Index according to the locomotor activity (HI loc), indicating difference score between the training sessions III and II, t=1.267, df=12.95, P (two-tailed) =0.2276, ns (not significant) p>0.05 control vs. treatment. b) Habituation Index according to the object exploration time (HI obj), indicating difference score between training sessions III and II, t=1.981 df=14, P (two-tailed) = 0.0676, ns (not significant) p >0.05 control vs. treatment. c) Discriminative Index of object Novelty (DIN), indicating preference score between the exploration times of the novel object and the mean exploration time of the familiar objects, t=2.989, df=11.77, P (two-tailed) = 0.0115, *p<0.05 control vs. treatment. Unpaired t-test with Welch's correction. All values indicate the Mean ± SEM*

Results of spontaneous alternation behavior:

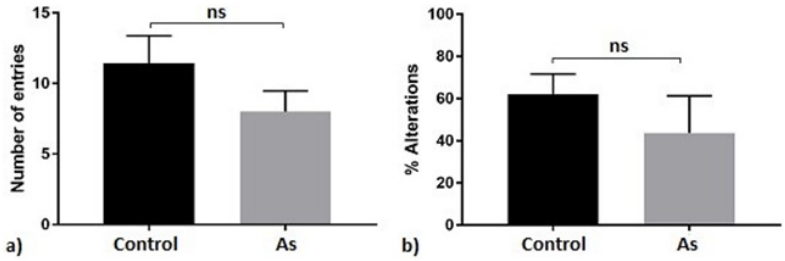


Fig. 5. Effects of chronic Arsenic exposure on young rat spontaneous alternation behavior and spatial working memory tested in the four-arm radial maze. Groups: Control, n=8; Arsenic (35 ppm) treatment, n=8. a) The number of total arm entries, t=1.401, df=11.19, P (two-tailed) =0.1885, ns (not significant) p >0.05 control vs. Arsenic treatment. b) Spontaneous alteration (%), t=0.9089, df=9.331, P (two-tailed) =0.3863, ns (not significant) p>0.05 control vs. treatment. Unpaired t-test with Welch's correction. All values indicate the Mean ± SEM

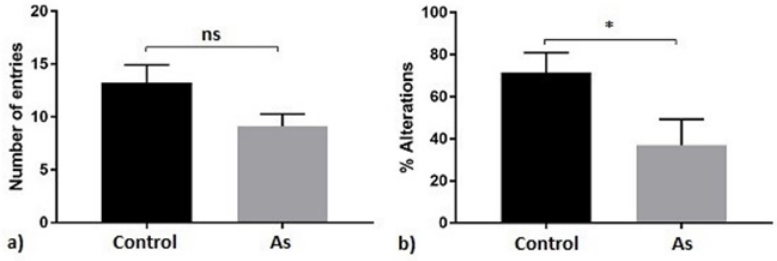


*Fig. 6. Effects of chronic Arsenic exposure on adult rat spontaneous alternation behavior and spatial working memory tested in the four-arm radial maze. Groups: Control, n=8; Arsenic (35 ppm) treatment, n=8. a) The number of total arm entries, t=2.025, df=12.43, P (two-tailed) = 0.0649, ns (not significant) p >0.05 control vs. Arsenic treatment. b) Spontaneous alteration (%), t=2.236, df=13.1, P (two-tailed) = 0.0434, *p<0.05 control vs. Arsenic treatment. Unpaired t-test with Welch's correction. All values indicate the Mean ± SEM*

Results of multi-branched maze test:

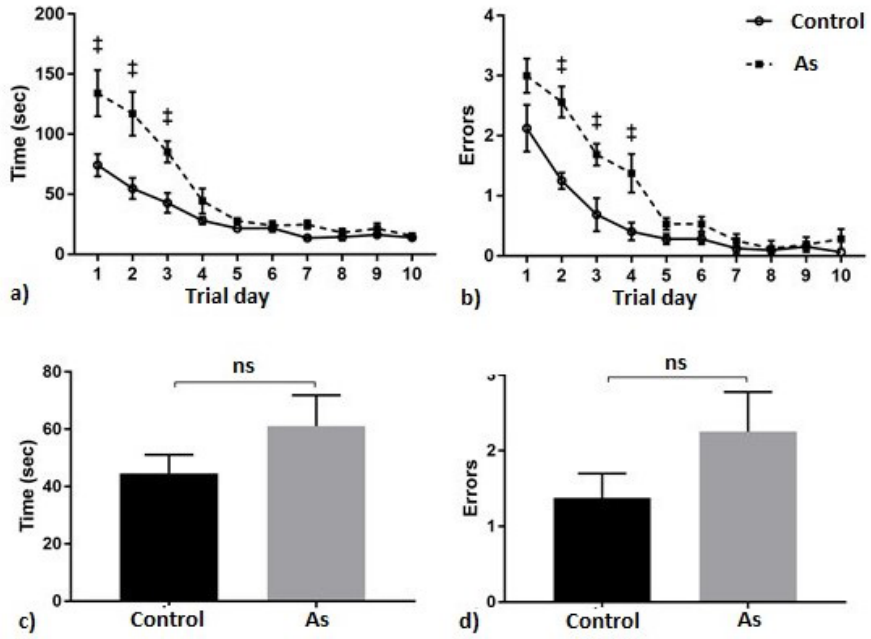


*Fig.7. Effects of chronic Arsenic exposure on young rat spatial learning and long-term memory tested in the Multi-Branched Maze. Groups: Control, n=8; Arsenic (35 ppm) treatment, n=8; Repeated measures one-way ANOVA followed by post hoc Tukey's multiple comparison tests: a) Time (sec) of maze passage for the ten days of trial, F (19, 120) = 27.74, P<0.001. b) Number of errors (enter into the blind alley section) made during ambulation though the maze for ten days of trial, F (19, 120) = 30.81 P<0.001. ‡ indicates statistically significant difference (p<0.05) between Control and Arsenic (35 ppm) treatment group. Unpaired t-test with Welch's correction: c) Time (sec) of maze passage t=4.321, df=9.802, P (two-tailed) =0.0016, and d) Number of errors made in one day trial of long-term memory assessment after 2 months of maze training, t=5.196, df=10.14, P (two-tailed)=0.0004. **p<0.01, ***p<0.001. All values indicate the Mean ± SEM*

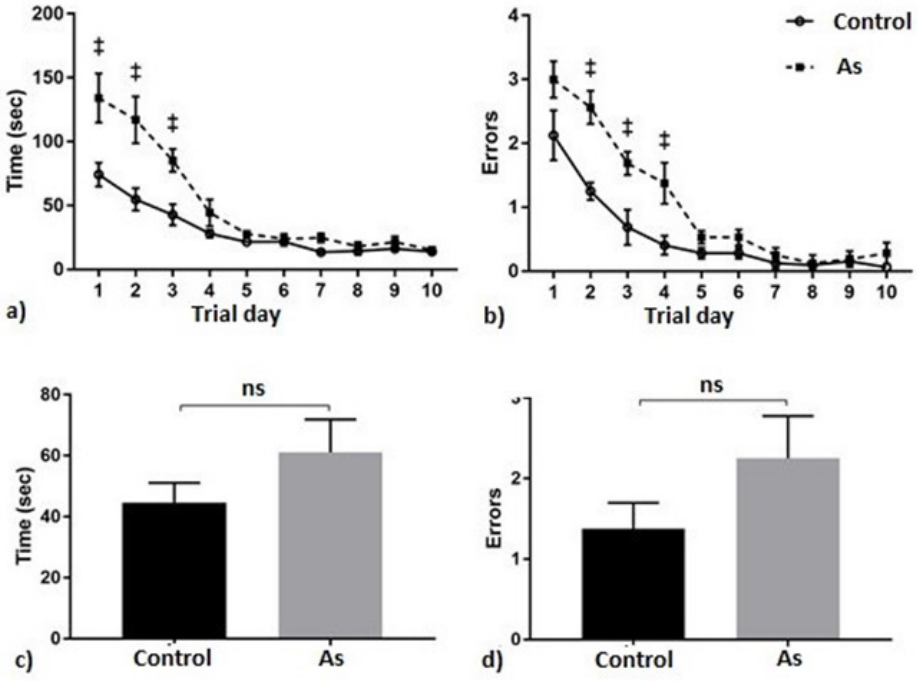


Fig. 8. Effects of chronic Arsenic exposure on adult rat spatial learning and long-term memory tested in the Multi-Branched Maze. Groups: Control, n=8; Arsenic (35 ppm) treatment, n=8; Repeated measures one-way ANOVA followed by post hoc Tukey's multiple comparison tests: a) Time (sec) of maze passage for ten days of trial, F (19, 140) = 20.59, P<0.001. b) Number of errors (enter into the blind alley section) made during ambulation though the maze for ten days of trial, F (19, 140) = 23.5, P<0.001. ‡ indicates statistically significant difference (p<0.05) between Control and Arsenic (35 ppm) treatment group. Unpaired t-test with Welch's correction: c) Time (sec) of maze passage t=1.314 df=11.5, P (two-tailed) = 0.2144 and d) number of Errors made in one day trial of long-term memory assessment after 2 months of maze training, t=1.416 df=11.64, P (two-tailed)= 0.1829. ns (not significant) p>0.05. All values indicate the Mean ± SEM

According to the literature the paucity of data about neurobehavioral changes after chronic exposure to arsenic, and about the specific arsenic species to which human populations are exposed, hinders direct comparisons between animal and human studies. Acute exposure to arsenic in humans has been shown to result in problems of memory, difficulties in concentration, mental confusion and anxiety. Rodent studies indicate that neurobehavioral deficits are observed after exposure to low doses of arsenic, as arsenic trioxide (1.5–12 mg/kg), sodium arsenate (5 mg/kg) or sodium arsenite (3–10 mg/kg), with time of exposure ranging from 2 weeks to 4 months. Deficits observed include changes in locomotor behavior, and deficits in learning tests; brain tissue levels above 6000 ng As/g wet tissue were associated with behavioral deficits [1,10,16,20]. The results of present study indicate that control rats unlike the arsenic exposed ones clearly react to the object novelty by exploring the new object more than familiar ones. It is interesting to note, that while the control rats showed the increase in exploration when a familiar object was moved to an unfamiliar location, the arsenic exposed rats did not demonstrate such enhanced exploration. It is known that behavioral effects dependent on dose, duration of exposure and developmental stage of the animals. In our experiments adult animals are more susceptible than young ones.

The results of multi-branched maze test performance have shown that arsenic exposed young animals need the same time to learn the correct maze performance as the control ones. There was no difference in errors made either (Fig.7).

The process of learning in the multi-branched maze was considerably difficult in the adult arsenic exposed group. During the first four days they need more time and made more errors for passing the maze compared to control rats. However, from the day 5 of the maze session successful trials of maze-passage increased and no differences have been observed between experimental and control animals (Fig.8).

For evaluation of memory tests, animals were subjected to maze session 2 months later after learning test termination. The results of the test are presented in Fig.7 and Fig.8. These diagrams show the comparison of data between exposed and control groups. We have found differences in maze test performance, during fulfilling memory tasks by arsenic exposed animals in comparison to control ones. This distinction was mostly notable in young groups, as the differences in duration of maze passage and number of errors made in maze test performance were statistically significant (P<0.05) among these animals.

Arsenic is neurotoxicant that can impair cognitive capacity. Most epidemiological research has focused on cognition in children, and reports on the effect of arsenic exposure on adult cognition are limited. However, a series of studies has recently revealed a significant correlation between arsenic exposure and altered adult cognition [9,15,20].

In the present study we investigated how arsenic impacts memory types of different aged rats.

Our data indicated that arsenic exposure to 68 mg/L (35 ppm) caused spatial memory damage, the morphological and biochemical bases of which could be the ultra-structural changes and reduced gene expression in hippocampus, posterior and pre-

frontal cortex. Behavioral study showed that in young rats arsenic exposure affects long-term memory whereas in adult rats much disturbances were revealed in short-term memory. It is known that the mechanisms of short-term memory are different from those of long-term memory. So we can hypothesize that mechanisms of arsenic effect on animal behavior might be dependent on the age of the treated animal.

Our findings are in line with several investigations showing that in children chronically exposed to arsenic, urine levels of this metalloid were inversely correlated with verbal IQ scores, including verbal comprehension and long-term memory [5].

Conclusions.
Our experiments revealed that 68 mg/L (35 ppm) Sodium (meta) arsenite (when animals got arsenic from drinking water for three months) induces more significant effect on body weight gain in adult rats rather than in young ones. Arsenic exposure may result in rat's emotional instability despite the animals' age. According to the spontaneous alteration test, obtained data revealed that behavior is changed only in adult rats compared to control ones. Also it was found that Arsenic consumption at the same concentration induces considerable difficulties in learning process (multi-branched maze test results) in the adult arsenic exposed group. Considering all above mentioned results, we can conclude, that Arsenic exposure affects short-term memory more dramatically in adult animals rather than of young ones, whereas difficulties in long-term memory were detected among young animals.

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SUMMARY

EFFECT OF ARSENIC EXPOSURE ON BEHAVIOR OF RATS OF VARIOUS AGE GROUPS

[1]Bikashvili T., [1,2]Lordkipanidze T., [2]Gogichaishvili N., [1,2]Pochkhidze N.

[1]I. Beritashvili Center of Experimental Biomedicine, Tbilisi; [2]Ilia State University, Tbilisi, Georgia

Arsenic is ranked first among toxicants posing a significant potential threat to human health based on known or suspected toxicity. Recent animal studies suggest that the brain is the major target of arsenic exposure. The present study demonstrates the effect of Arsenic compounds on behavior changes in different age (young and adult) groups of rats. In order to study anxiety behavior,

learning and memory processes we used open field, elevated plus maze, spontaneous alteration behavior and multi-branched maze tests. Our experiments revealed that 68 mg/L (35 ppm) Sodium (meta) arsenite (when animals got arsenic from drinking water for three months) induces more significant effect on body weight gain in adult rats rather than in young ones. Arsenic exposure may result in rat's emotional instability despite the animals' age. According to the spontaneous alteration test, obtained data revealed that behavior is changed only in adult rats compared to control ones. Also it was found that Arsenic consumption at the same concentration induces considerable difficulties in learning process (multi-branched maze test results) in the adult arsenic exposed group. We have found differences in maze test performance, during fulfilling memory tasks by arsenic exposed animals in comparison to control ones. This distinction was mostly notable in young groups. These data show that Arsenic exposure affects short-term memory more dramatically in adult animals rather than of young ones, whereas difficulties in long-term memory were detected among young animals.

Keywords: arsenic, arsenic exposure, arsenic neurotoxicity, behavior, memory, rat.

РЕЗЮМЕ

ВЛИЯНИЕ МЫШЬЯКА НА ПОВЕДЕНИЕ КРЫС РАЗНЫХ ВОЗРАСТНЫХ ГРУПП

[1]Бикашвили Т.З., [1,2]Лордкипанидзе Т.Г., [2]Гогичаишвили Н.Г., [1,2]Почхидзе Н.О.

[1]Центр экспериментальной биомедицины им. И.С. Бериташвили, Тбилиси; [2]Государственный университет им. Ильи Чавчавадзе, Тбилиси, Грузия

Мышьяк занимает ведущее место среди токсичных веществ, представляющих наибольшую опасность для здоровья человека ввиду своей известной или вероятной токсичности. Последние исследования на животных показали, что головной мозг является одной из основных целей воздействия мышьяка. В представленной работе показано, влияние соединений мышьяка на изменение поведения крыс разных возрастных групп (молодые и взрослые). Для исследования тревожно-эмоционального поведения, процессов обучения и памяти использованы тесты: открытого поля, спонтанно альтернативного поведения, приподнятого крестообразного и многоходового лабиринта. Проведенные эксперименты показали, что 68 мг/кг (35 ppm) натрий (мета) арсенит (когда животные получали мышьяк с питьевой водой в течение трёх месяцев) индуцировал более значительный эффект на прирост массы тела у взрослых, чем у молодых животных. Воздействие мышьяка может привести к эмоциональной нестабильности крыс, несмотря на их возраст. Полученные данные спонтанного альтернативного теста показали, что поведение изменяется только у взрослых экспериментальных крыс в сравнении с контрольными. Обнаружено также, что потребление мышьяка в той же концентрации вызывает значительные нарушения в процессе обучения взрослых крыс (результаты теста многоходового лабиринта). При выполнении теста памяти обнаружено различие между крысами, принимающими мышьяк и контрольными, что более четко проявилось в группах молодых животных. Согласно полученным данным, воздействие мышьяка более выявлено на кратковременную память взрослых крыс, тогда как у молодых крыс его воздействие происходит на долговременную память.

რეზიუმე

დარიშხანის ზემოქმედება სხვადასხვა ასაკის ვირთაგვების ქცევაზე

[1]თ. ბიკაშვილი, [1,2]თ. ლორთქიფანიძე, [2]ნ. გოგიჩაიშვილი, [1,2]ნ. ფოჩხიძე

[1]ი. ბერიტაშვილის ექსპერიმენტული ბიომედიცინის ცენტრი,თბილისი; [2]ილიას სახელმწიფო უნივერსიტეტი, თბილისი, საქართველო

წარმოდგენილ ნაშრომში ნაჩვენებია დარიშხანის ნაერთების გავლენა სხვადასხვა ასაკის (ახალგაზრდა და ზრდასრული) ვირთაგვების ჯგუფის ქცევით ცვლილებებზე. ემოციური ქცევის,დასწავლისა და მეხსიერების პროცესების შესასწავლად გამოყენებული იყო ღია ველის, ამაღლებული ჯვარედინი ლაბირინთის,სპონტანური ალტერაციული ქცევის და მრავალსვლიანი ლაბირინთის ტესტები. ექსპერიმენტებმა აჩვენა,რომ 68 მგ/ლ (35 ppm) ნატრიუმის (მეტა) არსენიტი (ცხოველები იღებდნენ დარიშხანს სასმელი წყლიდან 3 თვის განმავლობაში) წონის მატებაზე უფრო მნიშვნელოვან ზეგავლენას ახდენს ზრდასულ ცხოველებში, ვიდრე ახალგაზრდებში. დარიშხანის ზემოქმედებამ შეიძლება გამოიწვიოს ემოციური მდგომარეობის არასტაბილურობა ორივე ასაკის ვირთაგვებში. სპონტანური ალტერაციული ტესტის მიხედვით, ქცევა იცვლება მხოლოდ ზრდასულ ცხოველებში. ამასთან, ნაჩვენებია, რომ დარიშხანის იმავე დოზით გამოყენება იწვევს მნიშვნელოვან დარღვევებს ზრდასული ვირთაგვების დასწავლის პროცესში (მრავალსვლიანი ლაბირინთის ტესტის შედეგების მიხედვით). მეხსიერების ტესტის შესრულებისას განსხვავება საკონტროლო და დარიშხანმიღებულ ცხოველებში განსაკუთრებით შესამჩნევია ახალგაზრდა ვირთაგვების ჯგუფებში. მიღებული შედეგები ადასტურებს, რომ დარიშხანის ზემოქმედება ზრდასრულ ვირთაგვებში გამოიხატება ხანმოკლე მეხსიერების,ახალგაზრდა ვირთაგვებში კი - ხანგრძლივი მეხსიერების გაუარესებით.

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ПРОТИВОСУДОРОЖНЫЙ ЭКСТРАКТ КОРНЕЙ ГОЛОВЧАТКИ ГИГАНТСКОЙ (*CEPHALARIA GIGANTEA*)

[1]Гогитидзе Н. М., [1]Мушкиашвили Н.И., [2]Гедеванишвили М.Д., [1]Табатадзе Н.А., [1]Деканосидзе Г.Е.

[1]Тбилисский государственный медицинский университет, Институт фармакохимии им. И. Кутателадзе;
[2]Тбилисский государственный университет им. И. Джавахишвили, Грузия

В практике антиэпилептичесекой терапии в настоящее время находят применение различные группы лекарственных средств, специфически активных при соответствующих формах заболевания. Среди них при генерализованной форме типа абсансов препаратами первой линии являются этосуксимид и вальпроат натрия [11], хотя они и различаются по фармакологическому механизму действия: этосуксимид, угнетает “низкопороговые ” кальциевые каналы Т-типа в нейронах таламуса, тогда как вальпроат характеризуется преимущественно ГАМК-ергическим эффектом [12]. Следовательно, возможность выбора при лечении абсансов ограничена в основном двумя препаратами и необходимость расширения арсенала противоабсансных средств также очевидна. С этой точки зрения привлекает внимание экстракт головчатки - *Cephalaria gigantea* [6], который традиционно применяли в грузинской народной медицине для лечения судорожных состояний. Основываясь на данных народной медицины можно предположить, что экстракт цефалярии (ЭЦ) явдяется эффективным, преимущественно, в случаях генерализованных форм эпилепсии типа абсансов. Некоторым подтверждением этого предположения являются результаты скрининга экстракта на пентилентетразоловой (PTZ) модели эпилепсии [1], которая как известно, больше соответствует генерализованной форме заболевания - вещества, проявляющие противосудорожные свойства на данной модели рассматриваются в первую очередь в качестве потенциально активных при миоклонических судорогах и абсансах [12].

В сухом ЭЦ корней головчатки содержатся различные химические соединения, в т.ч. алкалоиды, тритерпеновые сапонины, фенилкарбоновые кислоты и фенилгликозиды [2,14].

Целью исследования явилось дальнейшее выявление противосудорожных свойств экстракта цефалярии на двух моделях экспериментальной эпилепсии и оценка седативного действия и степени безвредности суммарного экстракта.

Материал и методы. I. Противосудорожная активность ЭЦ на *PTZ-модели*. В опытах использованы аутбредные крысы линии Вистар обоего пола весом 150- 200 г (выращены в виварии Института фармакохимии). Животные получали стандартный гранулированный корм и воду из поилок. 12 крысам контрольной группы вводили перорально дистиллированную воду в объеме 0,5 мл однократно. 12 крыс группы сравнения перорально получали 45 мг/кг фенобарбитала в виде 0.1N раствора в NaOH. В опытных группах крысам вводили перорально 0.5 мл суспензии ЭЦ различной концентрации (диапазон доз от 150 до 800 мг/кг). Во всех группах крысам спустя 45 мин. вводили 112 мг/кг PTZ внутримышечно. Действие каждой дозы экстракта испытывали на 12 крысах. Основным признаком противосудорожного действия служил, в первую очередь, факт отсутствия тонических и клонических судорог; у крыс, у которых судорожная активность всетаки обнаруживалась, учитывали длительность латентного периода и летальные исходы. На основании этих признаков определяли среднестатистическую эффективную дозу экстракта (ED_{50}). В другом варианте опыта этой же серии была испытана эффективность предварительного введения ЭЦ. Крысы были разделены на 2 группы по 10 животных; в контрольной группе при помощи зонда вводили 0.5 мл питьевой воды, а в опытной группе - ЭЦ перорально в дозе 400 мг/кг один раз в день в течение 7 дней и спустя 60 мин. вводили стандартную судорожную дозу PTZ .

II. Аудиогенные судороги у крыс линии Крушинского-Молодкиной [10] (виварий Института экспериментальной биомедицины; эксперименты с аудиогенными крысами выполнены в отделе нейрофизиологии этого же института, руководитель профессор З. И.Нанобашвили) вызывали при помощи звукового раздражителя (звонок 90 децибелл длительностью 60 сек). В экспериментальные группы были включены животные, у которых помимо реакции страха и избегания, а также клонуса лицевых мышц развивался дикий бег, после чего наступали клонические и тонические поведенческие судороги (11 крыс); Степень судорожных реакций оценивали по шкале Джоуба [9]; Животные были разделены на 2 группы.

Группа (а). Однократное внутрибрюшинное введение ЭЦ в дозе 100 мг/кг; оценку судорожных реакций на звонок производили спустя 60 мин после введения, а также в последующие 3 дня: учитывали реакцию на звонок без введения ЭЦ ; измеряли продолжительность скрытого периода и дикого бега, и, соответственно, длительность скрытого периода развития поведенческих судорог у 6-ти крыс.

Группа (б). Внутрибрюшинное введение 100 мг/кг ЭЦ в течение 7 дней; спустя 60 мин. после 7 введения производили звуковое раздражение и оценивали степень аудиогенных судорожных реакций. Реакцию на звуковое раздражение (без введения ЭЦ) оценивали и в последующие 8 дней у 5-ти крыс.

III. Седативные свойства ЭЦ изучали на мышах обоего пола весом 20-25 г, которым вводили 0.2 мл экстракта в дозе 400 мг/кг перорально; спустя -15 мин внутрибрюшинно вводили пентобарбитал натрия (нембутал) 45 мг/кг. В контрольной группе мыши получали только нембутал. В обеих группах учитывалась продолжительноть сна в мин; группы были составлены из 10 мышей обоего пола.

В этой же серии изучали возможную гепатотоксичность экстракта при помощи стандартного теста – экстракт в дозе 400 мг/кг вводили мышам весом 25 г подкожно с оливковым маслом в объеме 0.05 мл/10 г веса тела (растворитель - пропиленгликоль), и через сутки внутрибрюшинно вводили 45 мг/кг пентобарбитала натрия; сравнивали среднее время сна у контрольных (интактных) и опытных животных.

IV.Токсикологическая характеристика ЭЦ. Крысам массой приблизительно 200 г перорально однократно вводили от 500 до 5000 мг/кг ЭЦ посредством зонда и наблюдали в течение 14 дней. Величину токсических доз (TD_{50}) расчитывали в 5 группах, содержащих по 6 животных. Учитывали нарушения

двигательной активности, обусловленные депрессией ЦНС по Ирвину]. Установить летальные дозы ЭЦ, при пероральном введении не удалось ввиду того, что даже в случае введения максимально допустимых объемов ЭЦ летальные исходы не наблюдались. Была охарактеризована также токсичность экстракта в условиях хронического (в течение 1 года) введения ED_{50} и утроенной дозы ED_{50} (из поилок в виде сиропа). Общую оценку результатов проводили в соответствии с Рекомендациями доклинического исследования лекарственных препаратов [3].

Все количественные данные обработаны статистически при помощи компьютерной программы “Биостат -2008“.

Результаты и их обсуждение. I. На модели PTZ- судорог выявлено, что противосудорожной активностью в различной степени обладают определенные дозы ЭЦ, а среднеэффективная противосудорожная доза (ED_{50}) составила 400±96.7 мг/кг/перорально. В контрольной группе животных, получавших только PTZ все животные погибали в результате развития тонически-клонических судорог. В группе крыс, получавших предварительно фенобарбитал судороги не наступали вовсе. В опытных группах максимальный эффект – отсутствие судорог приблизительно у 85% животных, был получен в результате перорального введения 800 мг/кг экстракта. Однако даже у крыс, у которых развились судороги (15%), латентный период с момента введения PTZ увеличился примерно в 5 раз и обе крысы выжили. В результате введения 400 мг/кг судороги проявились у 6 крыс, однако все они также выжили; при введении 150 мг/кг судороги наблюдались у 9 крыс, причем выжили только 3 из них, т.е. зависимость противосудорожного действия и летальных исходов от дозы очевидна.

В результате предварительного введения 400 мг/кг ЭЦ в течение 7 дней судорожные явления наблюдались только у одной крысы из 10, причем только спуся 40 мин после введения PTZ, но и эта крыса выжила (таблица 1).

II. Противосудорожный эффект экстракта был явно выражен также на модели аудиогенных судорог. У крыс, предрасположенных к судорогам на звуковое раздражение, характерным показателем является развитие поведенческих судорог, а также реакция дикого бега [13], длительность латентного периода и его продолжительность. Дикий бег после подачи звукового раздражителя у всех чуствительных животных (n=11) развивался спустя 3-8 сек. (латентный период бега) и продолжался 4-6 сек., затем возникали поведенческие судорожные припадки, однако без летальных исходов.

В результате однократного внутрибрюшинного введения ЭЦ у 2 из 6 крыс судороги не развились вовсе; у остальных 4 как латентный период бега, так и его продолжительность оказались увеличенными 15-18 сек. и 10-12 сек., соответственно, в ответ на звуковое раздражение. Восстановление чувствительности к звуковому раздражителю у этих 2 крыс наблюдалось только спустя 48 ч, когда развивалась картина судорожной реакции, подобная контрольной.

В результате предварительного 7-дневного введения ЭЦ аудиогенные судороги полностью отсутствовали у 3 из 5 крыс. У остальных 2 животных дикий бег хотя и наблюдался, скрытый период оказался существенно продленным. Отсутствие реакции на звуковой раздражитель у 3 крыс сохранялось еще в течение 7 дней после последнего введения ЭЦ (таблица 2).

III. Седативное действие ЭЦ. В группе мышей, получавших пентобарбитал (нембутал) средняя продолжительность сна составила около 20 мин.; в результате предварительного перорального введения экстракта продолжительность сна увеличилась примерно в 2 раза.

В опыте по определению возможной гепатотоксичности ЭЦ выяснилось, что терапевтическая доза препарата введенная за день до барбитурата не продлевает сон, т.е. не нарушает детоксикационной функции печени (таблица 3).

Таблица 1. Противосудорожная активность ЭЦ на PTZ модели

Группы (n=12)	**Доза мг/кг**	**Латентный период (мин/число крыс с судорогами)**	**Продолжительность судорог (сек)**	**Число животных без судорог**	**Смертность**
PTZ	112 п/к	5±1.7/12	15±4.7	0	100%/12
Фенобарбитал	45	-	-	12 /100%	0
ЭЦ (однократно)	800	25 и 27/2	5 и 6	10/83%	0
	400	20±3.5/6	6±2.7	6/50%	0
	150	10±3.7/9	12±3.6	3/25%	75 %/9
ЭЦ (n=10) (многократно)	400	40 /1	6	9/90%	0

Таблица 2. Противосудорожная активность ЭЦ на модели аудиогенных судорог

Группы	**Латентный период бега (сек)**	**Число животных без судорог/число животных в группе**	**Отсутствие чувствительности к раздражителю (в днях)**
Чувствительные животные	3-8	0/11	-
Однократное введение ЭЦ	15-18	2/6	2
Предварительное введение ЭЦ (7 дней)	18-20	3/5	7

Таблица 3. Влияние ЭЦ на продолжительность барбитурового сна

Проба на гепатотоксичность		Проба на седативные свойства	
Нембутал 45мг/кг	**Экстракт цефалярии 400 мг/кг +нембутал (спустя 24 *ч*)**	**Нембутал 45мг/кг**	**Экстракт цефалярии 400 мг/кг+ нембутал (спустя 15 мин)**
26x1* 24x3 27x3 15x1	25×1 24×2 23×1 26x2	20x1 24x1 23x3 19x1	50x1 52x2 49x2 55×1
26.29±3.59	**24.67±1.21**	**22.33±2.79**	**51.5±2,26**
p>0,05**		p<0,05	

** - продолжительность сна в мин **x** кол-во мышей;*
*** - по сравнению с продолжительностью нембуталового сна в контроле*

Таблица 4. Экстракты и природные химические соединения, проявляющие противосудорожную активность на модели PTZ-судорог (по [8], модифицированно)

	Лекарственные растения	**Химический состав**	**Модель судорог**	**Эффективная доза**	**Способ введения**
Экстракты	*Cephallaria gigantea*	Алкалоиды, полифенолы Тритерпеновые сапонины	PTZ*, AS**	100-400 -600 мг/кг	в/б, п/о
	Desmodium triflorum	Нафтохиноны, (плумбагин), флаваноиды	PTZ , MES***	400 мг/кг	п/о
	Abutilon indicum	Стероиды, сапогенины	PTZ, MES	100-400 мг/кг	п/о
	Carissa carandas Linn	кумарины,флавоноиды Гликозиды, тритерпеноиды	PTZ, MES	10 мл/кг	п/о
	Opuntia vulgaris	Алкалоиды, сапонины	PTZ	5 мл/кг	в/б
	Astragalus mongholicus Bunge	сапонины	PTZ	50, 100, 200мг/кг	в/б
Индивидуальные вещества	*Aconitum* (многие виды)	Алкалоиды Аконитин	PTZ	0.1-1.0 μм	Срез гипокампа
	Hippeastrum vittatum	Монтанин	PTZ	30-60 мг/кг	в/б
	*Rauwolfia serpentin*a	Раубазин	PTZ, BC****	7.5-40.6 мг/кг	в/в
	Passiflora caerulea	Флаваноиды Кризин	PTZ	40 μм	в/в
	Scutelaria baicalensis	Баикалин	PTZ , MES	5-10 мг/кг	в/б
	Cannabis sativa	Терпеноиды	PTZ , MES	58 мг/кг	-
	Mentha spicata	Канабидиол Карвон	PTZ , MES	100-400 мг/кг	-

PTZ – пентилентетразоловые судороги;AS – аудиогенные судороги;*
**** MES –максимальный электрошок; ****BC –бикукулиновые судороги*

IV**.** Токсикологическая характеристика ЭЦ. Пероральное введение максимального объема и дозы (технически осуществимое) ЭЦ не вызывало смертельных исходов, хотя при этом удалось установить значение токсических доз, в т.ч. TD_{50}, которая составила 2600±340 мг/кг. Токсическое действие ЭЦ в острых опытах проявилось, преимущественно, в виде явлений угнетения функций ЦНС: птоза, взъерошенности, скученности и понижения рефлекторной активности, что по-видимому, связано также со специфическим седативным свойством ЭЦ.

В условиях хронического эксперимента выявлено, что ни введение эффективных противосудорожных доз (ED_{50} - 400 мг/кг), равно как и увеличенных в 3 раза доз в течение одного года не привело к каким-либо существенным изменениям в общем состоянии и поведении животных, к отклонениям в гематологических и биохимических показателях, а также к морфологическим изменениям в паренхиматозных органах.

Опыты с введением экстракта на модели PTZ-судорог подтвердили данные традиционной медицины о противосудорожных свойствах ЭЦ; противосудорожная активность обнаруживалась при различных способах введения - пероральном, внутрибрюшинном, а также однократном и многократном предварительном. Существенно отметить, что в 15% случаев у крыс, получавших 800 мг/кг, единичные судорожные явления хотя и наблюдались, однако летальных исходов не наблюдалось. Наличие противосудорожных свойств ЭЦ на этой же модели обнаруживается также и в условиях предварительного повторного введения уменьшенной в 2 раза дозы (400 мг/кг) в течение 7 дней. Следовательно, в условиях повторного введения данной дозы препарат оказался не менее эффективным, чем при однократном введении максимальной дозы (800 мг/кг). Относительно механизма противосудорожного действия экстракта можно сослаться на известное мнение, что на PTZ-модели проявляют активность вещества, способные взаимодействовать с GABA/бензодиазепиновыеми рецепторами [5]. Подтверждением наличия противосудорожных свойств ЭЦ безусловно является его эффективность при аудиогенных судорогах - и в данном случае положительный эффект проявлялся как в условиях однократного, так и повторных внутрибрюшинных введений. Однако, наилучший эффект был получен в последнем случае, т.е. в группах с предварительным 7-дневным введением ЭЦ, также как на модели PTZ судорог. Следовательно, можно ожидать значительного противосудорожного эффекта именно в условиях систематического применения ЭЦ. Действительно, в результате предварительного введения ЭЦ в случае PTZ-судорог эффективность явно повысилась: судороги развились у одной из 10-ти крыс, тогда как в случае однократного введения той же дозы, судороги развились у 6 из 12 крыс, а в случае аудиогенных судорог, как указано выше, чувствительность к звуковому раздражителю отсутствовала в течение 7 дней в условиях многократного введения, а в условиях однократного введения чувствительность отсутствовала только в течение 2 дней. Аудиогенные судорожные припадки являются разновидностью генерализованной конвульсивной эпилепсии, в развитии которой первостепенную роль играют стволовые структуры головного мозга [12]. Можно предположить, что у животных, генетически детерминированных к судорожным реакциям, понижение чувствительности на звуковое раздражение после введения ЭЦ обусловлено снижением уровня возбудимости нейронов четверохолмия и/или мотроных областей ретикулярной формации.

Противосудорожные свойства на модели PTZ были установлены также у экстрактов и индивидуальных веществ, полученных преимущественно из растений, произрастающих в субтропических и тропических зонах [4, 7, 8, таблица 4].

По химическому составу наиболее близкими к ЭЦ являются экстракты и индивидуальные химические соединения растений, содержащих алкалоиды и/или тритерпеновые сапонины, или те и другие одноременно. Следует отметить,что противосудорожные свойства упомянутых в таблице растений были установлены также и на других моделях эпилепсии, однако данные противосудорожной активности на модели аудиогенных судорог не приводятся. Результаты опыта по изучению влияния ЭЦ на продолжительность барбитуратного сна свидетельствуют, что специфическая противосудорожная активность экстракта соответсвует его седативным свойствам. О седативных свойствах ЭЦ можно судить также и по проявлениям его угнетающего влияния на ЦНС в токсикологических экспериментах. Вариант опыта с продлением нембуталового сна (проба на гепатотоксичность) свидетельтвует, что эффект не обусловлен токсичностью экстракта. И наконец, с токсикологической точки зрения экстракт цефалярии оказался достаточно безвредным.

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SUMMARY

ANTISEIZURE ACTIVITY OF *CEPHALARIA GIGANTEA* ROOT EXTRACT

[1]Gogitidze N., [1]Mushkiashvili N., [2]Gedevanishvili M., [1]Tabatadze N., [1]Dekanosidze G.

[1]Tbilisi State Medical University I.Kutateladze Institute of Pharmacochemistry; [2]Iv. Javakhishvili Tbilisi State University, Georgia

Antiseizure activity of *Cephalaria gigantea* root extract was studied using PTZ- and/or audiogenic seizure models in outbred Wistar and inbred Krouchinsky- Molodkina rats respectively. In PTZ - model onset of tonic- clonic seizures, latencies to the beginning of the seizure activity, and mortality, and similarly in audiogenic seizures behavioral convulsive reactions , facial automatisms and latency to wild running were evaluated. The extract is used traditionally in Georgian folk medicine as anticonvulsant drug. In this study it was evidenced experimentally that extract demonstrates anticonvulsant properties as in both model, as in both routs of administration – peroral and intraperitoneal. Extract appeared most effective in case of preliminary repetitive administration: in PTZ model seizures were eliminated in 9 of 10 animals, and in audiogenic model convulsive response was no more observable during 7 days of treatment termination. It was found also that sedative properties are characteristic of this antiseizure extract according to the sleeping prolongation in barbiturate treated mice. Safety of the extract was evaluated in toxicological acute and chronic experiments, and consequently it is considered a substance of moderate general toxicity.

Keywords: Cephalaria extract, PTZ seizures, audiogenic seizers, anticonvulsant activity, sedative effect.

РЕЗЮМЕ

ПРОТИВОСУДОРОЖНЫЙ ЭКСТРАКТ КОРНЕЙ ГОЛОВЧАТКИ ГИГАНТСКОЙ (*CEPHALARIA GIGANTEA*)

[1]Гогитидзе Н. М., [1]Мушкиашвили Н.И., [2]Гедеванишвили М.Д., [1]Табатадзе Н.А., [1]Деканосидзе Г.Е.

[1]Тбилисский государственный медицинский университет, Институт фармакохимии им. И. Кутателадзе; [2]Тбилисский государственный университет им. И. Джавахишвили, Грузия

В работе представлены данные экспериментального изучения экстракта головчатки (*Cephalaria gigantean)*, который традиционно применяется в грузинской народной медицине для лечения судорожных состояний. Противосудорожное действие экстракта изучено на моделях пентилентетразоловых (PTZ) и аудиогенных судорог (аутбредные крысы линии Вистар и крысы линии Крушинского-Молодкиной, соответственно). Эффективность экстракта оценивалась в случае PTZ модели по отсутствию тонических и клонических судорог; у крыс, у которых судорожная активность всетаки обнаруживалась, учитывали длительность латентного периода и летальные исходы, а в случае аудиогенной модели - по реакциям страха и избегания, а также клонуса лицевых мышц, развитию дикого бега и появлению клонических и тонических поведенческих судорог. Экстракт испытан при пероральном и внутрибрюшинном способах введения. Установлено, что противосудорожная активность обнаруживается в условиях как однократных, так и предварительных повторных введений экстракта на обеих моделях, однако в результате предварительного введения экстракта его эффективность явно повысилась - в случае PTZ-модели судороги развились только у одной из 10 крыс, а в случае аудиогенных судорог, чувствительность к звуковому раздражителю отсутствовала в течение 7 дней после прекращения инъекций. Судя по продлению барбитуратного сна у мышей, экстракт цефалярии обладает также и седативными свойствами. Результаты токсикологического изучения свидетельствуют об умеренной токсичности препарата.

რეზიუმე

ანტიკონვულსიური ექსტრაქტი მცენარე სკიპალოს (ჩეჰჰალარია გიგანტეა) ფესვებიდან

[1]ნ. გოგიტიძე, [1]ნ. მუშკიაშვილი, [2]მ. გედევანიშვილი, [1]ნ. ტაბატაძე, [1]გ. დეკანოსიძე

[1]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, ი. ქუთათელაძის ფარმაკოქიმიის ინსტიტუტი; [2]ივ. ჯავახიშვილის თბილისის სახელმწიფო უნივერსიტეტი, საქართველო

სკიპალოს ექსტრაქტი, რომელსაც ქართულ ხალხურ მედიცინაში კრუნჩხვითი შეტევების სამკურნალოდ იყენებენ,შესწავლილ იქნა პენტილენტეტრაზოლური (თძ) და აუდიოგენური კრუნჩხვების მოდელებზე (ვისტარის აუტბრედულსა და კრუშინსკი-მოლოდკინას ხაზის ვირთაგვებში). PTZ ტესტის შემთხვევაში ექსტრაქტის ანტიკონვულსიურ ეფექტურობად კრუნჩხვითი მოვლენების გაქრობა, ან ლატენტური პერიოდის გახანგრძლივება და სიკვდილიანობა, ხოლო აუდიოგენური მოდელის შემთხვევაში კი - ველური სირბილის გახანგრძლივება და ქცევითი ტონურ-კლონური კრუნჩხვების გაბათილება იყო მიჩნეული. ექსტრაქტი გამოკვლეულია პერორალური და მუცლისშიდა შეყვანის მეთოდებით. ექსტრაქტი ეფექტური აღმოჩნდა როგორც ერთჯერადი, ისე წინასწარი განმეორებითი შიგნით მიღებისა ან ინიექციების პირობებშიც,მაგრამ წინასწარი გამოყენების შედეგად მისი ეფექტურობა გაიზარდა - PTZ მოდელზე კრუნჩხვები არ განვითარებულა 10-დან 9 ცხოველში, ხოლო აუდიოგენური მოდელის შემთხვევაში კრუნჩხვითი რეაქციები ბგერით გაღიზიანებაზე მკურნალობის შეწყვეტიდან მხოლოდ მე-7 დღეს გამოვლინდა. ამავე დროს, ბარბიტურატული ძილის მნიშვნელოვანი გახანგრძლივება თაგვებში იმის მაჩვენებელია, რომ ექსტრაქტი სედაციური თვისებებითაც გამოირჩევა. ტოქსიკოლოგიურ ექსპერიმენტებში მიღებული შედეგების მიხედვით, ექსტრაქტი ნაკლებად ტოქსიკურ პრეპარატებს მიეკუთვნება.

IMPACT OF FOOD ENRICHED WITH DIETARY FIBER ON PATIENTS WITH CONSTIPATION PREDOMINANT IRRITABLE BOWEL SYNDROME

Sulaberidze G., Okujava M., *Liluashvili K., Tughushi M., Abramashvili M.

Tbilisi State Medical University, Deapartment of Interal Medicine and Department of Pharmacotherapy;
**JSC Curatio, Tbilisi, Georgia*

Motility disorder of gastrointestinal tract and in particular Irritable Bowel Syndrome (IBS) is common and debilitating chronic disease with profound impact on the patient's quality of life and medical system costs [1]. Current developments show that causes of IBS are multifold, leading to complexity of treatment and requirement of more precise investigation of different pharmacological and non-pharmacological approaches [2,3].

The pathophysiology and clinical presentation of IBS is only partially explained with inflammation, infections, impairment of intestinal motility and brain-intestine axis [4]. The importance of visceral hypersensitivity and increased afferent stimulation for development of IBS is established. Increased afferent stimulation of the intestine is linked with enhanced physiologic impulses, changed motility and secretory function and development of pain and related symptoms [5]. Variation of intestinal microbiome is considered as one of the etiologic reasons of IBS as well. The recent studies suggested importance of changed intestinal microbiota related infections and short-chain fatty acids, the end products of bacterial fermentation in the intestine. Psychological distress and somatization of amplified symptoms related to dietary inadequacy is significant co-factor of IBS development, exacerbates the functional symptoms of the disease, has an impact on the quality of life and causes resistance to drug treatment [6].

Despite many patients with IBS perceive food to be important trigger for symptom's development, influence of dietary patterns and gender on IBS subtype appearance and the symptom severity is not well studded yet [7,8]. Most studies recently available represent retrospective assessment of food and nutrient intake and have high risk for recall bias [9,10]. Dietary fiber is widely recognized to have beneficial effects on health in general and on bowel function in particular, when consumed in sufficient amount, however, most often average fiber intake with food is less than half of recommended amount [11].

The aim of the study was investigation and comparison of the dietary fiber intake among women with constipation-predominant irritable bowel syndrome (IBS-C) and without, improvement of the dietary fiber intake using interventions with less rough changes of food related behavior and study of its effects on the bowel function, general wellbeing and compliance of patients.

Material and methods. In total 100 healthy women, without any clinical signs of gastrointestinal disorders and 98 women who met Rome III criteria for IBS-C were enrolled in the dietary fiber intake assessment survey. There was no significant difference in average age among the groups (33.7±16.7 years and 39.2±12.3 years, $p>0.1$ respectively).

One month dietary history questionnaire was applied for baseline evaluation of food intake for both, healthy controls and patients with IBS-C. The questionnaire was based on 48 commonly consumed food items in Georgia that are recognized as main sources of dietary fiber. For each food item two type of questions were suggested: food frequency and portion size questions with possible options of semi-quantitative answers.

The average daily amount of consumed foods and their composition was converted into nutrients (fiber, carbohydrates, protein, fats) and energy. For questionnaire data entry and estimations the simple MS Excel designed database was used. The proxy tables with data of nutritive values of selected food items was constructed and appropriate calculations were provided. All information regarding nutritive value of foods was derived from the bulletin of United States Department of Agriculture (USDA) [12].

For evaluation of bowel function, digestive feelings and general wellbeing the clinical assessment tool was adopted based on Digestive Wellbeing Questionnaire (DWQ) provided by Lawton Cl. [13]. All Patients with IBS-C involved in the study were evaluated at baseline, after 7 and 14 days of dietary interventions with fiber enriched products. Each clinical indicator was assessed with frequency of appearance or grade of severity. To obtain the quantitative data the severity grades were scored with numeric values. Stool type as the parameter of bowel function was assessed according to Bristol Stool Form Scale (BSFS) [14]. Data from the questionnaires were entered into the simple MS Excel designed database for analysis.

As comparative analysis of food and nutrient intake revealed significant deficit of dietary fiber in IBS-C patients, the dietary supplementation up to the Tolerable Upper Intake Level (UL) (40 gr of dietary fiber for patients with functional constipation) was provided with fiber enriched food – bread and muesli, with trade mark "Margi" [15], containing increased amount of preliminary processed wheat bran. The milling technology used allows to destroy the hydrophobic film of grain coat and makes the next technological stage remaining physiologic digestion of food – impregnation and action of the acid medium - more effective. The so processed bran becomes more easily digestible. The content of nutrients and energy per 100g of product was in:
Bread: fiber – 9.51g, carb. – 33.72g, protein – 7.56g, fats – 1.31g, energy – 177kcal
Muesli: fiber – 22.4g, carb. – 29.87g, protein - 7.33g, fats – 1.47g, energy – 212kcal.

For replenishment of the detected lack of the dietary fiber the IBS-C patients were prescribed to take 100-300g of bread and/or 40-110g of muesli at usual breakfast. The amount of added dietary fiber was 21.32±4.9g/daily.

The sample characteristics for categorical variables were calculated and presented in portions and for continuous parametric variables - in mean values and standard deviations. For estimation of the difference in continuous variables between independent samples t-test was used. All statistical tests applied were two-sided and at the 5% significance level. All statistical processing were performed by the means of MS MINITAB statistical package MINITAB® Release 14.12.0.

Results and their discussion. The average intake of dietary fiber was significantly lower in the group of women with IBS-C (17.9±5.8) compared with healthy population (21.6±8.9, p=0.013). Less than lower recommended level of daily dietary fiber intake (<25 g) occurred in 66.7% of healthy respondents and 90% of women with IBS-C (p=0,003) (Fig. 1). The average amount of daily fiber in women with deficiency from both groups was approximately 16g.

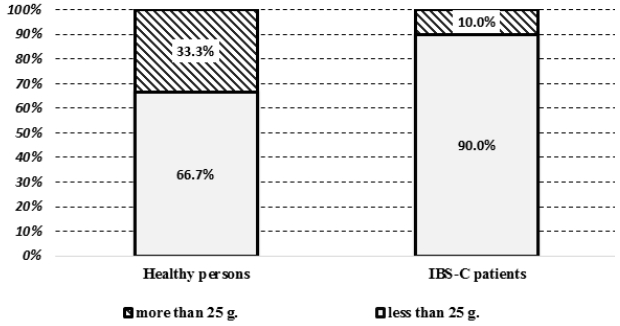

Fig. 1. Dietary Fiber Intake Pattern (%) Compared to Lower Recommended Level (25 g.)

The difference in average consumption of carbohydrates (191.4g and 190.5g, *p=0.946*) and energy (1086.0kcal and 1122.8kcal, *p=0.628*) between the groups was not considerable, but divergence of carbohydrate, as well as dietary fiber sources appeared.

Consumption of fiber from bread, other wheat products and cereals was significantly higher in patients with IBS-C, while healthy women used more fiber from non-starch vegetable, fruits and cookies, cakes and sweets (Fig. 2).

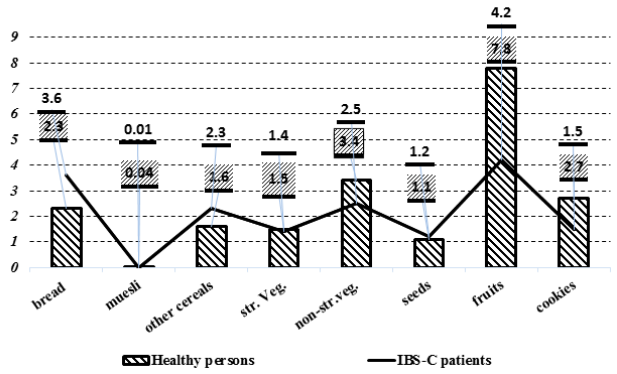

Fig. 2. Average Daily Intake of Fiber (grams) from Main Foods

Respectively women with IBS-C got main part of dietary carbohydrates from bread, wheat products and cereals, but healthy group used significantly higher amount of carbohydrates from fruits (Fig. 3).

From initially enrolled 98 IBS-C patients 82 continuously received dietary fiber rich food during 14 days of observation, consequently the compliance rate was 83.7%. After two weeks of adding dietary fiber rich food on breakfast the stool was of normal consistency (Bristol scale level 3 and 4) in 76 cases (94%) and was significantly improved relatively to baseline state (20%, p<0.0001 respectively). Before the intervention stool was very hard or hard in 28% and 64% respectively and changed to less hard and no hard type (28% and 64%). Herewith, after 14 days of supplementation of diet with fiber rich foods the bowel movement frequency increased significantly from 0.27 daily up to 1.54 daily.

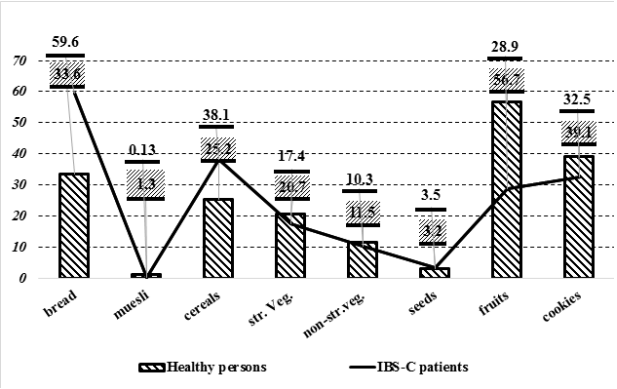

Fig. 3. Average Daily Intake of Carbohydrates (grams) from Main Foods

Statistically significant improvement was observed in abdominal pain and bloating, the score decreased from baseline 0.72 to 0.13 points and from 1.12 to 0.22 respectively (p<0.001). The score relevant for difficulty of defecation decreased from 1.61 up to 0.22 points (p<0.001), the sensation of incomplete evacuation was decreased from baseline 1.92 to 0.18 points (p<0.001). Analyses showed significant decrease of alertness related to digestive feelings and general wellbeing after continuous consumption of dietary fiber (from 0.95 up to 0.19 and from 0.41 up to 1.2 points, p<0.001) (Fig. 4).

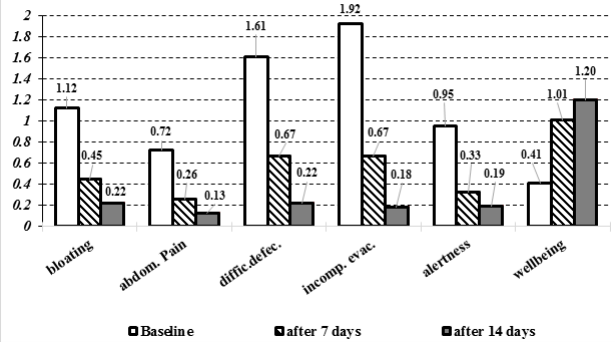

Fig. 4. Symptoms (Points) During the Dietary Supplementation with Fiber Rich Wheat Products

Conclusions:
Research data reviled significantly lower daily intake of dietary fiber among patients with IBS-C compared with healthy group.

The main source of dietary fiber in IBS-C group was bread and cereals, therefore introduction of dietary fiber rich bread and muesli in the breakfast didn't affect diet-related habits and determined high compliance of patients.

Two week long intervention significantly improved the bowel function and irritation related complains, the feeling of general wellbeing was considerably better on the endpoint as well.

Conflict of Interest. This study was the part of the project funded by Shota Rustaveli National Science Foundation (governmental non-profit organization) and terms of financing exclude any conflict of interest.

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SUMMARY

IMPACT OF FOOD ENRICHED WITH DIETARY FIBER ON PATIENTS WITH CONSTIPATION PREDOMINANT IRRITABLE BOWEL SYNDROME

Sulaberidze G., Okujava M., *Liluashvili K., Tughushi M., Abramashvili M.

*Tbilisi State Medical University, Deapartment of Interal Medicine and Department of Pharmacotherapy; *JSC Curatio, Tbilisi, Georgia*

The causes of motility disorder of gastrointestinal tract and in particular Irritable Bowel Syndrome IBS are multifold, leading to complexity of treatment and requirement of more precise investigation of different pharmacological and non-pharmacological approaches. The aim of the study was investigation and comparison of the dietary fiber intake among women with constipation-predominant irritable bowel syndrome (IBS-C) and without, improvement of the dietary fiber intake using interventions with less rough changes of food related behavior and study of its effects on the bowel function, general wellbeing and compliance of patients.

In total 100 healthy women, without any clinical signs of gastrointestinal disorders and 98 women who met Rome III criteria of IBS-C were enrolled in the dietary fiber intake assessment survey. The dietary habits of all participants, as well as bowel function, digestive feelings and general wellbeing of patients at baseline, on the 7th and 14th day of dietary intervention was assessed by the means of adopted questionnaires. The dietary supplementation was provided during the breakfast with fiber enriched food – bread and muesli.

Research data reviled significantly lower daily intake of dietary fiber among patients with IBS-C compared with healthy group. The main source of dietary fiber in IBS-C group was bread and cereals, therefore introduction of dietary fiber rich bread and muesli in the breakfast didn't affect diet-related habits and determined high compliance of patients. Two week long intervention significantly improved the bowel function and irritation related complains, the feeling of general wellbeing was considerably better on the endpoint as well.

Keywords: dietary fiber, irritable bowel syndrome, constipation.

РЕЗЮМЕ

ЗНАЧЕНИЕ БОГАТОЙ РАСТИТЕЛЬНЫМИ ВОЛОКНАМИ ПИЩИ ДЛЯ ПАЦИЕНТОВ С СИНДРОМОМ РАЗДРАЖЕННОГО КИШЕЧНИКА С ПРЕОБЛАДАНИЕМ ЗАПОРОВ

Сулаберидзе Г.Т., Окуджава М.В., *Лилуашвили К.Н., Тугуши М.Г., Абрамашвили М.М.

*Тбилисский государственный медицинский университет, департамент общей терапии; департамент фармакотерапии; *АО Курацио, Тбилиси, Грузия*

Причины развития нарушения моторной функции желудочно-кишечного тракта и в частности, синдрома раздражённого кишечника разнообразны, что обусловливает сложность лечения и необходимость изучения различных фармакологических и нефармакологических подходов.

Целью исследования явилась коррекция приема растительных волокон вместе с пищей без грубого нарушения поведенческих особенностей среди женщин с синдромом раздражённого кишечника с преобладанием запоров (СРК-З), а также изучение эффекта, проведенного вмешательства на функцию кишечника, общее самочувствие и следования пациентами измененной диете.

В исследовании принимали участие 100 женщин не имеющих жалоб со стороны желудочно-кишечного тракта и 98 женщин

с СРК-3 в соответствии с критериями, предложенными Rome III. Для определения привычного рациона все участники исследования были опрошены посредством диетического вопросника, а для оценки функции кишечника, пищеварения и общего самочувствия - клинического вопросника до увеличения приема растительных волокон и спустя 7 и 14 дней с начала вмешательства.

На основании полученных данных следует заключить, что в пищевом рационе женщин с СРК-С содержание пищевых растительных волокон значительно меньше по сравнению с здоровыми лицами. Основным источником пищевых растительных волокон среди пациентов с СРК-С является хлеб и хлопья, поэтому включение в состав завтрака хлеба и мюсли с высоким содержанием растительных волокон не вызывает значительных поведенческих изменении и является основой высокого уровня следования пациентами измененной диете. Двухнедельная изменение завтрака пациентов достоверно улучшило функцию кишечника, уменьшило жалобы, связанные с пищеварением и повысило общее самочувствие пациентов.

რეზიუმე

დიეტური ბოჭკოთი მდიდარი საკვების მნიშვნელობა უპირატესად ყაბზობით მიმდინარე გაღიზიანებული ნაწლავის სინდრომის მქონე პაციენტებისთვის

გ. სულაბერიძე,მ. ოკუჯავა,*კ. ლილუაშვილი,მ. ტუღუში, მ. აბრამაშვილი

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, ზოგადი თერაპიის დეპარტამეტი და ფარმაკოთერაპიის დეპარტამენტი; *სს "კურაციო",თბილისი,საქართველო

კუჭ-ნაწლავის ტრაქტის მოტორიკის მოშლით მიმდინარე დაავადებების და კერძოდ გაღიზიანებული ნაწლავის სინდრომის მიზეზი მრავალგვარია, რაც განაპირობებს მკურნალობის სირთულეს და სხვადასხვა ფარმაკოლოგიური და არაფარმაკოლოგიური მიდგომების შესწავლის აუცილებლობას. კვლევის მიზანს წარმოადგენდა ქალებში უპირატესად ყაბზობით მიმდინარე გაღიზიანებული ნაწლავის სინდრომის (IBS-C) დროს საკვებთან ერთად მცენარეული ბოჭკოს მიღების კორექცია კვებასთან დაკავშირებული ქცევის უხეში ცვლილების გარეშე და ამ ინტერვენციის ეფექტის შესწავლა ნაწლავის ფუნქციაზე, ზოგად თვითგრძნობასა და პაციენტების დამყოლობაზე.

კვლევაში მონაწილეობდა 100 ზოგადად ჯანმრთელი ქალი,რომელთაც არ ჰქონდათ კუჭნაწლავის ტრაქტის დისფუნქციის კლინიკური ნიშნები და 98 ქალი, რომლებსაც რომი III კრიტერიუმების მიხედვით აღენიშნებოდათ IBS-C. დიეტური კითხვარის საშუალებით შესწავლილი იყო კვლევაში ჩართული ყველა პირის ჩვეული კვების რაციონი, ხოლო დავადების მქონე პირებში კლინიკური კითხვარით შეფასდა ნაწლავის ფუნქციური მდგომარეობა, საკვების მონელებასთან დაკავშირებული ჩივილები და ზოგადი თვითგრძნობა სადღეღამისო რაციონში მცენარეული ბოჭკოს რაოდენობის გაზრდამდე,დიეტური ინტერვენციიდან 7 დღის და 14 დღის შემდეგ.

კვლევამ გამოავლინა IBS-C-ის მქონე პაციენტების ჩვეულ რაციონში მცენარეული ბოჭკოს სარწმუნოდ მცირე შემცველობა ჯანმრთელ პოპულაციასთან შედარებით. IBS-C-ის მქონე პაციენტებში მცენარეული ბოჭკოს ძირითადი წყარო იყო პური და ბურღულეული, ამიტომ მცენარეული ბოჭკოს მაღალი შემცველობის პურისა და მიუსლის დამატება საუზმეზე არ განაპირობებდა კვებასთან დაკავშირებული ქცევის მნიშვნელოვან ცვლილებას,რაც პაციენტების მაღალი დამყოლობის საფუძველს წარმოადგენს. ორ კვირიანმა ინტერვენციამ დაკვირვების საბოლოო ეტაპზე სარწმუნოდ გააუმჯობესა ნაწლავის ფუნქცია, გაღიზიანებასთან დაკავშირებული სიმპტომები და ზოგადი თვითგრძნობა.

ROLE OF PRIMARY HEALTH CARE IN RE-HOSPITALIZATION OF PATIENTS WITH HEART FAILURE

Verulava T., Jincharadze N., Jorbenadze R.

Ilia State University. G. Chapidze Emergency Cardiology Center, Tbilisi, Georgia

In Georgia, like in other countries, heart failure, a major cause of morbidity and mortality among the elderly, is a serious public health problem. According to the statistics, 69% of death comes from cardiovascular diseases [6].

Hospital readmission is one of the potential indicators of poor care or missed opportunities to better coordinate care [9] and was endorsed as a measure of hospital performance [15]. Heart failure is one of the most common principal discharge diagnoses [12]. Re-hospitalization rates are quite varying according to the diagnoses. According to some authors, re-hospitalization after coronary artery bypass grafting is 13.2% within 30 days of surgery [11]. After hospitalization for heart failure, 15-day readmission rates have been estimated at 13% and 30-day readmission rates at approximately 25% [7,8].

Hospital readmission for Heart failure as well as other chronic diseases creates a huge impact on the healthcare system as well as on the patient [1]. Re-hospitalization increases medical expenses and it has negative impact on patients' health and financial situation of family [3,13].

Multiple patient risk factors, including age, sex, social and economic situation, lower median household income, low quality of

Table. Principal discharge diagnosis associated with readmissions of patients without Acute Myocardial Infarction (AMI), with Acute Myocardial Infarction (AMI), and with Repeat Revascularization

Principal diagnosis	Total (%) (n=103)	No AMI in Index (%) (n=74)	AMI in Index (%) (n=29)	Revascularization During Readmission (%) (n=24)
Chronic ischemic heart disease	32.4	33.2	32.2	89
Heart failure	15.2	11.3	10.8	1
Unstable angina	11.7	10.5	9.6	1
Myocardial infarction	8.2	7.3	6.8	5
Arrhythmia	6.3	6.1	5.9	0
Acute respiratory failure	6.2	6	5.6	0
Other	19	25.6	29.1	4

medical service were significant predictors of readmission [11]. Lack of a comprehensive approach to heart failure management involving careful inpatient education, discharge planning, and coordinated delivery of outpatient care has been cited as a major reason for the continued high rates of hospital readmissions for heart failure. [5].

Generally, it is impossible to eliminate re-hospitalization. In some cases, re-hospitalization is unavoidable, because of the nature of disease; that is why predicting re-hospitalization is impossible. In efforts to identify opportunities to improve quality of care, several interventions have been proven to lower readmission rates after Heart failure hospitalization, including improved hospital [2] and post discharge care, [13] pre-discharge planning, [14] home-based follow-up, [16] and increasing the level of patient's education.[4,10].

Our research objective was to study recent trends in 30-day all-cause readmission rates after Heart failure hospitalization in order to improve clinical understanding of the risk for re-hospitalization after Heart failure admission and to inform efforts of policy-makers as increased attention is focused on this measure of hospital quality.

Material and methods. Methodological basis of this research is Literature in the sphere of re-hospitalization. Our research included quantity and quality components. Within the Quantitative research, we have analyzed data of re-hospitalized patients during 2014 year from biggest cardiology hospital in Georgia. Within the qualitative study, in-depth survey of medical staff and patients conducted. Restriction of methodology was following factors: A little time for research, researching only one cardiology centre.

Results and their discussion. According to the research, Re-hospitalization rate during 30 days was 1.5% (47.6% female and 52.4% male patients). Re-hospitalization has the correlation with the patient's age, sex and disease. Compared with patients who were not readmitted, patients who were readmitted were older (age 71 years vs. 67 years) and more likely to be female (62% vs. 38%) (Table).

Research showed that re-hospitalization also depends on the disease. Compared with patients who were not readmitted, patients who were readmitted have diabetes (32% vs. 29%), heart failure (23% vs. 15%), renal failure (7.5% vs. 3.5%), and ischemic heart disease (23% vs. 13%) (Table).

Patients who readmitted were more likely to die within 30 days of discharge compared with patients who were not readmitted (5.2% vs. 1.3%). The 30-day readmission rate of patients who had an acute myocardial infarction (AMI) was higher than that of non-AMI patients (AMI 22.4%, non-AMI 9.4%) (Table).

The majority of 30-day re-hospitalization was associated with a chronic ischemic heart disease (32.4%), heart failure (15.2%), unstable angina (11.7%), myocardial infarction (8.2%) arrhythmia (6.3%), and acute respiratory failure (6.2%). These diseases are high-risk groups of re-hospitalization, which considered for discharging patient's surveillance (Table).

Among all readmissions, 23.3% of patients had an associated revascularization procedure (percutaneous coronary intervention 21.6%, coronary artery bypass grafting 2.1%). The majority (89%) of admissions with revascularization procedures were associated with chronic ischemic cardiac disease (Table).

Research showed that there is connection between re-hospitalization and healthcare financing system. Specifically, rate of re-hospitalization is higher when state programs financing patients (68%). Re-hospitalization rate in patients with private insurance is 32%.

Among re-hospitalized patients, 65 patient (63.1%) were re-hospitalized only once, 29 patients (28.2%) were re-hospitalized twice, 5 patient (4.9%) was re-hospitalized four time, 1 patient (1%) was re-hospitalized 5 times.

We have interweaved re-hospitalized patients and the results showed that main reason of re-hospitalization was not fulfilling necessary medical treatment, not fulfilling required medication or terminating medication, by patients' decisions. 33.3% of patient have bought required medications partially, 13.3% did not buy necessary medications at all. Therefore, these patients do not take necessary medications or they just take it partially. Main reason is poverty (caused by unemployment or small pension). 46.6% of respondents think that they cannot effort necessary medications because of financial difficulties. Majority of patients are unemployed or are pensioners (63%), that is why they cannot effort taking expensive medications for long time. Doctors also confirm this assumption. They mention that 60% of discharged patients cannot effort necessary medications. Patients have no financial opportunity to get doctor consultation again or to get preventive medical treatment. It is also interesting that patients usually systematically get consultations from doctors by phone,

Doctors think that is because of financial difficulties, State Health insurance system do not pay outpatient visits fully.

According to doctors, main reason of re-hospitalization is that, patients do not fulfill doctor's prescriptions after discharging from hospital. Research showed that 40% patients who had not fulfill doctor's prescriptions, were turned back to hospital.

Research showed that re-hospitalization mainly is a non-predictive process. Doctors' records confirm this opinion. At the time of discharging patients, doctors confirm improving health of patient; they also mention that predictions may be unfavorable. This happens in case if doctors cannot eradicate health problems of patients and hospitalization becomes necessary.

The role of continuous medical supervision from Family doctor is important for decrease Re-hospitalization rate. According to questionnaire results, 46.7% of patients have not family doctor, 13.3% of patients have family doctor but visits doctor very seldom, and 40% of patients have family doctors and visits them often. 60% of patients prefer to visit to cardiologist of hospital and they do not visit family doctors. 33.3% of patients have not chosen cardiologist for a long-term medical supervision. 20% of patients have their own doctor but visit them very seldom, 46.7% of patients have private doctors and visit them often. This date shows that institution of family doctor has to be developed. Patients mainly prefer hospital cardiologist then family doctors. Patients also have problem of self-care. Sometimes, by the doctor directions patient have to take 10-15 various drugs and very often patients do not fulfill this direction. This problem may be solved with home care service. Patients think that state healthcare system must fully cover dispensary visits of doctors and diagnostic analysis.

According to the hospital cardiologists, 57% of them have no any communication with primary healthcare doctors, which take care of patients after discharging them from hospital.

In this case is a very important deeply informing patient about self-care, fulfilling doctor's prescriptions at time of discharging. Research showed that important reasons of re-hospitalization are, not taking necessary preventive measures after discharging patient and lack of scheduled visits, this happens because of low level of primary health care system. Institution of family doctor is not popular among patients; they simply do not trust family doctors. Patients usually prefer to visit specialists with specific spheres.

Conclusion, Recommendations.
Heart failure patients account for one of the largest group of patients with frequent hospital readmissions.

Primary health care plays a significant role in the reduction of re-hospitalization rate. In this regard, it is important to increase the role, authority and prestige of the family doctor. Study recommended the creation of a monitoring group, which will include cardiologist, family doctor, and nurse to develop collaboration strategy for managing disease. Consistent and coordinated care after discharging patients from hospital decreases re-hospitalization rate. Study Suggested improving the discharge procedure of patients.

It is important to improve dispensary, continuous medical supervision on patients with chronic diseases, to put into practice systematic communication with patients, remind them about doctor visits.

Study recommended expanding outpatient services package in state healthcare programs, especially for patients with chronic diseases. Study suggested improving day care centers, in order to assess the appropriateness of inpatient treatment, which will reduce unnecessary hospitalization and re-hospitalization costs.

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SUMMARY

ROLE OF PRIMARY HEALTH CARE IN RE-HOSPITALIZATION OF PATIENTS WITH HEART FAILURE

Verulava T., Jincharadze N., Jorbenadze R.

Ilia State University. G. Chapidze Emergency Cardiology Center, Tbilisi, Georgia

Re-hospitalization of cardiac patients is a great financial burden not only for healthcare system, but also for patients. Main aim of the research is to identify features and reasons of re-hospitalization and to determine ways of reducing.

Within the Quantitative research, we have analyzed data of re-hospitalized patients during 30 days. Within the qualitative study, in-depth survey of medical staff and patient conducted.

Main reason of re-hospitalization is that patients do not fulfill doctor's prescriptions after discharging from hospital. This is because of financial difficulties and lack of developing family doctor institution in the country. Usually, after discharging patient from hospital, for medical supervision he/she addresses to family doctor very seldom. There is no coordination between family and hospital doctors.

Primary health care plays a significant role in the reduction of re-hospitalization rate. In this regard, it is important to increase the role of the family doctor, to improve procedure of discharging patients, continuous medical supervision on patients, to expand outpatient services package in state healthcare programs, to improve day care centers.

Keywords: primary care, re-hospitalization, family doctor, heart failure.

РЕЗЮМЕ

РОЛЬ ПЕРВИЧНОЙ МЕДИКО-САНИТАРНОЙ ПОМОЩИ В ПОВТОРНОЙ ГОСПИТАЛИЗАЦИИ БОЛЬНЫХ С СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

Верулава Т.Н., Джинчарадзе Н.Н., Джорбенадзе Р.А.

Государственный университет Ильи; Центр неотложной кардиологии им. Г. Чапидзе, Тбилиси, Грузия

Повторная госпитализация кардиологических больных является большим финансовым бременем не только для системы здравоохранения, но и для пациентов. Основной целью исследования является выявление особенностей и причин повторной госпитализации и определить пути сокращения.

В рамках количественного исследования, мы проанализировали данные пациентов повторно госпитализированы в течение 30 дней. В рамках качественного исследования проводилось углубленное собеседование медицинского персонала и пациента.

Основная причина повторной госпитализации в том, что пациенты не выполняют предписания врача после выписки из больницы. Это из-за финансовых трудностей и недоразвития института семейного врача в стране. Как правило, после выгрузки пациента из больницы, он/она для медицинского наблюдения к семейному врачу обращается очень редко, и нет координации между семейного врача и врачей больницы.

Первичная медико-санитарная играет существенную роль в снижении повторной госпитализации. В связи с этим важно повысить роль семейного врача, чтобы улучшить непрерывного медицинского наблюдения на пациентах..

რეზიუმე

პირველადი ჯანდაცვის როლი კარდიოლოგიური პაციენტების რეჰოსპიტალიზაციაში

თ. ვერულავა, ნ. ჯინჭარაძე, რ. ჯორბენაძე

ილიას სახელმწიფო უნივერსიტეტი; აკად. გ. ჩაფიძის სახ. გადაუდებელი კარდიოლოგიის ცენტრი, თბილისი, საქართველო

კარდიოლოგიურ ავადმყოფთა რეჰოსპიტალიზაცია დიდი ფინანსური ტვირთია როგორც ჯანდაცვის სისტემისათვის, ასევე პაციენტებისათვის. კვლევის მიზანია კარდიოლოგიურ პაციენტებში რეჰოსპიტალიზაციის თავისებურებების, მისი გამომწვევი მიზეზების შესწავლა და შემცირების გზების ღონისძიებათა შემუშავება.

თვისებრივი კვლევის ფარგლებში ჩატარდა სამედიცინო პერსონალის ჩაღრმავებული ინტერვიუ. რაოდენობრივი კვლევის ფარგლებში ჩატარდა ექიმების და პაციენტების გამოკითხვა წინასწარ სტრუქტურირებული კითხვარების მეშვეობით, რეჰოსპიტალიზებულ პაციენტთა ავადმყოფობის ისტორიების შესწავლა.

რეჰოსპიტალიზაციის ძირითად მიზეზს წარმოადგენს პაციენტთა მიერ საჭირო სამკურნალო ღონისძიებების არჩატარება. მისი გამომწვევი მიზეზებია ფინანსური სიძნელეები, ასევე, პირველადი ჯანდაცვის სისტემის, კერძოდ, ოჯახის ექიმის ინსტიტუტის ნაკლები განვითარება,რომლის მთავარი ფუნქციაა პაციენტის საავადმყოფოდან გაწერის შემდეგ მასზე უწყვეტი სამედიცინო მეთვალყურეობა. პაციენტი სტაციონარიდან გაწერის შემდეგ იაშვიათად,ან საერთოდ არ მიმართავს ოჯახის ექიმს; არ არის კოორდინირება ოჯახის ექიმსა და საავადმყოფოს მკურნალ ექიმს შორის.

განმეორებითი ჰოსპიტალიზაციის სიხშირის შემცირებაში დიდი მნიშვნელობა ენიჭება პირველადი ჯან-

დაცვის ეფექტური სისტემის არსებობას. ამ მხრივ, უცილებელია, ქვეყანაში ოჯახის ექიმის ინსტიტუტის შემდგომი განვითარების ხელშეწყობა; კოორდინაციის არსებობა კლინიკასა,პაციენტსა და პირველად ჯანდაცვის სისტემას შორის; ბინაზე გაწერისას პაციენტთა ინფორმირებულობის დონის ამაღლება, მათზე საგანმანათლებლო დონისძიებების ჩატარება დაავადების მკურნალობისა და პროფილაქტიკის საკითხებზე; ჯანდაცვის სახელმწიფო პროგრამებში ამბულატორიული მომსახურების პაკეტის გაფართოება.

ОЦЕНКА ЭФФЕКТИВНОСТИ ВНЕДРЕНИЯ ИНФОРМАЦИОНОЙ СИСТЕМЫ 1С: ПРЕДПРИЯТИЕ В СТАЦИОНАРЕ

Баймагамбетова А.А., Кулов Д.Б., Цай А.Е., Кайырбекова К.К., Сакенова М.Н.

Карагандинский государственный медицинский университет, Казахстан

В развитии Республики Казахстан в настоящее время отмечается социально-ориентированное направление. В связи с этим сфера экономических отношений в области здравоохранения остается одной из важнейших в политике государства.

Система здравоохранения, являясь по сути единой структурой, включающей взаимосвязанные и взаимозависимые между собой структуры и организации, единой целью которой является укрепление, поддержание или восстановление здоровья населения

В области здравоохранения Республики актуален ориентир на повышение качества и эффективности медицинского обслуживания. Поэтому в последнее время приняты меры по изменению принципов взаимодействия между государством, лечебно-профилактическими учреждениями, медицинским персоналом и населением. Однако для их реализации требуется ряд действий, учитывающих современную конъюнктуру в сфере экономики и обмена информацией.

Система здравоохранения, с одной стороны, нуждается в увеличении объема финансирования для проведения исследований и внедрения медицинских и управленческих технологий; с другой стороны, необходимо выявлять существующие малоэффективные ресурсы, требующие изменения и повышения эффективности [4], что возможно исключительно путем интеграции инновационных технологий в системе здравоохранения [1-3].

В этой связи современное управление работой медицинских организаций невозможно без применения информационных технологий, которые являются упорядоченной совокупностью методов и способов работы с информацией, включающих в себя получение, как пассивно, так и посредством поиска, анализа, хранения и накопления информации, с последующей ее защитой и передачей. В Казахстане эффективно развиваются локальные медицинские информационные системы и сети: ни одна медицинская организация не работает без использования компьютерной техники, в различной степени отличающиеся по объему информационных систем. В этой связи необходимо отметить, что системы и сети по сей день, в основном, используются исключительно локально, действуя разрозненно в разных направлениях деятельности лечебно-профилактического учреждения (ЛПУ). Фактически на региональном уровне информационные системы охватывают только финансово-экономические службы (бухгалтерия, планово-экономический отдел). Остро стоит вопрос о реальном повышении качества и доступности медицинской помощи, с это целью необходимо проведение комплексной автоматизации максимального объема видов деятельности в учреждениях [5].

На сегодняшний день на рынке информационных услуг отмечается тенденция к увеличению количества медицинских информационных систем, что, по всей вероятности, связано с активно развивающимися технологиями, коммуникациями, оснащение медицинских учреждений автоматизированными медицинскими проборами, в целом, повышением компьютеризации. Информационные системы используются не только в крупных медицинских центрах с большим объемом информации, но и в небольших организациях и отделениях [6,7,15].

В современной практике принципы и направление деятельности информационных систем в медицине основываются на объединении и систематизации электронных записей о больных [9,10,11,13], создании единого архива медицинских данных, их фиксации с целью своевременного ознакомления медицинских сотрудников о результатах работы автоматизированных лабораторий [8,14]. Перспективным для использования представляются возможности создания видеоконференций, дистанционных консультаций, консилиумов и прочих методов обмена информацией посредством сети интернет [12,15].

Одной из информационных систем, обеспечивающих автоматизацию работы медицинского персонала и уменьшение бумажного документооборота является система 1С: Предприятие, адаптированная к медицинским учреждениям. Данная система необходима не только для сокращения времени обмена информацией между сотрудниками, но и используется как информационная основа мониторинга и перспективного планирования развития учреждений здравоохранения.

Управление лечебным учреждением осуществляется путем прямого структурного управляющего воздействия на персонал, работающий в различных отделах. Качество управления отслеживается посредством налаживания обратной связи, с акцентом на основные контрольные точки управления.

В масштабе государства данными контрольными точками являются снижение смертности от заболеваний, увеличение рождаемости, уменьшение числа инвалидности, обеспечение роста численности населения. В рамках работы стационарной помощи основными параметрами являются сокращение сроков госпитализации, что означает уменьшить экономические затраты и увеличить количество пролеченных случаев, повысить квалификацию медицинского персонала. Вышеизложенное невозможно осуществить без получения адекватной информации, характеризующей различные аспекты состояния персонала организации. Ниже приводится разработанная схема управления ЛПУ (рис.).

Для объективной оценки качества врачебной помощи огромное значение имеет социологический опрос мнения работников. Основываясь на данных анкетирования сотрудников различных сфер деятельности организаций здравоохранения, представляется возможным выявлять существующие и ограничивающие качество работы проблемы, влияющие также на приведение в единое русло интересов участников лечебно-диагностического процесса. Подобный мониторинг позволяет своевременно установить обратную связь, предоставляя лицам, участвующим в управлении и организации работы, информацию о текущем состоянии, позитивных и негативных изменениях и процессах в работе, создавая условия для своевременного внесения корректив. В глобальном отношении подобный мониторинг позволяет расширить базу знаний об эффективности управленческой деятельности в сфере здравоохранения.

Исходя из вышеизложенного. целью настоящего исследования является оценка эффективности внедрения информационной системы 1С: Предприятие.

Материал и методы. Информационная система 1С: Предприятие. интегрированная в работу в 2010 году включает в себя платформу и прикладные решения, разработанные на ее основе, для автоматизации деятельности организаций.

Для проведения исследования разработан специальный опросник. Целью опроса являлось изучение мнения медицинских сотрудников относительно изменений в организации после внедрения информационной системы 1С: Предприятие. Исследование проводилось на базе «Областного центра травматологии и ортопедии им. Х.Ж. Макажанова» г. Караганды. В нем приняли участие 138 сотрудников больницы, из них 48 врачей и 90 представителей среднего персонала с опытом работы не менее 5 лет. В учреждении функционирует 7 отделений, в связи с этим распределение опросников проводилось: 7 врачей и 13 медсестер в 6 отделениях, 6 врачей и 12 медсестер в одном отделении. Средний возраст респондентов составил 45 лет. Среди вопросов, присутствующих в анкете, особое внимание уделялось скорости и качеству выполнения заданий, объему обрабатываемой информации на бумажных носителях, вопросам конфликтных ситуаций и заработной платы. Отдельно включен вопрос о сравнении работы до и после внедрения системы. Респонденты дали оценку и описали конкретные параметры и изменения, которые они заметили. Объективная оценка эффективности работы стационара представлена в соответствии с официальными статистическими данными о количестве пациентов, получивших квалифицированную помощь, количестве койко-дней на одного пациента, квалификации медицинского персонала.

Статистическая обработка полученных данных выполнена с использованием программ Excel, Statistica 10,0 (StatSoft, Inc, 2011) для операционной системы Windows 7.

Результаты и их обсуждение. По результатам анкетирования 105 (76%) респондентов выразили мнение о положительном влиянии внедрения программы 1С: Предприятие в работу. 35 (72,3%) врачей и 43 (48%) представителя среднего медицинского персонала отметили уменьшение затрат времени на заполнение бумаг. 7 (13,6%) врачей и 21 (23,0%) медицинская сестра не отметили значительной разницы в работе, объясняя это быстрой адаптацией к изменившимся условиям и недостаточным опытом работы до внедрения в лечебно-диагностический процесс информационной системы. Остальные сотрудники остались недовольными, объясняя свое отрицательное отношение недостаточными навыками работы с компьютерной техникой и трудностями в осваивании программы.

Среди факторов, повлиявших на выполнение обязанностей, врачи (86%) отмечают сокращение объема информации на бумажных носителях и времени на выполнение диагностических мероприятий.

Рис. Общая схема управления ЛПУ

86% врачей и 81% медсестер по вопросам, касающимся изменений уровня мотивации и энтузиазма сотрудников, ответили, что за последние 5 лет этот показатель снизился. Что касается объективных результатов развития медицинского обслуживания, за последние 5 лет количество обслуженного населения увеличилось на 6,8% при уменьшении количества койко-дней на одного пациента на 12%. Заслуживает внимания увеличение количества персонала, повысившего уровень своей квалификации с первой на высшую и со второй на первую категорию.

Социологический опрос показал высокую эффективность внедрения информационной системы 1С:Предприятие в работу медицинского персонала стационарной помощи. Основное изменение, которое стало заметным для персонала - это уменьшение объема бумажной работы и увеличение скорости обмена информацией относительно диагностических процедур. Однако для внедрения системы необходимо повысить уровень компьютерной грамотности служащих. Многие сотрудники, не имеющие опыта работы с компьютерной техникой, недостаточно быстро адаптирующиеся к новым программным системам, испытывали дискомфорт в работе в начале внедрения системы. Опыт работы информационной системы в исследуемом стационаре выявил, что со временем происходит приспособление сотрудников к работе с техникой и в результате увеличивается качество обслуживания и отмечается повышение компьютерной грамотности.

В мировой медицинской практике использование информационных систем обеспечило создание электронной базы пациентов [9,12], упорядочение учета движения лекарственных средств [7], определение объема и видов диагностических процедур, что позволяет рационально планировать работу лечебного учреждения, максимально уменьшая издержки. Необходимо, однако, помнить, что постояннодействующая обратная связь с сотрудниками, оцениваемая не только по личному мнению, но и посредством использования измеряемых контрольных точек, позволяет с достаточной оперативностью корректировать эффективность внедряемой информационной системы.

Таким образом, анализ результатов внедрения в практику здравоохранения информационной системы 1С:Предприятие позволил заключить, что:
1) информационная система позволяет осуществлять учет использования объема и методов диагностических процедур и движения лекарственных препаратов;
2) повышает производительность труда медицинского персонала, сокращает число дней, проведенных в стационаре одним больным, увеличивает количество обслуженного населения;
3) сокращает объем информации на бумажных носителях и время, затрачиваемое на диагностические мероприятия.

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SUMMARY

THE EVALUATION OF THE EFFECTIVENESS OF THE IMPLEMENTATION OF INFORMATION SYSTEM 1C: ENTERPRISE IN THE HOSPITAL

Baimagambetova A, Kulov D., Tsay A., Kairbekova K., Sakenova M.

Karaganda State Medical University, Kazakhstan

The aim of research was to assess the impact of the introduction of information system 1C: Enterprise on the work of medical staff.

It was evaluated staff satisfaction in terms of quality and speed of their duties, as well as sociological changes after the introduction in the work the information system 1C: Enterprise from 2010.

The research involved 138 employees of the hospital, including 48 doctors and 90 nurses with experience of at least 5 years. The average age of respondents was 45 years. The study was conducted through questionnaires, including questions relating to life expectancy, changing the speed and quality of execution of tasks, also attended to questions about the change in the frequency of conflict situations and wages. Separately, it was included open-ended question about the change in the level of motivation before and after the implementation of the information system. Respondents gave the evaluation and describe the specific changes they have noticed. Objective assessment of the effectiveness was evaluated according to the official statistics on the number of people served, the time spent on one patient, the level of qualification of medical personnel.

76% of employees have noted positive changes in the work after the implementation of the information system 1C: Enterprise in the work, there is a change of diagnosis rate, the quality of treatment, 72.3% of physicians and 48% of nurses have noted a decrease in time spent on paperwork. 13.6% of physicians and 23.0% of nurses did not notice any difference. Other members expressed dissatisfaction, because of the necessity of learning of a computer program. After the number of the served population program of work increased by 6.8%, decreased the number of days of hospitalization by 12%.

The use of modern information systems increases the level of health services and health workers, increasing productivity.

Keywords: Management; HR policy; management system; information system; efficiency.

РЕЗЮМЕ

ОЦЕНКА ЭФФЕКТИВНОСТИ ВНЕДРЕНИЯ ИНФОРМАЦИОНОЙ СИСТЕМЫ 1С: ПРЕДПРИЯТИЕ В СТАЦИОНАРЕ

Баймагамбетова А.А., Кулов Д.Б., Цай А.Е., Кайырбекова К.К., Сакенова М.Н.

Карагандинский государственный медицинский университет, Казахстан

Целью исследования явилась оценка влияния внедрения информационной системы 1С: Предприятие на работу медицинского персонала.

Оценена удовлетворенность сотрудников с точки зрения качества и скорости выполнения их обязанностей, а также социологических изменений после начала использования информационной системы 1С: Предприятие, предназначенной для автоматизации работы.

В исследовании приняли участие 138 сотрудников больницы, в том числе 48 врачей и 90 среднего персонала с опытом работы не менее 5 лет, средний возраст респондентов - 45 лет. Исследование проводилось с использованием вопросников о продолжительности службы, изменениях скорости и качества исполнения заданий, частоты конфликтных ситуаций, заработной плате. Отдельно был включен вопрос об изменении уровня мотивации до и после реализации программы. Респонденты дали оценку и описали конкретно происходящие изменения.

105 (76%) сотрудников отметили положительные изменения в работе после реализации программы 1С: Предприятие: отмечалось изменение скорости в диагностике, качестве лечения. 35 (72,3%) врачей и 43 (48%) представителя среднего медицинского персонала отметили уменьшение затрат времени на заполнение бумаг. 7 (13,6%) врачей и 21 (23,0%) медицинская сестра не заметили разницы. Некоторые сотрудники выразили недовольство, в связи с необходимостью освоения компьютерной программой. В результате реализации системы 1С: Предприятие на 6,8% увеличилось количество обслуживаемого населения, на 12% уменьшилось число дней госпитализации.

Использование современных информационных систем повышает уровень медицинских услуг и медицинских работников, в результате - производительность труда.

რეზიუმე

ინფორმაციული სისტემის 1C: საწარმოს სტაციონარში დანერგვის ეფექტურობის შეფასება

ა. ბაიმაგამბეტოვა, დ. კულოვი, ა. ცაი, კ. კაირბეკოვა, მ. საკენოვა

ყარაგანდის სახელმწიფო სამედიცინო უნივერსიტეტი, ყაზახეთი

კვლევის მიზანს წარმოადგენდა ინფორმაციული სისტემის 1 C: საწარმო დანერგვა და მისი შეფასება სამედიცინო პერსონალის სინამდვილეში.

კვლევაში მონაწილეობა მიიღო 138 პირმა, მათ შორის 48 ექიმი და 90 საშუალო პერსონალის წარმომადგენელი, საშუალო ასაკი – 45 წელი, მუშაობის სტაჟი – 5 წელი. კვლევაში გამოყენებული იყო კითხვარი, რომელიც მოიცავდა შემდეგ კითხვებს: სამსახურის ხანგრძლივობის, დავალების შესრულების დროის და ხარისხის შესახებ, ასევე კონფლიქტური სიტუაციების არსებობისა და შრომის ანაზღაურების შესახებ. ცალკე კითხვა იყო ინფორმაციული სისტემის 1C: საწარმო-ს დანერგვის შემდეგ კვლევის მონაწილეთა მოტივაციის შეცვლის შეფასება. 105 (76%) რესპოდენტმა აღნიშნა დადებითი ცვლილებები მუშაობაში სისტემის დანერგვის შემდეგ; სწრაფი დიაგნოსტიკის, მკურნალობის ხარისხის მიმართებით. 35 (72%) ექიმმა და 43 (48%) საშუალო პერსონალის წარმომადგენელმა დადებითად შეაფასა სამუშაო დროს ეკონომია სხვადასხვა ქაღალდების შევსებაზე. 7 (13%) ექიმმა და 21 (23%) მედპერსონალის წარმომადგენელმა გამოთქვა უკმაყოფილობა კომპიუტერული პროგრამების შეთვისების სიძნელის გამო. კვლევის შედეგად მიღებული მონაცემებიდან გამომდინარე, სტატიის ავტორებს გამოტანილი აქვთ დასკვნა, რომ ინფორმაციული სისტემის 1C: საწარმო-ს რეალიზაციის შედეგად რადიკალურად გაიზარდა მომსახურებული მოსახლეობის რაოდენობა და მომსახურების ხარისხი, შემცირდა სავადმყოფოში ყოფნის ხანგრძლივობა 12%-ით. კვლევის შედეგებით

გამოვლინდა,რომ საინფორმაციო სისტემის დანერგვას ჯანდაცვის დაწესებულებებში დიდი შედეგი აქვს,რო-გორც მომსახურე პერსონალის მუშაობისათვის,ასევე ავადმყოფების უკეთესი მომსახერეობისათვის.

УСЛОВИЯ ТРУДА И СОСТОЯНИЕ ЗДОРОВЬЯ РАБОТНИКОВ ТБИЛИССКОГО МЕТРОПОЛИТЕНА

Хунашвили Н.Г., Цимакуридзе Мар.П., Бакрадзе Л.Ш., Хачапуридзе Н.А, Цимакуридзе Майя П.

Тбилисский государственный медицинский университет, департамент гигиены окружающей среды и профессиональной медицины, Грузия

Комплексное изучение условий труда занятого населения является основой для установления вредности и опасности производственной среды и трудового процесса, приоритетов профилактических оздоровительных мероприятий в конкретной профессии и на конкретном рабочем месте, что является предпосылкой повышения эффективности задач, стоящих перед медициной труда [1,6,8,11] и является не только медицинской, но и значимой социально-экономической проблемой [7,9].

На современном этапе развития общества большинство сфер профессиональной деятельности человека по сей день характеризуется наличием комплекса неблагоприятных факторов, отрицательно влияющих как на здоровье работающих, так и на качество их жизни [5,10]. Сказанное в равной мере касается как сферы производства, так и обслуживания, в том числе, обслуживания транспортных средств.

В современных мегаполисах в деле решения социальных, в том числе, транспортных проблем, важное место занимает такое массовое транспортное средство, как метрополитен, являясь фактически, ведущим видом внутригородского транспорта.

Для метрополитена, как и для любой сферы производственной и бытовой деятельности человека, свойственно образование определенных факторов, влияющих на его работоспособность и состояние здоровья работников этой сферы, что подтверждает актуальность данной проблемы и заинтересованность в ней специалистов медицины труда [3,4].

Целью исследования явилось изучение условий труда и состояния здоровья работников Тбилисского метрополитена и разработка профилактических мероприятий.

Материал и методы. С целью оценки условий труда работников Тбилисского метрополитена проведены соответствующие гигиенические исследования на базе данного объекта. В частности, изучены содержание пыли (269 определений) и токсических веществ (372 анализов) в воздухе рабочих зон, параметры микроклимата (2575 замеров), а также уровни шума (86 определений), вибрации (44 определений) и освещения (73 замеров). Проведен анализ показателей трудового процесса (3419 наблюдений). На основании анализа результатов проведенных исследований с применением соответствующих национальных нормативных документов проведена гигиеническая оценка состояния изученных показателей и разработана гигиеническая классификация условий труда работников основных профессий данного объекта.

Для оценки влияния имеющихся на изученном объекте условий труда на здоровье работников проведены комплексные клинико-функциональные и лабораторные исследования, в частности, общеклинические обследования – изучение терапевтического, неврологического, офтальмологического статусов, показателей проходимости бронхов методом пневмотахометрии (по Б.Е. Вотчалу), электрокардиография в 12 стандартных отведениях, общеклинические и биохимические анализы крови (уровень сахара в крови и индекс протромбина), по показаниям – рентгенография.

Обследовано 150 работников Тбилисского метрополитена, разделившихся на 2 группы по характеру профессионального контакта с производственными вредностями: 1) I группа (основная) – лица, контактирующие с ведущими производственными факторами (n=115); II (контрольная) – работающие на данном объекте, но не имеющие контакта с производственными вредностями (n=35).
Полученный цифровой материал обработан с применением методов биостатистики.

Результаты и их обсуждение. Анализ результатов проведенных гигиенических исследований показывает, что условия труда работников Тбилисского метрополитена характеризуется комплексом неблагоприятных факторов производственной среды и трудового процесса.

В комплексе факторов производственной среды ведущими являются факторы физического характера – механические колебания (шум и вибрация), а также неблагоприятное освещение. Уровень шума зависит от интенсивности движения подвижного состава. Максимальный уровень звукового давления регистрируется в кабине машиниста при движении поезда (108 ДбА), что на 28 ДбА превышает предельно допустимый уровень (ПДУ – 80 ДбА). На 3 ДбА выше ПДУ уровень шума в машинном зале и в помещениях вспомогательной службы, на 5 ДбА – в нижнем коридоре перрона; в распределительном зале и в комнате дежурного уровень шума превышает ПДУ на 2 ДбА, когда двери открыты, а при стоянии поезда уровень шума находится в пределах ПДУ.

Повышение уровня звука в основном регистрируется на средних и высоких частотах (500÷1000 Гц) и на тех же рабочих местах. При движении поезда в кабине машиниста в октавной полосе 8000 Гц его уровень на 37 дБ превышает ПДУ (ПДУ – 69 дБ), а в помещениях вспомогательной службы – на 19 дБ (рис. 1). С учетом этого показателя условия труда оцениваются, как 3.4. и 3.1 классы вредности, соответственно.

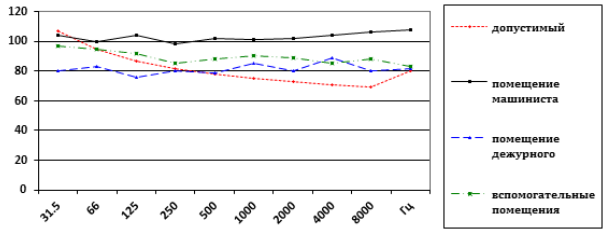

Рис. 1. Уровни шума (дБА) в основных помещениях Тбилисского метрополитена

Общая вибрация генерируется в машинном зале эскалаторов, в помещениях машиниста и дежурного. В большинстве случаев на всех измеренных частотах ее уровни повышены. В частности, в комнате машиниста ее уровень на 14-20 дБ превышает ПДУ при движении поезда, а при остановке поезда – на 3-9 дБ. Источником генерации вибрации является работа эскалаторов: в машинном зале эскалаторов при одновременной работе двух эскалаторов уровень вибрации на высокой частоте (63 Гц) лишь на 1 дБ превышает ПДУ; а при одновременной работе трех эскалаторов уровень вибрации на частотах 31,5 и 63 Гц - на 1 и 3 дБ, соответственно (рис. 2). По этому показателю Условия труда оцениваются, как 3.1, 3.4. и 3.2 классы вредности, соответственно.

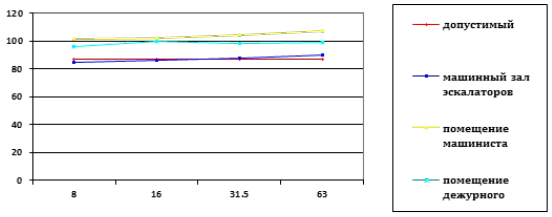

Рис. 2. Уровни вибрации (дБ) рабочего места в основных помещениях Тбилисского метрополитена

Исходя из специфики метрополитена, для освещения его помещений используется искусственное освещение, источником которого являются газоразрядные лампы низкого давления (люминесцентные). Естественное освещение употребляется только в наземных станциях, в некоторых их помещениях, а также в верхнем вестибюле каждой станции.

В помещениях нижнего вестибюля и в распределительном зале уровень искусственного освещения по показателю освещенности находится в пределах нормы (уровни удовлетворенности нормы составляют 107 и 113%, соответственно). На других рабочих местах его уровни ниже нормируемых величин. Самые низкие уровни освещения регистрируются в помещении кассира и в машинном зале эскалаторов (88 и 90% нормируемых величин, соответственно). Данные рабочие места характеризуются высокой точностью зрительной работы (III разряд), а при выполнении зрительной работы IV-VI разрядов уровень искусственной освещенности находится в пределах 90-95% нормируемых величин. Длительная работа в таких условиях отражается на работоспособности и состоянии здоровья работающего контингента. По этому показателю условия труда относятся к 3.1 классу вредности.

Основными причинами низкого уровня искусственного освещения производственных помещений являются нерациональное размещение осветительных арматур, использование источников света низкой мощности по сравнению с расчетными величинами, нерегулярная смена вышедших из строя источников света и т.д. Основными причинами дефицита естественного света в помещениях являются недостаточная площадь светоприемных сечений, а также их неудовлетворительное санитарное состояние.

Запыленность воздуха производственных помещений является значительной на большинстве рабочих местах. Так, в воздухе механического цеха службы сигнализации и связи содержание пыли превышает ПДК (ПДК – 10 мг/м^3) в 3,4 раза (3.2. класс вредности). К этому же классу относятся концентрации пыли камня и цемента при работе ремонтника путей службы путей и тоннелей - в 2,7 раза выше ПДК (ПДК – 6 мг/м^3), при обработке металла в механическом цехе службы движения – в 2,2 раза выше ПДК (ПДК – 6 мг/м^3). В этом же цехе при обработке материала запыленность воздуха частицами корунда и карборунда в 2,3 раза превышает ПДК (ПДК – 6 мг/м^3). В воздухе большинства рабочих мест содержание пыли соответствует 3.1 классу вредности. По этому показателю условия труда допустимому уровню соответствуют только на 7 рабочих местах. Следует отметить, что по изученному показателю, по средним данным, условия труда 3.3 и 3.4 классов вредности не установлены.

Пыль является высокодисперсной – частицы размером меньше 5 мкм составляют 68,5% общего количества пылинок с содержанием свободного диоксида кремния в пределах 3,4-7,8%.

Воздух рабочей среды характеризуется разнообразием и значительными концентрациями токсических веществ. Особенно опасен для здоровья марганец (I класс опасности), в виде аэрозоля конденсации, концентрации которого в воздухе рабочих мест сварщиков, токарей и слесарей объединенных мастерских в 5,2 раз превышают ПДК (ПДК – 0,05 мг/м^3) и соответствуют 3.2 классу вредности. К этому же классу опасности относится свинец, в виде пара, концентрации которого в воздухе некоторых рабочих мест превышают ПДК (ПДК – 0,01 мг/м^3) в 1,3-2,7 раза, что соответствует 3.1 классу вредности.

Высокие концентрации (4 раза выше ПДК) ксилола (IV класс опасности) обнаруживаются в воздухе механических цехов депо Глдани и Надзаладеви. В воздухе рабочих зон объединенных мастерских концентрация толуола (III класс опасности) в 4,1-6,5 раз превышает ПДК (ПДК – 50 мг/м^3), а концентрация бензола (II класс опасности) в 4,0 раза превышает ПДК (ПДК – 15 мг/м^3). В воздухе большинства рабочих мест концентрации исследуемых химических веществ соответствуют 3.1 классу вредности.

Формированию повышенных концентраций пыли и токсических веществ в воздухе основных рабочих мест Тбилисского метрополитена способствуют характер технологических

операций и обрабатываемого материала, а также организационное решение конкретного рабочего места (структура и уровень эффективности вытяжной вентиляции).

В связи с отсутствием источников тепловой энергии, формирование микроклимата зависит от периода года. В теплый период года в подземных помещениях средние величины температуры воздуха находятся в пределах 22,5-26,2^{0}C, при колебании от 16,4 до 33,4^{0}C. В общем, в 5,2% замеров показатели температуры воздуха превышают допустимую величину, предусмотренную для работ средней тяжести (28^{0}C). Величина температуры воздуха ниже допустимой (16^{0}C) в теплый период года не фиксируется.

В холодный период года средние величины температуры воздуха составляют 14,1÷22,0^{0}C, при колебании от 9,9 до 26,8^{0}C. В 5,9% случаев ее величины ниже допустимой (16^{0}C).

Средние величины относительной влажности воздуха превышают верхний предел оптимальных величин (60%) и составляют 59-73%. В теплый период года ее абсолютные величины колеблятся от 32 до 89%, а в холодный период года - в пределах от 26 до 86%. Наличие сравнительно высоких показателей влажности воздуха в подземном пространстве является вполне естественным.

Показатели скорости движения воздуха характеризуются низкими величинами - ниже 0,1 м/сек.

В целом состояние производственного микроклимата соответствует 2 и 3.1 классу вредности.

При комплексной оценке состояния условий труда работников Тбилисского метрополитена следует учесть характер рабочего процесса. В частности, среди этих факторов ведущими являются психоэмоциональная напряженность трудового процесса, работа в условиях дефицита оперативного времени и т.д. Длительная работа в таких условиях производственной среды и трудового процесса должна оказывать определенное влияние на психофизиологическое состояние работников и показатели их здоровья.

На основании комплексных гигиенических исследований разработана гигиеническая классификация условий труда работников основных профессий Тбилисского метрополитена. С учетом всех изученных факторов, на основании итоговой оценки, особенно неблагоприятное состояние условий труда установлено в кабине машиниста, где отмечаются экстремальные условия труда – 4 класса вредности. Ее определяющими факторами являются шум и вибрация – 3.4 класса вредности. В распределительном зале, на рабочем месте дежурного контроллера условия труда соответствуют 3.1 классу вредности. На других рабочих местах условия труда оцениваются 3.2 классом вредности.

Как и ожидалось, в результате изучения состояния здоровья работников данного объекта, выявлен целый ряд нарушений, связанных с воздействием неблагоприятных условий труда. В частности, установлено, что удельный вес практически здоровых лиц самим низким был среди линейных машинистов (3,4 случая на 100 обследованных, P<0,001), слесарей (7,7, P<0,001) и монтёров путей (11,8, p<0,001). Следует отметить, что среди обследованных сварщиков практически здоровые лица не обнаружены (рис. 3).

Рис. 3. Распределение практически здоровых лиц Тбилисского метрополитена по профессиям (на 100 обследованных)

В целом по объекту количество болевших лиц составляет 154,8 на 100 обследованных (в контрольной группе – 34,2). Количество болевших лиц в основной группе в 4,5 раза больше по сравнению с контрольной группой (t=13,5, p<0,001). У обследованных в основной группе 115 лиц установлено наличие 243 нозологических форм, что составляет 211,3 случая на 100 обследованных. Аналогичный показатель в контрольной группе составляет 15 случаев (42,9 на 100 обследованных). Таким образом, количество выявленных болезней в основной группе в 4,9 раз выше по сравнению с контрольной группой (t=12,4, p<0,001).

Выявление эффектов здоровья среди работников основных профессий и отсутствие данных патологий среди лиц контрольной группы, которые не имеют профессионального контакта с факторами риска, установленных на основании гигиенических исследований, указывает на причинно-следственную связь между этими двумя явлениями и диктует необходимость гигиенических регуляций.

В формировании структурных особенностей состояния здоровья работников Тбилисского метрополитена ведущими являются патологии сердечно-сосудистой, нервной и пищеварительной систем.

Уровень всех выявленных основных нозологических форм значительно выше в основной группе по сравнению с соответствующим показателем контрольной группы. Различие этих показателей отличается высокой степенью достоверности – p<0.001 (t=2.5-5.2). Структура выявленных заболеваний в основной и контрольной группах статистически достоверно отличается друг от друга – $\chi^2_{0,01}$=36. Таким образом, очевидно влияние условий труда Тбилисского метрополитена на формирование структурных особенностей выявленных нозологических форм.

Среди выявленных болезней ведущей является патология сердечно-сосудистой системы (в основном, в виде артериальной гипертензии) – 49,6 случаев на 100 обследованных (в 2,9 раза чаще по сравнению с контрольной группой – p<0,001); на втором месте находятся болезни нервной системы (в основном, неврастенический синдром и хронический пояснично-крестцовый радикулит) – 40,9 (в контрольной группе в 2,8 раза ниже – p<0,01), а на третьем – болезни пищеварительной системы (хронический холецистит, гастрит, колит; язвенная болезнь желудка и двенадцатиперстной кишки) – 28,7 случаев. Вместе с тем, в основной группе часто выявляются болезни опорно-двигательного аппарата (8,7 – p<0,01), органов дыхания (6,1 – p<0,01), мочеполовой системы (5,2 – p<0,01) и органа зрения (6,1 – p<0,01). В контрольной группе патология дыхательной, костно-суставной и мочеполовой систем, а также органа зрения не выявлена.

Болезни сердечно-сосудистой системы чаще всего фиксируются у монтеров пути (82,4 случаев – P<0.001), слесарей и

сварщиков (53,8 – p<0,05), а также (такой-же частотой) – у машинистов эскалатора и тоннельных рабочих (50,0 – p<0,05); в контрольной же группе встречается в 17,1 случаях на 100 обследованных (рис. 4).

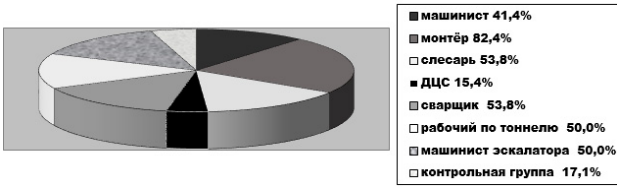

Рис. 4. Распределение болезней сердечно-сосудистой системы среди работников Тбилисского метрополитена по профессиям (на 100 обследованных)

Болезни нервной системы чаще всего выявляются среди машинистов линий (51,7 случаев на 100 обследованных – p<0,001) и у монтеров пути (4,1% – p<0,05), слесарей и дежурных центральной станции (ДЦС) (46,2% – p<0,05), машинистов эскалатора (43.8% – p<0.05). Болезни этой системы вовсе не выявлены среды сварщиков, а в контрольной группе выявляемость данной патологии на уровне 14,3 случаев на 100 обследованных (рис. 5).

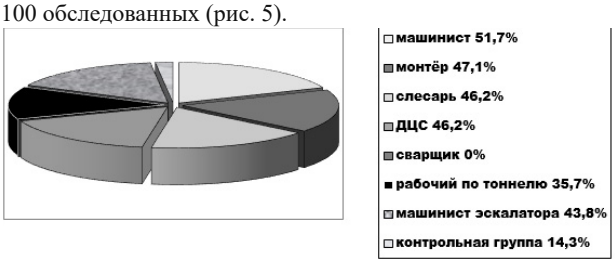

Рис. 5. Распределение болезней нервной системы среди работников Тбилисского метрополитена по профессиям (на 100 обследованных)

Частота болезней пищеварительной системы больше всех среди машинистов эскалатора (43,8 – p<0,01), слесарей (38,5 – p<0,01) и линейных машинистов (34,5 – p<0,01). В отличие от основной группы, в контрольной группе фиксируется низкий уровень болезней пищеварительной системы – 2.9 случаев на 100 обследованных (рис. 6).

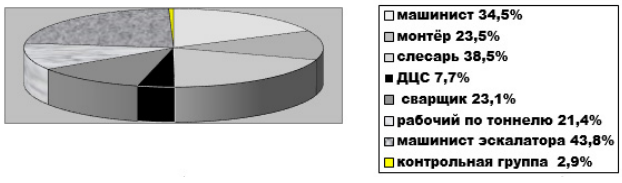

Рис. 6. Распределение болезней пищеварительной системы среди работников Тбилисского метрополитена по профессиям (на 100 обследованных)

По отдельным профессиям ведущими являются: патология дыхательной системы – у линейных машинистов (10,3 – p<0,05), костно-суставной системы – у слесарей (30,8 – p<0,05) и тоннельных рабочих (14,3 – p<0,05). Высок уровень болезней органа зрения у линейных машинистов (13,8 – p<0,05), мочеполовой системы – у линейных машинистов (13,8 – p<0,05) и слесарей (15,4 – P<0,05), что следует объяснить обусловленной особенностями трудового процесса напряженностью и наличием конкретных факторов риска на рабочем месте.

Анализ результатов проведенных клинико-функциональных исследований подтверждает, что под воздействием сформировавшихся в Тбилисском метрополитене комплексов профессиональных факторов в организме работающих развиваются определенные функциональные и органические изменения. Среди них превалируют болезни сердечно-сосудистой, нервной и пищеварительных систем. В развитии этих болезней определенную роль играют такие производственно-профессиональные факторы, как производственная пыль, токсические вещества, шум и вибрация. Выявленные среди работников большинства профессий повышенные уровни болезней пищеварительных органов обусловлены, по-видимому, нерациональным питанием.

Таким образом, на основании проведенными нами комплексных гигиенических, клинико-функциональных, лабораторных и биостатистических исследований установлены определенные закономерности формирования условий труда и состояния здоровья работников Тбилисского метрополитена и причинно-следственные связи между условиями труда и отдельными показателями состояния здоровья, что послужило основой для разработки комплексных профилактических мероприятий.

Выводы:

1. На основании анализа результатов комплексных исследований установлено неблагоприятное состояние условий труда и здоровья работников Тбилисского метрополитена;
2. На основании гигиено-клинических сопоставлений установлено наличие причинно-следственных связей между условиями труда и состоянием здоровья;
3. Полученные результаты является основой для разработки целенаправленных комплексных оздоровительных мероприятий с целью улучшения условий труда и, исходя из этого, для обеспечения высокого уровня работоспособности и сохранения здоровья работающих метрополитена.

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SUMMARY

WORKING CONDITIONS AND STATE OF HEALTH OF TBILISI SUBWAY EMPLOYEES

Khunashvili N., Tsimakuridze Mar., Bakradze L., Khachapuridze N., Tsimakuridze Maya

Tbilisi State Medical University, Department of Environmental Health and Occupational Medicine, Georgia

For the purpose of preventive events complex hygienic, clinical-functional, laboratory and biostatic researches are implemented on the basis of Tbilisi Subway. Conditions of work are characterized by complex of unfavorable factors of the working environment and the labor process. Working environment is characterized by combination of unfavorable state of physical factors and air pollution with dust and toxic substances. The levels of noise and vibration refer to the 3.4 class of harmfulness. The content of dust and toxic substances corresponds to 3.1-3.2 classes of working conditions harmfulness. In the indexes of health status, the leading diseases are pathology of cardiovascular, nervous and digestive systems. Cause-effect relationships between working conditions and individual health indicators have been already established, which served as the basis for the development of comprehensive preventive health measures.

Keywords: subway, conditions of work, functional state, health condition, prevention.

РЕЗЮМЕ

УСЛОВИЯ ТРУДА И СОСТОЯНИЕ ЗДОРОВЬЯ РАБОТНИКОВ ТБИЛИССКОГО МЕТРОПОЛИТЕНА

Хунашвили Н.Г., Цимакуридзе Мар.П., Бакрадзе Л.Ш., Хачапуридзе Н.А, Цимакуридзе Майя П.

Тбилисский государственный медицинский университет, департамент гигиены окружающей среды и профессиональной медицины, Грузия

С целью разработки профилактических мероприятий проведены комплексные гигиенические, клинико-функциональные, лабораторные и биостатические исследования на базе Тбилисского метрополитена. Условия труда характеризуется комплексом неблагоприятнх факторов производственной среды и трудового процесса. Производственная среда характеризуется сочетанием неблаприятного состояния физических факторов с загрязнением воздуха пылью и токсическими веществами. Уровни шума и вибрации относятся к 3.4 классу вредности. Содержание пыли и токсических веществ соответствует 3.1-3.2 классам вредности условий труда. В показателях состояния здоровья ведущими являются патология сердечно-сосудистой, нервной и пищеварительной систем. Установлены причинно-следственные связи между условиями труда и отдельными показателями состояния здоровья, что послужило основой для разработки комплексных профилактических оздоровительных мероприятий.

რეზიუმე

თბილისის მეტროპოლიტენის მუშაკთა შრომის პირობები და ჯანმრთელობის მდგომარეობა

ხუნაშვილი ნ., ციმაკურიძე მარ., ბაქრაძე ლ., ხაჭაპურიძე ნ., ციმაკურიძე მაია

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის გარემოს ჯანმრთელობისა და პროფესიული მედიცინის დეპარტამენტი, საქართველო

თბილისის მეტროპოლიტენის მუშაკთა შრომის პირობებისა და ჯანმრთელობის გამაჯანსაღებელი ღონისძიებების შემუშავების მიზნით ჩატარდა კომპლექსური ჰიგიენური,კლინიკურ-ფუნქციური,ლაბორატორიული და ბიოსტატისტიკური კვლევები. შრომის პირობები ხასიათდება საწარმოო გარემოსა და შრომის პროცესის არახელსაყრელი ფაქტორების კომპლექსით. ხმაურისა და ვიბრაციის დონე შეფასდა მავნეობის 3.4 კლასით. ჰაერში მტვრისა და ტოქსიკური ნივთიერებების შემცველობა შეესაბამება შრომის პირობების მავნეობის 3.1-3.2 კლასებს. ჯანმრთელობის მდგომარეობის მაჩვენებლებში წამყვანია გულ-სისხლძარღვთა, ნერვული და საჭმლის მომნელებელი სისტემების დაავადებები. დადგინდა მიზეზ-შედეგობრივი კავშირები შრომის პირობებსა და ჯანმრთელობის მდგომარეობის ცალკეულ მაჩვენებლებს შორის, რაც საფუძვლად დაედო კომპლექსური პროფილაქტიკური გამაჯანსაღებელი ღონისძიებების შემუშავებას.