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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

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

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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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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

CHRONIC MYELOID LEUKEMIA EXPECTED RELAPSE'S CLINICAL-LABORATORY INDEXES

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Chronic myeloid leukemia (CML) belongs to the group of chronic myeloproliferative diseases. It develops as a result of the malignant transformation of the polypotent stem cell, during which the myelopoesis on one or several lines shows clone proliferation with kept differentiation feature.

In the CML pathogenesis the trigger mechanism is somatic mutation of stem cell. The reason for mutation is translocation between chromosomes 9 and the 22. As a result the novel fusion gene is created (gene BCR-ABL). As a result of this translocation, with BCR gene fragment from the 22-th chromosome and ABL-gene fragment from the 9-th chromosome is created chimeric oncogene on the 22-th chromosome (ph-chromosome). The chimeric gene produces protein 210 (p210), rarely – p185 or p190. Because protein ABL contains tyrosine-kinase domain, the mutant gene product also is tyrosine-kinase with increased activity, after which cell's normal functioning is breached.Stem cell undergoes mutation and unrestrained proliferation [6].

Physiological cause of CML is the BCL-ABL gene's Bcr-Abl protein activity. Study of the Bcr-Abl protein tyrosine-kinase activity made it possible to create the target-therapy, giving the possibility to the scientists to specifically inhibit this activity using the tyrosine-kinase inhibitors (TKI). This medication can develop complete remissions in CML [3,4].

Diagnosis of the Chronic myeloid leukemia is based on ph-chromosome and BCR-ABL gene discovery using the cytogenetic, Fish (fluorescent hybridization method in situ) and PCR (polymerase chain reaction) methods [1].

Modern method of the CML treatment is the target-therapy, including inhibition of tyrosine-kinase activity inmalignant cells. It results decreasement of leukemic cells reproduction and tumor-causing protein quantity. Accordingly ph+ cells are decreased to minimum. [3,4].

`There are no clinic recommendations for stopping treatment in CML. The treatment can be stopped only in case and in the institution, where there is well-controlled research possibility. If there is IS-RQ-PCR test – the most sensitive accurate test for finding CML's leukemic cells in bone marrow and peripheral blood [2,5].

BCR-ABL tyrosine-kinase first selective inhibitor, used successfully today for CML treatment, is the Imatinib (Gleevec). As a result of the treatment in most cases there is remission, which, first of all, is clinical-hematologic (when there are no signs of the disease manifestation, i.e., when the liver and spleen sizes and peripheral blood indices become normal). Second, it is cytogenetic remission, when Philadelphia chromosome-positive cells are not found (ph+ is 0%). Third, the molecular remission, when using the molecular methods show no BCR-ABL pathologic gene (measured is BCR and ABL gene transcript level). [5].

Proceeding from that there are several levels of remission, there are different relapse levels, hematologic (when different organs are damaged and changes are in peripheral blood test), cytogenetic (when ph+ cells are found) and other molecular (when once more occurs transcript of BCL and AB gene).

Despite the type of the remission treatment with Imatinib is held permanently and the treatment is stopped only in cases there are complications concerning the medication use.

During treatment is necessary the leukemic cells number monitoring – with peripheral blood test, ph+ positive cells determination in bone marrow with cytogenetic research and BCR ABL gene transcript determination with molecular research [4,5].

Karyotyping is to be held in the period of hematologic remission in 3-rd and 6-th month and further every 6 month before getting the major cytogenetic response. After that, if the remission molecular assessment cannot be done – in every 12 months.

Research has established, that BCR-ABL gene transcript expression level in peripheral blood test is correlated with bone marrow's ph+ positive leukemic cells number and thus, using it, the remission monitoring is used to finally assess the CML's treatment answer – when the leukemic cell's residual number is lower than the level, found by cytogenetic research. [1].

Trully, the molecular-genetic methods better show the disease relapse (leukemic cells expression) and tell us about the undesirable condition, but such research is held by plan (once in 6-12 months or rarely) and their implementation materially and technically is not always possible. That's why the mentioned researches cannot be held for all the patients with frequency used in the world practice. As for the hematologic remission indexes (peripheral blood test and liver and spleen sizes), their monitoring during CML treatment is held monthly.

The goal of our work was detection of those clinical-laboratory changes at the CML hematologic relapse, which indicated the expected relapse, and proceed-

ing from this, showed us the necessity to hold the urgent cytogenetic-molecular researches.

Material and methods. In the Institute of Hematology and Transfusiology we have retrospectively checked clinical-laboratory data of 64 patients in the years 2003-2016. After treatment using Imitinib patients who were in remission in the period of January-April, 2017 had underwent program BCR and ABL gene percentage number detection by PCR (polymerase chain reaction) method.

According to the molecular research results, the patients were split on three groups: I – BCR-ALB gene expression less than 0,1% cells – low risk group; II – (-0,1-1,0% cells) medium risk group; III – (more than - 1% cells) – high risk group.

In the groups before the molecular research we analyzed retrospectively the condition of the patients (sizes of liver and spleen), peripheral blood indices (attention was paid to anemia, leykocytosis, thrombocytopenia, thrombocytosis, leukemic cells, eosinophilia and basophilia), remission duration, Imatinib dose decrease or irregular self-taking in.

As a result of treatment with Imatinib out of 64 patients with hematologic remission low expression of BCR and ABL gene (less than 0,1%) was found in 38 (59,3%) (low risk group) patients (Table 1).

Maximal duration of remission was 13 years, minimal – 2,5 years. In all cases, treatment with Imatinib was held with daily dose 400-600 mg. Doctor decreased the dose from 600 to 400 mg in 6 cases, because of the developed thrombocytopenia, and treatment after the 6-year remission was stopped by one patient because of pregnancy, in this case the disease became in chronic stage and after restored treatment the remission was achievedand it lasts 2 years. In the remission period hepatomegalia was found in 3 (7,9%) patients, and splenomegalia was not found at all.

Anemia (within HB 90,0-100,0 gr/l) as the treatment began, and during the remission period was found in 8 patients, during the treatment process was developed in 4 patients, and in total 12 patients (31,6%) had anemia. Mild leukocytosis during different periods was found in 3 patients, 6 patients had mild thrombocytopenia (140,0-160,0x10^9l). Thrombocytosis during the remission period was not found.

Eosinophilia (7-12%) was found in 12 patients (31,6%), leukemic cells and basophilia – were found in no case. Analyses of clinical-laboratory data for group wich patients express low BCR ABL gene quantity showed, that in this group during the remission period rather high frequency had anemia, periodic thrombocytopenia, leykocytosis and eosinophilia and this showed no expected remission breach, because in all cases despite the mentioned changes was received complete molecular response.

Moderate expression of the BCR ABL gene (up to 1%) was expressed in 8 (12,5%) patients (moderate risk group) their clinical-laboratory data see in Table 2.

In moderate risk group remission duration was 1-6 years. Treatment with Imatinib was held using the 400-600 mg. daily dose. One patient in the group stopped the treatment by 3 months after 4 years of remission and restored the treatment 6 month earlier before the molecular research. During this period hematologic remission was not breached.

Hepato-splenomegaly was not expressed in any case. Anemia and thrombocytopenia during the whole remission period was found in 2 out of 8 (25%) patients, and 2 (25%) patients 4 months before the molecular research showed thrombocytosis (600,0x10^9l), because of it in both cases the Imatinib daily dose was increased from 400 to 600 mg and in both cases the thrombocytes number became normal.

Because of low number of the patients in the moderate risk group, we could not get the significant results. However, the attention was paid to the 2 (25%) cases there was thrombocytosis, which was easily overcome by Imatinib increased dose.

In the high risk group (BCR - ABL gene high expression (1-67%)) were 18 (28.1%) patients (Table 3).

Remission duration was 0,5-14 years. 8 out of them (4,4%) stopped the treatment several times by themselves (7 patients periodically during 2-7 months, one patient – after 10years of remission – during 3 years) in this group hepatomegaly had 4 patients, splenopmegaly (170-180 mm) and leukocytosis (WBC– 44,0-120,0x10^9l) because of the disease relapse had 2 patients. One patient – for 7 months, the second one – after the three-year treatment stop (after the treatment restoration both of them had hematologic remission). Both patients had also the leukemia cells in blood and basophilia. Eosinophilia was shown in 6 (33,3%) cases, moderate anemia (within HGB- 90-100,0 g/l) was found in 6(33,3%) patients. Thrombocytopenia – was found in 4 (22,2%)cases, because of this Imatinib dose was from 600 to 400 mg. 12 (66,7%) patients before the molecular research – during one year showed high thrombocytosis (600,0-1200,0x10^9l), 8 out of them had the treatment regime breach, and 4 patient had thrombocytosis despite the regular treatment.

We should notice, that in the high risk group there were 4 patients, having no clinical-laboratory changes during the whole remission period and they underwent regular treatment in 2 patients remission duration was 6 months before the molecular research , the third had remission of 3 years, the fourth – during 4 years).

Thus, as a result of retrospective analyses of the high risk group clinical-laboratory changes we have found, that patients of this group showed anemia and thrombocytopenia insignificantly. Splenomegaly, leykocytosis, leukemic cells and basophilia were expressed only in connection with disease relapse only (in one case – three years, the second one -7 months after the treatment termination). Special attention was drawn to the patients in high risk group which had high thrombocytosis (66,7%), 70% of patients periodically terminated the Imatinib intakes, 2.2% during the whole remission process stopped no treatment.

Table 1. Clinical-laboratory data of treatment with Imatinib

Group	patients number	remission duration, years	imatinib dose daily	daily dose decreasement	non-reg. preparation intake	hepato-megaly	splenomegaly	anemis	leycocytosis	thrombocytopenia	thrombocytosis	leukemic cells	eosinophilia	baasophilia
low risk group	38 59,3%	2,5-13	400-600 mg	6 caused by thrombocytopenia	1	3 7,9%	-	12 31,6%	3 7,9%	6 15,8%	-	-	12 31,6%	-

Table 2. Clinical-laboratory data of moderate risk group patients

Group	patients number	remission duration, years	Imatinib daily dose	Daily dose decreasement	non-reg. preparation intake	hepato-megaly	splenomegaly	anemis	leycocytosis	thrombocytopenia	thrombocytosis	leukemic cells	eosinophilia	baasophilia
moderate risk group	8 12,5%	1-6	400-600 mg	-	1	-	-	2 25%	-	2 25%	2 25%	-	-	-

Table 3. The clinical-laboratory data of high risk group patients

Groups	patients number	remission duration, years	Imatinib dayly dose	Daily dose decreasement	non-reg. preparation intake	hepato megaly	splenomegaly	anemis	leukocytosis	thrombocytopenia	thrombocytosis	leukemic cells	eosinophilia	baasophilia
high risk group	18 28,1%	0,4-14	400-600mg	4 becauseaaa of thrombocytopenia	8 44,4%	4 22,2%	2 (relapse)	6 33,3%	2 (relapse)	4 22,2%	12 66,7%	2 (relapse)	6 33,3%	2 (relapse

Table 4. The clinical-laboratory retrospective data analyses of all patients

group	patients number	remission duration, years	Imatinib daily dose	Daily dose decreasement	non-reg. preparation intake	hepato megaly	spleno megaly	anemis	leukocytosis	thrombocytopenia	thrombocytosis	leukcemic cells	eosinophilia	baasophilia
low risk group	38 59,3%	2,5-13	400-600 mg	6 caused by thrombo-cyto-penia	1	3 7,9%	-	12 31,6%	3 7,9%	6 15,8%	-	-	12 31,6%	-
modera-te risk group	8 12,5%	1-6	400-600 mg	-	1	-	-	2 25%	-	2 25%	2 25%	-	-	-
high risk group	18 28,1%	0,4-14	400-600 mg	4 because of thrombo-cyto-penia	8 44,4%	4 22,2%	2 (re-lap-se)	6 33,3%	2 (re-lap-se)	4 22,2%	12 66,7%	2 (re-lap -se)	6 33,3%	2 (re-lap-se)

Proceeding from this, discontinued treatment regimen and the expressed progressing thrombocytosis can be taken as the possible relapse indicator.

Moreover, there were patients in the high risk group, having comparatively short remission (in 2 cases – remission duration was only 6 months, in one case- 3 years, one case– 4 years), this can be explained by insufficient treatment.

Results and their discussion. Thus, after the treatment using Imatinib during 0,5-14 years time, grouping of 64 patients with CML in remission stage according to the molecular research results, and clinical-laboratory data retrospective analyses (Table 4) showed, that hepatomegalia in all groups was expressed.

Moderate splenomegaly, leukocytosis, leukemic cells and basophilia was found only in high risk group and because of the treatment regimen termination, concerning the developed relapse.

Moderate anemia, thrombocytopenia and eosinophilia were found with the same frequency in all groups, this defined no remission quality and the relapse development risk. As for thrombocytosis, it was expressed only in the moderate risk group with the most number (66%) in high risk patients, most of them (70%) irregularly underwent the Imatinib treatment. This fact indicates, that irregular, non-systemic treatment and progressive high thrombocytosis in peripheral blood can be counted indicator of the expected relapse the chronic myeloid leukemia, and this indicated the urgent molecular-genetic research necessity in order to define the post-treatment tactics.

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SUMMARY

CHRONIC MYELOID LEUKEMIA EXPECTED RELAPSE'S CLINICAL-LABORATORY INDEXES

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Today Chronic Myeloid Leukemia (CML) relapse's final assessment and monitoring in the whole world is implemented by BCR-ABL gene quantitative detection – during the polymerase chain reaction (by PSR means).

Implementation of this monitoring materially and technically is not often available and remission during years is being assessed using monthly clinical-laboratory data.

Proceeding from this, the goal of our work was to find the clinical-laboratory features, indicating the expected relapse and require the urgent molecular research carry out.

In order to find the clinical-hematologic indicators of the Chronic Myeloid Leukemia expected relapse, BCR-ABL gene quantitative determination using the PSR method after the Imatinib treatment was done in 64 patients with CML who had remission (duration 0,5-14 years). The retrospective analyses of clinical-laboratory data was also held before the research.

According to the molecular research results, we have set the risk groups of the patients – low, moderate and high risk groups.

In the groups we have found the clinical-laboratory changes, existed before the research.

We have held the comparative analyses of the molecular research in groups and the clinical-laboratory changes in them. As a result, we have established, that moderate anemia (expressed often during the whole remission period among the patients of all three risk groups) does not indicate the expected relapse and that in the Chronic Myeloid Leukemia remission period the expected relapse indicator could be the patient's Imatinib irregular intakes, non-systemic treatment and high, inexplicable progressive thrombocytosis in peripheral blood. These factors indicate the necessity to hold the urgent molecular research in order to define the post-treatment tactics.

Keywords: Chronic myeloid Leukemia, BCR-ABL gene quantitative determination, Imatinib, cytogenetic-molecular researches.

РЕЗЮМЕ

КЛИНИКО-ЛАБОРАТОРНЫЕ ПОКАЗАТЕЛИ ОЖИДАЕМОГО РЕЦИДИВА ХРОНИЧЕСКОЙ МИЕЛОИДНОЙ ЛЕЙКЕМИИ

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Окончательная оценка и мониторинг ремиссии хронической миелоидной лейкемии по всему миру по сей день осуществляется количественным определением BCR-ABL гена посредством полимеразной цепной реакции (ПЦР).

Проведение такого мониторинга часто бывает технически и материально недоступным и в течение многих лет ремиссия оценивается посредством ежемесячных клинико-лабораторных исследований.

Исходя из вышеизложенного, целью данного исследования явилось определение тех клинико-лабораторных показателей, которые указывают на ожидаемый рецидив и необходимость проведения неотложных молекулярных исследований.

Для выявления клинико-гематологических показателей ожидаемого рецидива хронической миелоидной лейкемии в период ремиссии (длительность 0,5-14 лет), вызвнной иматинибом, 64 больным программно провели количественное определение BCR-ABL гена посредством ПЦР и ретроспективный анализ клинико-лабораторных данных за период перед молекулярными исследованиями.

Согласно результатам молекулярного исследования, выделена группа больных с низким, средним и высоким уровнями риска.

До проведения молекулярных исследований в каждой группе выявлялись клинико-лабораторные изменения.

Проведен сравнительный анализ данных клинико-лабораторных изменений и результатов молекулярных исследований; в результате установлено, что умеренная анемия, которая за весь период ремиссии часто проявлялась среди больных всех трех групп риска, не указывает на ожидаемый рецидив болезни, а в период ремиссии хронической миелоидной лейкемии показателем ожидаемого рецидива следует считать нерегулярное, несистематическое проведение лечения иматинибом и выявление в периферийной крови нарастающего тромбоцитоза. Эти показатели указывают на необходимость неотложного проведения молекулярных исследований с целью определения дальнейшей лечебной тактики.

რეზიუმე

ქრონიკული მიელოიდური ლეიკემიის მოსალოდნელი რეციდივის კლინიკურ-ლაბორატორიული მაჩვენებლები

თ. კირტავა, დ. ღირდალაძე, თ. ვაწაძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი; ჰემატოლოგიისა და ტრანსფუზიოლოგიის ინსტიტუტი, თბილისი, საქართველო

ქრონიკული მიელოიდური ლეიკემიის რემისიის საბოლოო შეფასება და მონიტორინგი სადღეისოდ მსოფლიოში პოლიმერაზული ჯაჭვური რეაქციის (პჯრ) საშუალებით BCR-ABL გენის რაოდენობრივი განსაზღვრით ხორციელდება.

ასეთი მონიტორინგის ჩატარება ხშირად ტექნიკურად და მატერიალურად ხელმისაწვდომი არ არის და წლების განმავლობაში რემისია ფასდება მხოლოდ ყოველთვიური კლინიკურ-ლაბორატორიული კვლევების მონაცემებით.

კვლევის მიზანს შეადგენდა იმ კლინიკო-ლაბორატორიული მაჩვენებლების გამოვლენა, რომლებიც მოსალოდნელ რეციდივზე მიუთითებდენ და მოლეკულური კვლევების გადაუდებლად ჩატარების აუცილებლობაზე მიანიშნებენ.

ქრონიკული მიელოიდური ლეიკემიის მოსალოდნელი რეციდივის კლინიკურ-ჰემატოლოგიური მაჩვენებლების გამოვლენის მიზნით იმატინიბით მკურნალობის შემდგომ რემისიაში 0,5-14 წლამდე ხანგრძლივობით მყოფ 64 ავადმყოფს პროგრამულად ჩაუტარდა BCR-ABL გენის რაოდენობრივი განსაზღვრა პჯრ მეთოდით. მოლეკულური კვლევების წინა პერიოდში ჩატარდა ავადმყოფთა კლინიკურ-ლაბორატორიული მონაცემების რეტროსპექტული ანალიზი.

მოლეკულური კვლევის შედეგების მიხედვით გამოიყო ავადმყოფთა დაბალი, საშუალო და მაღალი რისკის ჯგუფები. ჩატარდა სხვადასხვა ჯგუფის ავადმყოფთა მოლეკულური კვლევის შედეგებისა და კლინიკურ-ლაბორატორიული ცვლილებების შედარებითი ანალიზი. დადგინდა, რომ ზომიერი ანემია, რომელიც მთელი რემისიის პერიოდში ხშირად ვლინდება სამივე რისკის ჯგუფის ავადმყოფებში, არ მიუთითებს დაავადების მოსალოდნელ რეციდივზე. ქრონიკული მიელოიდური ლეიკემიის რემისიის პერიოდში მოსალოდნელი რეციდივის მაჩვენებლად შეიძლება ჩაითვალოს ავადმყოფთა მიერ იმატინიბით არარეგულარული, უსისტემო მკურნალობა და მაღალი, მზარდი თრომბოციტოზი პერიფერიულ სისხლში. ეს მაჩვენებლები მიუთითებს მოლეკულური კვლევების გადაუდებლად ჩატარების აუცილებლობაზე მკურნალობის შემდგომი ტაქტიკის განსაზღვრის მიზნით.

THE PROGNOSTIC SIGNIFICANCE OF COMBAIND EXPRESSION OF ZAP-70 AND CD38 IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Chronic lymphocytic leukemia (CLL) is the most common leukemia in the USA and Europe, including Georgia and is predominant in elderly males, with the median age 65 years at the moment of diagnosis.

The duration of the disease is heterogeneous: patients with indolent (CLL) don't require treatment for many(years), when others because of aggressive duration reguires intensive immediate treatment [14].

The Rai and Binet [1,11] clinical stagingsystems are valuable in classifying CLL patients broad prognostic subgroups, however clinical stages have some limitations and this has led to a search for novel parameters with improved predictive power. There is increasing interest in the use of prognostic markers which may predict survival and guide management in patients diagnosed with the early stages of CLL. Randomized studies and a meta- analysis indicate that early initiation of chemotherapy does not show benefit in CLL and may increase mortality, when patients with symptomatic and/or progressed disease should be immediately treated [8,9].

More then 1 decade ago immunophenotypic avaluation by flow cytometry of Z- chain associated protein- kinase –70 (ZAP–70) and CD38 have to used to predict the clinical course of CLL [4]. Measuring CD38 and ZAR–70 markers is rapid and convenient by flow cytometry, they the first biological markers to be extensively studied as a surrogate marker [15].

Expression of one or Both of this markers generally indicates a worse prognosis. Both markers are used as surrogates for IgVH mutational status are independent prognostic factors , expression higher then 20% of ZAP–70^{+} cells in CLL cases having unmutated IgVH status and they have strongly correlation with this and shows poor prognosis [8,12,15].

Elevated CD38^{+} expression – usually >30% of CLL cells – correlated with advanced disease stage and disease progression but one third patients show discordant results . Discordance between ZAP – 70 and CD38 axpression is observed in 30-40% of patients and is associated with outcomes intermediate between concordant- positive and concordant – negative cases [13].

Our aim was to assess the inter links of the mentioned markers based on our materials, the attitude according to the disease stage, and to document which of them had leading meaning for prognosis and treatmend of the disease.

Material and methods. The clinical group was composed from patients who were diagnosed with CLL in the period from 2008 to March 2017 at the Institute of Haematology and transfusiology, Tbilisi,Georgia.

The diagnosis of B-CLL was made on the basis of clinical, morphologic and immunophenotypic criteria. During research 104 patients are alive. Diagnosis were determined by flow cytometry by heparinized samples of peripheral bload for cells patients, but CD38 and ZAP-70 were determined only for 58 CLL patients. All of patients were distributioned according to the Rai stading System. At the time of the study. 17 patients had 0 stage (29,3%), 15 patients I stage(25,8%), 16 patients – II stage (27,5%), 5 patients – III stage (8,6%) and 4 patients IV stage (6,89%).

Our CLL study contingent were divided in two groups, based on level of ZAP-70^{+}cell <20% and CD38^{+} cells<30% 32 patients(thefirst group) and level of ZAP-70^{+} cells>20% and CD38^{+}cells >30% (II 26 p. group) in the begining of disease. We have calculated the life time to 27 patients from the I group and 18 patients from II group.

We didn't include in study group patients whose diagnosis and CD 38 and ZAP-70 markers were determined from 2016, 01 to 2017, 04. We calculated life expectancy only in 27 patients from the I group and in 18 patients from II group.

We have used the Rai staging system and other tests such are – bone marrow examination, biochemistry analysis. Peripheral lymphe nodes and abdominal ultrasonography and Computer tomography we exemined by rutine methods.

Results and their discussion. Several biological markers can predict disease progression and therapeutic outcomes in patients with early stages of CLL- including IgHV gene mutational status, ZAP-70, CD38, CD49d and cytogenic abnormalities (10).

In the present study we have investigated the expression of CD38 and ZAP-70 markers to assesments their prognostic value in CLL, correlation to Rai-stages and relattioships Between this markers and outcome of therapy.

In this study were involved 58 patients, 31 males and 27 females, average age - 65 years.

We have used the Rai staging system and divided all patients in two groups; I group - 32 patients – ZAP-70^{+} cells were less then 20%, II group – 26 patients - (ZAP – 70^{+} cells more then 20%).

In the I group 62,4% (n=20) patients were in 0-1 stages, 28,1% (n=9) patients in II stage - 9,35% (n=3) in III-IV stages.

In the II- group – 49,97% (n=13) in the 0-I stages, 26,9% (n=7) - II stage and 22,9 (n=6) – III-IV stages (Fig. 1).

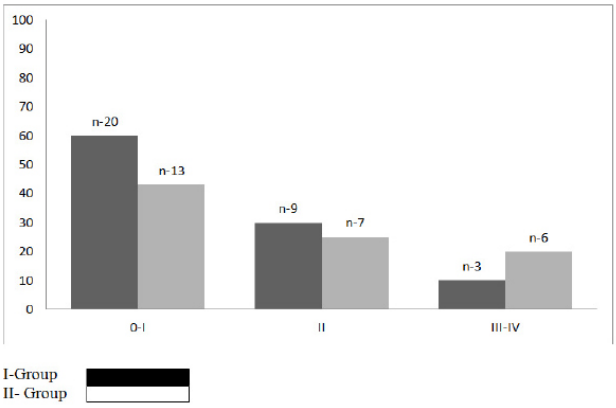

Fig 1. Distribution, Absolute number and percentage of patients in all stages CLL

Leukocytes number and spleen size was more incresed in stages III-IV of II group, then in other stages of this group (Table 1).

Table 1. The patients distribution according to the stages and clinical – hematological indices during CLL debut

I group				II group		
stage	**patients number and%**	**leukocytes $10^{9/L}$**	**spleen size mm**	**patients number and%**	**leukocytes $10^{9/L}$**	**spleen size mm**
0 – I	20 (62,4%)	30,3 ± 12,4 (n=20)	(-) n=20	13 (49,9%)	21,2 ± 4,3 (n=13)	(-) n=13
II	9 (28,1%)	78,4 ± 9,7 (n=9)	176,1 (n=9)	7 (26,9%)	72,1 ± 23,4 (n=7)	171,0 (n=7)
III - IV	3 (9,35%)	56,4 ± 20,1 (n=3)	175,3 (n=3)	6 (22,9%)	118 ± 12,1 (n=6)	202,3 (n=6)

Table 2. CD38 and ZAP-70$^+$ cells absolute number and percentge in CLL (In Both group)

Rai stages	I group				II group			
	CD38$^+$ (-)- not deted (<10%) (% - n)	**CD38$^+$ (>30%) (% - n)**	**ZAP-70$^+$ (< 20%) (% - n)**	**ZAP-70$^+$ (> 20%) (% - n)**	**CD38$^+$ (<30%) (% - n)**	**CD38$^+$ (>30%) (% - n)**	**ZAP-70$^+$ (<20%) (% - n)**	**ZAP-70$^+$ (>20%) (% - n)**
0 –I	(-) 20 <10%-12 100%	0	20 (62,5%)	0	5 (19,2%)	8 (30,76%)	0	13 (50%)
II	0	0	9 (28,1%)	0	4 (15,3%)	3 (11,5%)	0	7 (26,9%)
III - IV	0	0	3 (9,3%)	0	4 (15,38%)	2 (7,69%)	0	6 (23,07%)

Table 3. Combination of Absolute number and percentage of patients with the different levels of CD38$^+$ and ZAP -70$^+$cells in CLL

I group n - 32		II group n – 26			
CD38$^-$ and <10%	**ZAP-70$^+$ (< 20%)**	**CD38$^-$ or <30%**	**ZAP-70$^+$ >20% - <40%**	**CD38$^+$ >30%**	**ZAP-70$^+$ >40% - 80%**
(-) n=20 <10% n=12	n=32	(-) n=3 <30% n=6	9	(-) n=6 >30% 11	26

In the I group CD38 and ZAP-70 markers study has show that the CD38$^+$cells practicaly were not detected in the patients of this group. Among the patients of the II group, having hte ZAP-70$^+$ cells, more that 20% in all the patients CD38$^+$ cells in the average amount and even proportion, were shown at all stages (Table 2).

In the I group patients the average life expactancy was 62 months (out of 32 patients of the group 13 patients (40,6%) during years needed no treatment.

The II group patients showed the average lite expectancy was 39 months, despite the modern chemo therapy treatment CRFC, FC Bendamustin, Cyllopospomide.

In the first group were ZAP-70$^+$ <20% CD38 was negative practically in all cases. But in II group ZAP-70$^+$cells were more then >40% in 17 (65%) cases. In 9 (35%) cases ZAP-70$^+$cells were increazed more slightly < 40% (avarage 30,3%) and in this 9 patients were ZAP-70$^+$cells were more then 20%, but less then 40% - CD38$^+$ cells in 3 cases were not detected and in other 6 case its level was < 30%. In remained 17 cases, ZAP-70$^+$cells were increased more then 40-80% CD38$^+$ cells in 6 patients were not detected and in other 11 patients CD38 cells were increasing – this 6 patients like others were refractory to chemothrapeutic regimens – FC, RFC, Bendamustin, Cyclophosphamid (Table 3).

The importance of ZAP -70$^+$ as an independent prognostic marker has been shown in numerous earlier studies [3,5,7,8].

Our study shows the same results in ZAP -70$^+$ cases when its number was <20% (I group - 32 patients) the patients has favorable prognosis (the big part of this patients n=13 (40%) didn't need treatment during a long period), other patients, which needs treatments - treatment was effective and this patient's life expectancy was long (62 months).

When ZAP -70$^+$cells were>20% (II group – 26 patients) prognosis was unfavorable, patients treatment was non effective and accordingly live expectancy was shorter (average 39 month).

Despite the number of CD38 positive or negative cells [3,6].

In the works where compared were ZAP-70$^+$ and ZAP-70$^-$ cases events treatment results and the research was held on the minimal residual disease existence, in ZAP-70$^+$ positive cases treatment the remission obtained was always incomplete, and on the contrary, where the ZAP-70$^+$ was negative – complete [2,3,5].

In our study we didn't reveal the importance of CD38 as a prognostic independent marker and there were not correlation between CD38$^+$ and CD38$^-$ cells numbers in CLL prognosis.The data of this study agree with the researchers didn't strongly confirm CD38 prognostic impact [3,15].

Sine our study data confirm that ZAP-70 marker has the advantageous prognostic meaning, we reckon the information on CLL disease debut on ZAP-70 marker expression can be used not only for defining the aggressive duration of the disease, but also in greater part, to define the refracterity towards the modern chemotherapy regimens.

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SUMMARY

THE PROGNOSTIC SIGNIFICANCE OF COMBAIND EXPRESSION OF ZAP-70 AND CD38 IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Our aim was to assess the inter links of the markers CD38 and ZAP-70 based on our materials, the attitude according to the disease stage, and to document which of them had leading meaning for prognosis and treatment of the disease.

In our study we have used flow cytometry for detection CD38 and ZAP-70$^+$ markers expression. (58 patients to assessments their prognostic value in chronic lymphocytic leukemia (CLL), Correlation to Rai stages and relationships between this markers and outcome of therapy).

We divided all patients in two groups based on level of ZAP-70$^+$ cell and CD38$^+$cells,(I group-patients) ZAP-70$^+$ cells <20% CD38$^+$<30% and ZAP-70$^+$ cells >20% and CD38>30%,(II group) because our in investigation shows, that ZAP -70$^+$ is very importance independent prognoctic marker as why in ZAP-70$^+$ cases when its number was <20%, patients had favorable prognosis – the big part of them (13(40.6%) didn't need treatment during a long period, but which need the treatment was effective and this patients life expectancy was long (62 mounts).

When ZAP-70 cells were>20% (II group n=26) prognosis was unfavorable, patients treatment was not effective and accordingly life expectancy was shorter (39 mounts).

Despite CD38 positive or negative cells number.

During research where compared were ZAP-70$^+$ and ZAP-70$^-$ cases events treatment results and the research was held on the minimal residual disease existence, in ZAP-70$^+$ positive cases treatment the remission obtained was always incomplete, and on the contrary, where the ZAP-70$^+$ was negative – complete.

In our study we didn't reveal the importance of CD38 as a prognostic independent marker and there were not correlation between CD38$^+$ and CD38$^-$ cells numbers in CLL prognosis.

Because our study data confirm that ZAP-70 marker is more importance marker then CD38 and it has seriously prognostic significance, we think that information about ZAP-70 marker expression.

Because our study data confirm that ZAP-70 marker has the advantageous prognostic meaning, we reckon the information on CLL disease debut on ZAP-70 market expression can be used not only for defining the aggressive process of the disease, but also in greater part, to define the refracterity towards the modern chemotherapy regimens.

Keywords: markers CD38 and ZAP-70, chronic lymphocytic leukemia.

РЕЗЮМЕ

ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ КОМБИНИРОВАННОЙ ЭКСПРЕССИИ ZAP-70 И CD38 ПРИ ХРОНИЧЕСКОЙ ЛИМФОЦИТАРНОЙ ЛЕЙКЕМИИ

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Целью данного исследования явилось определение взаимосвязи между маркерами CD38 и ZAP-70, их отношения к стадии заболевания и определение прогноза и тактики лечения.

С помощью проточной цитометрии изучена экспрессия маркеров CD38 и ZAP-70 у 58 больных хронической лимфоцитарной лейкемией, определена их взаимосвязь со стадией болезни, течением и продолжительностью жизни. Установлено, что в случаях когда ZAP–70^+ <20% болезнь протекает благополучно (из этой группы 13 (40,6%) больным не требовалось назначение лечения в течение длительного времени), а проводимое лечение было эффективным (средняя продолжительность жизни больных этой группы составила 62 месяца). Во II группе (26 больных), в которой количество ZAP-70^+ клеток было >20%, заболевание протекало неблагоприятно, отмечалось быстрое прогрессирование, современные программы химиотерапии оказались неэффективными (RFC, FC, бендамустин), средняя продолжительность жизни больных не превышала 39 месяцев. Количество клеток $CD38^+$ или CD 38^- не влияли на течение и исход заболевания.

На основании данных проведенного исследования, корреляции между количеством клеток $CD38^+$, $CD38^-$ и ZAP-70^+ не выявлено. Количество клеток ZAP-70^+ играет решающую роль в прогнозировании успешного лечения. Авторами делается заключение, что в дебюте заболевания число клеток ZAP-70^+ может быть использовано не только для определения агрессивного течения заболевания, но и установления возможной рефрактерности болезни к современным химиотерапевтическим средствам.

რეზიუმე

CD38 და ZAP-70 კომბინირებული ექსპრესია და მათი პროგნოზული მნიშვნელობა ქრონიკული ლიმფოციტური ლეიკემიის მიმდინარეობაში

თ. კირტავა, თ. ვაწაძე, ე. აზმაიფარაშვილი, დ. ღირდალაძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი; ჰემატოლოგიისა ტრანსფუზიოლოგიის ინსტიტუტი, თბილისი, საქართველო

შრომის მიზანს წარმოადგენდა CD38 და ZAP-70 მარკერების ურთიერთკავშირის და ქრონიკული ლიმფოციტური ლეიკემიის (ქლლ) სტადიასთან მათი დამოკიდებულების შეფასება, ასევე, მათგან დაავადების მიმდინარეობისა და მკურნალობის პროგნოზის უპირატესი ფაქტორის გამოვლენა.

გამდინარე ციტომეტრიის გამოყენებით შესწავლილი იყო 58 ავადმყოფის CD38 და ZAP-70 მარკერების ექსპრესია ქლლ-ის დროს, მათი დამოკიდებულება დაავადების სტადიასთან, მიმდინარეობასა და სიცოცხლის ხანგრძლივობასთან.

ჩატარებული კვლევებით დადგინდა, რომ <20% ZAP-70^+ შემთხვევაში (I ჯგუფი,32 ავადმყოფი) დაავადების მიმდინარეობა იყო კეთილსაიმედო, მათგან 13 (40,6%) ავადმყოფს საერთოდ არ დასჭირდა მკურნალობა ხანგრძლივი პერიოდის განმავლობაში. დანარჩენ 19 ავადმყოფს ჩაუტარდა ეფექტური მკურნალობა; ამ ჯგუფის ავადმყოფების სიცოცხლის საშუალო ხანგრძლივობა შეადგენდა 62 თვეს.

II ჯგუფის 26 ავადმყოფში (ZAP-70^+ უჯრედების რაოდენობა - >20%) დაავადების მიმდინარეობა აღმოჩნდა არაკეთილსაიმედო, დაავადება სწრაფად პროგრესირებდა, თანამედროვე ქიმიოთერაპიული პროგრამები აღმოჩნდა არაეფექტური (RFC, FC, ბენდამუსტინი), სიცოცხლის საშუალო ხანგრძლივობამ შეადგინა 39 თვე, $CD38^+$ ან $CD38^-$ უჯრედების რაოდენობის მიუხედავად.

კვლევის შედეგების მიხედვით, კორელაცია $CD38^+$, $CD38^-$ და ZAP-70^+ უჯრედების რაოდენობას შორის არ გამოვლინდა. დაავადების მკურნალობის ეფექტურობის პროგნოზირებისათვის ZAP-70^+ უჯრედების რაოდენობას აქვს გადამწყვეტი მნიშვნელობა. ამიტომ, ინფორმაცია ქლლ-ს დებიუტში ZAP-70^+ უჯრედების რაოდენობის შესახებ შეიძლება გამოყენებულ იქნას არამარტო დაავადების აგრესიული მიმდინარეობის განსაზღვრისთვის, არამედ, დიდი ალბათობით, თანამედროვე ქიმიოთერაპიული საშუალებებით მკურნალობის მიმართ რეფრაქტერობის დასადგენად.

RESULTS OF MINIMAL INVASIVE TREATMENT IN LOCALIZED ACQUIRED CUTIS LAXA TYPE 1 AND TYPE 2 – CASE REPORT AND DISCUSSION

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Cutis laxa is a rare connective tissue disorder presenting with abnormal skin wrinkling and skin laxity. The underlying pathomechanism is a loss of elasticity that is not necessarily restricted to skin only but may include other organs as well. Two major types of cutis laxa can be differentiated, i.e. congenital and acquired; inherited and non-inherited. The congenital type is related to a variety of mutations in genes regulating elastin synthesis and metabolism or structural disturbances of the extracellular matrix [6]. Major inherited disorders are autosomal recessive cutis laxa (types IA, IB, IIA, IIB, III), autosomal dominant cutis laxa, X-linked recessive cutis laxa, adult late-onset cutis laxa, Urban-Rifkin-Davis syndrome, Macrocephaly-Alopecia-Cutis Laxa-Scoliosis syndrome (MACS), and Arterial Tortuosity Syndrome (ATS). Non-inherited disorders include transient neonatal cutis laxa, neonatal cutis laxa with Marfan phenotype, acquired cutis laxa type 1, and acquired cutis laxa type 2 (Marshall's syndrome, post-inflammatory elastolysis and cutis laxa) [3]. The acquired type is rarer and a possible consequence of chronic inflammation [5,9].

Case reports. *Case 1:* We report a 62-year-old female Caucasian patient, born to non-consanguineous parents, who developed an asymptomatic fine wrinkling and loose skin on the neck and décolleté about three years ago. The skin color turned into a yellowish tone (Fig. 1). No other body areas were involved. Her medical history was unremarkable. She did not take any medications. The family history was negative for skin diseases. A skin biopsy revealed a flattened, slightly atrophic epidermis combined with a loss of elastin fibers in the upper and mid dermis. There was a mild lymphocytic infiltration. The diagnosis of localized cutis laxa acquisita type 2 was confirmed.

The only relevant exogenous factor that could be identified was an excessive sun exposure during leisure times. Results of routine laboratory investigations were in the normal range. Her Fitzpatrick skin type was II.

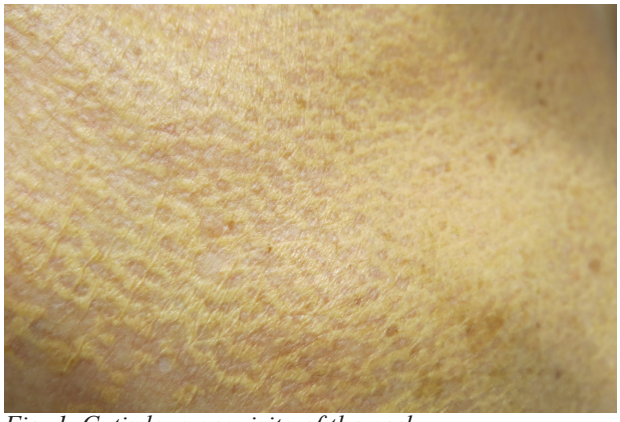

Fig. 1. Cutis laxa acquisita of the neck

Case 2. A 46-year-old tall Caucasian female presented with loose facial skin and wrinkling including blepharoptosis. The disease started about three years ago with erythematous lesions.

No other body parts were affected, there were no findings of internal involvement (pulmonary, cardiovascular, gastrointestinal or urogenital). Her medical history was negative for any drug therapy. She was otherwise healthy and very athletic. There was no family history of comparable findings or complaints.

The clinical and histopathologic findings argued for localized (facial) acquired cutis laxa type 1. She was treated repeatedly by dermal filler injection and botulinum toxin with excellent results (Fig. 2). An upper lid blepharoplasty was performed at a later time.

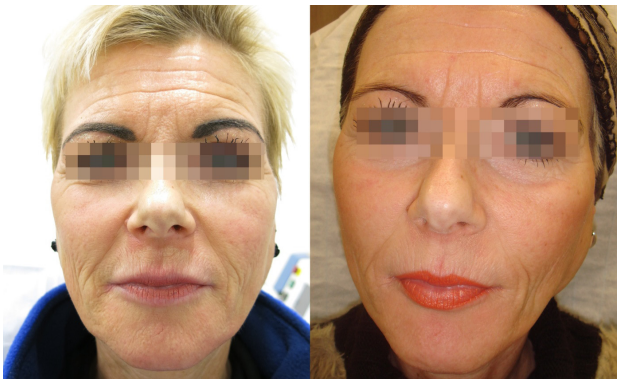

Fig. 2. Localized cutis laxa type 1 before treatment (left) and after deep subdermal placement of hyaluronic acid-based soft tissue filler (right)

Results and their discussion. Although ageing skin develops increased skin laxity over time in sun-exposed areas due to dermal UVA-induced photodegradation of extracellular matrix, it has not reached the level seen in cutis laxa. In our patient 1, the macroscopic appearance of a loose and pendulous skin of neck and décolleté together with the loss of elastin fibers in skin confirmed the diagnosis of localized acquired cutis laxa. According to recent classification, the disorder was classified as type 2, although there was no history of Sweet's syndrome or any other neutrophilic dermatosis [3]. Diagnosis is based upon clinical presentation and histopathology. We suggested medical peelings and radiofrequency therapy, but the patient did not return.

Recently, an increased expression of mRNA for elastin and fragmented tropoelastin have been observed in affected skin. Fibroblasts had a higher mitotic activity in cell culture [8]. The discrepancy of increased mRNA

for elastin but loss of elastin fibers in affected skin may be explained by a disturbed translation and/ or increased elastin turnover.

The second patient suffered from acquired cutis laxa type 1, localized on the face. This type is known to affect internal organs in about 50% of cases. Medications, infections and neoplasia may be triggering factors [3,7]. Treatment options include surgery for ptosis of skin including blepharoplasty, and minimal invasive procedures such as soft tissue fillers and radiofrequency. Since the underlying metabolic disturbances cannot be corrected, the improvement is of temporary nature and treatment needs to be repeated. There is no effective drug treatment available [9]. Hyaluronic acid may stimulate elastin production [4]. Hyaluronic acid together with extracellular matrix is an excellent tool to expand adipose-derived stem cells [1]. The latter has been accounted for prolonged effects of hyaluronic acid-derived soft tissue filler facial restoration [2,10].

Prevention of acquired cutis laxa is another target. Sun protection, treatment of inflammatory skin diseases such as Sweet's syndrome, or urticaria, and careful monitoring of possible adverse effects during drug therapy are suggested options. Their usefulness in acquired cutis laxa, however, has yet to be proven.

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SUMMARY

RESULTS OF MINIMAL INVASIVE TREATMENT IN LOCALIZED ACQUIRED CUTIS LAXA TYPE 1 AND TYPE 2 – CASE REPORT AND DISCUSSION

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Cutis laxa is a disease of premature ageing. While the congenital type is characterized by mutations of genes involved in extracellular matrix turnover, acquired cutis laxa is a rare disease that can be induced by a variety of exogenous factors. We present a case of acquired type 2 cutis laxa of the neck due to excessive exposure to natural sunlight and a type 1 facial acquired cutis laxa, both significantly improved by minor invasive procedures. The etiology, prevention and treatment options are discussed.

Keywords: Ageing, cutis laxa, extracellular matrix, elastin metabolism.

РЕЗЮМЕ

РЕЗУЛЬТАТЫ МИНИМАЛЬНО-ИНВАЗИВНОГО ЛЕЧЕНИЯ ПРИ ПРИОБРЕТЕННОМ ЛОКАЛИЗОВАННОМ CUTIS LAXA I И II ТИПА - КЛИНИЧЕСКИЙ СЛУЧАЙ И ОБСУЖДЕНИЕ

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Cutis Laxa - болезнь преждевременного старения. Хотя врожденный тип характеризуется мутацией генов, вовлеченных в оборот внеклеточного матрикса, приобретенная Cutis Laxa является редким заболеванием, которое может быть вызвано различными экзогенными факторами. Представлены два клинических случая приобретенной Cutis Laxa: II типа в области шеи, вызванного чрезмерным воздействием естественного солнечного света и Cutis Laxa I типа в области лица. Состояние обоих пациентов значительно улучшилось в результате применением минимально инвазивных лечебных процедур. В статье обсуждаются этиология, профилактика и лечение заболевания.

რეზიუმე

შეძენილი ლოკალიზებული I და II ტიპის CUTIS LAXA-ს მინიმალური ინვაზიური მკურნალობის შედეგები - კლინიკური შემთხვევები და განხილვა

უ. ვოლინა

დრეზდენის ტექნიკური უნივერსიტეტი, აკადემიური კლინიკური ჰოსპიტალი, დერმატოლოგიისა და ალერგოლოგიის განყოფილება, დრეზდენი, გერმანია

Cutis Laxa - ნაადრევი სიბერის დაავადებაა. დაავადების თანდაყოლილი ტიპი უჯრედული მატრიქსის ცვლაში ჩართული გენების მუტაციით ხასიათდება. შეძენილი Cutis Laxa იშვიათი დაავადებაა, რომელიც შეიძლება სხვადასხვა ეგზოგენური ფაქტორით იყოს გამოწვეული. სტატიაში წარმოდგენილია შეძენილი Cutis Laxa-ს ორი კლინიკური შემთხვევა: მეორე ტიპის – კისრის მიდამოში,გამოწვეული ბუნებრივი მზის სინათლის გადაჭარბებული ზემოქმედებით და პირველი ტიპის – სახის მიდამოში. მინიმალურად ინვაზიური სამკურნალო პროცედურების გამოყენების შედეგად ორივე პაციენტის მდგომარეობა მნიშვნელოვნად გაუმჯობესდა. სტატიაში განხილულია დაავადების ეტიოლოგია,პროფილაქტიკა და მკურნალობა.

КОНУСНО-ЛУЧЕВАЯ ТОМОГРАФИЯ В ДИАГНОСТИКЕ ОДОНТОГЕННЫХ ГАЙМОРИТОВ (СЛУЧАИ ИЗ ПРАКТИКИ)

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Одонтогенный гайморит - воспалительное заболевание слизистой оболочки верхнечелюстной пазухи, возникающее в результате распространения патологического процесса из зубочелюстной области. Этой проблеме, стоящей на стыке двух специальностей – оториноларингологии и стоматологии, посвящено множество публикаций. Увеличению частоты одонтогенных верхнечелюстных гайморитов способствует ряд социальных факторов:

а) резкое снижение платежеспособности населения ведет к запоздалому обращению за стоматологической помощью, несмотря на широкую сеть государственных и частных стоматологических кабинетов;

б) широкое распространение хозрасчетных стоматологических и зубопротезных кабинетов приводит к тому, что протезирование, пломбирование, наращивание “проблемных” зубов по настоянию клиента производится без учета или с игнорированием медицинских противопоказаний, что в дальнейшем, приводит к развитию гайморита при видимом благополучии в полости рта.

в) недооценка со стороны отологингологов связи гайморита с заболеваниями зубов - некоторые одонтогенные процессы, особенно протекающие скрытно, рассматриваются как риногенные с соответствующими последствиями - частыми рецидивами воспаления. Стоматологи в большинстве случаев распознают симптоматику заболеваний верхнечелюстных пазух, возможность их повреждения и инфицирования в процессе лечения зубов.

Предпосылки одонтогенного гайморита:

1. Анатомические - чем больше пневматизирована верхнечелюстная пазуха, тем ниже опускается её дно в альвеолярный отросток и тем тоньше становится костная пластинка, отделяющая корни зубов от полости пазухи.

Немаловажную роль играет также наличие искривленной носовой перегородки, так как в случаях сращения искривленной носовой перегородки с носовыми раковинами отсутствует аэрация гайморовых пазух, затрудняется отток содержимого, создавая благоприятные условия для его скопления и инфицирования.

Иногда в верхнечелюстной пазухе встречаются дополнительные ячейки, фиброзные тяжи, что также отрицательно сказывается на пассаже содержимого и способствует развитию синусита.

Размеры соустья гайморовых пазух вариабельны при его небольшом диаметре; в случае его неправильной формы, возникает риск обтурации полости

пазухи ввиду отека слизистой оболочки, в результате чего полностью нарушается отток содержимого.

2. Механические - перфорация дна полости верхнечелюстной пазухи, осложнения при лечении пульповой камеры и корневых каналов. Причинами повреждения дна верхнечелюстной пазухи являются: разрушение тканей над верхушкой корня зуба патологическим процессом; анатомо-физиологическая близость дна пазухи к корням зубов; нарушение правил удаления зуба, что механически нарушает целостность дна гайморовой пазухи, в полость пазухи попадают фрагменты зуба и части медицинского инструментария. Инородные тела свободно располагаются в полости пазухи, в толще измененной слизистой оболочки, подслизистого слоя, либо дифференцируются в структуре жидкостного содержимого.

При очистке корней от путридных масс иногда происходит их проталкивание за апикальное отверстие. В случаях, когда между периодонтом и слизистой оболочкой верхнечелюстной пазухи отсутствует кость, возможно прямое попадание продуктов распада из корневого канала или патологически измененных тканей периодонта в полость пазухи.

При расширении каналов корней зуба возможно механическое проникновение игл, нервэкстрактора, бора и других инструментов, а также пломбировочного материала через верхушечное отверстие корня в периодонт и верхнечелюстную пазуху.

3. Наличие патологического процесса, вызывающего разрушение нижней стенки верхнечелюстной пазухи - пульпит, периостит, остеомиелит, радикулярная киста, гранулема, опухоль, пародонтоз, пародонтит.

Одонтогенный гайморит часто возникает как следствие периостита или остеомиелита при распространении процесса с альвеолярного отростка на пазуху. Причиной одонтогенного гайморита иногда могут быть нагноившиеся одонтогенные кисты, проросшие в полость пазухи. Причиной хронического воспаления в полости верхнечелюстной пазухи реже являются зубы, ретинированные и дистопированные в полость пазухи.

4. Общность иннервации, кровообращения и лимфооттока.

Одним из значимых факторов в патогенезе одонтогенного синусита является обтурация естественного отверстия и затруднение оттока содержимого из пазухи. Вследствие отека слизистой оболочки носа и верхнечелюстной пазухи уменьшается проходимость естественного выводного отверстия пазухи, что приводит к нарушению ее вентиляционно-дренажной функции. При полной обтурации отверстия за счет всасывания слизистой оболочкой кислорода в пазухе создается отрицательное давление, возникают явления застоя, что усугубляет отек слизистой оболочки. В результате падения давления в пазухе, гипоксии, гиперкапнии, накопления недоокисленных продуктов создаются благоприятные условия для роста и размножения аэробов и факультативных анаэробов. Таким образом, возникает порочный круг, определяющий возникновение болезни. Если его не разорвать, в слизистой оболочке возникнут необратимые изменения, которые понижают эффективность консервативного лечения синусита и мероприятий по санации полости рта и препятствуют восстановлению проходимости естественного отверстия пазухи.

Основными методами лучевой диагностики одонтогенного гайморита являются обзорная рентгенография, панорамная зонография, спиральная компьютерная томография (СКТ) и метод конусно-лучевой компютерной томографии (КЛКТ) придаточных пазух носа, конусно-лучевая компьютерная томография зубочелюстной системы и придаточных пазух носа [2,6].

Метод конусно-лучевой томографии до недавнего времени применялся только для диагностики патологии зубочелюстной системы. В связи с появлением конусно-лучевых томографов с сенсором, превышающим размеры зубочелюстной системы, стало возможным выполнение такой методики, как конусно-лучевая томография придаточных пазух носа. Немаловажной особенностью метода является его низкая лучевая нагрузка, которая составляет 40-50 мЗв, что особенно важно при выполнении исследований в динамике у пациентов группы риска.

Целью исследования явилась оценка возможности конусно-лучевой томографии в диагностике одонтогенных гайморитов.

Материал и методы. С помощью метода КЛКТ обследованы пациенты Института стоматологии АМН Украины, отоларингологического отделения Института пластической хирургии «Виртус», клиники челюстно-лицевой хирургии и ЛОР отделения Военно-медицинского клинического центра Южного Региона г. Одессы, Центра реконструктивной и восстановительной медицины Одесского медицинского университета. Наблюдались 50 пациентов до и после оперативного вмешательства в динамике до и после консервативного лечения. Из них мужчин было 26 (52%), женщин – 22 (44%), детей – 2 (4%), возраст пациентов варьировал в пределах от 10 до 89 лет.

Основными причинами одонтогенного гайморита являлись: периодонтит – у 18 (36%) пациентов, остеомиелит верхней челюсти – у 1 (2%), нагноившиеся кисты верхней челюсти – у 17 (34%), ятрогенные перфорации верхнечелюстной пазухи (корни, протолкнутые в верхнечелюстную пазуху), инородные тела, ретенированные зубы – у 14 (28%) пациентов. Оперативное лечение проведено 42 (82%) пациентам, наблюдение в динамике - 38 (78%). На конусно-лучевом томографе «Morita» (Япония) проводились конусно-лучевая томография двух челюстей в окклюзии и верхненижнечелюстного сустава (ВНЧС), включая гайморовы пазухи, средние зоны лица, придаточные пазухи носа.

Конусно-лучевая томография двух челюстей в окклюзии и ВНЧС, включая гайморовы пазухи, выполнялась пациентам с полной либо частичной вторичной адентией для планирования дентальной имплантации, а также с целью исключения воспалительного процесса в верхнечелюстных синусах. Область сканирования составила 12.0x16.0 см^2. Параметры сканирования 90-120 кВ, 7.0-8.5 мА, толщина среза от 0.02 см до 3.0 см. Голова пациента фиксировалась височными зажимами для исключения динамической нерезкости,окклюзионная плоскость выставлялась параллельно подбородочному уступу. Центрирование лазерного луча (разметка) выполнялось строго по окклюзионной плоскости.

Параметры сканирования при выполнении методики конусно-лучевой томографии средней зоны лица, придаточных пазух носа и верхней челюсти оставались неизменными, изменялось положение лазерного луча в зависимости от выбора зоны исследования.

При выполнении конусно-лучевой томографии средней зоны лазерный луч устанавливался по Франкфуртской горизонтали: при придаточных пазухах носа - на переносице, при верхней челюсти – по альвеолярным отросткам верхней челюсти.

Для определения наличия жидкостного содержимого в полости пазух, голова пациента наклонялась на 30 градусов вперед, либо назад относительно горизонтально расположенной плоскости подбородочного уступа.

При наклоне головы уровень жидкости изменялся согласно углу наклона головы, что позволяло дифференцировать полиповидные разрастания слизистой оболочки и кистовидные образования от свободной жидкости. При анализе изображения с помощью программы EZ2009, использовалась методика денситометрии. Анализ содержимого полостей придаточных пазух носа выявил, что средняя плотность полиповидноутолщенной слизистой оболочки и кистовидных образований составила от +40 до +80 ед.Н, жидкостное содержимое - от +10 до +22 ед.Н., плотность инородных тел (пломбировочный материал, фрагменты медицинского инструментария) - от +600 до +3300 ед.Н. Плотность определялась на участке площадью 0.5-3.0 см^2. Учитывались усредненные показатели плотности (рис. 1а, б).

Дополнительными методами являлись панорамная томография зубных рядов, внутриротовая рентгенография, спиральная компьютерная томография и рентгенография придаточных пазух носа в носоподбородочной проекции.

Клинический случай 1. Пациент Ч., 63 года. Обратился на консультацию к челюстно-лицевому хирургу с жалобами на затрудненное носовое дыхание, зловонные выделения желто-зеленого цвета из полости носа в течение 3 недель. Выполнена КЛКТ придаточных пазух носа верхней челюсти (рис. 2).

Клинический случай 2. Пациент А., 38 лет. Обратился к отоларингологу с жалобами на длительные выделения с неприятным запахом из носа, головные боли в течение 2 недель. Выполнена КЛКТ придаточных пазух носа, включая верхнюю челюсть (рис. 3а,б).

Пациенту выполнено оперативное вмешательство (операция Колдуэлла-Люка), полость пазухи полностью санирована. Спустя 2 месяца проведена повторная КЛКТ верхней челюсти и гайморовых пазух (рис. 3б).

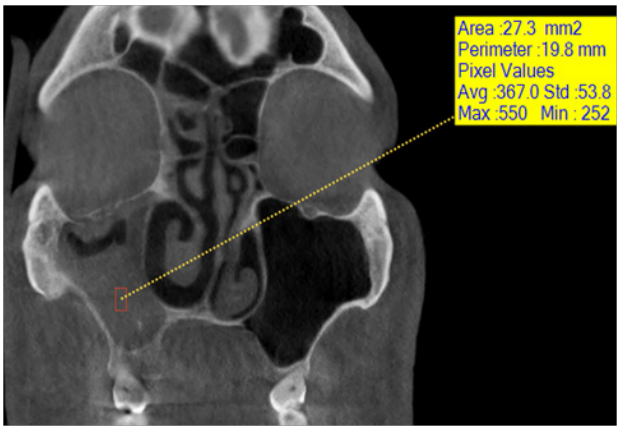

Рис. 1а. КЛКТ придаточных пазух носа, включая верхнюю челюсть. Фронтальная реконструкция на уровне средней трети костной части носовой перегородки. Полость правой гайморовой пазухи наполнена содержимым неоднородной плотности. Соустье правой гайморовой пазухи не прослеживается, обтурировано за счет реактивного утолщения слизистой оболочки полости пазухи. Соустье гайморовой пазухи слева - прослеживается. Для исключения динамической нерезкости голова фиксирована с помощью височных зажимов

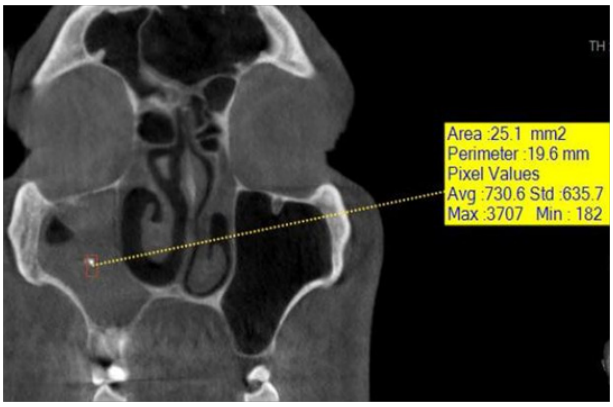

Рис. 1б. В структуре содержимого определяется инородное тело высокой плотности до 0.2 см в диаметре, плотностью +635 ед.Н. - пломбировочный материал

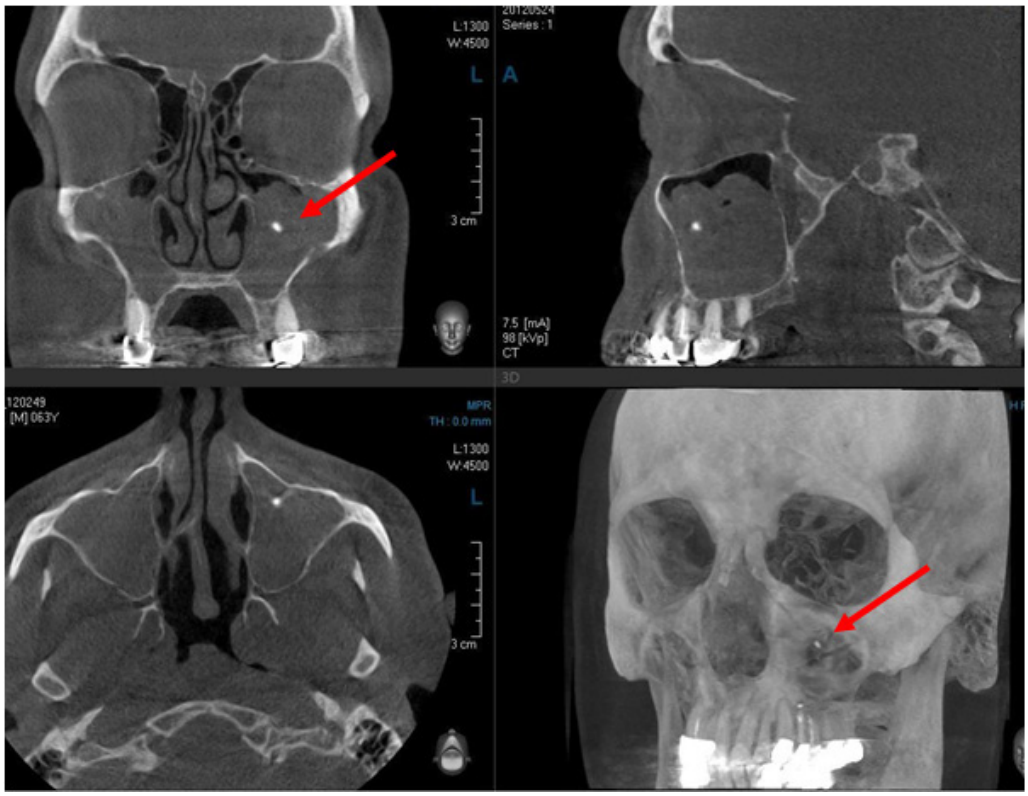

Рис. 2. Фронтальная, сагиттальная и аксиальная реконструкции, режим максимально интенсивных проекций. Обе пазухи выполнены полиповидноутолщенной слизистой. В полости левой гайморовой пазухи, на фоне полиповидноутолщенной слизистой оболочки определяется инородное тело высокой плотности - пломбировочный материал указан стрелками

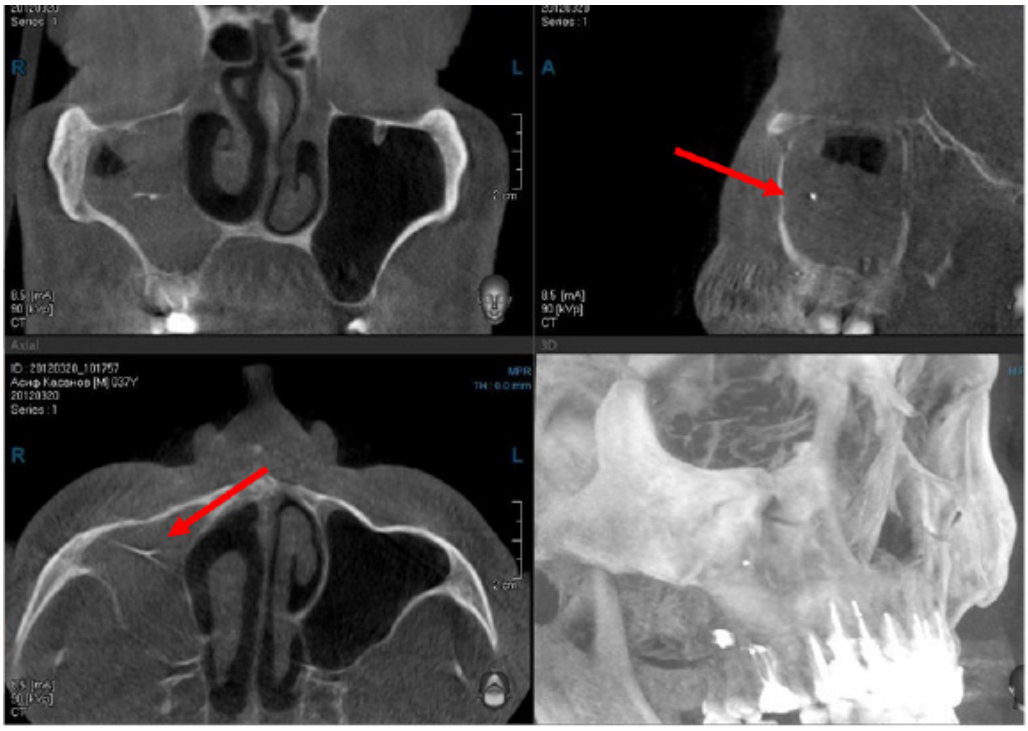

Рис. 3а. КЛКТ придаточных пазух носа. Фронтальная, сагиттальная и аксиальная реконструкции, режим максимально интенсивных проекций. В полости правой гайморовой пазухи на фоне полиповидноутолщенной слизистой оболочки определяются 2 инородных тела высокой плотности - пломбировочный материал

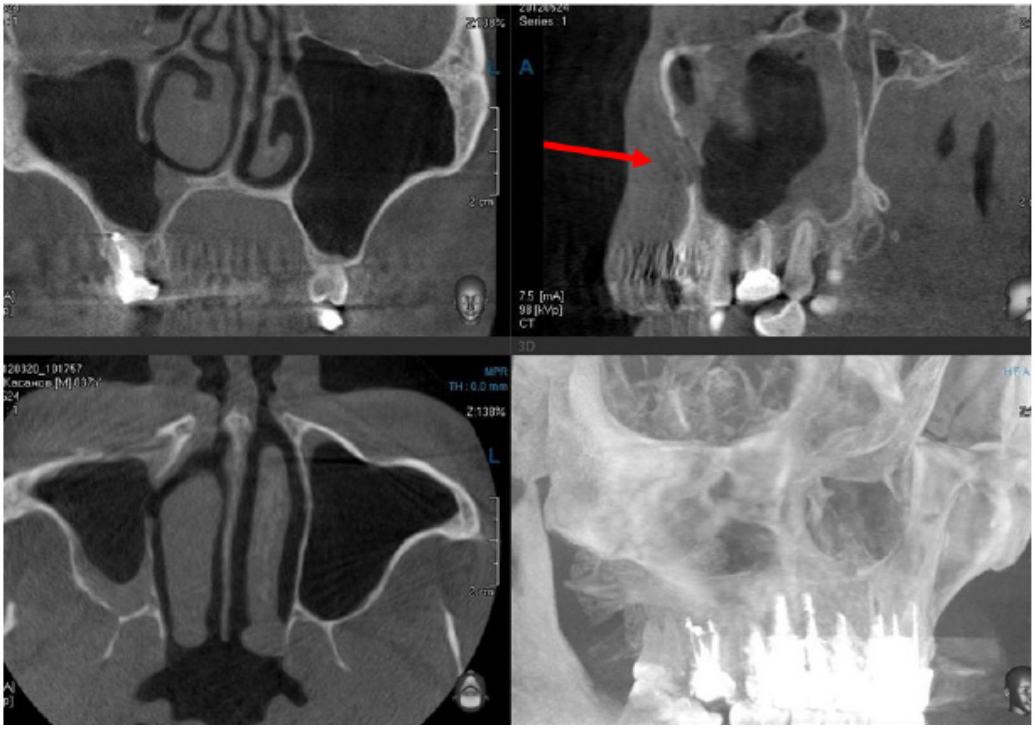

Рис. 3б. КЛКТ придаточных пазух носа. Фронтальная, сагиттальная и аксиальная реконструкции, режим максимально интенсивных проекций. Послеоперационный дефект передней стенки гайморовой пазухи справа (указан стрелкой), слизистая оболочка задней стенки гайморовой пазухи равномерно утолщена

Клинический случай 3. Пациентка Ю., 22 года обратилась с жалобами на постоянные ноющие боли в области верхней челюсти справа, неприятные выделения из носа. Выполнена ортопантомография (рис. 4а), КЛКТ придаточных пазух носа, включая верхнюю челюсть (рис. 4б).

Пациентке выполнено оперативное вмешательство, удалены 15 и 16 зубы, выполнена пластика дефекта верхней челюсти с помощью титановой пластины, восстановлен дефект нижней стенки гайморовой пазухи, операция «синус-лифтинга». Спустя 2 месяца поторная КЛКТ верхней челюсти, включая гайморовы пазухи (рис. 4 в,г,д).

Результаты и их обсуждение. Конусно-лучевая томография позволила выявить этиологию (травматическая, инфекционная, медикаментозная), локализацию периодонтита, размеры радикулярных кист и их локализацию, остеомиелит верхней челюсти, нагноившиеся кисты верхней челюсти, перфорации верхнечелюстной полости, корни, протолкнутые в верхнечелюстную пазуху, инородные тела, ретенированные зубы.

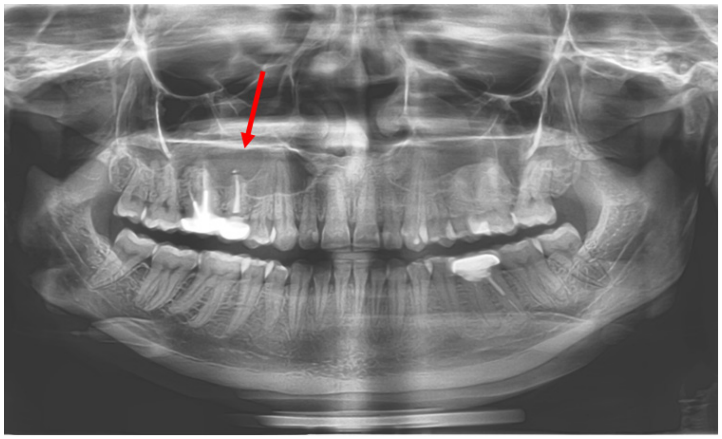

Рис. 4а. Ортопантомография. В области 15-16 зубов верхней челюсти справа отмечается неравномерное расширение периодонтальной щели, каналы пломбированы (указано стрелкой). Пломбировочный материал прослеживается на всем протяжении негомогенно

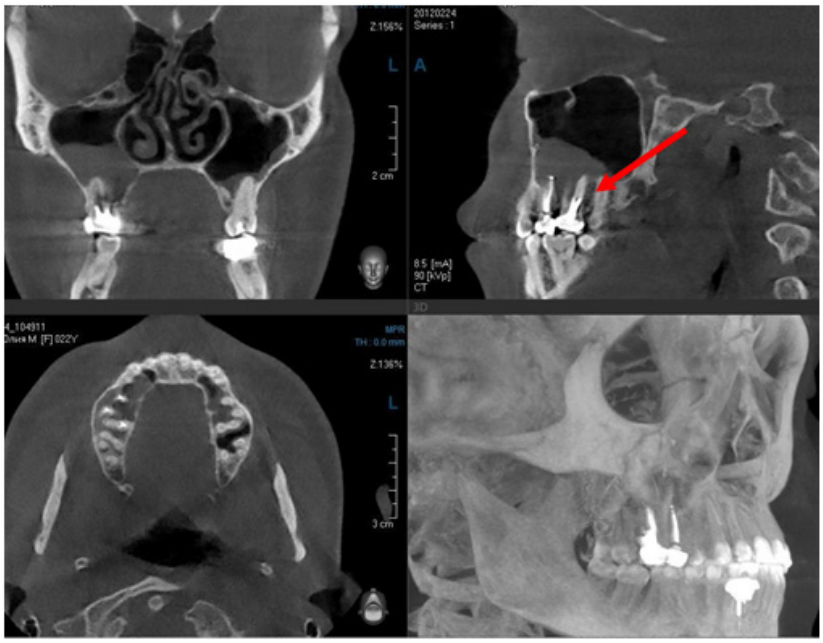

Рис. 4б. Конусно-лучевая томография двух челюстей в окклюзии, включая ВНЧС и гайморовы пазухи. В области 15-16 зубов отмечается снижение плотности костной ткани верхней челюсти, над корнями зубов - полиповидное разрастание слизистой оболочки. Фронтальная, сагиттальная и аксиальная реконструкции, режим максимально интенсивных проекций

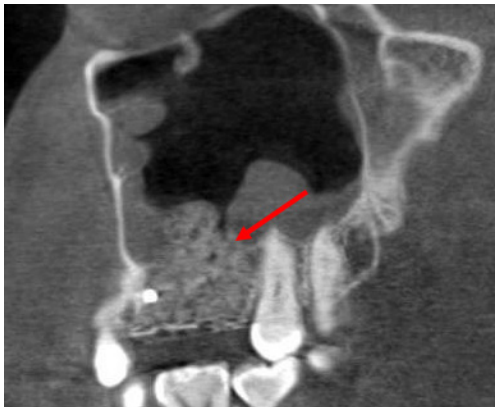

Рис. 4в. КЛКТ верхней челюсти, включая гайморовы пазухи. Сагиттальная проекция на уровне правой гайморовой пазухи. Дефект верхней челюсти заполнен титановой пластиной. 15 и 16 зуб удалены. В области удаленных зубов дифференцируется костнозамещающий материал, заполненный дефект нижней стенки гайморовой пазухи указан стрелкой

При анализе изображений, полученных с помощью конусно-лучевой томографии в полости гайморовых пазух, и верификации одонтогенного гайморита определяли уровень содержимого неоднородной плотности, полиповидные разрастания слизистой оболочки, выполняющие просвет пазухи полностью, либо частично. В структуре содержимого, в толще полиповидноутолщенной слизистой оболочки определялись инородные тела (пломбировочный материал, фрагменты медицинского инструментария, некорректно установленные импланты, фрагменты зубов), включения различной плотности.

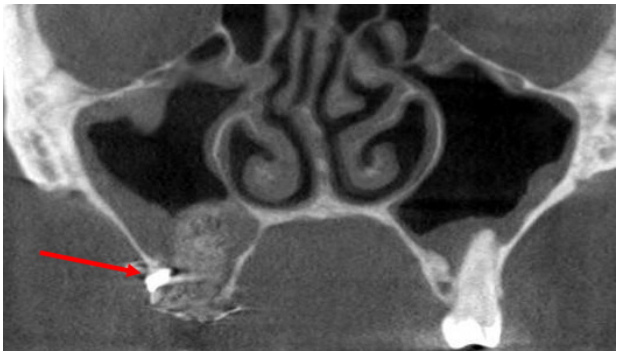

Рис. 4г. КЛКТ верхней челюсти, включая гайморовы пазухи. Фронтальная реконструкция на уровне гайморовых пазух. В области удаленных 15-16 зубов - костнозамещающий материал (операция «синуслифтинга»). Титановая пластина интимно прилежит к нижней стенке гайморовой пазухи, полностью заполняет ее дефект. Пластина фиксирована к альвеолярным отросткам с помощью титанового винта (стрелки)

На основании полученных данных, разработан объем и способ оперативного вмешательства, выбрана тактика консервативного лечения. Наблюдение пациентов в динамике позволило оценить качество выполнения оперативного вмешательства, определить эффективность консервативной терапии.

Пациентам выполнялась гайморотомия по Колдуэллу-Люку, в случае необходимости, с резекцией верхушек корней зуба, удалением кистовидного образования на корне зуба. При наличии свища между ротовой полостью и полостью гайморовой пазухи выполнялась пластика нижней стенки гайморовой

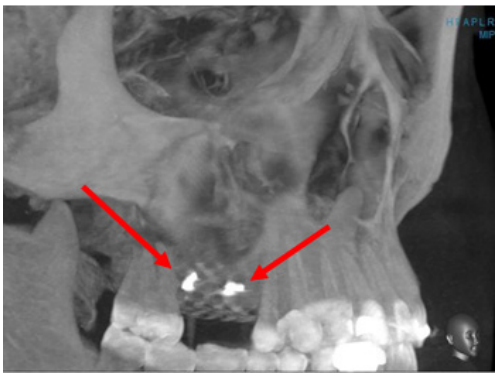

Рис.4д КЛКТ верхней челюсти, включая гайморовы пазухи. Объемное представление в режиме максимально интенсивных проекций. Дифференцируется титановая пластина,заполняющая дефект верхней челюсти, фиксированная двумя титановыми винтами (указано стрелками)

пазухи. Критериями оценки качества проведенного оперативного вмешательства являлись удовлетворительная пневматизация полости гайморовой пазухи, отсутствие инородных тел, содержимого в полости пазухи и дефекта нижней стенки гайморовой пазухи.

Заключение. Конусно-лучевая томография является информативным методом лучевой диагностики для выявления одонтогенного гайморита. Разрешающая способность конусно-лучевой томографии позволяет дифференцировать ткани периодонта, верифицировать наличие одонтогенных кист, кистогранулём, инородных тел в полости гайморовых пазух, а также визуализировать реактивные изменения слизистой оболочки придаточных пазух носа. Сопутствующее программное обеспечение позволяет лечащему врачу самостоятельно анализировать трехмерное качественное изображение интересующей его области.

Возможности конусно-лучевой томографии позволяют при минимальной лучевой нагрузке получить качественное изображение твердых и мягких тканей придаточных пазух носа и зубочелюстной системы. Возможность сочетанного изображения верхней челюсти и придаточных пазух обеспечивает выявление одонтогенного гайморита и разработку оптимальной тактики дальнейшего консервативного лечения или оперативного вмешательства.

Низкая лучевая нагрузка предоставляет возможность выполнения многократных повторных исследований с целью оценки эффективности оперативного лечения или консервативной терапии на различных этапах реабилитационного периода, а также полученного косметического и функционального результата.

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SUMMARY

CONE BEAM COMPUTED TOMOGRAPHY IN DIAGNOSTICS OF ODONTOGENIC MAXILLARY SINUSITIS (CASE REPORTS)

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Diagnostic studies performed by cone beam computed tomography Morita 3D made possible to obtain high resolution images of hard tissues of upper jawbone and maxillary sinus, to detect bony tissue defects, such as odontogenic cysts, cystogranulomas and granulomas. High-resolution and three dimensional tomographic image reconstructions allowed for optimal and prompt determination of the scope of surgical treatment and planning of effective conservative treatment regimen. Interactive diagnostics helped to estimate cosmetic and functional results of surgical treatment, to prevent the occurrence of surgical complications, and to evaluate the efficacy of conservative treatment.

The obtained data contributed to determination of particular applications of cone beam computed tomography in the diagnosis of odontogenic maxillary sinusitis, detection of specific defects with cone beam tomography as the most informative method of diagnosis; as well as to determination of weak and strong sides, and helped to offer mechanisms of x-ray diagnostics to dental surgeons and ENT specialists.

Keywords: cone beam computed tomography, maxillary sinusitis, bony tissue defects.

РЕЗЮМЕ

КОНУСНО-ЛУЧЕВАЯ ТОМОГРАФИЯ В ДИАГНОСТИКЕ ОДОНТОГЕННЫХ ГАЙМОРИТОВ (СЛУЧАИ ИЗ ПРАКТИКИ)

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Целью исследования явилась оценка возможности конусно-лучевой томографии в диагностике одонтогенных гайморитов.

Наблюдались 50 больных одонтогенным гайморитом до и после оперативного вмешательства в динамике до и после консервативного лечения. Из них мужчин было 26 (52%), женщин – 22 (44%), детей – 2 (4%), возраст пациентов варьировал в пределах от 10 до 89 лет.

На конусно-лучевом томографе «Morita» (Япония) проводились конусно-лучевая томография двух челюстей в окклюзии и верхненижнечелюстного сустава, включая гайморовы пазухи, средние зоны лица, придаточные пазухи носа.

Конусно-лучевая томография является информативным методом лучевой диагностики для выявления одонтогенного гайморита, разрешающая способность конусно-лучевой томографии позволяет дифференцировать ткани периодонта, верифицировать наличие одонтогенных кист, кистогранулём, инородных тел в полости гайморовых пазух, а также визуализировать реактивные изменения слизистой оболочки придаточных пазух носа.

Сопутствующее программное обеспечение позволяет лечащему врачу самостоятельно анализировать трехмерное качественное изображение интересующей его области.

Возможности конусно-лучевой томографии позволяют при минимальной лучевой нагрузке получить качественное изображение твердых и мягких тканей придаточных пазух носа и зубочелюстной системы. Возможность сочетанного изображения верхней челюсти и придаточных пазух обеспечивает выявление одонтогенного гайморита и разработку оптимальной тактики дальнейшего консервативного лечения или оперативного вмешательства.

Низкая лучевая нагрузка предоставляет возможность выполнения многократных повторных исследований с целью оценки эффективности оперативного лечения или консервативной терапии на различных этапах реабилитационного периода, а также полученного косметического и функционального результата.

რეზიუმე

ოდონტოგენური ჰაიმორიტის დიაგნოსტიკა კონუსურ-სხივური კომპიუტერული ტომოგრაფიის მეშვეობით (კლინიკური შემთხვევები)

ე. დემიდოვა, გ. ხურციძე

ოდესის ეროვნული სამედიცინო უნივერსიტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა კონუსურ-სხივური კომპიუტერული ტომოგრაფიის გამოყენების ეფექტურობის შეფასება ოდონტოგენური ჰაიმორიტის დიაგნოსტიკაში.
კვლევაში მონაწილეობას ღებულობდა 50 პაციენტი ოდონტოგენური ჰაიმორიტით,26 (52%) მამაკაცი,22 (44%) - ქალი და 2 (4%) ბავშვი 10-დან 89 წლის ასაკში, ოპერაციამდე და ოპერაციის შემდეგ, ასევე კონსერვატიულ მკურნალობამდე და მკურნალობის შემდეგ. კონუსურ-სხივური კომპიუტერული ტომოგრაფიის ("Morita 3", იაპონია) მეშვეობით ჩატარებულმა კვლევებმა ავტორებს მისცა ზედაყბის მაგარი ქსოვილების და მაქსილური სინუსის მაღალი რეზოლუციის გამოსახულების მიღების და ძვლის ქსოვილის დეფექტების,ანუ ოდონტოგენური

კისტების,ციტოგრანულომებისა და გრანულომების დიაგნოსტიკის საშუალება.

მაღალმა რეზოლუციამ და სამგანზომილებიანი ტომოგრაფიული გამოსახულების რეკონსტრუქციამ ოპტიმალურად მოკლე დროში განსაზღვრა ოპერაციული მკურნალობის მასშტაბი, შემუშავდა შესაბამისი სამოქმედო გეგმა და კონსერვატიული მკურნალობის ოპტიმალური ტაქტიკა. ქირურგიული გართულებების თავიდან აცილების მიზნით, ინტერაქტიული დიაგნოსტიკის საშუალებით განისაზღვრა ქირურგიული მკურნალობის კოსმეტიკური და ფუნქციური შედეგები.

კონუსურ-სხივური კომპიუტერული ტომოგრაფია წარმოადგენს ინფორმაციულ მეთოდს ოდონტოგენური ჰაიმორიტის სხივური დიაგნოსტიკისთვის; კონუსურ-სხივური კომპიუტერული ტომოგრაფიის მაღალი რეზოლუცია იძლევა პერიოდონტის ქსოვილების დიფერენცირების, ოდონტოგენური კისტების, კისტოგრანულომების, ჰაიმორის ღრუში უცხო სხეულების არსებობის ვერიფიცირების, ასევე, ცხვირის დანამატის წიაღების ლორწოვანი გარსის რეაქტიული ცვლილებების ვიზუალიზების საშუალებას.

თანამდევი პროგრამული უზრუნველყოფა მკურნალ ექიმს აძლევს მისთვის საინტერესო მიდამოს ხარისხიანი სამგანზომილებიანი გამოსახულების დამოუკიდებელი ანალიზის საშუალებას.

კონუსურ-სხივური კომპიუტერული ტომოგრაფიის შესაძლებლობები იძლევა ცხვირის დანამატი წიაღების მაგარი და რბილი ქსოვილების და ყბა-კბილთა სისტემის ხარისხიანი გამოსახულების მიღების საშუალებას მინიმალური სხივური დატვირთვით. ზედა ყბისა და დანამატი წიაღების შერწყმული გამოსახულების მიღების შესაძლებლობა განსაზღვრავს ოდონტოგენური ჰაიმორიტის გამოვლენის და შემდგომი კონსერვატიული და ოპერაციული მკურნალობის ოპტიმალური ტაქტიკის შემუშავების შესაძლებლობას.

LIPOPROTEIN ASSOCIATED PHOSPHOLIPASE A2 AS A MARKER OF VULNERABLE ATHEROSCLEROTIC PLAQUE IN PATIENTS WITH INTERNAL CAROTID ARTERY STENOSIS

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Atherosclerosis as the main reason of stroke can be observed in a majority of population in highly developed countries. More than 80% of patients have the stroke developed due to ischemia [7]. Stroke represents the third most common cause to death worldwide, affecting 15 million people from which 5 million do not survive, and the other 5 million become disabled. Stroke is the most common reason for premature permanent invalidism of elderly people [16]. Around 10-15% of strokes appear as the result of severe atherosclerosis of internal carotid artery [5]. Several studies have shown that besides the size of stenosis of internal carotid artery (ICA), the other influential risk is the composition of atherosclerotic plaque [8]. Around 20-30% of patients with asymptomatic stenosis ICA feature soft echogenic atherosclerotic plaques with a high potential of embolization. Up to 70% of echogenic plaques are the cause of symptomatic stenosis ICA. The patients with echogenic plates have 2 to 4 times higher occurrence of stroke as a result of ulceration followed by a thrombus formation [5,23].

Latest period of development of biochemical and imaging methods reveals pathological anatomy and pathological physiology processes taking place in the atherosclerotic plaque which might help to detect the patients with a high risk of stroke [14].

One of the options to detect the above mentioned patients is to identify the level of lipoprotein associated phospholipase A2 (Lp-PLA2) in the patient blood. Lipoprotein associated phospholipase A2 is the enzyme produced by inflammatory cells (monocytes macrophages, T-lymphocytes, mast cells) in the atherosclerotic plaque [18,19,22]. Lp-PLA2 is involved in the hydrolysis of oxidized phosphatidylcholines to form pro-atherogenic and pro-inflammatory substances such as lysophosphatidylcholine and oxidized fatty acids. Oxidized LDL particles are the main cause of atherosclerosis formation and development. These substances are involved in endothelial dysfunction and local inflammatory reaction resulting in necrotic core formation in the atherosclerotic plaque [17,33]. When circulating, Lp-PLA2 is bound to molecules of LDL in up to 80%, while the rest is bound to molecules HDL, VLDL and Lp (a) [31]. The advantage of Lp-PLA2 as an inflammatory marker is in its high vascular specificity. The concentration of Lp-PLA2 in blood does not increase due

to various causes of inflammation as is the case with many inflammatory markers e.g. CRP, fibrinogen [4,11]. Due to the nature of Lp-PLA2, determining its level might help to detect the patients with soft atherosclerotic plaque and high risk of stroke.

Material and methods. *Patient selection*

The research was carried out at Clinic of Vascular Surgery, East Slovak Institute of Cardiovascular Diseases (VÚSCH, a.s.), Faculty of Medicine, University of Pavol Jozef Šafárik in 70 patients with hemodynamically significant stenosis of internal carotid artery, out of which 26 (37%) were female and 44 (63%) were male. The average age was 70 ± 8. All the patients were familiar with the research and had signed the informed consent prior to its start. The research was approved by the ethics committee of VÚSCH a. s. on 7 December 2015.

Biomedical research excluded the patients with acute or chronical liver disease, heart failure, heart ischemia, heart chamber fibrillation, hear valves disorders, uncontrolled hypertension, decompensated diabetes mellitus, patients with trauma, autoimmune disease, malignant cancer and also the patients with acute or chronic infection.

The patients, n = 70, were divided into two groups, based on symptomatology. The first group contained 40 (57%) asymptomatic patients with stenosis of internal carotid artery of up to 70 %, the second group contained 30 (43%) symptomatic patients with stenosis of internal carotid artery of more than 50 %, of which 20 patients (66%) have had a stroke, or transient ischemic attack (TIA), 10 patients (33%). All the patients were indicated to carotid endarterectomy as a surgical prevention of stroke.

A group of 20 healthy individuals with no clinical demonstration of acute or chronic disease was used for biochemical blood analysis.

Based on the histology results of atherosclerotic plaque examination, the patients were divided into two groups, too. The first was group of 38 patients (54%) with soft atherosclerotic plaque, and the second was group of 32 patients (46%) with calcified atherosclerotic plaque.

Clinical examination of patients

Ultrasonography examination of carotid arteries

Ultrasonography examination was performed with the use of 8 MHz linear multi frequency USG device Philips HD 11 XE, featuring duplex doppler sonography and colour mapping of the blood flow.

The size of stenosis of internal carotid artery was measured in all patients with the use of evaluation of peak systolic velocity (PSV peak systolic velocity) and evaluation of end diastolic velocity (EDV). Physiological values considered for internal carotid artery were PSV 120 cm/s maximum and EDV 40 cm/s maximum [6]. Based on the measurement, the percentage of stenosis was calculated as recommended by Society of Radiologists in Ultrasound [13].

Vulnerability of atherosclerotic plaque was evaluated in B mode with gray-scale median value. Based on echogenicity of atherosclerotic plaque, the patients were divided into four groups [29]. The first one contained 19 patients (27%) with soft, fully anechogenic atherosclerotic plaque, the second had patients with mixed atherosclerotic plaque with predominance of soft – anechogenic sections (echogenic sections were less than 50%) in 17 patients (24%), the third group had patients with mixed atherosclerotic plaque with predominance of calcified section (anechogenic sections were less than 50%) in 12 patients (17%), and the last group had patients with calcified – fully echogenic atherosclerotic plaque in 22 patients (32%).

Histology analysis of atherosclerotic plaque

Eversion carotid endarterectomy was performed in all patients to obtain the atherosclerotic plaque for histological examination. Atherosclerotic plaques were fixed in 10 % formalin solution, decalcified and paraffin embedded in form of small blocks. Then, 5μm blocks were cut off the paraffin to undergo a histological examination. The blocks were examined in longitudinal section at the point of greatest stenosis. The colouring used was hematoxylin-eosin. According to histological examination, the patients were divided into two groups, one containing patients with soft atherosclerotic plaque, 38 patients (54%) and the second containing patients with calcified atherosclerotic plaque, 32 patients (46%).

Biochemical examination of blood

All the patients were taken their blood for biochemical testing early morning prior to surgery. Lipid status was tested (T-Chol, LDL, HDL, TG) along with fibrinogen concentration and CRP. A blood sample for Lp-PLA2 and IL-4 determination was centrifuged for 10 minutes at 2500 revolutions. The serum was then frozen at – 80 °C until its further analysis. To determine the concentration of Lp-PLA2, ELISA kit was used (Human lipoprotein associated phospolipase A2, Cussabio, USA, detection range 1.56 ng/ml - 100 ng/ml, sensitivity 0.39 ng/ml, detection wavelength 0.39 ng/ml). Concentration of IL-4 was also determined with the use of ELISA kit (Human IL-4 platinum ELISA, eBioscience, San Diego USA, detection range 7.8 - 500 pg/mL, sensitivity 1.3 pg/mL). Samples LP-PLA2 and IL-4 were determined on Synergy H4 multiplate reader, BioTek Vermont, USA.

Statistical analysis

Results were evaluated with the use of descriptive statistics method (multiplicity, arithmetic averages ± standard error of means – (S.E.M.), percentage representation) with the use of Anova one way test (MINITAB Inc. version 11.24, Coventry, United Kingdom). The relations between the two variables – the group of symptomatic and asymptomatic patients were evaluated with the use of Anova one way test (MINITAB Inc. version 11.24, Coventry, United Kingdom). Correlations were evaluated with the use of Pearson test (MINITAB Inc. version 11.24, Coventry, United Kingdom, Microsoft Office Excel 2013). The relations among more than two variables (symptomatic, asymptomatic patients and control group) were evaluated with the use of Tukey test (MINITAB Inc. version 11.24,

Table 1. Level of biochemical and inflammatory markers in symptomatic and asymptomatic patients

	Symptomatic patients n = 30 (43%)	Asymptomatic patients n = 40 (57%)	Control group n = 20	p
T-Chol (mmol/l)	4.68 ± 0.27[a]	4.37 ± 0.19[a]	3.70 ± 0.08[b]	*
LDL (mmol/l)	3.09 ± 0.20[a]	2.85 ± 0.13[a]	2.07 ± 0.08[b]	***
HDL (mmol/l)	1.01 ± 0.04[b]	0.99 ± 0.03[b]	1.77 ± 0.08[a]	***
TG (mmol/l)	1.89 ± 0.22[ab]	2.13 ± 0.22[a]	1.22 ± 0.14[b]	*
CRP (mg/l)	8.36 ± 1.91[a]	5.06 ±1.02[a]	0.95 ± 0.21[b]	**
Fib (g/l)	4.14 ± 0.20[a]	3.79 ± 0.15[a]	2.88 ± 0.18[b]	***
IL-4 (pg/ml)	65.77 ± 3.78[a]	42.69 ± 1.73[b]	31.60 ± 0.55[c]	***
Lp-PLA2 (µg/l)	285.30 ± 2.05[a]	274.35 ± 3.38[b]	221.82 ± 1.13[c]	***

The values in the tables show the average ± S.E.M. (standard error of means), percentage, n=number of patients
a, b, c – values represent statistically significant differences between the groups, values of p<0.05 are considered statistically significant (Tukey test, MINITAB Inc., Coventry, United Kingdom)
*Significant changes marked with *** are statistically significant when P<0.001, ** when P<0.01 and * - when P<0.05 (Anova one way test, MINITAB Inc., Coventry, United Kingdom)*
T-Chol - total cholesterol, LDL - low density lipoprotein, HDL - high density lipoprotein, TG - triglycerides, CRP - C reactive protein, Fib - fibrinogen, IL-4 - interleukin 4, Lp-PLA2 – lipoprotein associated phospholipase A2

Table 2. Markers level in patients with soft and calcified plaque

	Soft plaque n = 38 (54%)	Hard plaque n = 32 (46%)	P
T-Chol (mmol/l)	4.62 ± 0.23	4.38 ± 0.21	N.S.
LDL (mmol/l)	3.01 ± 0.17	2.89 ± 0.16	N.S.
HDL (mmol/l)	1.01 ± 0.04	0.99 ± 0.03	N.S.
TG (mmol/l)	2.43 ± 0.28	1.60 ± 0.09	*
CRP (mg/l)	8.08 ± 1.61	4.78 ± 1.16	**
Fib (g/l)	4.07 ± 0.17	3.80 ± 0.17	N.S.
IL-4 (pg/ml)	65.56 ± 2.92	38.83 ± 1.61	***
Lp-PLA2 (µg/l)	293.72 ± 1.65	263.50 ± 1.90	***

The values in the tables show the average ± S.E.M. (standard error of means), percentage, n = number of patients
*Significant changes marked with *** - are statistically significant when P<0.001, ** - when P<0.01 and * - when P<0.05 (Anova one way test, MINITAB Inc., Coventry, United Kingdom)*

Coventry, United Kingdom), where different letters represent statistically significant relations for P<0.05.

Results and their discussion. Our group of 70 patients had 40 (57%) asymptomatic patients and 30 (43%) symptomatic patients of which 20 (66%) patients were after a stroke and 10 (33%) patients had transient ischemic attack.

Lipids status (T-Chol, LDL, HDL, TG) and the level of inflammatory markers (fibrinogen, CRP) in patients are shown in Table 1.

The highest concentrations of T-Chol, LDL, HDL, CRP and Fib were measured in symptomatic patients, however, these did not feature a significant difference compared with the group of asymptomatic patients (P>0.05). Significant difference (P<0.05) between the symptomatic and asymptomatic patients was found in concentration of TG. Significant differences were found in the following markers: T-Chol (P<0.005), LDL (P<0.001), HDL (P<0.001), CRP (P<0.01) and Fib (P<0.001), when comparing the two groups (symptomatic and asymptomatic patients) with a control group of healthy individuals. Out of specific markers IL-4 and Lp-PLA2, a significant difference was found in IL-4 (P<0.001) and in Lp-PLA2 (P<0.001). According to histological examination, the patients were divided into two groups. There were 38 (54%) patients with soft atherosclerotic plaque and 32 (46%) patients with calcified atherosclerotic plaque. The levels of tracked markers in both groups are shown in Table 2.

When evaluating concentration of tracked parameters in patients with soft atherosclerotic plaque and patients with calcified atherosclerotic plaque, significant differences were found in these markers: TG (P<0.05), CRP (P<0.01), IL-4 (P<0.001) and Lp-PLA2 (P<0.001). Other markers (T-Chol, LDL, HDL and Fib) did not demonstrate significant differences between the two groups. Concentration of Lp-PLA2 in patients with soft and calcified atherosclerotic plaque is shown in Fig. 1.

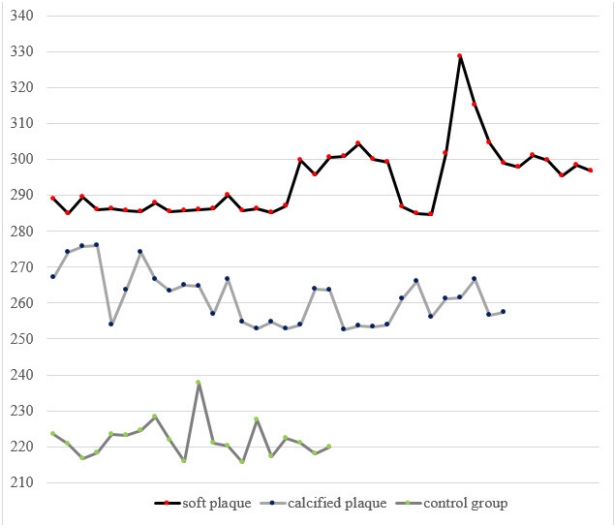

Fig. Concentration of Lp-PLA2 (μg/l) in patients with soft and calcified atherosclerotic plaque and a control group

Correlations

Evaluation of correlations revealed that concentration of Lp-PLA2 correlates with T-Chol (P<0.05), LDL and Fib (P<0.01), HDL, TG, CRP and IL-4 (P<0.001). Concentration of IL-4 in our set of patients correlates with T-chol, LDL and TG (P<0.05), Fib (P<0.01), CRP and Lp-PLA2 (P<0.001). Correlation relations are shown in Table 3.

Our research showed the highest concentration of Lp-PLA2 285.30 ± 2.05 (P<0.001) in symptomatic patients, similarly, the highest concentrations of Lp-PLA2 293.72 ± 1.65 (P<0.001) were observed in patients with soft atherosclerotic plaque with high embolization activity. Majority of symptomatic patients 23 (77%) featured a soft atherosclerotic plaque that was a cause of neurological symptomatology. Several histopathological studies have interpreted the occurrence of higher concentrations of Lp-PLA2 in patients with vulnerable atherosclerotic plate with a large lipid core and thin fibrous cap, similarly to our case [22, 32, 33]. The concentration of Lp-PLA2 correlates more with the composition of plaque rather than its size [21]. Beňovská et al. (2010) interprets higher concentrations of Lp-PLA2, over 300 μg/l, in patients after a stroke. The lowest concentration of Lp-PLA2 221.82 ± 1.13 (P<0.001) obtained in our research was in the control group of healthy individuals. Results confirm that Lp-PLA2 can be considered as an individual parameter to assess a stroke as presented in bibliography [28]. In Rotterdam study, Oei et al. (2005) showed a higher activity of Lp-PLA2 in patients after a stroke. Multicentre Lp-PLA2 Studies Collaboration evaluating the use of Lp-PLA2 for risk assessment of cardiovascular attacks, strokes and sudden cardiac death had confirmed the linkage between Lp-PLA2 and coronary arteries disease, but did not confirm such an intensive linkage to stroke occurrence which is explained by studies heterogenity [30]. In general, it can be concluded that the evaluation of ischemic stroke was less dealt with in the previous studies compared to cardiovascular diseases.

Surgery treatment (carotid endarterectomy) is indicated in patients with symptomatic stenosis of internal carotid artery within 50 – 99% and also asymptomatic patients with stenosis within 70 – 99%. The surgery is highly beneficial in symptomatic patients where the risk of recurrent stroke is up to 30% within 30 days. The benefit of surgery is not so apparent in asymptomatic patients where the risk of stroke is 3,2 % [2,27]. Nambi et al. (2009) in his ARIC study referred to the fact that measurement of Lp-PLA2 concentration in patients with atherosclerotic disease of carotid arteries had significantly contributed to identification of patients with a high risk of ischemic stroke.

In general, inflammatory process is well understood as the key factor in formation and development of atherosclerosis. The inflammation is also responsible for atherosclerotic plaque destabilization which can result in a stroke along with carotid arteries disease. Several studies from last decades showed higher values of systemic inflammatory markers (CRP, IL-4, IL-6) in patients with arteries atherosclerosis, the concentration of which can correlate with progress or even rupture of the atherosclerotic plaque [1,9,24]. At present, C-reactive protein is not only the marker of acute inflammatory reaction but also the marker of systemic chronic inflammatory reaction in atherosclerosis. The linkage between a higher level of CRP and the course of acute vascular syndromes such as stroke has been confirmed in several studies [1,3,10]. CRP level is higher

Table 3. Correlation relations between Lp-PLA2, IL-4 and other tracked parameters

	Lp-PLA2	**IL-4**
T-Chol (mmol/l)	*	*
LDL (mmol/l)	**	*
HDL (mmol/l)	***	N.S.
TG (mmol/l)	***	*
CRP (mg/l)	***	***
Fib (g/l)	**	**
IL-4 (pg/ml)	***	-
Lp-PLA2 (μg/l)	-	***

*Correlation relations according to Pearson - significant changes marked with *** are statistically significant when P<0.001, ** when P<0.01 and * when P<0.05 (Pearson test, MINITAB Inc., Coventry, United Kingdom*

mainly in patients with soft vulnerable atherosclerotic plaque. The higher levels mean a risk factor of atherosclerotic process progress followed by vascular complications. Some studies show that CRP levels do not correspond with the process of atherogenesis as much as assumed before, and do not reflect actual formation of atherosclerotic plaques. These studies define higher levels of CRP as a result of patient polymorbidity [11]. The opposite studies refer to a direct impact of CRP upon the process of arteries changes within the atherosclerotic process [15, 34]. Our study shows the highest concentration of CRP in patients with soft atherosclerotic plaque 8.08 ± 1.61 mg/l. In comparison with calcified atherosclerotic plaque 4.78 ± 1.16 mg/l group of patients, the levels of CRP were significantly lower, $P<0.01$. Toth (2010) claims that simultaneous determination of CRP and Lp-PLA2 helps to identify the risk of stroke. Similarly, Atherosclerosis Risk in Communities (ARIC) study mentions that concurrent increase of CRP and Lp-PLA2 concentration can help do detect the patients with high risk of stroke [24].

Although IL-4 is traditionally considered to be anti-inflammatory cytokine, several studies alike Lee et al. (2010) have claimed its important role in the process of formation and progress of vascular inflammation which, in the end, leads to a plaque destabilization. Profumo et al. (2007) and Gabrile et al. (2016) referred to higher levels of IL-4 in patients with symptomatic stenosis of internal carotid artery. Higher levels of IL-4 in our patients set were detected in symptomatic patients, resp. in patients with soft atherosclerotic plaque $P<0.001$, which points out a pro inflammatory activity of IL-4 within chronic inflammatory process of atherosclerosis.

Conclusion

The paper deals with higher concentrations of Lp-PLA2 in patients with a soft atherosclerotic plaque with a high embolization potential. Higher concentration of Lp-PLA2 and systemic inflammatory markers (CRP, IL-4) could be used along with ultrasonography to detect mainly asymptomatic patients who are in urgent need of surgical or endovascular treatment as a prevention of stroke.

Conflict of Interest. There is no conflict of interest.

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SUMMARY

LIPOPROTEIN ASSOCIATED PHOSPHOLIPASE A2 AS A MARKER OF VULNERABLE ATHEROSCLEROTIC PLAQUE IN PATIENTS WITH INTERNAL CAROTID ARTERY STENOSIS

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The aim of this study was to compare the concentration of inflammatory vascular markers and morphological structure of atherosclerotic plaque in symptomatic and asymptomatic patients with the stenosis of internal carotid artery (ICA).

The research was carried out in 70 patients with hemodynamically significant stenosis of ICA out of which 40 (57%) were asymptomatic patients and 30 (43%) were symptomatic patients, of which 20 patients (66%) have had a stroke, or transient ischemic attack (TIA), 10 patients (33%). All the patients were indicated to carotid endarterectomy as a surgical prevention of stroke. All the patients were taken their blood for biochemical testing (T-Chol, LDL, HDL, TG, Fibrinogen, CRP and specific markers IL-4 and Lp-PLA2) early morning prior to surgery.

The highest concentrations of T-Chol, LDL, HDL, CRP and Fibrinogen were measured in symptomatic patients, however, these did not feature a significant difference compared with the group of asymptomatic pa-

tients (P>0.05). Significant difference was found in IL-4 (P<0.001) and in Lp-PLA2 (P<0.001).
When evaluating concentration of tracked parameters in patients with soft atherosclerotic plaque and patients with calcified atherosclerotic plaque, significant differences were found in these markers: TG (P<0.05), CRP (P<0.01), IL-4 (P<0.001) and Lp-PLA2 (P<0.001).

The paper deals with higher concentrations of Lp-PLA2 in patients with a soft atherosclerotic plaque. Higher concentration of Lp-PLA2 and systemic inflammatory markers (CRP, IL-4) could be used along with ultrasonography to detect mainly asymptomatic patients who are in urgent need of surgical or endovascular treatment as a prevention of stroke.

Keywords: Lp-PLA2, internal carotid artery stenosis, soft plaque, carotid endarterectomy, stroke.

РЕЗЮМЕ

ЛИПОПРОТЕИН-АССОЦИИРОВАННАЯ ФОСФОЛИПАЗА А2, КАК МАРКЕР УЯЗВИМОЙ АТЕРОСКЛЕРОТИЧЕСКОЙ БЛЯШКИ У ПАЦИЕНТОВ СО СТЕНОЗОМ ВНУТРЕННЕЙ СОННОЙ АРТЕРИИ

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Повышенная концентрация Lp-PLA2 может способствовать раннему выявлению пациентов с высоким риском инсульта.

Целью исследования явилось сравнение концентрации воспалительных сосудистых маркеров и морфологической структуры атеросклеротической бляшки у пациентов с симптоматическим и ассимптоматическим стенозом внутренней сонной артерии.

В исследование включены 70 пациентов с гемодинамически значимым стенозом внутренней сонной артерии (ВСА), из них 40 (57%) были ассимптоматическими, 30 (43%) - симптоматическими пациентами, 20 (66%) пациентов имели инсульт, 10 (33%) – транзиторную ишемическую атаку.

Всем пациентам рекомендована каротидная эндартерэктомия как хирургическая профилактика инсульта. До операции у всех пациентов была забрана кровь для биохимического исследования (T-Chol, LDL, HDL, TG, фибриноген, CRP и специфические маркеры IL-4 и Lp-PLA2).

Самые высокие концентрации T-Chol, LDL, HDL, CRP и фибриногена выявлены у симптоматических пациентов, однако они статистически не отличались от группы ассимптоматических пациентов (P>0,05). Значительная разница обнаружена при оценке IL-4 (p<0,001) и Lp-PLA2 (p<0,001). При оценке концентрации отслеживаемых параметров у пациентов с мягкой атеросклеротической бляшкой и пациентов с кальцифицированной атеросклеротической бляшкой обнаружены статистические различия в следующих маркерах: TG (P<0,05), CRP (P<0,01), IL-4 (P<0,001) и Lp-PLA2 (p<0,001).

Повышенная концентрация Lp-PLA2 выявлена у пациентов с мягкой атеросклеротической бляшкой. Повышение концентрации Lp-PLA2 и системных воспалительных маркеров (CRP, IL-4) наряду с ультрасонографией атеросклеротической бляшки сонных артерий, может использоваться для выявления групп высокого риска с ассимптоматическим стенозом ВСА, которым необходима хирургическая или эндоваскулярная профилактика инсульта.

რეზიუმე

ლიპოპროტეინ-ასოცირებული ფოსფოლიპაზა A2, როგორც ათეროსკლეროზული ფოლაქის მარკერი ავადმყოფებში შიგნითა საძილე არტერიის სტენოზით

[1]პ. სტეფანიკი, [1,4]ი. კოპოლოვეცი, [2]ზ. ჰერტელიოვა, [3]ტ. სტეფანი, [1]მ. ფრანკოვიცოვა

[1]სისხლძარღვთა კლინიკა, აღმოსავლეთ სლოვაკიის გულ-სისხლძარღვთა დაავადების ინსტიტუტი «VÚSCH»; [2]პ. შაფარიკას სახ. უნივერსიტეტი, სამედიცინო ფაკულტეტი, კოშიცე; [3]შინაგანი მედიცინის კლინიკა, ლ. პასტერის სახ. საუნივერსიტეტო კლინიკა, სამედიცინო ფაკულტეტი, კოშიცე, სლოვაკიის რესპუბლიკა; [4]უმაღლესი სახელმწიფო სასწავლო დაწესებულება "უჟგოროდის ნაციონალური უნივერსიტეტი", სამედიცინო ფაკულტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა ანთებითი სისხლძარღვოვანი კონცენტრაციის მარკერების შედარება ათეროსკლეროზული ფოლაქის მორფოლოგიურ სტრუქტურასთან პაციენტებში შიგნითა საძილე არტერიის სიმპტომური და ასიმპტომური სტენოზით.

კვლევაში ჩართული იყო 70 ავადმყოფი შიგნითა საძილე არტერიის (შსა) ჰემოდინამიკურად მნიშვნელოვანი სტენოზით, მათ შორის 40 (57%) - ასიმპტომური, 30 (43%) - სიმპტომური პაციენტი, 20 (66%) პაციენტი იყო ინსულტით, 10 (33%) - ტრანზიტორული იშემიური შეტევით.

ყველა პაციენტს დაენიშნა კაროტიდული ენდარტერექტომია,როგორც ინსულტის ქირურგიული პროფილაქტიკა. ოპერაციამდე პაციენტებს ჩაუტარდა სისხლის ბიოქიმიური გამოკვლევა (T-Chol, LDL, HDL, CRP, ფიბრინოგენი და სპეციფიკურ მარკერებზე IL-4 და Lp-PLA2).

გამოვლინდა T-Chol, LDL, HDL, CRP და ფიბრინოგენის კონცენტრაციის მაღალი მაჩვენებლები სიმპტომურ პაციენტებში, რომლებიც სტატისტიკურად სარწმუნოდ არ განსხვავდებოდნენ ასიმპტომურ პაციენტების მონაცემისაგან (P>0,05). მნიშვნელოვანი სხვაობა გამოვლინდა IL-4 (p<0,001) და Lp-PLA2 (p<0,001) მაჩვენებლებში. ზემოაღნიშნული პარამეტრების შეფასებისას პაციენტებში რბილი ათეროსკლეროზული ფოლაქით და კალციფიცირებული ათეროკსლეროზული ფოლაქით გამოვლინდა სტატისტიკური სხვაობა შემდეგ მარკერებში: TG (P<0,05), CRP (P<0,01), IL-4 (P<0,001) და Lp-PLA2 (p<0,001).

Lp-PLA2-ის მომატებული კონცენტრაცია გამოვლინდა ავადმყოფებში რბილი ათეროსკლეროზული ფოლაქით. Lp-PLA2 კონცენტრაციის და სისტემური ანთებითი მაჩვენებლების (CRP, IL-4) მატება საძილე არტერიების ათეროკლეროზული ფოლაქით, სონოგრაფიულ მონაცემებთან ერთად, შეიძლება გამოყენებული იყოს შსა-ის ასიმეტრიული სტენოზის მაღალი რისკის ჯგუფის გამოსავლენად.

МОДИФИЦИРОВАННАЯ СИСТЕМА ТРОМБОПРОФИЛАКТИКИ У БОЛЬНЫХ ХИРУРГИЧЕСКОГО ПРОФИЛЯ

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Венозные тромбоэмболичиские осложнения (ВТЭО) остаются потенциально опасными для жизни больных, особенно, у пациентов после хирургических вмешательств [8]. На фоне достижения общего снижения послеоперационной летальности у хирургических больных тромбоз глубоких вен и связанная с ним тромбоэмболия легочной артерии остаются доминирующими послеоперационными осложнениями и являются значимой проблемой для современной хирургии [3]. Несмотря на внедрение в клиническую практику протоколов тромбопрофилактики, частота развития ВТЭО остается на высоком уровне, в частности у пациентов после протезирования тазобедренного сустава, операций на мочевыделительной системе, на толстой и прямой кишке, при реваскуляризирующих операциях. Применение профилактических доз нефракционированного гепарина (НФГ) сопровождается развитием послеоперационного тромбоза в 30,1% наблюдений, низкомолекулярного гепарина (НМГ) – в 16,1%, плацебо – в 54,2% [9], что диктует необходимость разработки более эффективной тромбопрофилактики послеоперационных венозных тромбозов.

Целью исследования явилось снижение частоты развития послеоперационного тромбоза вен бассейна нижней полой вены при плановых хирургических вмешательствах путем применения модифицированного способа тромбопрофилактики.

Материал и методы. I группу исследования составили 482 пациента, прооперированных в хирургических отделениях КЗТОС «Тернопольской университетской больницы» в течение 2012-2014 гг. Тромбопрофилактика оперированным пациентам осуществлялась в соответствии с утвержденными отраслевыми междисциплинарными клиническими рекомендациями «Венозный тромбоэмболизм. Диагностика. Лечение. Профилактика» [1].

Пациентам I группы проведена оценка риска развития послеоперационного венозного тромбоэмболизма (ПВТЭ) с применением шкалы J. Caprini, согласно которой у 133 пациентов установлена очень высокая степень риска развития ПВТЭ, у 172 – высокая степень риска, у 142 – умеренная степень риска и у 35 больных - низкая степень риска развития ПВТЭ.

Рядом исследователей [5,10] высказана мысль о несовершенстве шкалы J. Caprini. Они указывают на то, что в ряде наблюдений уровень риска развития ПВТЭ находится на границе соседних степеней риска, а во многих случаях степень риска развития ПВТЭ не соответствует действительному положению вещей. Согласно нашим исследованиям, подобное происходит ввиду неучета уровня хирургического стресса у оперируемого пациента при установлении степени риска развития ПВТЭ.

Согласно вышеизложенному, у пациентов при определении степени риска развития ПВТЭ по шкале

J. Caprini следует одновременно осуществлять определение уровня хирургического стресса. Уровень стресса устанавливался по содержанию глюкозы и кортизола в крови в дооперационном периоде, во время травматического этапа хирургического вмешательства и в раннем послеоперационном периоде [4]. Анализируя полученные данные установлено, что группу пациентов с высоким уровнем хирургического стресса (группа IA, n=183 (37,97%) пациента) составили 133 больных с очень высокой степенью риска развития ПВТЭ и 50 больных с высокой степенью риска ПВТЭ по шкале J. Caprini; группу IB - n=139 (28,84%) больных с умеренным уровнем хирургического стресса - 122 пациента с высокой степенью риска развития ПВТЭ и 17 больных со средней степенью риска развития ПВТЭ и группу IC - n=160 (33,08%) больных с низким уровнем хирургического стресса – 125 больных со средней степенью риска развития ПВТЭ и 35 больных с низкой степенью.

В группу IA, больные с высоким уровнем хирургического стресса, включены пациенты, которым выполнены ортопедические операции, среди которых тотальное цементное эндопротезирование тазобедренного сустава - 41 (22,41%) случай, металлоостеосинтез перелома шейки бедренной кости - 60 (32,79%) случаев, металлоостеосинтез перелома бедренной кости - 24 (13,12%); колпроктэктомия - 4 (2,19%); правосторонняя гемиколэктомия - 32 (17,49%) случая; панкреатодуоденальная резекция - 4 (2,19%) пациента; гастрэктомия - 8 (4,37%) больных; аорто-бифеморальное аллопротезирование инфраренальной аневризмы брюшной аорты - 9 (4,92 %) случаев.

В группу IB, больные с умеренным уровнем хирургического стресса, вошли пациенты, которым проведены оперативные вмешательства по поводу хирургической патологии гастро-дуоденальной зоны - 29 (20,87%) пациентов, гепато-панкреато-билиарной системы - 49 (35,68%), мочевыводящей системы - 31 (22,30%) больной, облитерирующего атеросклероза брюшного отдела аорты и магистральных артерий нижних конечностей - 30 (21,57%).

Группу IC составили больные с низким уровнем хирургического стресса - 160 (31,23%) пациентов, у которых применены малоинвазивная технология оперативного лечения на гепатобилиарной и мочевыделительной системах - 92 (57,50%) случая и больные с пластикой вентральных грыж - 68 (42,50%) пациентов.

Оперативное вмешательство способствует росту гиперкоагуляционных свойств крови [2]. Инициация гиперкоагуляционного синдрома осуществляется на травматическом этапе хирургического вмешательства с максимальным его ростом ко 2-3 часу раннего послеоперационного периода. Формирование гиперкоагуляционного синдрома происходит, в основном, за счет увеличения содержания тромбин-фибринной фракции (IIa фактор) в сыворотке крови. Превалирующее влияние на IIa фактор гемокоагуляционного каскада проявляет только НФГ [6]. Промежуток времени между окончанием операции и первой инъекцией НМГ (6 или 12 ч после окончания хирургического вмешательства), обладает преимущественным влиянием на Ха фактор, достаточный для формирования тромбоза в венозной системе. В указанный промежуток времени необходимо осуществить поступление в организм НФГ в дозе, которая должна соответствовать уровню хирургического стресса. На 2-4 сутки послеоперационного периода НФГ вводится в половинной дозе от первоначальной, не нарушая схему одновременного применения НМГ, согласно рекомендаций ACCP 2016 года [7].

216 пациентов (2014-2015 гг.) составили II группу наблюдения, куда включены 92 пациента, которые, с точки зрения нозологии патологического процесса, объема и сложности оперативного лечения соответствовали пациентам I группы. При установлении степени риска развития ПВТЭ по шкале J. Caprini с учетом степени хирургического риска, в группу пациентов с высоким уровнем хирургического стресса вошли 92 (42,73%) больных (IIA), в группу пациентов с умеренным уровнем хирургического стресса - 57 (26,39%) больных (IIB) и в группу пациентов с низким уровнем хирургического стресса - 67 (31,02%) (IIC группа).

Результаты и их обсуждение. Послеоперационный тромбоз вен системы нижней полой вены (НПВ) у пациентов I группы развился в 92 (19,17%) случаев. Чаще всего послеоперационный тромбоз диагностировали в группе IA (высокий уровень хирургического стресса) - 45 (24,59%) наблюдений, в IB группе (умеренный уровень хирургического стресса) - 26 (18,84%) наблюдений, а в группе IC (низкий уровень хирургического стресса) послеоперационный тромбоз обнаружили в 21 (13,21%) случае.

Из 92 наблюдений послеоперационного тромбоза у пациентов I группы в 80 (86,96%) случаях тромботической процесс диагностирован в глубоких венах системы НПВ, в 12 (13,04%) – в системе подкожных вен нижних конечностей. Из 80 наблюдений у 13 (16,25%) диагностирован флотирующий тромб. Больные с флотирующим тромбом составили группу риска развития ТЭЛА и указанной группе пациентов с целью предупреждения развития ТЭЛА проведено оперативное вмешательство - тромбэктомия по неотложным показаниям.

У пациентов II группы, у которых применяли модифицированный способ тромбопрофилактики, в послеоперационном периоде диагностировано 23 (10,65%) случая тромбоза вен бассейна НПВ. Чаще всего послеоперационный тромбоз проявлялся в группе IIA (высокий уровень хирургического стресса) - 12 (13,04%) наблюдений, в группе IIB (умеренный уровень хирургического стресса) - 6 (10,53%), а в группе IIC (низкий уровень хирургического стресса) послеоперационный тромбоз обнаружен в 5 (7,46%) случаях.

У 18 (78,26%) из 23 (10,65%) пациентов с послеоперационным тромбозом в системе НПВ тромботической процесс локализовался в глубокой венозной системе, у 5 (21,74%) больных - варикотромбофлебит. Во всех наблюдениях послеоперационный тромбоз как в глубоких венозных магистралях, так и в поверхностной венозной системе нижних конечностей не носил эмбологенный характер.

При анализе полученных результатов исследования установлено, что включение фактора хирургического стресса в шкалу риска развития послеоперационного тромбоза по J. Caprini (2012) объективизирует систему определения риска развития послеоперационного венозного тромбоза. При этом утверждается, что для больных с высоким уровнем хирургического стресса характерным является высокий риск развития послеоперационного тромбоза, для пациентов с умеренным уровнем хирургического стресса - умеренный риск, а для пациентов с низким уровнем хирургического стресса - низкий риск развития послеоперационного венозного тромбоза.

Применение модифицированного способа тромбопрофилактики при оперативных вмешательствах у пациентов II группы способствовал снижению частоты развития послеоперационного тромбоза вен системы НПВ в 1,8 ($p<0,001$) раза, что нашло свое отражение в группах пациентов с разным уровнем хирургического стресса. Так, у пациентов II группы с высоким уровнем хирургического стресса частота развития ПВТО снизилась в 1,9 ($p<0,001$) раза в сравнении с аналогичными пациентами I группы, у пациентов II группы с умеренным уровнем хирургического стресса частота развития ПВТО уменьшилась в 1,8 ($p<0,001$) раза в сравнении с пациентами I группы, у пациентов II группы с низким уровнем хирургического стресса частота развития ПВТО снизилась в 1,8 ($p<0,001$) раза по сравнению с аналогичными пациентами I группы.

Выводы. Определение уровня хирургического стресса у пациентов с установленным риском развития послеоперационного тромбоза вен системы НПВ по шкале J. Caprini (2012) объективизирует систему установления риска развития послеоперационного тромбоза вен бассейна НПВ и дает возможность выделить группы с высоким, умеренным и низким уровнем риска развития послеоперационного тромбоза.

Включение НФГ в систему тромбопрофилактики при плановых оперативных вмешательствах дает возможность снизить частоту развития послеоперационного тромбоза вен бассейна НПВ в 1,8 ($p<0,001$) раза.

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SUMMARY

MODIFIED SYSTEM OF THROMBOPROPHYLAXIS IN PATIENTS WITH SURGICAL PROFILE

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The aim of the study was to reduce the incidence of postoperative thrombosis in the veins of the inferior vena cava basin under planned surgical interventions by using a modified thromboprophylaxis method. Two groups of patients were studied in a total of 698 patients who underwent a risk assessment of postoperative venous thromboembolism (PVTE) using the J. Caprini scale (2012). According to the patients indicated in determining the degree of risk of HTHP development according to the J. Caprini scale, the level of surgical stress was simultaneously determined. The level of the latter was established by the content of glucose and cortisol in the blood in the preoperative period, during the traumatic stage of surgical intervention and in the early postoperative period. Introduction to the J. Caprini system of the degree of surgical stress objectifies the system for

determining the risk of postoperative venous thrombosis. Inclusion of UFH (the prevailing influence on factor II) in the system of thromboprophylaxis of LMWH (predominant influence on Xa factor) with planned surgical interventions made it possible to reduce the incidence of postoperative thrombosis of the veins in the NIP basin by 1.8 (p<0.001) times.

Keywords: surgical stress, thromboprophylaxis, venous thromboembolic complications.

РЕЗЮМЕ

МОДИФИЦИРОВАННАЯ СИСТЕМА ТРОМБОПРОФИЛАКТИКИ У БОЛЬНЫХ ХИРУРГИЧЕСКОГО ПРОФИЛЯ

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Целью исследования явилось снижение частоты развития послеоперационного тромбоза вен бассейна нижней полой вены при плановых хирургических вмешательствах путем применения модифицированного способа тромбопрофилактики.

Исследовались две группы больных (n=698), которым была проведена оценка риска развития послеоперационного венозного тромбоэмболизма (ПВТЭ), используя шкалу J. Caprini (2012). Наряду с определением степени риска развития ПВТЭ по шкале J. Caprini, осуществлялось определение уровня хирургического стресса. Уровень стресса устанавливали по содержанию глюкозы и кортизола в крови в дооперационном периоде, во время травматического этапа хирургического вмешательства и в раннем послеоперационном периоде. Введение в систему J. Caprini степени хирургического стресса объективизирует систему определения риска развития послеоперационного венозного тромбоза. Включение низкофракционного гепарина (преобладающее влияние на IIa фактор) в систему тромбопрофилактики низкомолекулярного гепарина (преобладающее влияние на Xa фактор) при плановых оперативных вмешательствах позволило снизить частоту развития послеоперационного тромбоза вен бассейна нижней полой вены в 1,8 (p<0,001) раза.

რეზიუმე

თრომბოპროფილაქტიკის მოდიფიცირებული სისტემა ქირურგიული პროფილის ავადმყოფებში

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[1]უკრაინის სახელმწიფო უმაღლესი საგანმანათლებლო დაწესებულება "ბუკოვინის სახელმწიფო სამედიცინო უნივერსტეტი", ჩერნოვცი; [2]უკრაინის სახელმწიფო უმაღლესი საგანმანათლებლო დაწესებულება უკრაინის ჯანდაცვის სამინისტროს ი. გორბაჩევსკის სახ. ტერნოოპლის სახელმწიფო სამედიცინო უნივერსტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა გეგმიური ქირურგიული ჩარევის დროს ქვედა ღრუ ვენის აუზის პოსტოპერაციული თრომბოზის განვითარების სახშირის შემცირება თრომბოპროფილაქტიკის მოდიფიცირებული მეთოდის გამოყენებით.

გამოკვლეულია ავადმყოფების 2 ჯგუფი (n=698); J. Caprini-ს სკალის მეშვეობით (2012); შეფასდა პოსტოპერაციული ვენური თრომბოემბოლიზმის განვითარების რისკი, ოპერაციამდე, ქირურგიული ჩარევის ტრავმულ ეტაპზე და ადრეულ პოსტოპერაციულ პერიოდში, სისხლში გლუკოზის და კორტიზოლის შემცველობის განსაზღვრის მეშვეობით შეფასდა ქირურგიული სტრესის დონე. J. Caprini-ს სისტემაში ქირურგიული სტრესის ხარისხის ჩართვამ განაპირობა პოსტოპერაციული ვენური თრომბოზის განვითარების რისკის განსაზღვრის სისტემის ობიექტივიზირება. დაბალფრაქციული ჰეპარინის (უპირატესი მოქმედებით IIa ფაქტორზე) ჩართვა თრომბოპროფილაქტიკაში დაბალმოლეკულური ჰეპარინით (უპირატესი მოქმედებით Xa ფაქტორზე) იძლევა ქვედა ღრუ ვენების აუზის პოსტოპერაციული თრომბოზის განვითარების სიხშირის 1,8-ჯერ (p<0,001) შემცირების საშუალებას გეგმიური ოპერაციული ჩარევის დროს.

FACTORS ASSOCIATED WITH POST-STROKE FATIGUE WITHIN THE FIRST 3 MONTH AFTER STROKE

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Although post-stroke fatigue (PSF) is a commonly reported problem that negatively affects rehabilitation, recovery and survival rate after stroke, up to now PSF remains a neglected problem in routine clinical practice [17]. A variety of potential causes or risk markers for PSF have been examined, without any consistent findings [13]. As known, PSF is multidomain entity which consist of different components such as physical, mental, emotional, so on [9]. To the best of our knowledge, up to now there has been no research on the determinants of different PSF components at different stages after stroke. But, in order to elaborate effective treatments and support for patients with PSF, first of all, it is crucial to understand how various socio-demographic, personal and psychological factors could contribute to onset and further longevity of definite PSF domains. It is therefore necessary to identify possible risk factors for global PSF as well as PSF definite domains for development of effective prevention measures.

The objectives of this study were to identify socio-demographic, personal and psychological factors associated with certain PSF domains within first 3 months after stroke.

Material and methods. Initially we enrolled in the study 234 patients. Patients were included in the study if they had an acute stroke (ischemic or hemorrhagic), agreed to participate in the study and were able to provide informed consent. Exclusion criteria were major medical illness that could cause seconndary fatigue (oncological, hematological diseases, cardiac, liver, kidney and respiratory insufficiency, progressive angina pectoris, acute myocardial infarction), alcohol abuse, consciousness impairments, insufficient cognitive ability (Mini-Mental State Examination scores less than 24) [3], depressive and anxious disorders (Hospital Anxiety and Depression Scale scores more than 10 for both pathologies) [19], impaired speech function to participate (severe dysphasia or dysarthria), impaired language or written ability to complete the study questionnaires, severe functional disabilities (modified Rankin scale scores ≥4).

Patients' characteristics had been evaluated consequently in definite time points: at hospital stay, in 1 and 3 months after stroke. During the first post-stroke month 31 patients and during the next 2 months 27 more patients were dropped out due to different reasons. So, in 3 months after stroke we had examined 176 patients.

Data were collected in the face-to-face interviews using structured questionnaires and patient's medical records.

PSF was measured by self-report multidimensional fatigue inventory-20 (MFI-20) questionnaire. MFI-20 is a 20-item questionnaire which covers the following fatigue dimensions: global, physical, mental, activity-related and motivational. A cut-off of 12 out of 20 for every sub-scale has been suggested for use with people with stroke [15].

Socio-demographic factors such as age, gender, marital status (married/single), formal education level (higher/non-higher), pre-stroke employment status (employed/unemployed) were recorded. Pre-stroke fatigue was diagnosed retrospectively if patients reported fatigue lasting longer than 3 months before the stroke [8]. Patients' tobacco smoking status was classified as "non-smoker" (who didn't smoke at least 1 year before the stroke) or "current smoker" (who smoked regularly for the last 1 year before stroke). Subjects were grouped by the level of alcohol consumption (number of drinks per week): none or moderate (≤7 for women and ≤14 for men) and heavy (>7 for women and >14 for men) [12]. Signs of anxiety and depression were assessed by Hospital Anxiety and Depression Scale (anxiety and depression sub-scales using a cut-off of 4, which has been recommended for persons who have had a stroke) [14]. Apathy symptoms were assessed by the Starkstein apathy scale (a cut-off point ≥14 from the total score of the scale was used to dichotomize the patients into apathetic and non- apathetic) [16]. Mild cognitive impairments (MCI) were evaluated by the Montreal cognitive assessment (cut-off scores less than 26) [11]. Sleepiness was measured using Epworth scale (scores ≥10 indicate excessive daytime sleepiness) [6]. Patients were asked if they experienced chronic pain in the last week. For anthropometric characteristics were used body mass index (cut-off 30 kg/m^2) and waist circumference (cut-off 102 cm for males and 88 cm for females). The co-morbidities included arterial hypertension, ischemic heart disease, atrial fibrillation and diabetes mellitus.

Continuous variables were represented as mean±standard deviation and categorical data were represented by number (n) and percentage. Univariate and multivariate logistic regression analysis were performed to analyze the odds ratio with 95% confidence intervals of significant factors associated with patients with PSF. Variables having a P value <0,05 in the univariate analysis were selected and evaluated by multivariate logistic regression models with the forward selection method. P values <0,05 were considered significant. Statistical analysis were performed using SPSS 14.0 statistics software.

Results and their discussion. Patients' age ranged from 43 to 79 years (63,3±8,4 years). There were 112 (47,9%) males and 122 (52,1%) females. 201 (85,9%) patients suffered of ischemic strokes, 33 (14,1%) had hemorrhagic strokes.

Table 1 indicates significant prevalence of PSF within first 3 months post-stroke period. Also, it's important that PSF is a heterogeneous entity with quite different

Table 1. Frequencies of certain domains PSF dimensions during first 3 post-stroke months

PSF dimension	Time point after stroke onset		
	stay in hospital	1 month	3 month
global	72 (30,8%)	65 (32%)	73 (41,5%)
physical	74 (31,6%)	66 (32,5%)	73 (41,5%)
mental	59 (25,2%)	67 (33,0%)	75 (42,6%)
activity-related	103 (44,0%)	51 (25,1%)	33 (18,8%)
motivational	36 (15,4%)	33 (16,3%)	25 (14,2%)

Table 2. Factors associated with global PSF domain from multivariate logistic regression models

Factors	Time point after stroke onset		
	stay in hospital	1 month	3 months
employing status	-	2,24 (1,05-4,79), p=0,04	2,85 (1,29-6,29), p=0,01
pre-stroke fatigue	2,26 (1,06-4,83),p=0,04	-	-
anxiety	3,41 (1,28-9,05), p=0,01	-	2,94 (1,16-7,44), p=0,02
excessive daytime sleepiness	2,07 (1,13-3,78), p=0,02	2,48 (1,27-4,84), p=0,01	-
pain	-	2,66 (1,18-5,99), p=0,02	2,34 (1,07-5,12), p=0,03

dynamics of its components during observation period.

As article is limited we present only significant results. First of all, in multivariate regression logistic analysis many variables (such as gender, marital status, education level, smoking status, level of alcohol consumption, apathetic impairments, arterial hypertension, atrial fibrillation, ischemic heart disease, diabetes mellitus, body mass index, waist circumference) were not significantly associated with any PSF aspect at any time point after stroke onset.

Table 1 reveals that patients who had employment status before stroke onset, experienced higher risk of global PSF in 1 and 3 months after stroke. Maybe this phenomenon is present because working patients tend to be more active and in majority of cases try to return to working life after the acute stroke phase.

Pre-stroke fatigue is associated with global PSF only during hospital staying. The relationship between pre-stroke fatigue and PSF has previously been reported in other studies [13]. It is important to take into consideration that the prevalence of fatigue in the general population is relatively high, and PSF measured in the early period after a stroke may not necessarily be caused by the stroke itself but it could be the sequel of pre-stroke fatigue.

Our study showed that anxiety signs are associated with three times increased risk of general PSF in different time points within 3 months post-stroke period. This fact is in accordance with literature data: in recent years, many investigators have demonstrated that anxiety symptoms are independent predictors of PSF [13].

Excessive daytime sleepiness is associated with global PSF within 1 month after stroke. As known, excessive daytime sleepiness are common co-morbidities of acute stroke [1]. This phenomenon can be caused by fragmented sleep (particularly obstructive sleep apnea), dopaminergic and noradrenergic impulse disruption as stroke consequence and the use of some medications (sedatives, hypnotics, so on) [2]. As a consequence of sleepiness patients are less likely to be as active as they can be, and they complain of PSF. But in its turn, PSF may lead to increased sleep demands for restoration. So, it's quite difficult to evaluate causal relationship between excessive sleepiness and PSF.

Chronic pain increases the risk of PSF development more than twofold at 1 and 3 months after stroke. In overwhelming majority of cases participants described pain in form of shoulder pain, muscle pain and tension type headache. Resulting from pain, there can be a decline in the amount of physical activities performed by patients after stroke. Moreover, chronic pain has exhaust influences on nervous system and could provoke mental and emotional fatigue.

In general, PSF physical domain, according to MFI-20 sub-scale, can be predominantly described as sensation of inability to do physical tasks. Table 3 shows that working status is associated with more than twice increase of physical PSF risk at 3 months after stroke. Probably, the returning to work and attempts of being active in the professional life may become a factor increasing this PSF domain for the working patients. Association between pain and physical PSF can be explained by the fact that people with pain (especially of musculoskeletal origin) may avoid physical activity due to increased severity of pain. In it's turn, lack of physical activity can further worsen PSF, including its physical component.

Mental fatigue, according to corresponding MFI-20 sub-scale, is mainly described as "loss of concentration". As is seen from table 4, working status is associated with more than twofold increasing of mental PSF in 3 months after stroke. This phenomenon can be explained, at least partially, in the same way as about physical PSF – returning to work requires increased efforts, including mental efforts also. This is important, as mental PSF may be significant

Table 3. Factors associated with physical PSF domain from multivariate logistic regression models

Factors	Time point after stroke onset		
	stay in hospital	1 month	3 months
employing status	-	-	2,71 (1,26-5,83), p=0,01
pain	2,65 (1,45-4,82), p=0,002	2,18 (1,17-4,07), p=0,01	-

Table 4. Factors associated with mental PSF domain from multivariate logistic regression models

Factors	Time point after stroke onset		
	stay in hospital	1 month	3 months
employing status	-	-	2,45 (1,12-5,37), p=0,02
anxiety	3,21 (1,27-8,09), p=0,01	-	2,87 (1,14-7,18), p=0,02
excessive daytime sleepiness		2,45 (1,26-4,79), p=0,01	2,70 (1,31-5,59), p=0,01
MCI		2,26 (1,12-4,56), p=0,02	2,81 (1,32-6,02), p=0,01

Table 5.Factors associated with activity-related PSF domain from multivariate logistic regression models

Factors	Time point after stroke onset		
	stay in hospital	1 month	3 months
employing status	-	-	2,75 (1,19-6,35), p=0,02
pain	-	2,18 (1,02-4,68), p=0,04	-

obstacle to post-stroke patients who are on their way to a return to previous working activities.

Anxiety symptoms are associated with threefold increased risk of mental PSF domain. It's natural, because anxiety symptoms, such as irritability, sensitivity to stress, concentration difficulties, and emotional instability may directly provoke and further aggravate the mental PSF aspect [5].

Excessive daytime sleepiness are associated with two and half time higher risk of mental PSF. This phenomenon likely may be explained in similar way as global PSF.

Connections between MCI and mental PSF can be explained by the fact that persons with MCI try to compensate the cognitive deficits by making extra effort («coping theory») [17]. But these persons able to perform mental activity just for short periods, and, notably, it will take longer than normal to regain energy after being exhausted [4]. Probably, the last explanation may be partially responsible for excessive daytime sleepiness.

As is seen from table 5, returning to work and chronic pain are associated factors of activity-related PSF. According to corresponding MFI-20 sub-scales, motivational and physical aspects of PSF are overlapping each other. So, above mentioned associations can be explained by the same way as physical component of PSF.

Table 6 shows that anxiety symptoms are associated with motivational PSF during hospital staying, but depression symptoms and chronic pain could predict motivational PSF aspect at 1 and 3 months after stroke. According to MFI-20, the essence of fatigue motivational component has close overlap with depressive signs [15]. Depression symptoms have been considered concomitant post-stroke experiences played an important role in triggering PSF [13]. Not only do these two types of experiences coexist but also are common shared experiences, making it difficult to differentiate between them as independent conditions [7]. Chronic pain may be associated with PSF in directs as well as in indirect way via depression [10].

This is the first study to examine factors that could be related to certain PSF domains using MFI-20 sub-scales within early post-stroke period.

It was determined that working status, pre-stroke fatigue, anxiety symptoms, excessive daytime sleepiness and pain can contribute to global PSF. Specific PSF domains have different risk factors, but majority of them are the same as for global PSF. The exceptions are as follows: MCI may contribute to mental PSF and depression signs

Table 6. Factors associated with motivational PSF domain from multivariate logistic regression models

Factors	Time point after stroke onset		
	stay in hospital	1 month	3 months
anxiety	4,03 (1,35-12,03), p<0,001	-	-
depression	-	4,00 (1,52-10,55), p<0,001	3,34 (1,13-9,81), p=0,03
pain	-	2,65 (1,08-6,49), p=0,03	2,84 (1,11-7,23), p=0,03

– to motivational PSF. Of course, we cannot exclude the possibility that other factors not evaluated in this study (e.g. clinical, neurological, biological) might also play a significant role in PSF development.

Wu and colleagues propose PSF as part of an evolving process, i.e. there may be specific factors associated with PSF at different stages after stroke [18]. From theoretical point of view, given the fact that certain PSF domain in definite time point after stroke are associated with different factors, probably each PSF domain, at least partially, has specific mechanism. So, the nature and pathogenesis of certain PSF aspects at different periods after stroke still need to be further scrutinized.

The clinical implications of our study are that the presence of all above mentioned factors within early post-stroke period may signal the increased probability of PSF development. Particular attention needs to be paid to modifiable variables (signs of depression and anxiety, chronic pain, excessive daytime sleepiness), because management of these factors may be helpful for preventing PSF.

Conclusions. 1. Employing status before stroke, pre-stroke fatigue, anxiety, excessive daytime sleepiness and chronic pain may be contributing factors to global PSF development within first 3 months after stroke.

2. Majority of risk factors for specific PSF domains are the same as for global PSF. The exception is MCI for mental PSF and depression signs for motivational PSF.

3. Management of modifiable risk factors (anxiety and depression signs, excessive daytime sleepiness, chronic pain) probably may be helpful for PSF prevention within first 3 months after stroke.

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SUMMARY

FACTORS ASSOCIATED WITH POST-STROKE FATIGUE WITHIN THE FIRST 3 MONTH AFTER STROKE

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Aim - identify socio-demographic, personal and psychological factors associated with certain post-stroke fatigue (PSF) domains within first 3 months after stroke.

There were examined patients consequently in definite time points after ischemic or hemorrhagic strokes: at hospital stay (234 patients), in 1 month (203 patients) and in 3 months (176 patients). Global PSF and certain PSF domains were measured by multidimensional fatigue inventory-20 (MFI-20) scale.

In multivariate logistic regression analysis the majority of variables (gender, marital status, education level, smoking status, level of alcohol consumption, apathetic impairments, arterial hypertension, atrial fibrillation, ischemic heart disease, diabetes mellitus, body mass index, waist circumference) were not significantly associated with any PSF domain risk at any time point after stroke. On the other hand, it had been found reliable associations between risk of global PSF and employing status before stroke, pre-stroke fatigue, anxiety symptoms, excessive daytime sleepiness, pain. Majority of risk factors for specific PSF domains (physical, mental, activity-related, motivational) are the same as for global PSF. The exception is mild cognitive impairments for mental PSF and depression signs for motivational PSF.

Management of modifiable risk factors (anxiety and depression signs, excessive daytime sleepiness, chronic pain) probably may be helpful for PSF prevention within first 3 months after stroke.

Keywords: post-stroke fatigue, socio-demographic, personal and psychological factors.

РЕЗЮМЕ

ФАКТОРЫ, АССОЦИИРОВАННЫЕ С ПОСТИНСУЛЬТНОЙ УСТАЛОСТЬЮ В ТЕЧЕНИЕ ПЕРВЫХ 3 МЕСЯЦЕВ ПОСЛЕ ИНСУЛЬТА

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Цель исследования - идентифицировать социально-демографические и психологические характеристики пациентов, ассоциированные с определенными компонентами постинсультной усталости в течение первых 3 месяцев после инсульта.

Проводилось последовательное обследование 234 пациентов в определенных временных интервалах после развития ишемического или геморрагического инсультов: в стационаре - 234 пациента, спустя 1 месяц - 203 пациента и спустя 3 месяца - 176 пациентов после развития инсульта. Наличие общей постинсультной усталости (ПИУ), как и определенных ее компонентов, определяли с помощью многомерной шкалы усталости (MFI-20).

Выявлены статистически достоверные корреляции между риском общей ПИУ и профессиональной занятостью пациентов перед развитием инсульта, наличием усталости в доинсультном периоде, тревожными проявлениями, повышенной дневной сонливостью, болевым синдромом. Риск развития отдельных компонентов ПИУ, как правило, достоверно ассоциировался с вышеперечисленными факторами, характерными для общей ПИУ. Исключением были легкие когнитивные нарушения для ментальной ПИУ и депрессивные проявления для мотивацинной ПИУ.

Коррекция модифицируемых факторов риска (тревожные и депрессивные проявления, повышенная дневная сонливость, болевой синдром) эффективна для профилактики ПИУ в раннем постинсультном периоде.

რეზიუმე

პოსტინსულტურ დაღლილობასთან ასოცირებული ფაქტორები ინსულტის შემდგომი პირველი სამი თვის განმავლობაში

ი. დელვა, ნ. ლიტვინენკო, მ. დელვა

უკრაინის სამედიცინო სტომატოლოგიური აკადემია, პოლტავა, უკრაინა

კვლევის მიზანს წარმოადგენდა პაციენტებში პოსტინსულტური დაღლილობის გარკვეულ კომპონენტებთან ასოცირებული სოციალურ-დემოგრფიული და ფსიქოლოგიური მახასიათებლების იდენტიფიცირება ინსულტის შემდგომი პირველი სამი თვის განმავლობაში.

ჩატარდა პაციენტების თანმიმდევრული კვლევა გარკვეულ ინტერვალებში იშემიური და ჰემორაგიული ინსულტის განვითარების შემდგომ: სტაციონარში - 234 პაციენტი, ერთი თვის შემდგომ - 203 პაციენტი და სამი თვის შემდგომ - 176 პაციენტი. ზოგადი პოსტინსულტური დაღლილობის (პიდ) არსებობა, ისევე როგორც მისი გარკვეული კომპონენტების, განისაზღვრებოდა დაღლილობის მრავალგანზომილებიანი შკალის გამოყენებით (MFI-20).

ჩატარებული კვლევის საფუძველზე გამოვლინდა ზოგადი პიდ-ის რისკის სტატისტიკურად სარწმუნო კორელაცია პაციენტის პროფესიულ დატვირთვასთან ინსულტის განვითარების წინა პერიოდში, ასევე, ზოგად დაღლილობათან ინსულტამდელ პერიოდში, შფოთვით გამოვლინებებთან, მომატებულ მძინარობასთან დღის საათებში და ტკივილის სინდრომთან. პიდ-ის ცალკეული კომპონენტის განვითარების რისკი სარწმუნოდ ასოცირდებოდა ზოგადი პიდ-ისთვის დამახასითებელ ზემოჩამოთვლილ ფაქტორებთან. გამონაკლისს შეადგენდა მსუბუქი კოგნიტური დარღვევები მენტალური პიდ-ისთვის და დეპრესიული გამოვლინებები - მოტივაციური პიდ-ისთვის.

ჩატარებული კვლევის შედეგების ანალიზის საფუძველზე ავტორების მიერ გამოტანილია დასკვნა იმის შესახებ, რომ მოდიფიცირებადი ფაქტორების (შფოთვითი და დეპრესიული გამოვლინებები, მომატებული დაღლილობა დღის საათებში, ტკივილის სინდრომი) კორექცია ეფექტურია პიდ-ის პროფილაქტიკისათვის ადრეულ პოსტინსულტურ პერიოდში.

INVESTIGATION OF BONE MINERALIZATION IN PATIENTS WITH CORONARY HEART DISEASE COMPLICATED BY CHRONIC HEART FAILURE, STAGE II-A

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Cardiovascular diseases (CVD) and osteoporosis are important causes of morbidity and mortality in the elderly [1,11]. Osteoporosis is a serious public health concern with an estimated worldwide incidence of over 200 million. Approximately 30% of postmenopausal women in developed countries have osteoporosis and at least 40% of women and 15-30% of men will sustain a fracture; the risk of a further fracture is increased by 50-100%. The worldwide annual incidence of hip fracture is 1.7 million [6].

Traditionally osteoporosis and CVD were considered unrelated and their coexistence has been attributed to independent processes exclusively related to age. However, the majority of the studies have shown that individuals with CVD have a higher risk of experiencing bone loss and thus greater predisposition to risk of fracture. On the other hand there is growing evidence that individuals with low bone mass have higher mortality for cardiovascular events compared to patients with cardiovascular disease with normal bone mass [11].

The nature of the putative link between osteoporosis and CVD remains unclear. It could be firstly explained by their common risk factors such as age, smoking, alcohol consumption, physical activity and menopause [7].

Moreover, vascular calcification is an independent risk factor for CVD. Potential links underlying both diseases may be related to the calcification process that is involved in atherosclerosis and bone mineralization. Mineralization is of particular interest because numerous noncollagenous bone-related proteins mediating bone resorption have also been implicated in calcification and ossification in the vascular intima [1]. Calcification of any artery or cardiac valve increases the risk of cardiovascular events and mortality threefold to fourfold and is accepted as a predictor of coronary heart disease (CHD) [5].

This study aims to investigate bone mineralization in patients with CHD complicated by stage II-A chronic heart failure.

Material and methods. The study involved 33 men with CHD complicated by Stage II-A chronic heart failure (according to the classification by N.D. Strazhesko, V.H. Vasilenko and G.F. Lung (1935).

The average age of patients was 57.91±9.30 years. Their BMI exceeded normal range (set at less than 25 kg/m^2) and was in the range of subcompensated obesity, 28.04±2.12 kg/m^2. Clinical characteristics of the patients were as follows: the disease duration ranged from 2 to 20 years, the underlying disorder mainly was cardiosclerosis. In patients history were found bad habits: 16 - smoking, 4 - alcohol abuse, 7 - caffeine abuse (4-5 cups of coffee per day). A history of fractures was found in 4 persons.

The patients did not have other severe comorbidities that could have caused changes in bone tissue. All study participants were hospitalized patients and had given written consent for their clinical data to be used in the study. All reported research conducted in accordance with the principles set forth in the Helsinki Declaration, 2008.

Diagnosis of CHD was confirmed using a set of characteristic anamnestic, clinical (typical angina attacks with physical and psycho-emotional stress), biochemical (increased total cholesterol and total lipids levels) and ECG (ST segment depression below the baseline, T-wave inversion) data. To corroborate diagnosis, we also used data obtained during physical examination, such as enlarged to the left heart boundaries, weakened sound of the top tone, stress of the second tone above the aorta, changes in blood pressure and heart rate.

In order to verify the diagnosis of heart failure we used main limiting factors of physical performance and clinical symptoms: dyspnea, tachycardia, and fatigue after exertion. The final diagnosis of chronic heart failure with systolic dysfunction was given based on the results of echocardiography test.

Dual-energy X-ray absorptiometry (DXA) is widely used for measuring bone mineral density (BMD) because of its recognized precision. The method utilizes two measurements, T-score and Z-score. The first one is calculated when the patient's BMD is subtracted from mean BMD of a population of healthy young adults, matched The T-score is calculated as a number of SDs the patient's measured BMD is above or below the mean for population of healthy 30-year adults, matched for sex and ethnicity. The Z-score is expressed in units of the population SD, but instead of comparing the patient's BMD to the mean of young adult population, it is compared with the mean BMD of a healthy population matched for age, sex and ethnicity. In this study, we evaluated the scores according to the WHO guidelines (WHO, Geneva, 1994): BMD >1.2 g/sm^2 is classified as osteosclerosis; a T-score ≥ –1 is regarded as normal, and T-score between –2.5 and -1 is classified as osteopenia [10].

The control population samples were selected from a densitometric database of healthy individuals maintained at the medical diagnostic center of Ternopil State Medical University and designated as Young Adults and Age Matched groups [10].

The results were analysed using Statistica 7.0 software and presented as mean with standard deviations.

To evaluate the distribution of the character together by sampling data we have used Lillieforsa and Kolmogorov-Smirnov tests. The differences between all groups were determined using one-way ANOVA, followed by post hoc Least Significant Difference test. A p-value of <0.05 was considered statistically significant.

Results and their discussion. Densitometry analysis of lumbar segment of patients with CHD complicated by Stage II-A chronic heart failure showed normal BMD or signs of osteodeficiency. Thus, at L_1 level osteopenia was diagnosed in 51,5% patients, L_2 – 51,5%, L_3 – 48,5% and L_4 – 45,5%. Among the osteodeficient states frequently was observed osteopenia I stage in 44,6%, osteopenia II stage – in 27,7%, osteopenia III stage – in 10,8% and osteoporosis was noted in 16,9% patients (Fig.).

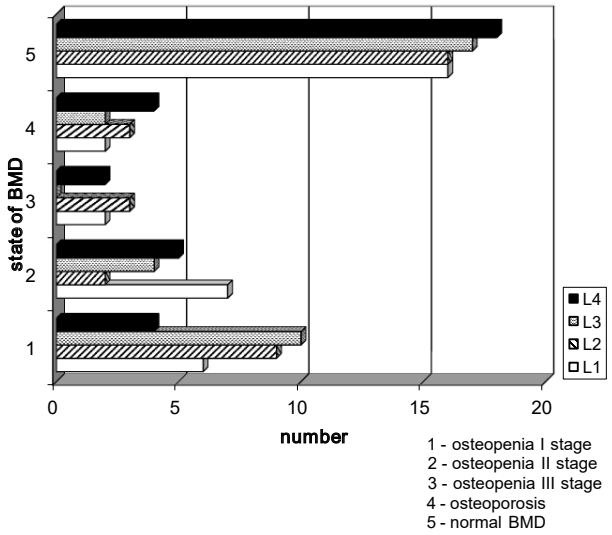

Fig. Distribution of male patients with CHD complicated by Stage II-A chronic heart failure by the BMD

The data presented in Table 1, have showed large number of patients with CHD complicated by Stage II-A chronic heart failure with normal BMD (50,8%). Herewith practically identical mineralization in all vertebrae was observed. The indices of bone tissue state, expressed in units of standard deviation determined by densitometric method and analyzed comparatively to young healthy people (T), and in accordance with their age group (Z), have confirmed this statement. The average value of BMD in T-score was (-0,17±0,08), which was not significantly differed (P>0,05) of mineralization due to Z -score (-0,11±0,06).

Densitometry analysis of lumbar segment of patients with CHD complicated by Stage II-A chronic heart failure showed that in case of osteopenia I stage BMD was significantly higher (P<0,001) at the L_1 level compared with three other vertebrae. Although according to T-score mineralization equally decreased in all investigated vertebrae approximately by 7.4 times vs normal BMD of this group patients (Table 2). It should be noted that in case of osteopenia I stage the indices of BMD are changing samely due to young healthy people (Young Adult) and their age group (Age Matched), because there is no significant difference (P>0,05). The average value of BMD in T-score was (-1,26±0,02), that in fact not differ from mineralization in Z-score (-1,19±0,07).

Densitometry analysis of lumbar segment of patients with CHD complicated by Stage II-A chronic heart failure showed that in case of osteopenia II stage BMD was the lowest at the L_1 level. The lowest index in Young Adult (T-score) was established at the L_4 level, which is significantly different from data of 2 patients at L_2 level ((-1,70); (-1,80)) and 4 patients at L_3 level (P<0,05) (Table 3). However investigated values do not correlate with BMD indices compared with those of age, since the mini-

Table 1.BMD of the lumbar spine of male patients with CHD complicated by Stage II-A chronic heart failure with normal bone tissue (M±m)

Vertebra number	BMD, g/cm²	Young Adult		Age Matched	
		%	T	%	Z
L_1 (n=16)	1,16±0,02	100,18±1,79	0,02±0,17	101,59±2,17	-0,14±0,21
P_1	>0,05	>0,05	>0,05	>0,05	>0,05
L_2 (n=16)	1,20±0,02	97,20±1,77	-0,28± 0,18	98,87±2,04	0,04±0,27
P_2	>0,05	>0,05	>0,05	>0,05	>0,05
L_3 (n=17)	1,21±0,02	99,35±1,60	-0,09±0,17	100,82±2,08	-0,24±0,20
P_3	>0,05	>0,05	>0,05	>0,05	>0,05
L_4 (n=18)	1,19±0,02	96,88±1,30	-0,32±0,13	98,12±1,76	-0,11±0,23
P_4	>0,05	>0,05	>0,05	>0,05	>0,05

note: P_1 *– significance of difference between indices* L_1 *and* L_2*;* P_2 *– significance of difference between indices* L_2 *and* L_3*;* P_3 *– significance of difference between indices* L_3 *and* L_4*;* P_4 *– significance of difference between indices* L_4 *and* L_1

Table 2. BMD of the lumbar spine of male patients with CHD complicated by Stage II-A chronic heart failure with I stage of osteopenia (M±m)

Vertebra number	BMD, g/cm²	Young Adult		Age Matched	
		%	T	%	Z
L_1 (n=6)	1,00±0,01	86,33±0,71	- 1,30±0,06	88,67±2,03	-1,10±0,21
P_1	<0,001	<0,05	>0,05	>0,05	>0,05
L_2 (n=9)	1,09±0,01	88,22±0,36	-1,21±0,05	88,78±1,50	-1,18±0,18
P_2	>0,05	>0,05	>0,05	>0,05	>0,05
L_3 (n=10)	1,09±0,01	87,90±0,43	-1,23±0,05	89,60±1,36	-1,09±0,16
P_3	>0,05	>0,05	>0,05	>0,05	>0,05
L_4 (n=4)	1,08±0,01	87,25±0,75	-1,28±0,08	87,00±2,58	-1,38±0,30
P_4	>0,05	>0,05	>0,05	>0,05	>0,05

note: P_1 *– significance of difference between indices* L_1 *and* L_2*;* P_2 *– significance of difference between indices* L_2 *and* L_3*;* P_3 *– significance of difference between indices* L_3 *and* L_4*;* P_4 *– significance of difference between indices* L_4 *and* L_1

Table 3. BMD of the lumbar spine of male patients with CHD complicated by Stage II-A chronic heart failure with II stage of osteopenia (M±m)

Vertebra number	BMD, g/cm²	Young Adult		Age Matched	
		%	T	%	Z
L_1 (n=7)	0,95±0,01	82,14±0,40	-1,71±0,03	83,43±1,96	-1,60±0,23
P_1	<0,001	>0,05	>0,05	>0,05	>0,05
L_3 (n=4)	1,02±0,01	82,25±0,63	-1,88±0,06	81,75±1,65	-1,85±0,21
P_2	>0,05	>0,05	<0,01	<0,05	<0,05
L_4 (n=5)	1,03±0,01	82,80±0,20	-1,66±0,02	87,80±1,53	-1,20±0,15
P_3	<0,001	>0,05	>0,05	>0,05	>0,05

note: P_1 *– significance of difference between indices* L_1 *and* L_2*;* P_2 *– significance of difference between indices* L_2 *and* L_3*;* P_3 *– significance of difference between indices* L_3 *and* L_4*;* P_4 *– significance of difference between indices* L_4 *and* L_1

mum values were in the third lumbar vertebra. Moreover, comparing the indices of "T" and "Z" score, it was established that maximum values of BMD were diagnosed in L_4, herewith the value of mineralization due to Young Adult was significantly lower (P<0,01) due to age. Besides, value of Age Matched (Z-score) at the L_4 level did'nt correspond to osteopenia II stage (-1,20±0,15) and was significantly higher compared to those of other vertebrae. The average value of BMD in T-score was (-1,75±0,05), that in fact not differ from mineralization in Z-score (-1,55±0,13).

Densitometry analysis of lumbar segment of patients with CHD complicated by Stage II-A chronic heart failure showed that III stage of osteopenia was detected in a small number of patients (n=7), moreover III stage of osteopenia was not determined at L_3 level. Assessing the level of mineralization we have found that BMD is the

lowest at L_1 level: from 0,89 to 0,91 g/cm^2. Considering the index Young Adult (T-score), it should be noted that its values at all levels practically did not differ from each other. Thus, at L_1 level T-score was (-2,10)-(-2,20), at L_2 and L_4 level – (-2,10)- (-2,30).

It was established that in case of III stage of osteopenia the indices of BMD are changing samely due to young healthy people (Young Adult) and their age group (Age Matched), because there is no significant difference (P>0,05). The average value of BMD in T-score was (-2,18±0,02), that in fact not differ from mineralization in Z-score (-2,11±0,09).

Densitometry analysis with established osteoporosis showed that in all lumbar vertebrae mineralization decreases vs patients with III stage of osteopenia about by 8,0% (p<0,05). Thus, BMD in patients ranged from 0,80 to 0,88 g/cm^2. Analysis of Age Matched indices showed, that bone mass loss in case of Stage II-A chronic heart failure and osteoporosis based on age regarding healthy people of similar age was almost the same, as compared with group of young healthy people Young Adult (P>0,05). The average value of BMD in T-score was (-3,12±0,14), that in fact not differ (P>0,05) from mineralization in Z-score (-2,60±0,22).

A number of studies have investigated the association between BMD and cardiovascular morbidity. Chen S.J. et al. suggest that patients with osteoporosis have higher risk of CHD than those without osteoporosis. Patients who have osteoporosis and have received treatment with bisphosphonates have a significantly lower risk for CHD than are those without treatment. Their findings suggest that osteoporosis is significantly associated with the risk of CHD in an Asian population [1]. In the placebo branch of the MORE study, osteoporosis (T-score<- 2.5 at the spine or the femoral neck) was associated with a fivefold higher risk of cardiovascular event (for example, stroke, myocardial infarction). In a group of 6800 men and women (MONICA and Västerbotten Intervention Programme databases), low hip BMD was associated with higher risk of myocardial infarction [12,14].

Potential mechanisms for the link between osteoporosis and cardiovascular disease remain unknown. One hypothesis puts forth that the coexistence of osteoporosis and CVD is due to their shared etiological factors (such as smoking, physical activity, alcohol intake, menopause, hypertension, etc), which may simultaneously promote or inhibit atherosclerosis and bone demineralization. However, in many epidemiologic studies, the association between osteoporosis and CVD remained even after the adjustment of some of these risk factors [4].

Secondly, common pathophysiological mechanisms are implicated in the progression of the two conditions: inflammatory cytokines, endogenous sex hormones, oxidized lipids, vitamin K deficiency, and vitamin D [4].

Thirdly, coexistence of osteoporosis and CVD may be due to common genetic factors. Genome-wide association studies have identified several genes and single nucleotide polymorphisms associated with BMD, and CVD risk factors or metabolic traits, including high density lipoprotein, low density lipoprotein, triglycerides, type 1 diabetes, type 2 diabetes, systolic blood pressure, diastolic blood pressure and waist hip ratio [3,2,9,13]. Furthermore osteoprotegerin and receptor activator of nuclear factor kappa B ligand regulate osteoclast activation and function but are also involved in the vascular calcification process and atherosclerosis. Bone morphogenetic protein (BMP2) is involved in osteoblastic differentiation by the stimulation of Runx2 expression; in humans, atherosclerotic lesions show an increased expression of BMP2 and Runx2 with respect to normal arteries and this may be responsible for arteries wall calcification [8].

Conclusions. 1. Structural and functional changes of bone tissue of the lumbar spine have been found in patients with chronic heart disease complicated by stage II-A chronic heart failure: I stage of osteopenia – in 44,6%, II stage of osteopenia – in 27,7%, III stage of osteopenia – in 10,8% and osteoporosis – in 16,9%.

2. It was established the same type of downward trend for BMD decreasing in L_1 of patients with different stages of osteopenia, but in case of osteoporosis mineralization decreased equally in all vertebrae.

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

INVESTIGATION OF BONE MINERALIZATION IN PATIENTS WITH CORONARY HEART DISEASE COMPLICATED BY CHRONIC HEART FAILURE, STAGE II-A

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The majority of the studies have shown that individuals with cardiovascular diseases have a higher risk of experiencing bone loss and thus greater predisposition to risk of fracture. On the other hand there is growing evidence that individuals with low bone mass have higher mortality for cardiovascular events compared to patients with cardiovascular disease with normal bone mass.

This research aims to investigate bone mineralization in patients with coronary heart disease complicated by stage II-A chronic heart failure.

The study involved 33 men with coronary heart disease complicated by Stage II-A chronic heart failure. Bone mineral density was measured using dual energy x-ray densitometry of lumbar region of spine.

Structural and functional changes of bone tissue of the lumbar spine have been found in 49,2% patients with coronary heart disease complicated by Stage II-A chronic heart failure, in particular, I stage of osteopenia – in 44,6%, II stage of osteopenia – in 27,7%, III stage of osteopenia – in 10,8% and osteoporosis – in 16,9%. It was established the same type of downward trend for BMD decreasing in L1 of patients with different stages of osteopenia, but in case of osteoporosis mineralization decreased equally in all vertebrae.

Keywords: coronary heart disease, bone mineral density.

РЕЗЮМЕ

ОЦЕНКА КОСТНОЙ МИНЕРАЛИЗАЦИИ У БОЛЬНЫХ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА, ОСЛОЖНЕННОЙ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ II-А СТАДИИ

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Большинство исследований показали, что лица с сердечно-сосудистыми заболеваниями имеют более высокий риск потери костной массы и, следовательно, большую предрасположенность к переломам. С другой стороны, все больше свидетельств того, что среди лиц с низкой костной массой отмечается более высокая смертность от сердечно-сосудистых заболеваний в сравнении с кардиологическими пациентами с нормальной костной массой.

Целью исследования явилось определение минерализации костей у пациентов с ишемической болезнью сердца, осложненной хронической сердечной недостаточностью II-А стадии.

В исследовании принимали участие 33 мужчины с ишемической болезнью сердца, осложненной хронической сердечной недостаточностью II-А стадии. Минеральную плотность костей измеряли посредством двухэнергетической рентгеновской денситометрии поясничной области позвоночника.

Выявлены структурные и функциональные изменения костной ткани поясничного отдела позвоночника у пациентов с ишемической болезнью сердца, осложненной хронической сердечной недостаточностью II-А стадии: I стадия остеопении - у 15 (44,6%), II стадия остеопении - у 9 (27,7%), III стадия остеопении - у 3 (10,8%), а остеопороз - у 6 (16,9%) больных. Установлен тот же тип нисходящего тренда снижения минеральной плотности костной ткани в L1 у пациентов с различными стадиями остеопении, однако в случае остеопороза минерализация уменьшалась одинаково во всех позвонках. Полученные результаты создают необходимость разработки направлений профилактики и лечения остеодефицита у больных хронической сердечной недостаточностью на фоне ишемической болезни сердца.

რეზიუმე

ძვლის მინერალიზაციის ხარისხის შეფასება ავადმყოფებში II-A სტადიის გულის ქრონიკული უკმარისობით, გართულებული იშემიური დაავადებით

ი. კრინიცკაია, მ. მარუშჩაკი, ტ. ზაეცი,
ი. სავჩენკო, გ. გაბორი

ი. გორბაჩევსკის სახ. ტერნოპოლის სახელმწიფო სამედიცინო უნივერსიტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა ძვლის მინერალიზაციის ხარისხის შეფასება ავადმყოფებში II-A სტადიის გულის ქრონიკული უკმარისობით, გართულებული იშემიური დაავადებით.

კვლევაში მონაწილეობდა 33 მამაკაცი გულის იშემიური დაავადებით, გართულებული II-A სტადიის გულის ქრონიკული უკმარისობით. ძვლების მინერალური სიმკვრივის განსაზღვრა ხდებოდა ორმაგი ენერგეტიკული რენტგენული დენსიტომეტრიით ხერხემლის წელის მიდამოში.

დადგენილია ძვლის ქსოვილის სტრუქტურული და ფუნქციური ცვლილებები ხერხემლის წელის მიდამოში: ოსტეოპენიის I სტადია - 15 (49,2%) ავადმყოფი, II სტადია – 9 (27,2%), III სტადია – 3 (10,8%), ოსტეოპოროზი – 6 (16,9%) ავადმყოფი. პაციენტებში ოსტეოპენიის სხვადასხვა სტადიით დადგენილია L1–ში ძვლის ქსოვილის მინერალური სიმკვრივის დაქვეითების ზემოაღნიშნული ტიპის დაღმავალი ტრენდი. ოსტეოპოროზის შემთხვევაში მინერალიზაციის მაჩვენებელი შემცირებული იყო ყველა მალაში.

RETROSPECTIVE STUDY OF EVALUATION OF PATIENTS WITH ST ELEVATION MYOCARDIAL INFARCTION AND INTACT CORONARY ARTERIES. EVALUATION OF TREATMENT APPROACHES; OUTCOME AND PROGNOSIS

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Acute myocardial infarction (MI) indicates irreversible myocardial injury resulting in necrosis of a significant portion of myocardium (generally >1 cm). Acute MI may be either of the nonreperfusion type, in which case the obstruction to blood flow is permanent, or of the reperfusion type, in which the obstruction or lack of blood flow is long enough in duration (generally hours) but is reversed or restored after myocardial cell death occurs [4]. ST elevation Myocardial Infarction (STEMI) with Normal Coronary Arteries (NCA) is well-documented pathology. Based on literature it can be found in 7-15% of patients diagnosed with STEMI. Myocardial infarction with 'normal' coronary arteries (MINCA) typically occurs in the under-50s [16]. In 2007, new definition of MI was proposed by the joint European Society of Cardiology/ American College of Cardiology Foundation/American Heart Association/World Heart Federation task force for the redefinition of myocardial infarction (MI). The joint task force defined MI as an evidence of myocardial necrosis in a clinical picture aligned with myocardial ischemia [2]. While the eventual etiology remains uncertain in most patients, long-term outcomes of patients with STEMI and normal coronary arteries appear favorable [1].

The exact cause of normal coronary arteries in STEMI remains unclear in many clinical cases. To diagnose this condition, it is important to determine the multiple potential underlying mechanisms that may be responsible, many of which require different treatments [5,8,17]. Up to 30% of women and 12% of men have STEMI but no evidence of obstructive (≥50%) coronary disease at the time of angiography [6,9]. From a mechanistic standpoint, these cases have been attributed to plaque disruption that cannot be reliably detected by invasive angiography, endothelial and microvascular dysfunction, or vasospasm [11,15,18]. In one study of patients with myocardial infarction and nonobstructive CAD, nearly 60% had abnormal cMRI findings in a transmural or subendocardial pattern (i.e., ischemic) [14,15]. Interestingly, the remaining 40% had subepicardial or midwall (i.e., nonischemic) or mixed (both ischemic and nonischemic) patterns of late gadolinium enhancement on cMRI [4]. The proposed mechanism for this might be related to focal ischemia in an area of vasospasm or plaque erosion, resulting in platelet aggregates and distal embolization [1]. This ischemic insult can be appreciated with T2 hyper intensity on cMRI, as myocardial edema is often a consequence of myocardial ischemia. Coronary vasospasm has been implicated as a cause of myocardial infarction when no obstructive CAD is identified at the

time of coronary angiography, and certain clinical presentations, such as cocaine and stimulant use, are risk factors for development of coronary vasospasm. Tobacco use has been implicated in coronary spasm, likely mediated through nicotine, which can be a potent vasoconstrictor.

Svatikova et al. [8] performed a randomized, placebo-controlled, crossover trial of 25 healthy volunteers who consumed 16 of a commercially available energy drink or placebo (matched in taste and color but without caffeine or stimulants) and studied effects on blood pressure, heart rate, and serum norepinephrine levels. Despite no differences in heart rate between energy drink use and placebo, there was a significant increase in systolic, diastolic, and mean blood pressure with energy drink use as compared to placebo. This was associated with a significant increase in norepinephrine levels after energy drink. These findings suggest that adrenergic stimulation with energy drinks may predispose patients to cardiovascular risk and may be particularly concerning in patients with unrecognized cardiac disorders or cardiac-related susceptibilities.

Another reason of STEMI with normal coronary arteries is Takotsubo cardiomyopathy (TCM). This is a transient cardiac syndrome that involves left ventricular apical akinesis and mimics acute coronary syndrome (ACS). It was first described in Japan in 1990 by Sato et al. Patients often present with chest pain, have ST-segment elevation on electrocardiography (ECG), and have elevated cardiac enzyme levels consistent with myocardial infarction (MI) [7]. However, when the patient undergoes cardiac angiography, left ventricular (LV) apical ballooning is present, and there is no significant coronary artery stenosis [2,12].

The data provided above are based on single retrospective analysis and case study results. The data available for retrospective analysis of different etiologies of MINCA are very limited. In many cases the possible reason remains unclear, which makes the treatment difficult and prognosis unclear [10,13].

Material and methods. We retrospectively investigated patients with ACS and normal coronaries, however in this paper we will provide a data about patients with STEMI and normal coronary arteries. In this research we included patients with STEMI; normal coronary arteries (<40% occlusion of any coronary artery); wall motion abnormalities detected by echocardiography and clinically significant persistent increase of cardiac markers. We did not include patients with transitory ST elevation without segmental asynergy or cardiac markers increase. We also did not include patients with micro-circular disease, which is the well-known pathology in terms of pathophysiology; epidemiology; clinical manifestations and prognosis. The research did not include patients with diagnosed pericarditis, myocarditis or cardiomyopathy or if data suggested having above diagnosis. In catheterization laboratory of cardiology department of our hospital, we retrospectively evaluated 165 patients with STEMI with positive cardiac markers and wall motion abnormalities detected either by echocardiography or by ventriculography. Seventeen (17) patients (10.3%) were fount with normal coronary arteries. In all cases, coronary angiography was performed within 12 hours from the initial episode. In all cases, ECG dynamic was characteristic to acute myocardial Infarction (MI).

All patients had prolonged episode of retrosternal pain positive Troponin test; non-transient ST elevation and wall motion abnormalities.

Results and their discussion. From 165 patients (114 male and 51 female) seventeen patients (6 male and 11 female) were found with normal coronary arteries. Fifteen patients were transferred from another hospital with diagnosis of Acute Coronary Syndrome (ACS) in order to perform coronary angiography. In two patients, STEMI was developed during being in hospital. The mid age for males was 54 for females 61 years.

While retrospective analysis of medical records it was revealed that in more than half of patients (8 female and 3 male) patients were suffered to significant emotional stress a few hours prior to coronary event (death of family members; witness of car incident etc.).

Three female patients were hard smokers (>2 packs per day). All male patients were hard smokers. The mean total cholesterol value was 182 mg/dl. Two from six males have the history of diabetes type 2 and in 4 male patients it was suspected cocaine abuse, however all four patients refused performing relevant confirmatory tests. Due to limitations of this study (retrospective design) we were not able to collect complete coagulation status for all patients.

ECG results:

ll patients had a ST elevation >1 mm in standard and >2 mm in two consecutive precordial leads. In tree cases (possible diagnose of Tacotsubo cardiopathy) ST elevation was detected in anterior, posterior and lateral leads. In one patient echocardiography findings were typical to Tacotsubo cardiopathy (apical dissinergy), however in two others echocardiography data are not available as they were discharged after removing the second bruising (due to personal issues-death of family members).

Cardiac Markers:

Elevation of Troponin-T was documented in all 17 patients. The mean value was 12.5 ng/ml. CK-MB was evaluated in 47% of patients and in all cases with recurrent ischemia to exclude repeated MI. To note: troponin increase was found from the first hours of hospital admission.

Coronary Angiography:

From 17 patients with no coronary atherosclerosis findings in 11 normal coronary flow was detected. In 6 patients slow coronary flow was found (TIMI 1) without local stenosis. The correlation between slow coronary flow and regional asinergy of left ventricle was not detected.

Study limitations:

- Due to limited number of patients it was impossible to perform comparative analysis in different age groups;
- No biopsy results are available which could exclude potential myocarditis
- Full coagulation panel was not available for all patients

- No tests were done to exclude cocaine abuse
- Echocardiography is missing in two patients with suspected Tacotsubo Cardiopathy
- No psychology testing were done (the only available notes about severe stress prior the initial event
- No catecholamine level was determined.

Prognosis

In 17 patients retrospectively observed in our research, we did not have lethal outcome within 6 month follow-up period. Either in hospital or after discharge we have not observed the cases with fatal or non-fatal adverse reactions. One male patient was re-admitted in 5.5 month after initial event with the same diagnose (the ECG was identical –ST elevation in the same leads). Repeated coronary angiography did not reveal coronary pathology. We suspect possible cocaine abuse in this patient, but patient again refused to perform relevant tests.

The above study is actually the first retrospective study with attempt to compare clinical; ECHO; ECG; angiography and laboratory data in patients with ST elevation Myocardial Infarction and Normal Coronary Arteries (MINCA). It gives 6 month follow up data in this limited cohort of patients. Despite limitations, it gives valuable results in understanding of the phenomena of MINCA. This is especially important in terms of finding the correlation between different investigation results and patients clinical status. Important to mention that in 7 patients with completely normal coronary arteries and normal coronary flow apical-septal and apical-lateral dyskinesia and hypo-kinesis was found. This is first research where segmental asinergy was documented in 88% of patients with MINCA.

It is extremely important that the most of patients (64.7%) were females and in most of cases they were affected by severe stress prior initial episode. We consider that in this population is important to order psychology testing followed by psychology rehabilitation and catecholamine detection. This will give an information about its role in disease development.

Incomplete coagulation results did not allow performing analysis of coagulation panel and its role in disease development. We do not doubt about potential role of coagulation abnormalities in this pathology, however cannot confirm it in the current research.

As was mentioned in all cases coronary angiography was performed within first 12 hours after symptoms start, however in most of cases (~82%) it was done within first 3 hours. It does not include the possible spontaneous thrombolysis but we do not have data to confirm it.

We cannot exclude the cocaine abuse in four male patients. Based on medical history it could not be excluded. We also cannot exclude myocarditis, as the biopsy results are not available.

With this limited retrospective research we raised important aspects of future research of patients with MINCA. Future prospective studies with involvement multidiscipline specialists and longer follow up is needed to understand whole mechanism; clinical variations, treatment approaches and outcome for this interesting and not a very rare pathology.

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SUMMARY

RETROSPECTIVE STUDY OF EVALUATION OF PATIENTS WITH ST ELEVATION MYOCARDIAL INFARCTION AND INTACT CORONARY ARTERIES. EVALUATION OF TREATMENT APPROACHES; OUTCOME AND PROGNOSIS

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Myocardial infarction with normal coronary arteries is a well known pathology. It may or may not be associated with left ventricle wall motion abnormalities. Data was reviewed retrospectively for patients with ST elevation myocardial infarction who underwent cardiac catheterization. From the total number of patients evaluated 10.3% (17) patients had Myocardial Infarction with normal coronary arteries. Females were more likely to present with MINCA then males. Coronary flow was normal in 11 from 17 patients with MINCA. In 6 cases slow coronary flow was detected. Myocardial segments with slow coronary flow did not correlate with wall motion abnormalities detected by echocardiography and ventriculography. In 8 females, Takotsubo cardiomyopathy was suspected. Data were analyzed retrospectively and we were not able to obtain full coagulation panel for all evaluated patients. Myocardial biopsy was not performed in either of patients under observation. Spontaneous thrombolysis was suspected in number of cases. Most angiography investigations were done within three hours after symptoms start. Prognosis of patients with ST-elevation Myocardial Infarction (STEMI) and normal coronary arteries was good. No fatal or non-fatal complications during hospitalization. During 6 month, follow up one male patient was re-hospitalized due to Acute Coronary Syndrome (ACS) in 5.5 month after initial event. Repeated coronary angiography did not reveal the abnormalities.

Our study is first attempt for collecting retrospectively different data for patients with STEMI and NCA. Important is that no correlation was found between wall motion abnormalities and coronary flow limitations (if present). Compared to other studies we found higher incidences of wall motion abnormalities detected by echocardiography and/or ventriculography.

Future prospective design studies in STEMI and NCA are warranted to understand the pathophysiology and define right treatment approaches. Stress may be considered as prominent factor, but future studies are needed with psychological evaluation; autonomous nerves system testing and catecholamine levels determination to verify its role in this pathology.

Keywords: Myocardial infarction; coronary arteries; wall motion abnormality; systolic function; ST elevation.

РЕЗЮМЕ

РЕТРОСПЕКТИВНЫЙ АНАЛИЗ ПАЦИЕНТОВ С ИНФАРКТОМ МИОКАРДА С ЭЛЕВАЦИЕЙ СЕГМЕНТА ST И НОРМАЛЬНЫМИ КОРОНАРНЫМИ СОСУДАМИ. ОЦЕНКА ТАКТИКИ ЛЕЧЕНИЯ, ИСХОДА И ПРОГНОЗА

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Целью исследования явился анализ состояния пациентов с инфарктом миокарда с подъемом сегмента ST и разработка тактики лечения.

Ретроспективно изучены 165 пациентов (114 мужчин и 51 женщина), подвергшиеся коронарографии по поводу инфаркта миокарда с подъемом сегмента ST, из них у 17 (10,3%) пациентов обнаружены нормальные коронарные артерии. У женщин данная патология наблюдалась чаще, чем у мужчин. У 11 пациентов наблюдался нормальный коронарный кровоток, у 6 обнаружено замедление коронарного кровотока. Участки с замедленным коронарным кровотоком не соответствовали таковым с нарушением локальной сократимости левого желудочка при эхокардиоскопии или вентрикулографии. Среди обследованных у 8 женщин было подозрение на кардиомиопатию Такотсубо. Так как исследование проведено ретроспективно не было возможности собрать полную картину свертываемости крови у всех пациентов и исключить спонтанный тромболизис. Все ангиографии были проведены в течение 3 часов после начала события. Также нет данных о биопсии миокарда, так как она не проводилась. По данным проведенного анализа, наблюдался хороший прогноз. Осложнения во время госпитализации или после выписки из стационара не обнаружены. У одного пациента наблюдался повторный инфаркт с ST элевацией спустя 5,5 месяцев после исходного события. Повторная ангиография наличие коронарной патологии не выявила.

Проведенный ретроспективный анализ - первая попытка оценить этиологию, течение, исход и прогноз пациентов с инфарктом миокарда с элевацией сегмента ST, у которых не имелось коронарной патологии. В ходе анализа наблюдался относительно

высокий процент пациентов с нарушением сегментной сократимости желудочка в сравнении с другими исследованиями, хотя они не коррелировали с участками замедления коронарного кровотока при наличии таковых. Для определения этиологии механизма, тактики лечения и прогноза таких пациентов необходимо проведение дальнейших исследований с включением психологических тестов, миокардиальной биопсии, изучением уровня катехоламинов и автономной нервной системы.

რეზიუმე

ST-სეგმენტის ელევაციით მიოკარდიუმის ინფარქტის და ინტაქტური კორონარული არტერიების მქონე პაციენტების რეტროსპექტული კვლევა: მკურნალობის ტაქტიკის, გამოსავლის და პროგნოზის შეფასება

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შპს „ალექსანდრე ალადაშვილის სახელობის კლინიკა“ თბილისი, საქართველო

რეტროსპექტულად შეფასდა პაციენტთა (n=165, 114 – მამაკაცი, 51 – ქალი) მონაცემები, რომელთაც ჩაუტარდათ კორონარული ანგიოგრაფია ST-სეგმენტის ელევაციით მიმდინარე მიოკარდიუმის ინფარქტის გამო. პაციენტთა 10.3%-ში (17 პაციენტი) კორონარების ათეროსკლეროზული დაზიანება არ გამოვლინდა. მისი სიხშირე უფრო მაღალი იყო ქალებში, მამაკაცებთან შედარებით. გამოკვლეულ პაციენტთაგან 11-ს აღენიშნებოდა ნორმალური კორონარული ნაკადი, დანარჩენ 6 - კორონარული ნაკადის შენელება. მიოკარდიუმის სეგმენტები შენელებული კორონარული ნაკადის კორონარების აუზში არ კორელირებდა სეგმენტური ასინერგიის უბნებთან, რაც გამოვლინდა ექოკარდიოგრაფიულად ან ვენტრიკულოგრაფიით. გამოკვლეულ პაციენტთა შორის 8 შემთხვევაში (ყველა - ქალი) საეჭვო იყო ტაკოცუბოს კარდიომიოპათიის არსებობა. ანალიზი გაკეთდა რეტროსპექტულად და, რიგ შემთხვევებში, ვერ მოხერხდა სრული კოაგულაციური სპექტრის შეფასება; ასევე, არ ჩატარებულა მიოკარდიუმის ბიოფსია; ვერ მოხერხდა სპონტანური თრომბოლიზისის გამორიცხვა (პაციენტთა უმეტესობაში დიაგნოსტიკური ანგიოგრაფია ჩატარდა სიმპტომების გამოვლენიდან 3 საათში).

კვლევის შედეგებით გამოვლინდა, რომ ST-სეგმენტის ელევაციით მიმდინარე მიოკარდიუმის ინფარქტით პაციენტებში, რომელთაც კორონარული სისხლძარღვების დაავადება არ გამოუვლინდათ, პროგნოზი კეთილსაიმედოა. არც ერთ მათგანს არ აღენიშნა გართულებები ჰოსპიტალიზაციის პერიოდში, ან მის შემდგომ. მხოლოდ ერთ მამაკაცში საწყისი ეპიზოდიდან 5,5 თვის შემდეგ დაფიქსირდა ST-სეგმენტის ელევაციით მიმდინარე განმეორებითი მიოკარდიუმის ინფარქტის შემთხვევა. განმეორებითმა კორონაროგრაფიამ კვლავ არ გამოავლინა კორონარული დაავადების არსებობა.

სხვა მონაცემებისაგან განსხვავებით, კვლევაში გამოვლინდა სეგმენტური ასინერგიის უბნების არსებობის უფრო მაღალი მაჩვენებელი, გამოვლენილი ექოკარდიოგრაფიულად ან ვენტრიკულოგრაფიით, თუმცა იგი არ კოლელირებდა კორონარული ნაკადის შენელებული უბნების აუზებთან (ასეთის არსებობის შემთხვევაში).

დაავადების ეტიოლოგიის, განვითარების მექანიზმის, მკურნალობის ტაქტიკის და პროგნოზის სარწმუნო ტენდენციების გამოსავლენად მომავალში აუცილებელია პროსპექტული დიზაინის კვლევები, რომელიც უნდა მოიცავდეს ფსიქოლოგიურ ტესტირებას, ავტონომიური ნერვული სისტემის ფუნქციის შეფასებას, კატექოლამინების დონის განსაზღვრას და მიოკარდიუმის ბიოფსიას.

THE SAFETY AND EFFICACY OF AMIODARONE AND CARVEDILOL COMBINATION IN TREATMENT OF PATIENTS WITH SEVERE CARDIAC RHYTHM DISORDERS

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Isolated cardiac rhythm disorders can be considered as one of the manifestations of heart failure along with dyspnea, palpitation, fatigue and edema. Ventricular arrhythmias play significant role in progression of symptoms of heart failure and sudden death [4]. Significant part (1/3-2/3 patients depending on functional class (F.C)) of heart failure patients dies suddenly due to fatal arrhythmias [6]. Therefore, control of fatal arrhythmia is extremely important in controlling of heart failure symptoms and fatal rhythm disorders. The risk of sudden cardiac death from ventricular fibrillation (VF) or ventricular tachycardia (VT) in patients with ischemic cardiomyopathy related to structural heart disease has been favorably impacted by the wide adaptation of implantable cardioverter defibrillators (ICDs) for both primary and secondary prevention [4]. This trend is in direct opposition to a general decline in stand-alone antiarrhythmic drugs for ventricular indications [6] however, even patients with inserted ICD still require aggressive antiarrhythmic therapy due to frequent shocks, which is distressing for most of patients. Beta-Blockers and Amiodarone are considered as potential treatment to control ventricular arrhythmias in heart failure patients. There is no doubt that B-blockers are gold standard of care in heart failure patients and should be prescribed to every patient with II-IV F.C patients unless contraindicated or not tolerated [17]. From the number of different classes of B-Blockers available on the market Carvedilol can be considered as treatment of choice [13].

Carvedilol therapy has been reported to be more effective than other beta-blockers in patients with chronic heart failure (CHF). Amiodarone is an anti-arrhythmic medicine that has also been reported to be effective in patients with CHF. But the usefulness of combined therapy with carvedilol and amiodarone has not been reported [8,15]. Obviously, Amiodarone is the only antiarrhythmic drug, which can be considered for long-term therapy of heart failure patients. However, it does not improve the total mortality. There is no evidence, which confirms that Amiodarone can decrease the global mortality in heart failure patients, moreover single studies suggest that it can worsen heart failure symptoms in III and IV F.C patients [9]. At the same time, Amiodarone significantly decreases the risk of sudden death in patients after myocardial infarction. In fact, Amiodarone is not a treatment of choice for III and IV F.C heart failure patients, even in patients with increased risk of sudden death due to ventricular rhythm disorders considering potency of increase of cases of cardiac decompensation.

Combination use of Amiodarone and Carvedilol was tested in a number of studies with limited study population. Based on these results it can be associated with increased risk of bradycardic events (6% of patients developed symptomatic bradycardia which required pacemaker insertion). Combination therapy with amiodarone and carvedilol was well tolerated and seems to be effective in severe heart failure in terms of improved symptoms, reduced heart rate and increased ejection fraction. Prophylactic pacemaker implantation should be considered due to a significant rate of bradycardic events [12].

The another study demonstrated that combined therapy with carvedilol and amiodarone is more effective in improving cardiac symptoms, exercise capacity, cardiac function and cardiac sympathetic nerve activity in patients with Dilated Cardiomyopathy (DCM) [5,15].

The consideration above is extremely important and favorable for patients with ICD or cardiac pacemakers [4,10,14]. Patients are fully protected from development of symptomatic bradycardia or atrioventricular blockade. These patients with high risk of ventricular rhythm disorders or frequents shock due to ICD can especially benefit from the combined antiarrhythmic treatment [1,7].

Based on judgement above we considered whether it is possible adding Carvedilol in patients with heart failure who already receives treatment with Amiodarone due to severe ventricular arrhythmias. We observed number of patients in our hospital where the decision was made to switch patient from Amiodarone to Carvedilol due to worsening of heart failure symptoms. It was found that within the first week of treatment, when Amiodarone plasma concentration was still high and Carvedilol was started, we have achieved complete arrhythmia control in most of our patients. Within next weeks, when Amiodarone plasma concentration progressively decreased ventricular rhythm disorders appeared again as Carvedilol alone was not able to control them. The consideration above justifies the possibility of using both medications at the same time.

Material and methods. We have evaluated the studies with combination of B-blocker and Amiodarone therapy and found that the number of studies provides valuable information about safety and efficacy of this combination. However, the studies are limited; population under the study is small and in general, this limited information does not give a definite response whether combination of B-Blockers and Amiodarone is possible; can be safe and effective in heart failure patients to control severe ventricular rhythm disorders [1,2,5,12,14].

To evaluate efficacy and safety of combination of Amiodarone and Carvedilol at Cardiology Department of our hospital we retrospectively evaluated 142 patients with anamnesis of myocardial infarction. All of them have

Table 1. Patients' characteristics

Patients group	History of (Myocardial Infarction) MI	Hypertension	Diabetes	Atrial Fibrillation	Heart Failure Functional Class (FC)
I group (46)	46 (100%)	30 (65%)	18 (39%)	12 (26%)	II F.C. 18 (39%); III F.C. 24 (52%); IV F.C. 4 (9%)
II group (52)	52 (100%)	27 (51%)	16 (30%)	14 (27%)	II F.C. 22 (42%); III F.C. 29(55%); IV F.C. 1 (3%)
III group (44)	44 (100%)	22 (54%)	16 (36%)	11 (25%)	II F.C. 16(36%); III F.C. 24(55%); IV F.C. 4 (9%)

Table 2. Efficacy and safety of combination therapy heart failure patients

Value	I group	II group	III group
Total mortality	18%	11.5%^^	4.5%
Cardiovascular mortality	15,2%	7,6%^^	2,5%
Mortality due to arrhythmia	4.3%	3,8%^^	2.2%*
Mortality due to decompensation of heart failure	8,2%	1,3%^^	1,1%

^ - significant difference compared to first group
*- * significant difference compared to first group*

heart failure II-IV F.C. Adding Carvedilol to Background Amiodarone therapy was done in case of unsuccessful control of ventricular arrhythmia; in case of progression of heart failure symptoms despite optimal therapy or when the rhythm restore was considered in new onset atrial fibrillation patients. All patients were evaluated retrospectively and were receiving standard background therapy for heart failure.

We evaluated three different groups of patients: first group were receiving Amiodarone (46 patients); second group were receiving Carvedilol (52 patients) and third group were receiving combination of Amiodarone and Carvedilol (44 patients). Detailed information about concomitant medical history of the different treatment group of patients are provided in Table 1.

All evaluations were done retrospectively: echocardiography; ECG; Holter monitoring; fasting plasma glucose; serum electrolytes. Patients were enrolled in analysis having different types of hemodynamically significant ventricular arrhythmias confirmed by 1st Holter monitoring. ¼ part of all patients enrolled in retrospective evaluation were found with new onset atrial fibrillation and sinus rhythm restore was the goal of treatment. The minimal observation period was 6 month, maximal up to 5 years.

The Amiodarone dosage used for this retrospective analysis was 1000 mg per week. The average Carvedilol daily dose was 25 mg, but it vary from 6.26 to 25 mg (the dose titration was done based on titration algorithm). No dose change was done due to combination with Amiodarone.

Results and their discussion. While analysis of study results we found that the most frequent adverse event was bradi arrhythmias (Heart rate <50 beats per minute (BPM)); First degree AV block and Sino auricular blockade (RR<2000 msec) in 2 patients of first group (4.3%). The above issue was the reason for Amiodarone discontinuation. For same reason the dose of Carvedilol was decreased in three patients of second group (5.7%) and in three patients of third group (6.8%). There was no need for pacemaker insertion in either of patients.

There was noted transient hypotension (<110 mm.Hg for systolic); dizziness and abdominal discomfort. There was no need to discontinue or modify background antiarrhythmic therapy due to above events. We observed not clinically significant tendency of increase of non-serious adverse reactions in third group of patients.

Based on data provided above we did not find statistically significant increase of adverse reactions in third group of patients where Amiodarone and Carvedilol were used as a combination therapy compared to groups where the medications were used as mono antiarrhythmic therapy.

While analysis of data we found that in third group of patients the best results in terms of decrease of total mortality and death due to arrhythmia were reported. It was also noted the tendency of decrease of cardio-vascular deaths and deaths due to decompensation of heart failure, but the difference was not statistically significant compared to Carvedilol group, but was statistically significant compared to Amiodarone group (Table 2).

After reviewing repeated Holter monitoring results in 95.5% of patients of third group complete control of ventricular arrhythmia were achieved. In patients of first group ventricular arrhythmia was still present in 24% of patients. In second group, ventricular arrhythmia was still present in

33% of patients. In all patients of third group restoring of sinus rhythm were noted (100%); in first group of patients restoring of sinus rhythm were observed in 66.6% patients with atrial fibrillation. The percentage of patients with atrial fibrillation with restored sinus rhythm in second group was 57.1%. In all patients with atrial fibrillation belonging to first and second group, target ventricular response was achieved in all patients with atrial fibrillation.

Based on above data Carvedilol in Combination with Amiodarone can be considered as better method of pharmacologic cardioversion in selected population with atrial fibrillation rather either of medications alone. The above data are based on very limited patient population. More trials with more patients are needed to get definite recommendations.

While evaluation of echocardiography results adding Carvedilol to Amiodarone therapy led to visible improvement of left ventricular parameters compared to group of patients with Amiodarone. Visible decrease of left ventricle end diastolic and end-systolic dimensions along with significant increase of ejection fraction were noted in second and third group of patients. Improvement of functional class was noted in parallel in II and III heart failure F.C patients.

Known benefit of Carvedilol on left ventricular functional parameters were not decreased in group where Carvedilol was used in combination with Amiodarone. Moreover. Adding Carvedilol to Amiodarone treatment led to additive effect by decreasing death due to arrhythmia and controlling ventricular arrhythmias. Combination use of Amiodarone and Carvedilol did not lead to statistically significant increase of adverse reactions compared to groups where these medications were used as a single antiarrhythmic treatment

The provided study has significant limitations. The data were assessed retrospectively and there was not possible to obtain more information or order more investigations where clinically indicated. Study population was not big enough to provide with the definite recommendations. However, the approach to use combination of Carvedilol and Amiodarone can be considered as one of the options in heart failure patients after myocardial infarction with increased risk of sudden dearth due to ventricular arrhythmia.

Large prospective parallel group clinical trials are needed to provide more information about efficacy and safety of this combination therapy.

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SUMMARY

THE SAFETY AND EFFICACY OF AMIODARONE AND CARVEDILOL COMBINATION IN TREATMENT OF PATIENTS WITH SEVERE CARDIAC RHYTHM DISORDERS

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Different arrhythmias are cause of sudden death in many patients with heart failure. Amiodarone is usually used for prevent this arrhythmias, but it is not drug of choice for treatment the patients with heart failure. We retrospectively analyzed 142 patients with moderate and severe heart failure and history of myocardial infarction. These patients have received amiodarone, carvedilol or combination of these two medications together with standard therapy. In our retrospective analysis, the combination therapy with Amiodarone and Carvedilol had highly significant decrease arrhythmic death compare with carvedilol and amiodarone groups. This therapy is more effective in recovering of sinus rhythm in patients with atrial fibrillation and for control ventricular arrhythmias. The effects of carvedilol on left ventricular remodeling, systolic function and symptomatic status are not affected adversly by concurrent treatment with amiodarone. Carvedilol is an effective additional therapy for the patients with chronic heart failure already receiving Amiodarone. Carvedilol can be added to Amiodarone in patients with severe ventricular rhythm disorders and increased risk of sudden death without expecting of increase adverse events (than either drug alone) or loss of clinical efficacy.

Keywords: heart failure, ventricular arrhythmia, Amiodarone, Carvedilol, combination therapy with Amiodarone and Carvedilol

РЕЗЮМЕ

ОЦЕНКА ЭФФЕКТИВНОСТИ И БЕЗОПАСНОСТИ КОМБИНАЦИИ АМИОДАРОНА И КАРВЕДИЛОЛА ПРИ ЛЕЧЕНИИ ТЯЖЕЛЫХ НАРУШЕНИЙ РИТМА СЕРДЦА

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Нарушение ритма сердца является частой причиной гибели пациентов с сердечной недостаточностью. Для контроля сердечного ритма часто используется амиодарон, однако он не является препаратом выбора при сердечной недостаточности. Ретроспективно проанализированы данные 142 пациентов с сердечной недостаточностью и перенесенным инфарктом миокарда, которые получали амиодарон, карведилол или комбинацию этих препаратов на фоне стандартной терапии. В группе комбинированного использования амиодарона и карведилола наблюдалось статистически достоверное уменьшение смертности от аритмии в сравнении с группами с изолированным использованием этих препаратов. Подобная комбинация более эффективна для восстановления синусового ритма и контроля желудочковых аритмий. Положительный эффект карведилола на ремоделирование левого желудочка, систолическую функцию и клинические проявления сердечной недостаточности не снижался при сопутствующем лечении амиодароном. Согласно проведенному анализу, применение карведилола у пациентов с высоким риском тяжелых желудочковых аритмий и внезапной смерти сопровождается дополнительной эффективностью и не вызывает увеличения риска нежелательных явлений в сравнении с изолированным использованием этих препаратов.

რეზიუმე

ამიოდარონის და კარვედილოლის კომბინაციის ეფექტურობის და უსაფრთხოების შეფასება გულის რითმის მძიმე დარღვევების დროს

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შპს „ალექსანდრე ალადაშვილის სახელობის კლინიკა", თბილისი, საქართველო

სხვადასხვა არითმია გულის უკმარისობით პაციენთთა დაღუპვის ხშირ მიზეზს წარმოადგენს. ამიოდარონი უხშირესად გამოიყენება ასეთი

არითმიების სამკურნალოდ, მაგრამ იგი არ არის არჩევის პრეპარატი გულის უკმარისობით პაციენტებში. რეტროსპექტულად გავაანალიზებულია საშუალო და მძიმე გულის უკმარისობით და მიოკარდიუმის ინფარქტის ანამნეზით 142 პაციენტის მონაცემები, რომლებიც იღებდნენ ამიოდარონს, კარვედილოლს და ამიოდარონის და კარვედილოლის კომბინაციას სტანდარტულ მკურნალობასთან ერთად. ამიოდარონის და კარვედილოლის ჯგუფში გამოვლინდა არითმოგენული სიკვდილის სარწმუნო შემცირება იზოლირებულად ამიოდარონის და კარვედილოლის ჯგუფებთან შედარებით. ამასთანავე ეს კომბინაცია იყო უფრო ეფექტური სინუსური რითმის აღსადგენად მოციმციმე არითმიით პაციენტებში და პარკუჭოვანი არითმიების გასაკონტროლებლად. კარვედილოლის დადებითი მოქმედება მარცხენა პარკუჭის რემოდელირებაზე, სისტოლურ ფუნქციასა და გულის უკმარისობის კლინიკურ გამოვლინებებზე არ მცირდებოდა ამიოდარონთან კომბინაციის შემთხვევაში. ავტორთა მონაცემებით, კარვედილოლის დამატება მძიმე პარკუჭოვანი არითმიების და უეცარი სიკვდილის მაღალი რისკის მქონე პაციენტებში, რომლებიც იღებენ ამიოდარონს ხასიათდება დამატებითი ეფექტურობით და შეიძლება განიხილებოდეს, როგორც ერთ-ერთი შესაძლო მკურნალობა. ამასთანავე, ეს კომბინაცია სარწმუნოდ არ ზრდის მოსალოდნელი გვერდითი მოვლენების სიხშირეს პრეპარატების იზოლირებულად გამოყენების შემთხვევებთან შედარებით.

INFLUENCE OF BETA-BLOCKERS AND IVABRADIN ON LONG-TERM PROGNOSIS OF PATIENTS WITH STABLE ANGINA

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Patients with stable forms of ischemic heart diseases (IHD) belong to a group of very high risk because of cardiovascular mortality in them ranges from 1.3% to 10% per year, and in 2-10% of patients developed non-fatal myocardial infarction (MI) [4,5]. Reducing mortality from cardiovascular disease (CVD), which is achieved in many developed countries in recent years, basically associated with the widespread introduction of treatment's standards [2,6]. According to the recommendations of the European Society of Cardiology, the main strategy for treatment of stable IHD is prevention of MI and death that improves prognosis. This strategy does accentuation on obligatory admission of at least four groups of medicine, which effectiveness of influence on prognosis was clearly demonstrated in the implementation of extensive randomized placebo-controlled trials [1].

The course of IHD can be very diverse: some patients have angina with stable course without significant aggravation of clinical picture from years to years, in others - is progressing rapidly, resulting in myocardial infarction, heart failure and death, in the third – immediately starts with the acute coronary syndrome [5]. Mostly clinical symptoms and the patient's prognosis are determined, on the one hand – by the ratio of morphological and functional components of the disease pathogenesis, the other - the adequacy of the chosen drug, interventional or surgical treatment [4]. The most important daily task of practicing cardiologist is the choice tactics of treatment of each patient with coronary insufficiency. The separation of angina on various forms justified only on clinical positions because of different clinical syndromes of IHD is a manifestation of the same disease process. Evaluation of the severity of condition and long-term prognosis of IHD is a very complicated problem. As known, the course and long-term prognosis in patients with chronic forms of IHD significantly correlated with coronary angiography data and indicators of myocardial function, such as left ventricular ejection fraction [3,5]. It is established inverse relationship between the severity of coronary atherosclerosis and survival of patients with coronary artery disease [6].

Material and methods. We examined 90 patients with stable angina (SA), which in addition to nitrates, aspirin ("Bayer AG" 100 mg per day) and rosuvastatin (Mertenil, "Gedeon Richter" 10 mg per day) received bisoprolol (Concor "Nycomed") in dose of 1.25 – 7.5 (5.41 ± 1.36) mg / day) - a group I, 30 patients; carvedilol (Koriol, "KRKA") in dose of 6.25-12.5 (9.75 ± 1.69) mg / day - group II, 30 patients; and ivabradine (Koraksan, "Servier") in dose of 5-15 (9.81 ± 2.13) mg / day - the third group, 30 patients.

We analyzed the following indicators to identify the impact on long-term prognosis (after 1 year of observation) of prescribed treatment: patient adherence to treatment, cases of myocardial infarction and circulatory decompensation, which resulted in necessity of patient's hospitalization during the year of observation, calculating the probability of achieving a key prognostic endpoint by patient (the occurrence of MI or unstable angina, need for revascularization, cardiovascular death) using the concept of the odds ratio and determination of important

components in the progression of the disease (patient age, increased heart rate (HR) above 60 beats / min, adherence to treatment, availability of unhealthy habits and increased endothelin-1 (ET-1) and homocysteine (Hc).

Results and their discussion. The results of research indicate that in the period of observation among all patients with SA in general, 4 patients died (4.44%). It was found that they completely stopped taking all intended drugs. Results of achieving a key prognostic endpoint by patients in studied groups (cardiovascular death, MI, or hospitalization for unstable angina, or the need for revascularization) are presented in Table 1.

The authors previously conducted research have shown that markers of unfavorable prognosis in patients with hemodynamically significant atherosclerosis of coronary artery, verified by selective coronary angiography and cardiac ventriculography, is multivessel coronary lesions, the presence of deletions in the gene ACE and ACE activity, presence of classic risk factors such as systolic blood pressure, diabetes type 2, smoking, obesity, dyslipidemia, physical inactivity and burdened heredity on CVD [7].

A comparative analysis of the dynamics of odds ratio OR was provided in SA patients with risk of MI, US, necessity of revascularization and cardiovascular death after 12 months of treatment.

Using a model of univariate regression analysis, leads to the conclusion that the risk of achieving patients with stable angina a key prognostic endpoint increased with age as follows - for every subsequent 5 years after 50 had to increase the risk of the achieving endpoint to 1.32 times (Table 2).

In addition, the chance to reach the endpoint increased by 2.87 times with elevation of heart rate every 10 beats / min more than 60 beats / min., by 5.89 times in case of prescribed treatment failure and by 2.12 times in the presence of harmful habits of the patient, such as smoking (Fig. 1).

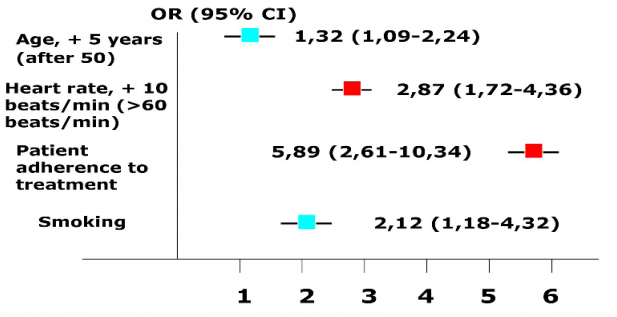

Fig. 1. Analysis of factors that influence on achievement the endpoint by patients (all patients with stable IHD) after 12 months of observation

Much attention is paid to biomarkers of inflammation among other potential biomarkers of progression in chronic IHD. The processes that lead to erosion or disintegration of atherosclerotic plaque include a number of mechanisms of inflammation, in particular such as endothelial dysfunction [5].

Because of biomarkers of endothelial dysfunction responsible for different aspects of the progression in chronic IHD, the study of their relationship can contain unique information for clinicians in terms of predicting of adverse cardiovascular events and observation period for certain categories of patients.

The effect of raising Hc and ET-1 on achievement the endpoint by patients with SA (ie of adverse cardiovascular events) was analysed. Revealed that hyperhomocysteinemia increases the risk of achieving the endpoint by patients with SA (OR – 5.8 (CI: 2.31-14.57, p <0.05)). A similar trend is observed for the level of ET-1: increasing its value elevate the risk of endpoint appearance in patients with SA (OR – 8.18 (CI: 3.16-21.21, p <0.05)) as shown in Fig. 2.

Table 1. The incidence of unfavorable coronary events in the groups of patients with stable angina after 12 months of observation

Events	Group I		GroupII		Group III	
	abs.	%	abs.	%	abs.	%
Unstable angina	9	30	7	23.33	8	26.67
Myocardial infarction	3	10	4	13.33	1	3.33*
Need for revascularization	8	26.67	6	20	5	16.67*
Cardiovascular death	1	3.33	2	6.67	1	3.33

*note: * - significant difference between formed groups of patients*

Table 2. Markers of patients achieving target point after 12 months of observation (univariate regression analysis results)

Sign	Odds ratio (95% CI)
Age, + 5 years (after 50)	1.32 (1.09 – 2.24)
Heart rate, + 10 beats/min (>60 beats/min)	2.87 (1.72 – 4.36)
Patient adherence to treatment	5.89 (2.61 – 10.34)
Smoking	2.12 (1.18 – 4.32)

Table 3. Adherence to treatment in patients with stable angina with different variants of the disease

Group of medicine	Patients with endpoints	Patients without endpoints
Acetylsalicylic acid	84.31%	89.74%
Nitrates	82.35%	48.71%*
Statins	50.98%	76.92%*
β-AB / ivabradine	58.82%	82.05%*

*note: * - significant difference of indices between patients*

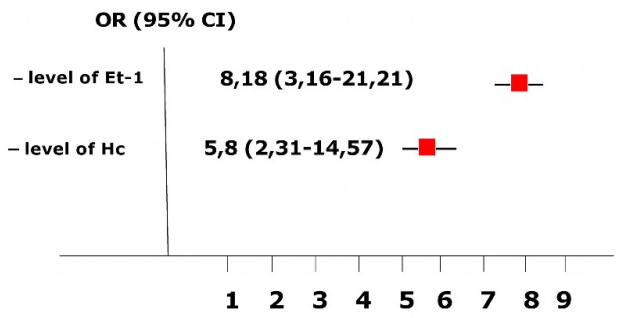

Fig. 2. Analysis of factors that influence on achievement the endpoint by patients (all patients with stable IHD) after 12 months of observation

We also conducted a comparative analysis of the impact on prognosis of compliance guidelines to standard medical therapy in patients with SA. For this purpose, all patients with SA were divided into two groups: patients who have reached endpoints; patients who have not reached the endpoint.

The analysis of patient adherence to treatment in both groups presented in Table 3.

Attracted attention to the fact, that the group of patients who did not achieve endpoint during the year characterized by indisputable higher adherence to treatment, including medicines, such as statins, β-AB / ivabradine. Another group of patients is much more committed to treatment by nitrates drug. This fact may be caused by progression of SA symptoms.

Conclusion. Summarizing the results of this research we concluded that in compared patients groups developed cardiovascular death and unstable angina with almost equal frequency. As for cases of myocardial infarction and the need for revascularization, their number was smaller in patients who in addition to standard treatment received ivabradine. Prognosis of patients with stable angina after 12 months of treatment primarily depends on their adherence to treatment, age, heart rate, presence of harmful habits, and markers of endothelial dysfunction, including endothelin-1 and homocysteine.

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SUMMARY

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The purpose of the study was to evaluate the influence of beta-blockers and ivabradine on long-term prognosis of patients with stable angina.

90 patients with stable angina that have been involved in present study along with nitrates, antiplatelet agents and statins received bisoprolol (Group I), carvedilol (Group II) and ivabradine (Group III). We analyzed the following indicators: patient adherence to treatment, cases of myocardial infarction and circulatory decompensation, which resulted in necessity of patient's hospitalization during the year of observation, calculating the probability of achieving a key prognostic endpoint by patient using the concept of the odds ratio and determination of important components in the progression of the disease.

We concluded that in compared patients groups developed cardiovascular death and unstable angina with almost equal frequency. As for cases of myocardial infarction and the need for revascularization, their number was smaller in patients who in addition to standard treatment received ivabradine. Prognosis of patients with stable angina after 12 months of treatment primarily depends on their adherence to treatment, age, heart rate, presence of harmful habits, and markers of endothelial dysfunction, including endothelin-1 and homocysteine.

Keywords: stable angina, bisoprolol, carvedilol, ivabradine, long-term prognosis.

РЕЗЮМЕ

ВЛИЯНИЕ БЕТА-АДРЕНОБЛОКАТОРОВ И ИВАБРАДИНА НА ОТДАЛЕННЫЙ ПРОГНОЗ У ПАЦИЕНТОВ СО СТАБИЛЬНОЙ СТЕНОКАРДИЕЙ

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Целью исследования явился анализ влияния бета-блокаторов (бисопролола, карведилола) и блокатора if-канала ивабрадина на отдаленный прогноз у пациентов со стабильной стенокардией.

Обследовано 90 больных хроническими формами ишемической болезни сердца, которые кроме нитропрепаратов, антиагрегантов и статинов получали бисопролол (I группа), карведилол (II группа) и ивабрадин (III группа). В статье проанализированы следующие показатели: приверженность пациентов к лечению, развитие инфаркта миокарда и случаев декомпенсации кровообращения, которые обусловили необходимость госпитализации больного в течение года, вычисление вероятности достижения пациентами конечной точки. Для анализа параметров использована современная концепция отношения шансов с выделением значимых составляющих в прогрессировании заболевания.

Сделан вывод, что у пациентов сравниваемых групп, почти с одинаковой частотой развивалась сердечно-сосудистая смерть и нестабильная стенокардия. Что касается случаев развития инфаркта миокарда и потребности в реваскуляризации, то их количество было намного меньше у пациентов, у которых дополнительно к базисной терапии был назначен ивабрадин. Прогноз пациентов со стабильной стенокардией через 12 месяцев лечения прежде всего зависел от их приверженности к лечению, от возраста, частоты сердечных сокращений, наличия вредных привычек, а также от уровня маркеров эндотелиальной дисфункции, в частности эндотелина-1 и гомоцистеина.

რეზიუმე

β-ადენობლოკატორების და ივაბრადინის გავლენა შორეულ პროგნოზზე პაციენტებში სტაბილური სტენოკარდიით

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უკრაინის უმაღლესი სახელმწიფო საგანმანათლებლო დაწესებულება «ბუკოვინის სახელმწიფო სამედიცინო უნივერსიტეტი», ჩერნოვცი, უკრაინა

კვლევის მიზანს წარმოადგენდა β-ბლოკატორის (ბისოპროლოლი და კარვედილოლი) და if-არხის ბლოკატორის (ივაბრადინი) შორეულ პროგნოზზე ზეგავლენის ანალიზი პაციენტებში სტაბილური სტენოკარდიით.

შესწავლილია 90 ავადმყოფი გულის იშემიური დაავადების ქრონიკული ფორმით, რომლებიც,ნიტროპრეპარატებთან,ანტიაგრეგანტებთან და სტატინებთან ერთად, დამატებით იღებდნენ ბისოპროროლს (I ჯგუფი), კარვედილოლს (II ჯგუფი) და ივაბრადინს (III ჯგუფი). კვლევის პერიოდში გაანალიზდა შემდეგი მონაცემები: პაციენტების განწყობა მკურანალობის მიმართ,მიოკარდიუმის ინფარქტის და სისხლის მიმოქცევის დეკომპენსაციის განვითარების შემთხვევები,რაც განაპირობებს ავადმყოფის ჰოსპიტალიზაციის აუცილებლობას და მთელი წლის განმავლობაში დაკვირვების ქვეშ ყოფნას. პარამეტრების გაანალიზების მიზნით გამოყენებული იყო შანსების დამოკიდებულების თანამედროვე კონცეფცია დაავადების პროგრესირებაში მნიშვნელოვანი შემადგენლის გამოყოფით.

დადგენილია, რომ შედარების ჯგუფში თითქმის ერთნაირი სიხშირით ვითარდებოდა გულ-სისხლძარღვოვანი სიკვდილი და არასტაბილური სტენოკარდია. მიოკარდუმის ინფარქტის განვითარების შემთხვევები და რევასკულარიზაციის მოთხოვნა უფრო მცირე იყო პაციენტებში,რომელთაც,ბაზისურ თერაპიასთან ერთად დანიშნული ჰქონდათ ივაბრადინი. სტაბილური სტენოკარდიით ავადმყოფების პროგნოზი 12

თვის შემდეგ,პირველ რიგში,დამოკიდებული იყო ავადმყოფის განწყობაზე მკურანალობისადმი,მის ასაკზე,გულის შეკუმშვების სიხშირეზე,უარყოფითი ჩვენებების არსებობაზე და ენდოთელური დისფუნქციის მარკერებისმ (ენდოთელინ-1 და ჰომოცისტეინი) დონეზე.

ANXIETY LEVELS IN PATIENTS WITH PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA IN RELATION WITH THE PATIENT DEMOGRAPHICS, TYPE OF SUPRAVENTRICULAR TACHYCARDIA AND THEIR PERSONALITY TYPE

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Paroxysmal supraventricular tachycardia (PSVT) is a common arrhythmia occurring with an incidence of 2,5 per 1000 in general population [11]. This arrhythmia encompasses three different mechanisms of tachycardia which are: Atrioventricular Nodal Reentrant Tachycardia (AVNRT), Atrioventricular Reentrant Tachycardia (AVRT) and Atrial Tachycardia (AT) [2]. The most common mechanism is atrioventricular nodal re-entrant tachycardia (AVNRT) occurring in 50-60% of cases. The atrioventricular re-entrant tachycardia (AVRT) is the second most common form of PSVT occurring in up to 30% of cases and the least common form is atrial tachycardia which occurs in about 10% of cases [4]. Although the PSVT occurs in all age groups it's mechanism varies depending on patient demographics [8,10].

The episodes of paroxysmal supraventricular tachycardia are often accompanied with such symptoms as palpitations, dizziness, dyspnea, and diaphoresis and these symptoms frequently are very severe and sometimes even disabling [3]. The episodes of PSVT are also known to cause significant anxiety [1], depression and panic disorder [5]. These symptoms may cause misdiagnosis of the paroxysmal supraventricular tachycardia as panic attack [12].

As the relationship between cardiovascular diseases and psychopathology is shown to be associated with certain personality types [9] and cardiovascular reactivity [6] we decided to evaluate the incidence of different personality types among patients with documented paroxysmal supraventricular tachycardia and associated anxiety levels according to their personality type, age, gender and the mechanism of PSVT.

Material and methods. *Study population.*

Study population consisted of 62 consecutive patients who underwent an electrophysiological study and successful radiofrequency catheter ablation for AV Nodal Reentrant Tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT) and atrial tachycardia (AT) at the Jo Ann Medical Center, Tbilisi, Georgia between July 2016 and April 2017. Exclusion criteria were age less than 18 years, severe heart failure (NYHA III-IV), severe renal failure with hemodialysis, history of stroke with neurological disability, significant psychiatric illness, pregnancy.

Data collection

In addition to demographic (age, gender) and anthropometric (height, weight) data all patients were asked to fill out the personality type questionnaire (Myers Briggs Type Indicator, MBTI) which consisted of 70 questions and the State-Trait Anxiety Inventory (STAI).

The MBTI is an introspective self-report questionnaire designed to indicate psychological preferences in how people perceive the world and make decisions. The questionnaire is based on Carl Gustav Jung's theory according to which there are four principal psychological functions by which humans experience the world – sensation, intuition, feeling and thinking. The MBTI questionnaire constructs the personality type using the four dichotomies which have to answer four principal questions: 1. Does the person focus more on external or inner world to receive energy. This is called Extraversion (E) or Introversion (I). 2. How the person perceives information. Sensing (S) means the person prefers to focus on basic information received directly and Intuition (N) means the person prefers to interpret and add meaning. 3. The third question is about how we make decisions. Thinking (T) means that a person makes a decision mainly through logic. Feeling (F) means that, as a rule, he or she makes a decision based on emotion, i.e. based on what they feel they should do. 4. The fourth criterion reflects how a person implements the information he or she has processed. Judging (J) means that a person organizes all of his life events and, as a rule, sticks to his plans. Perceiving (P) means that he or she is inclined to improvise and explore alternative options.

According to the MBTI questionnaire, the patients were assigned one of the 16 personality types (ESTJ, ISTJ, ENTJ, INTJ, ESTP, ISTP, ENTP, INTP, ESFJ, ISFJ, ENFJ, INFJ, ESFP, ISFP, ENFP, INFP).

State-Trait Anxiety Inventory (STAI) is an introspective psychological inventory which consists of 40 items and is used to assess state (situational) and trait (general) anxiety.

The mechanism of the patient's supraventricular tachycardia was determined during the electrophysiological study and catheter ablation procedure. After obtaining an informed consent the procedure was performed on conscious sedation with standard techniques described elsewhere and with the electrophysiological recording and stimulation system EP Tracer (Sschwarzer Cardiotek GmbH, Heilbronn, Germany) and the RF generator EP-Shuttle (Stockert GmbH, Freiburg, Germany).

Unpaired Student T-test was used to compare mean state and trait anxiety scores between different personality types, age groups, and gender. Age groups were defined as < 50 years old and ≥50 years old.

Results and their discussion. 62 patients were included in the study. There were 44 were female (71%) and 18 male (29%) patients. The mean age was 48.26 ±15.15 (ranged from 18 to 74 years). 40 patients (64.5%) had AV Nodal Re-entrant Tachycardia (AVNRT), 17 (27.4%) had AV Reciprocating Tachycardia (AVRT) and 5 (8.1%) had Atrial Tachycardia (AT). 15 (24.2%) patients had ISTJ personality type, 13 (21%) patients had ESFJ, 13 (21%) ESTJ, 11 (17.7%) ISFJ, 3 (4.8%) ENTJ, 2 (3.2%) INFJ, 1 (1.6%) ISFP, 1 (1.6%) ESFP, 1 (1.6%) ISTP, 1 (1.6%) ENTP, 1 (1.6%) INTJ. There were no ENFP, INFP, ESTP, INTP and ENFJ personality types in this group.

We found no significant difference in State (p=0.893) or Trait (p=0.315) anxiety scores according to gender although higher scores were found in females (Fig. 1). Mean State anxiety score was 41.53±13.51 in females and 38±9.22 in males (p=0.315) and mean Trait anxiety score was 44.70±12.62 in females and 44.28±5.73 in males (p=0.893). Older patients also tended to have higher anxiety scores although the difference was not statistically significant (Fig. 2). The mean State anxiety score for patients ≥50 years old was 41.94±12.83 and for patients <50 years old was 38.90±11.98 (p=0.344). Mean Trait anxiety score for patients ≥50 years old was 46.78±11.33 and for patients <50 years old was 42.14±10.26 (p=0.100).

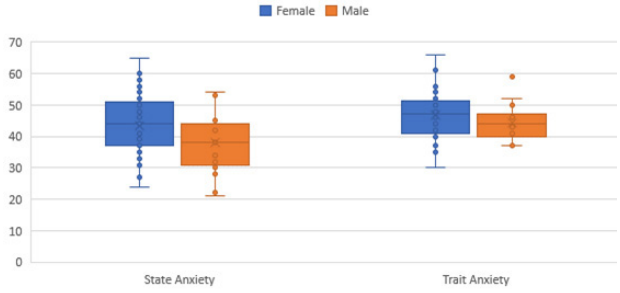

Fig. 1. Anxiety levels by gender

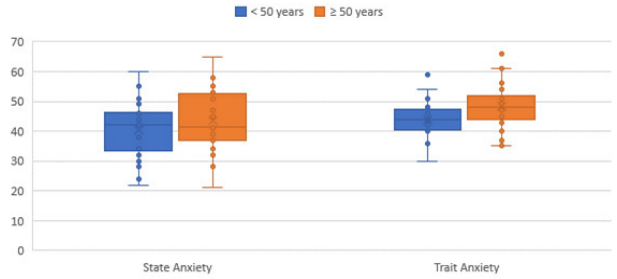

Fig. 2. Anxiety levels by age

We found statistically significant difference in trait anxiety levels between patients with different SVT types. The patients with AVNRT had significantly higher Trait anxiety scores (mean 46.82±10.52) than the patients with AVRT or AT (mean 40.59±10.91) (p=0.032) (Fig. 3). State anxiety score was not significantly different between patients with different SVT types. Mean State anxiety score for AVNRT patients was 40.95±11.60 and for AVRT and AT patients 39.68±14.03 (p=0.706).

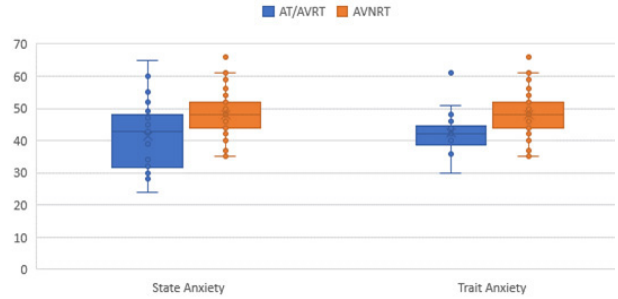

Fig. 3. Anxiety levels by type of SVT

There was no significant association between anxiety scores and personality types. Mean Trait anxiety score was 44.43±13.60 for introverts (I) and 44.71±7.93 for extroverts (E) (p=0.293). Mean State anxiety score was 38.63±14.09 for introverts (I) and 42.29±10.50 for extroverts (E) (p=0.404). Mean Trait anxiety score was 44.20±11.50 for sensing (S) types and 47.43±5.53 for intuitive (N) types (p=0.425). Mean State anxiety score was 39.89±12.41 for sensing (S) and 45.14±12.52 for intuitive (N) types (p=0.827). Mean Trait anxiety score was 43.45±10.52 for thinking (T) and 45.89±11.58 for feeling (F) types (p=0.538) and mean State anxiety score was 40.55±12.50 for thinking (T) and 40.43±12.58 for feeling (F) types (p=0.867). Mean Trait anxiety score was 44.63±11.34 for judging (J) and 43.75±4.27 for perceiving (P) types (p=0.339). Mean State anxiety score was 40.88±12.65 for judging (J) and 35.00±7.70 for perceiving (P) types (p=0.414).

The paroxysmal supraventricular tachycardia is associated with significant anxiety [7]. In our patients not a single patient had a trait anxiety score below 30 (lowest possible score is 20 indicating low anxiety) and 50 (80.6%) patients had trait anxiety score 40 or higher (highest possible score is 80). As for state or situational anxiety, 53 (85.48%) had a state anxiety score ≥30 and 34 (54.8%) of patients had a state anxiety score ≥40 before ablation. On

the other hand, there is insufficient data whether different personality types express different anxiety patterns or whether the anxiety levels differ according to age, gender or specific type of paroxysmal supraventricular tachycardia.

In our patients the most common personality types were ISTJ, ESFJ, ESTJ and ISFJ. State anxiety scores were higher in extroverts (E), intuitive (N) and judging (J) types although the difference was not statistically significant suggesting lesser role of personality type in the anxiety levels of the patients with paroxysmal supraventricular tachycardia.

Also females showed greater anxiety levels which agrees with the literature that females are more likely to have symptoms ascribed to psychiatric origins but again our data did not reach statistical significance. Patients 50 years of age or older had higher anxiety levels probably reflecting fear of having a heart attack.

Interestingly the mechanism of supraventricular tachycardia was significantly associated with patients' anxiety levels. Specifically, patients with Atrio-ventricular Nodal Re-entrant Tachycardia (AVNRT) had significantly higher trait anxiety levels than the patients with Atrial Tachycardia (AT) or Atrio-ventricular Reciprocating Tachycardia (AVRT). The reason for this association is not clear. On the other hand, the state anxiety levels were not significantly different between patients with different types of supraventricular tachycardia which is not surprising because the fear of the procedure was not expected to be associated with the SVT mechanism. We can speculate that the AVNRT causes more severe symptoms because of simultaneous contractions of atria and ventricles during tachycardia which may translate to more trait anxiety in patients but more studies are needed to clarify this association.

So our data shows that state and trait anxiety levels are not different in patients with different personality types, but show some trend that age and gender may have influence on anxiety levels. On the contrary the mechanism of tachycardia, namely AVNRT vs AVRT and AT, significantly correlates the trait anxiety levels and this association is not affected by state anxiety which shows no difference between the patients with different mechanism of SVT.

Conclusion. Anxiety is an important factor to be considered in patients with paroxysmal supraventricular tachycardia. It doesn't seem to be associated with different personality types. Female and older patients tend to show higher anxiety levels. The atrioventricular Nodal Reentrant Tachycardia (AVNRT) is associated with significantly higher trait anxiety levels compared to other types of paroxysmal supraventricular tachycardia.

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SUMMARY

ANXIETY LEVELS IN PATIENTS WITH PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA IN RELATION WITH THE PATIENT DEMOGRAPHICS, TYPE OF SUPRAVENTRICULAR TACHYCARDIA AND THEIR PERSONALITY TYPE

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The aim of the study was to evaluate the incidence of different personality types and state and trait anxiety levels in patients with paroxysmal supraventricular tachycardia

and their association with patients age, gender and the mechanism of the paroxysmal SVT.
62 patients with documented paroxysmal supraventricular tachycardia who underwent endocardial eletrophysiological study and catheter ablation of the paroxysmal SVT were included in the study. The patients were asked to fill out the Myers-Brigss Type Indicator and State-Trait Anxiety Inventory questionnaires and the results were analyzed and correlated with the arrhythmia mechanism determined during electrophysiological study and catheter ablation procedure, and the patients' demographics (age and gender).

There was no significant difference in State (mean 41.53±13.51, p=0.893) or Trait (mean 44.70±12.62, p=0.315) anxiety scores according to gender although higher scores were found in females. Older patients (≥50 years old compared to <50 years old) had higher anxiety scores but with no statistical significance (p=0.344 for state anxiety and p=0.100 for trait anxiety). The patients with AVNRT had significantly higher Trait anxiety scores (mean 46.82±10.52) than the patients with AVRT or AT (mean 40.59±10.91) (p=0.032). State anxiety score was not significantly different between patients with different SVT types (p=0.706).
Anxiety is an important factor to be considered in patients with paroxysmal supraventricular tachycardia. It doesn't seem to be associated with different personality types. Female and older patients tend to show higher anxiety levels. The atrioventricular Nodal Reentrant Tachycardia (AVNRT) is associated with significantly higher trait anxiety levels compared to other types of paroxysmal supraventricular tachycardia.

Keywords: Anxiety, paroxysmal supraventricular tachycardia.

РЕЗЮМЕ

УРОВЕНЬ ТРЕВОГИ У ПАЦИЕНТОВ С ПАРОКСИЗМАЛЬНОЙ СУПРАВЕНТРИКУЛЯРНОЙ ТАХИКАРДИЕЙ В СВЯЗИ С ДЕМОГРАФИЧЕСКИМИ ДАННЫМИ, ПСИХОЛОГИЧЕСКИМ ТИПОМ И МЕХАНИЗМОМ ПАРОКСИЗМАЛЬНОЙ СУПРАВЕНТРИКУЛЯРНОЙ ТАХИКАРДИИ

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Целью данного исследования явилось определить распространение психологических типов и уровень ситуационной и общей тревоги у пациентов с пароксизмальной суправентрикулярной тахикардией и связь этих даных с возрастом, полом и механизмом пароксизмальной суправентрикулярной тахикардией.

В исследование были включены 62 пациента с документированной пароксизмальной наджелудочковой тахикардией (НЖТ), которым проводилось эндокардиальное электрофизиологийеское исследование и катетерная абляция пароксизмалжной НЖТ. Пациенты заполняли вопросники Myers-Brigss Type Indicator и State-Trait Anxiety Inventory. Проанализированы результаты и их связь с механизмом пароксизмальной НЖТ, установленным во время катетерной абляций, и с демографическими данными пациента (пол, возраст).

По половому признаку статистически значимой разницы в уровнях ситуационной (mean 41.53±13.51, p=0.893) и общей (mean 44.70±12.62, p=0.315) тревоги не выявлено, однако у женщин наблюдался более высокий уровень тревоги. ЧТо касается возраста, ≥50 лет по сравнению с <50 лет разница между уровнями ситуационной и общей тревоги также не была статистически значимой (p=0.344 для ситуационной и p=0.100 для общей тревоги), хотя у пожилых наблюдался более высокий уровень тревоги. У пациентов с АВ-узловой пароксизмальной тахикардией наблюдался значительно высокий уровень общей тревоги (mean 46.82±10.52) по сравнению с пациентами с АВ-реципрокной и предсердной тахикардиями (mean 40.59±10.91) (p=0.032). Уровень ситуационной тревоги у этих пациентов значительно не отличался (p=0.706).

У пациентов с пароксизмальной наджелудочковой тахикардией наблюдается высокий уровень тревоги, что, по-видимому, не связано с психологическим типом человека. У женщин и пожилых наблюдается более высокий уровень тревоги. АВ-узловая реципрокная тахикардия связана со значительно более высоким уровнем общей тревоги по сравнению с АВ-реципрокной и предсердной тахикардиями.

რეზიუმე

შფოთვის დონე სუპრავენტრიკულური პაროქსიზმული ტაქიკარდიის მქონე პაციენტებში და მისი კავშირი პაციენტის დემოგრაფიულ მონაცემებთან, ფსიქოლოგიურ ტიპთან და პაროქსიზმული სუპრავენტრიკულური ტაქიკარდიის ტიპთან

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კვლევის მიზანს წარმოადგენდა პაროქსიზმული სუპრავენტრიკულური ტაქიკარდიის მქონე პაციენტებში ფსიქოლოგიური ტიპების გავრცელების და შფოთვის დონის და ამ მონაცემების კავშირის შეფასება ასაკთან, სქესთან და პაროქსიზმული სუპრავენტრიკულური ტაქიკარდიის მექანიზმთან.

კვლევაში ჩართული იყო 62 პაციენტი დოკუმენტირებული პაროქსიზმული სუპრავენტრიკულური ტაქიკარდიით, რომელთაც ჩაუტარდათ ენდოკარდიული ელექტროფიზიოლოგიური კვლევა და პაროქსიზმული სუპრავენტრიკულური ტაქიკარდიის კათეტერული აბლაცია. პაციენტები ავსებდნენ Myers-Brigss Type Indicator da State-Trait Anxiety Inventory კითხვარებს. ჩატარდა მიღებული შედეგების ანალიზი და მათი კორელაცია ელექტროფიზიოლოგიური კვლევის და აბლაციის დროს დადგენილ პაროქსიზმული სუპრავენტრიკულური ტაქიკარდიის მექანიზმთან და პაციენტის დემოგრაფიულ მონაცემებთან (ასაკი, სქესი).

სქესის მიხედვით სტატისტიკურად მნიშვნელოვანი განსხვავება სიტუაციური (mean 41.53±13.51, p=0.893) და ზოგადი (mean 44.70±12.62, p=0.315) შფოთვის მონაცემებს შორის არ გამოვლინდა, თუმცა ქალებს შფოთვის უფრო მაღალი დონე აღენიშნათ. 50 წლის ზემოთ პაციენტებს შფოთვის უფრო მაღალი დონე ჰქონდათ, განსხვავება არც აქ იყო სტატისტიკურად მნიშვნელოვანი (p=0.344 სიტუაციური შფოთვისთვის და p=0.100 ზოგადი შფოთვისთვის). პაციენტებს AV-კვანძოვანი რეენტრული ტაქიკარდიით აღენიშნებოდათ მნიშნელოვნად მაღალი ზოგადი შფოთვა (mean 46.82±10.52) შედარებით AV-რეციპროკული ტაქიკარდიის და წინაგულოვანი ტაქიკარდიის მქონე პაციენტებთან (mean 40.59±10.91, p=0.032). სიტუაციური შფოთვა მნიშვნელოვნად არ განსხვავებოდა ტაქიკარდიის მექანიზმის მიხედვით (p=0.706).

დადგენილია, რომ AV-კვანძოვანი რეენტრული ტაქიკარდია, პაროქსიზმული სუპრავენტრიკულური ტაქიკარდიის სხვა ფორმებთან შედარებით, ასოცირებულია ზოგადი შფოთვის მნიშვნელოვნად მაღალ დონესთან.

ECHOCARDIOGRAPHIC CHARACTERISTICS OF DIFFERENT WHO/ISH CARDIOVASCULAR DISEASE RISK GROUPS

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Use of risk prediction charts to estimate cardiovascular disease (CVD) risk is a major advance in CVD prevention compared to the older practice of identifying and treating individual CVD risk factors [37]. Many systems for assessing the CVD status of individual patients have been described [2,5,13,16,19,20,24,36,37,40,49,52], but there is no universal system for CVD risk prediction: the CVD risk scores have different accuracy in different populations and tend to over predict in low-risk populations and under predict in high-risk populations [6]. Existing CVD risk estimations, such as Framingham, ASSIGN, and SCORE CVD risk scoring systems, are based on risk prediction in samples of the general population [13,24]. While the WHO (World Health Organization)/ISH (International Society of Hypertension) risk prediction charts, offer an advantage, since the charts have been developed specifically for each WHO sub region [6]. Data collection for the CVD risk estimation in Georgian population for WHO/ISH system was conducted in collaboration with David Tvildiani Medical University [45]. The risk prediction charts acknowledge that many cardiovascular risk factors tend to appear in clusters; Most of them include age, sex, smoking, blood lipids, blood pressure and presence of diabetes mellitus as their core variables [2,5,6,13,16,19,20,24,36,40,49,52]. It is also known that other risk factors, such as obesity, high waist–hip ratio, low physical activity, low socioeconomic status, family history of premature CVD, low HDL-C, elevated triglycerides, serum creatinine, and C-reactive protein, albuminuria, hyperuricemia and fibrinogen, as well as variables of target organ damage (TOD) such as left ventricular hypertrophy (LVH) can also modify cardiovascular risk [1,28,29,37]. The noninvasive echocardiography is a valuable tool to identify presence of subclinical cardiac damage (CD), such as – left ventricle (LV) systolic or diastolic dysfunction, enlarged left atrium (LA), and increased LV mass. CD detected by noninvasive echocardiography can play important role in correctly reclassifying patients from one to another risk group [8,12,25,26,34,39,42,45,47-49]. Recent ESH (European Society of Hypertension) / ESC (European Society of Cardiology) Guidelines for the management of Arterial Hypertension recommend a simple flow-chart for estimating the combined effect of risk factors, target organ damage and comorbidities on global risk of fatal cardiovascular events. According to 2013 ESH/ESC algorithm, hypertensive patients of grade 1 with TOD are at higher cardiovascular risk than hypertensive patients with concomitant risk factors but no TOD [26].

Detection of TOD not only provides an estimate of total cardiovascular risk in the initial work-up of hypertensive patients, but also may document treatment-induced improvement in damaged organs; in particular, regression of LVH has been associated with a lower incidence of fatal and nonfatal cardiovascular events [28,35]. Impaired echocardiographic variables, such as LVH, LV dysfunction and

LA enlargement have been associated with poor cardiovascular outcome in persons with hypertension independently of inpatient and/or outpatient BP (Blood pressure) levels and other conventional risk factors [11].

In the study published in October 2016 we assessed association between echocardiographic characteristics and individual cardiovascular risk factors [41]. This study is continuation of our previous work and we aim to analyze association of echocardiographic TOD variables with the CVD risk groups defined by WHO/ISH.

Material and methods. Population of this study is part of the study population of a larger study [44,46], carried out by David Tvildiani Medical University in collaboration with WHO. The study is a population based cross-sectional study conducted in Sachkhere Medical Center in Georgia, from September 2008 to December 2010. The study protocol was approved by the Sachkhere Medical Center and David Tvildiani Medical University Ethics committees. The study participation was voluntary. All participants gave written informed consent to participate.

Consecutive sample of 177 participants, who underwent routine transthoracic echocardiography during the period of "Cardiovascular Risk Assessment of the Georgian Population study" [46] were included in our study. Patients with clinically manifested cardiovascular disease were excluded (31 [17.5%] participants).

To assess CVD risk of remaining 146 persons WHO/ISH risk prediction chart for EUR B was used [14]. Study population was categorized in three groups: Group 1 included population with risk less than 10% according to WHO/ISH, in Group 2 there were united two WHO/ISH risk categories (10-10.9% and 20-29.9%) and Group 3 represented population of 30-39.9% and more than 40% of CVD risk.

The CVD risk was assessed using a modeling approach with age, sex, smoking, blood pressure, blood cholesterol, and presence or absence of diabetes mellitus. The definition we employed for Hypertension is in accordance with JNC-VII definitions [51]. Diabetes was defined as fasting glucose ≥7 mmol/L (126 mg/dl) or use of insulin or oral hypoglycemic medications. Persons who smoked regularly during the previous 12 months were classified as smokers. In addition to WHO/ISH CVD risk factors BMI (Body Mass Index) and Waist Circumference (WC) were assessed.

Out of 146 patients included in the final statistical analysis 66.4% were women; mean age was 55 years (40-70 years). Distribution of the study population in WHO/ISH groups (group I <10%, group II - 10-10.9% and 20-29.9% and group III 30-39.9% and >40%) and corresponding cardiovascular risk factors are shown in Table 1.

Echocardiography was performed on Philips Sonos 7500 with Secondary Harmonic Imaging on basis of the recommended technique for transthoracic quantitative evaluations [22].

Among WHO/ISH risk groups mean difference of

Table 1. Distribution of cardiovascular risk factors in different in WHO/ISH risk groups

Variable ± SD	Value		
	Group I <10%	Group II 9-28.9 %	Group III >30 %
population	n=116 (79.5%)	n=25 (17.1%)	n=5 (3.4%)
gender, man	n=36 (31%)	n=9 (36%)	n=2 (40%)
gender, women	n=80 (69%)	n=16 (64%)	n=3 (60%)
Age range, y	40-70	41-70	58-70
Mean Age, y	**53.94 ±8.85***	**56.76 ± 8.93***	**63.60± 5.32***
SBP range (mmHg)	80-170	115-210	150-190
mean SBP (mmHg)	**129.18 ± 17.39****	**159.2± 22.39****	**172.00 ± 16.43****
DBP range (mmHg)	50-100	70-120	80-110
mean DBP (mmHg)	**80.91 ± 11.12****	**95.20± 13.03****	**96 ± 11.4****
BG range (mmol/l)	3.12-15.04	3.95- 16.79	4.83 -15.26
mean BG (mmol/l)	**5.34 ± 1.52****	**6.28±2.72****	**9.04 ± 5.17****
WC range (cm)	64-170	79-123	92-127
mean WC (cm)	104.16 ± 16.76	102.0 ± 10.74	110.60 ± 15.58
BMI range ($kg/m^{2)}$	19.30 -48.80	22.30 -37.80	25.40 - 43.40
mean BMI ($kg/m^{2)}$	31.43 ± 6.40	29.48 ± 4.40	31.80 ± 7.36
TCH range (mmol/l)	3.13-7.64	2.89 -7.80	5.70 - 8.31
mean TCH (mmol/l)	**5.05 ± 0.99****	**5.81 ± 1.40****	**6.86 ± 1.10****
Smoking	**n=11 (9.5%)***	**n=5 (20%)***	**n=1 (20%)***

*SBP - Systolic Blood Pressure ; DBP - Diastolic Blood Pressure; BG - Blood Glucose. \ WC - Waist Circumference, BMI - Body mass index; TCH - Total Cholesterol, *- P<0.05, ** - P<0.01*

Table 2. Distribution of echocardiographic characteristics in different WHO/ISH risk groups

Variable ± SD	Value		
	Group I	Group II	Group III
LA range (mm)	25-53	31-51	39-55
mean LA (mm)	**40.49 ± 5.02***	**41.4 ± 4.25***	**46.20 ± 5.72***
LVD range (mm)	39-59	41-64	47 - 58
mean LVD (mm)	48.41 ± 4.4	50.32± 5.43	51.80 ± 4.09
IVS range (mm)	6.0 - 14.0	7.50 - 13.50	9.00 - 14.00
mean IVS (mm)	10.41 ± 1.57	10.52 ± 1.32	10.90 ± 2.13
PWT range (mm)	6.0 - 14.0	7.50 - 13.50	9.00 - 14.00
mean PWT (mm)	10.27 ± 1.52	10.38 ± 1.18	10.80 ± 2.17
LVEDV range (ml)	42-115	63 -175	65 - 189
mean LVEDV (ml)	101.45 ± 23.71	107.04 ± 29.31	108. 53 ± 31.42
PSP range (mmHg)	0-50	16-48	25 -79
mean PSP (mmHg)	**27.63 ± 8.71***	**29.04± 7.71***	**40.80 ± 22. 23***
EF range (%)	57-75	53-69	51 -65
mean EF (%)	**61.86 ± 4.81***	**60.92 ± 5.42***	**55.60 ± 4.31***

*LA - Left atrium diameter; LVD - Left ventricular end-diastolic dimension; IVS - Interventricular septum thickness; PWT - Left ventricular posterior wall thickness; LVEDV - Left ventricular end-diastolic volume; EF - Left ventricular ejection fruction; PSP - Pulmonary Systolic Pressure; * - P<0.05, ** - P<0.01*

the following TOD variables were assessed: left ventricular end-diastolic diameter (LVD), interventricular wall thickness (IVS), Posterior wall thickness (PWT), left ventricular end diastolic volume (LVEDV), left ventricular ejection fraction (EF), left atrium diameter (LA) and pulmonary systolic pressure (PSP).

Left ventricular systolic function was evaluated by the method of discs (Simpson's rule) [22,34]. Pulmonary systolic pressure was assessed by continues-wave Doppler of tricuspid regurgitation [3].

Following criteria were used to exclude patients from the study: LVEF < 50 %, severe valvular heart disease defined by EAE (European Association of Echocardiography) and ASE (American Society of Echocardiography) recommendations [22, 39], and atrial fibrillation.

Statistical analysis was performed in IBM SPSS Statistics version 21. Descriptive statistics (means, standard deviations and proportions) were calculated for cardiovascular risk factors and echocardiographic characteristics for each WHO/ISH group. To assess statistically significant difference between mean values of echocardiographic characteristics among cardiovascular risk groups we used ANONA method. A p-value <0.05 was defined as statistically significant.

Results and their discussion. As it was expected the mean values of age, SBP, TCH, BG and smoking prevalence were statistically different in different WHO/ISH risk groups. Opposite this neither WC nor BMI were statistically associated with risk groups. Mean WC (≥102/88 cm for men/women) and mean BMI (≥30) were slightly elevated in groups I and III and in upper norm in group II (Table 1).

Distribution of echocardiographic characteristics among CVD risk groups defined by WHO/ISH are presented in Table 2. The mean value of LA in group I was 40.49±5.02 mm, 41.4±4.25 mm in sub group II and 46.20±5.72 mm in sub group III. The mean PSP in group I was- 27.63±8.71 mmHg, 29.04±7.71 mm in group II - Hg and 40.80±22.23 mm Hg in group III. The mean EF in group I was 61.86±4.81%, 60.92±5.42% in group II and 55.60±4.31% in group III.

The mean IVS in group I was - 10.41±1.57 mm, 10.52±1.32 mm in group II and 10.90±2.13 mm in group III. Mean PWT in group I was 10.27±1.52 mm, 10.38±1.18 mm in group II and 10.80±2.17 mm in group III. Mean LVD in group I was 48.41±4.4 mm, 50.32±5.43 mm in group II and 51.80**±4.09 mm** in group III. Mean LVEDV in group I was 101.45±23.71 ml, 107.04±29.31 ml in group II - and 108. 53±31.42 ml in group III.

The distribution of echocardiography characteristics in WHO/ISH groups was statistically different for LA, PSP and EF. The mean LA was increased in all risk groups (40.84 ±4.5 mm) [41] and different groups of WHO/ISH classifications differed by degree of LA enlargement. In groups I and II LA were only mildly dilated, while in group III was revealed moderate LA enlargement. The mean PSP was in normal range in groups I and II and mildly to moderate elevated in group III. The mean EF was in normal range for all the groups with tendency of reduction from group I to group III.

Unlike this we have not found statistically significant differences in other echocardiographic variables, as IVS, PWT, LVD and LVEDV and they were in normal range for all risk groups.

As anticipated we found statistically significant differences in the distributions of gender, age, smoking status, TCH and BG levels across the WHO/ISH risk groups of our study population, since the WHO/ISH risk charts take into account these variables. In addition to these individual CVD risk factors included in the WHO/ISH scoring system, we found that the mean DBP was normal in WHO/ISH group I and elevated (Hypertension grade I) in the groups II and III.

The differences in Obesity variables (WC and BMI) were not statistically different. Both mean WC (≥ 102/88 cm for men/women) and BMI (≥30) were slightly elevated in groups I and III and in upper norm in group II.

From the echocardiographic parameters assessed in this study, mean LA size was increased in all three WHO/ISH groups and different groups statistically significant differed by degree of LA enlargement: in groups I and II LA were only mildly dilated, while in group III was revealed moderate LA enlargement. The mean PSP was in normal range in groups I and II and mildly to moderate elevated in group III. These differences were also statistically significant. It is important to mention, that although EF was in normal range tendency of EF decrease from risk group I to the group III was noted and these differences were statistically significant too.

Other echocardiography variables (LVD, IVS, PWT, LVEDV and EF) were within the normal range in all three WHO/ISH risk groups and between these variables we didn't find statistically significant differences.

According to the findings above and considering that our study population is without any clinical presentation of cardiovascular disease and still have statistically significant tendency toward increase in LA and PSP and decrease in EF we argue that those variables can be considered as early predictors of cardiovascular disease.

The role of echocardiographic assessment of subclinical abnormalities for stratification of risk for cardiovascular outcomes was an aim of several recently published studies [6,10-12,19,20,32,37,41,42,46-48]. It is also known that traditional cardiovascular risk factors correlate with echocardiographic parameters [21,32,41,46]. Based on results of our previous study echocardiographic characteristics were significantly correlated with age and determinants of obesity [42]. Based on the results of Tsang et al study impaired echocardiographic variables, such as LA enlargement, LV systolic dysfunction and etc. enhanced risk stratification for the development of first age-related cardiovascular events in elderly cohort, incremental to clinical risk profiling alone [48]. Cuspidi et al revealed that in the detection of CD by echocardiography allowed to reclassify a large proportion of patients from moderate to high risk when ultrasound examinations were added to routine risk assessment thus leading to a potentially inadequate therapeutic management especially of low-medium risk patients [12]. Based on results of another study of the same authors in never-treated hypertensive patients echocardiography evaluation decreased the proportion of low-risk and medium risk patients accordingly to 11.1%, and 35.7%, whereas more than 50% of the patients previously classified at low-medium risk were found to be at high absolute risk (risk was stratified according to the WHO/ISH criteria) [7]. The study of Schillaci et al have demonstrated that in low-risk untreated hypertensive individuals in whom treatment would be postponed or avoided according to current WHO–ISH guidelines echocardiography alters risk stratification 29% of the cases based on the initial WHO–ISH work-up and identifies treatment [42]. Besides this echocardiography may documents regression of TOD [27,36].

There are also studies which reviled that impaired echocardiographic variables, particularly LA size [4,15,24] and volume are markers of LV diastolic dysfunction [17,18,23] a strong predictor of death and heart failure hospitalization [30,31] and an important tool for refining cardiovascular risk stratification and therapeutic interventions [9].

According to the findings of our study and considering that our study population is without any clinical presentation of cardiovascular disease and still have statistically significant tendency toward increase in LA and PSP we argue that those variables can be considered as early predictors of cardiovascular disease. Furthermore, it is recommended to include echocardiographic examination as part of the CVD risk evaluation protocol in selected population.

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SUMMARY

ECHOCARDIOGRAPHIC CHARACTERISTICS OF DIFFERENT WHO/ISH CARDIOVASCULAR DISEASE RISK GROUPS

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The objective of the study was to analyze association of echocardiographic TOD variables with the CVD risk groups defined by WHO/ISH.

A cross-sectional study was conducted between (September 2008 – December 2010) Consecutive sample of 146 participants were enrolled in the study, 97 (66.4 %) women and (49) 33,6 % men, mean age. Study population was categorized in three groups according to WHO/ISH risk categories: Group 1 included population with risk less than 10% according to WHO/ISH, in Group 2 there were united two WHO/ISH risk categories (10-10.9% and 20-29.9%) and Group 3 represented population of 30-39.9% and more than 40% of CVD risk. Routine Echocardiography was conducted. The data was analyzed using SPSS, version 21.

The distribution of echocardiography characteristics in WHO/ISH groups was statistically different for LA, PSP and EF ($P<0.05$). In groups I and II LA were only mildly dilated, while in group III was revealed moderate LA enlargement. The mean PSP was in normal range in groups I and II and mildly to moderate elevated in group III. The mean EF was in normal range for all the groups with tendency of reduction from group I to group III. Unlike this we have not found statistically significant differences in other echocardiographic variables, as IVS, PWT, LVD and LVEDV and they were in normal range for all risk groups.

According to the findings of our study and considering that our study population is without any clinical presentation of cardiovascular disease and still have statistically significant tendency toward increase in LA and PSP we argue that those variables can be considered as early predictors of cardiovascular disease. Furthermore, it is recommended to include echocardiographic examination as part of the CVD risk evaluation protocol in selected population.

Keywords: CVD risk, WHO/ISH risk groups, Echocardiography, echocardiographic TOD variables.

РЕЗЮМЕ

ЭХОКАРДИОГРАФИЧЕСКАЯ ХАРАКТЕРИСТИКА РАЗЛИЧНЫХ ГРУПП РИСКА РАЗВИТИЯ СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ, ОПРЕДЕЛЕННЫХ ВСЕМИРНОЙ ОРГАНИЗАЦИЕЙ ЗДРАВООХРАНЕНИЯ, МЕЖДУНАРОДНЫМ ОБЩЕСТВОМ ПО ИЗУЧЕНИЮ АГ

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Целью исследования явился анализ связи эхокардиографических переменных с группами риска сердечно-сосудистых заболеваний, определенных Всемирной организацией здравоохранения/Международным обществом по изучению АГ (ВОЗ/МОГ).
С сентября 2008 г. по декабрь 2010 г. исследованы 146 пациентов, из них 99 (66,4%) женщин и 49 (33,6%) мужчин, средний возраст 55 лет (40-70 лет). Изучаемая популяция была разделена на три группы в соответствии с категориями риска, разработанными ВОЗ/МОГ: I группа включала пациентов с риском менее 10% в соответствии с критериями ВОЗ/МОГ, во II группе объединены две категории риска ВОЗ/МОГ - 10-10,9% и 20-29,9%, III группа представлена 30-39,9% и более 40% риска возникновения сердечно-сосудистых заболеваний. Проводилась рутинная эхокардиография.
Распределение характеристик эхокардиографии в группах ВОЗ/МОГ было статистически различным для левого предсердия (ЛП), систолическое давление в легких (СДЛ) и фракция выброса левого желудочка (ФВЛЖ) ($p<0,05$). У пациентов I и II групп среднее значение ЛП было незначительно расширено, в то время как в III группе обнаружено его умеренное увеличение. Среднее значение СДЛ находилось в нормальном диапазоне в I и II группах и было умеренно повышено в III группе. Среднее значение ФВЛЖ находилось в нормальном диапазоне у пациентов всех групп с тенденцией к снижению от I к III группе. Других эхокардиографических данных, таких как: толщина межжелудочковой перегородки, толщина задней стенки левого желудочка, конечный диастолический размер левого желудочка и конечный диастолический объем левого желудочка статистически значимых изменений не обнаружено, они были в нормальном диапазоне у всех пациентов групп риска.

Согласно результатам проведенного исследования и учитывая, что исследуемая популяция не имела клинического проявления сердечно-сосудистых заболеваний и по-прежнему имеет статистически значимую тенденцию к увеличению LA и PSP, мы утверждаем, что эти переменные можно рассматривать как ранние маркеры сердечно-сосудистых заболеваний и рекомендуем включать эхокардиографическое обследование в рамки протокола оценки риска сердечно-сосудистых заболеваний у данной категории больных.

რეზიუმე

სხვადასხვა WHO/ISH რისკ ჯგუფების ექოკარდიოგრაფიული მახასიათებლები

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კვლევის მიზანს წარმოადგენდა სხვადასხვა WHO/ISH კარდიოვასკულურ რისკ ჯგუფებში ექოკარდიოგრაფიული მახასიათებლების განაწილება.

კვლევა ჩატარდა 2008 წლის სექტემბრიდან,2010 წლის დეკემბრამდე,კვლევაში მონაწილეობდა 146 საკვლევი პირი, 97 (66.4%) ქალი და 49 (33,6%) მამაკაცი,საშუალო ასაკი 55 (40-70).

პაციენტებს უტარდებოდა სტანდარტული ექოკარდიოგრაფიული კვლევა კარდიოვასკულური რისკ-ფაქტორების არსებობაზე. პაციენტები განაწილდნენ სამ WHO/ISH რისკ-ჯგუფში: I ჯგუფში გაერთიანდნენ პაციენტები, რომელთა კარდიოვასკულური რისკი < 10%-ზე, II ჯგუფში რისკი მერყეობდა 10-10.9%-დან 20-29.9%-მდე, III ჯგუფში წარმოდგენილი იყო პაციენტებით რისკით 30-39.9% და 40%-ზე მეტი. შედეგების ანალიზისთვის გამოყენებულ იქნა პროგრამა SPSS, version 21.

სხვადასხვა WHO/ISH რისკ-ჯგუფებს შორის სტატისტიკურად სარწმუნოდ განსხვავდებოდნენ LA, PSP და EF ($P<0.05$). I და II რისკ-ჯგუფებში LA მხოლოდ მცირედაა დილატირებული, III რისკ-ჯგუფში კი აღინიშნება LA-ის ზომიერი დილატაცია. PSP-ის საშუალო მაჩვენებელი ნორმალურია I და II რისკ-ჯგუფებში და მსუბუქი ზომიერადაა მომატებული III რისკ-ჯგუფში. EF-ის საშუალო მაჩვენებელი ნორმის ფარგლებშია სამივე რისკ-ჯგუფში,თუმცა აღინიშნება ტენდენცია დაქვეითებისაკენ I-დან III ჯგუფში. განსხვავებით ზემოთ აღნიშნულისა,სტატისტიკურად სარწმუნო განსხვავება არ გამოვლინდა IVS, PWT, LVD და LVEDV ექოკარდიოგრაფიულ მახასიათებლებს შორის.

კვლევის შედეგების მიხედვით, იმის გათვალისწინებით, რომ აღნიშნული საკვლევი ჯგუფი წარმოადგენდა პოპულაციას კარდიოვასკულური დაავადებების გამოვლინების გარეშე და მიუხედავად ამისა,დაფიქსირდა LA-სა და PSP-ის ზრდის ტენდენცია,შეიძლება დავასკვნათ,რომ ეს მახასიათებლები წამოადგენენ კარდიოვასკულური დაავადებების ნაადრევ პრედიქტორებს. ავტორები იძლევიან რეკომენდაციას იმის შესახებ, რომ პაციენტების გარკვეული ჯგუფისთვის, ექოკარდიოგრაფიული კვლევა შეტანილი უნდა იყოს კარდიოვასკულური რისკის შეფასების პროტოკოლში.

ОПТИМИЗАЦИЯ ДИАГНОСТИКИ ПРИ СИНДРОМЕ ПЛЕВРАЛЬНОГО ВЫПОТА НЕЯСНОЙ ЭТИОЛОГИИ

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Плевральные выпоты встречаются в практике врачей всех специальностей. В последние годы во всем мире отмечается ухудшение эпидемиологической обстановки по туберкулезу и рост числа неспецифических заболеваний легких [2,5,8]. Исследователи сообщают о более чем 80 различных заболеваниях, которые часто являются причиной развития плевритов [1,3]. Ввиду произошедшей в последние десятилетия узкой специализации в различных областях медицины (пульмонология, кардиология, нефрология) дифференциальная диагностика плевральной патологии стала более сложной. У значительного числа больных определение этиологии основного заболевания длится 3-4 месяца [3,7]. Комплексное применение различных неинвазивных методов обследования позволяет уточнить наличие, локализацию, приблизительный объем и характер внутриплевральной жидкости (транссудат или экссудат), однако не позволяет судить о конкретной причине накопления жидкости [8]. Цитологическое исследование экссудата эффективно в 45-80% наблюдений при вторичном злокачественном поражении плевры и лишь в 20% при мезотелиоме [6,7,10]. Получить верификацию туберкулезного плеврита неинвазивными методами удается еще реже. Обнаружение микобактерий туберкулеза (МБТ) методами микроскопии не превышает 10-20%, а посевом – 25-50% [3,4,8]. В связи с этим, использование инвазивных методов для верификации этиологии плевритов в настоящее время приобретает особую значимость.

К хирургическим (инвазивным) методам диагностики плевритов относятся торакоцентез, чрезкожная игловая биопсия плевры, торакоскопия (в том числе видеоассистированная) [9,12,13] и диагностическая торакотомия. При анализе эффективности различных диагностических исследований в зарубежной литературе принято использовать следующие показатели: чувствительность, специфичность и точность [14,15].

Целью данного исследования явился сравнительный анализ эффективности некоторых хирургических процедур с последующим цитологическим, микробиологическим и гистологическим исследованием получаемого материала в общей схеме диагностического алгоритма при плевральном выпоте неясного генеза.

Материал и методы. Проведен анализ историй болезни 143, 95 (66,4%) мужчин и 48 (33,6%) женщин, поступивших в НИИ легочных заболеваний, которым в клинике проводилась диагностика и лечение по поводу синдрома плеврального выпота неясного генеза, а именно малоинвазивные хирургические процедуры: плевральная пункция (ПП), видеоассистированная торакоскопия (ВАТС) с биопсией плевры. Для оценки достоверности методов исследования больных с экссудативными плевритами использовали такие показатели, как чувствительность, специфичность и точность метода. Проанализированы данные, полученные при хирургических процедурах, проведенных пациентам с целью уточнения природы возникновения плеврального выпота. Общая характеристика данных на основании заключений клинических диагнозов приведена в таблице 1.

Изучены материалы цитологического, гистологического, микробиологического исследований пункции плевральной жидкости, а также биопсийного материала.

Согласно стандартному диагностическому алгоритму при синдроме плеврального выпота (СПВ) неясного генеза установлены окончательные диагнозы: у 87 (60,8%) пациентов – плеврит туберкулезной этиологии; у 33 (23,1%) – злокачественный плеврит, среди них у 7 (21,2%) – на фоне первичных опухолей плевры (мезотелиомы), у 26 (78,8%) больных определена метастатическая природа выпота. Неспецифическая природа плевритов отмечалась у 23 пациентов. У этих больных

Таблица 1. Общая характеристика случаев СПВ неясного генеза

Генез плеврального выпота	Общее количество случаев		Количество хирургических процедур		Кол-во ПП		Кол-во ВАТС	
	абс.	%	абс.	%	абс.	%	абс.	%
Туберкулезный	87	60,8	131	57,7	87	60,8	44	52,4
Опухолевой	33	23,1	58	25,6	33	23,1	25	29,8
Неспецифической природы	23	16,1	38	16,7	23	16,1	15	17,8
Всего	**143**	**100**	**227**	**100**	**143**	**100**	**84**	**100**

характер выпота был экссудативным, что указывает на инфекционно-воспалительный генез этих плевритов. Больные, у которых выпот представлял собой транссудат (нефротический синдром, коллагенозы, застойная сердечная недостаточность и др.), в исследование не включались. Дальнейшее лечение таких больных проводилось в специализированных стационарах и клиниках.

Следует отметить, что клиническая картина почти у всех больных СПВ была однотипной и не позволяла судить о причине развития плеврального выпота.

Всем пациентам с СПВ (n=143) выполнена плевральная пункция, которая осуществлена под местной инфильтрационной анестезией. Полученную жидкость разливали в три стерильные пробирки и отправляли на микробиологическое, биохимическое и цитологическое исследования. Осложнений после ПП ни в одном случае не наблюдалось. В случаях, когда верифицировать причину выпота не удавалось, больным производилась ВАТС под общей анестезией.

Достоверность различий сравниваемых величин определяли по параметрическому t-критерию Стьюдента и достоверной вероятности (p). Статистически значимыми считались различия при $p<0,05$.

Результаты и их обсуждение. *Результаты цитологического исследования плевральной жидкости и данных ВАТС.*

Проанализированы данные 87 (60,8%) пациентов с плевритом туберкулезной этиологии. Точный диагноз по результатам цитологического исследования установлен 45 (51,7%) больным, причем у 44 – по отпечаткам плевральных биоптатов, полученных в результате ВАТС, у 1 – по пункционной биопсии увеличенного регионарного лимфатического узла. По данным ПП лимфоцитарный характер выпота в 69 (79,2%) случаях позволил лишь предположить специфическую природу заболевания. У 44 из них впоследствии туберкулезная природа плеврита была подтверждена по цитологическим отпечаткам плевральных биоптатов (не учитывая гистологическое исследование биоптатов).

Цитологическое наличие единичных или скоплений опухолевых клеток установлено только у 8 (24,2%) из 33 (23,1%) больных с опухолевым плевритом. Из них в 4 случаях правильный диагноз установлен по материалу ПП и по отпечаткам биопсийного материала плевры, полученного при ВАТС. У 25 (75,8%) пациентов цитологический материал оказался неинформативным: наблюдалась картина, соответствующая цитологической при неспецифических плевритах. В одном цитологическом препарате выявлена стафилококковая флора.

У 23 (16,1%) больных неспецифическим плевритом исследовали клеточный состав плевральной жидкости и данные, полученные при ВАТС. **У 3** (13%) больных из 23 с неспецифическим плевритом в мазках выявлено небольшое количество лимфоцитов - 10 в поле зрения. У 16 (69,6%) больных обнаружены нейтрофилы - до 50-70 в поле зрения. В одном случае при плевральной пункции отмечалось повреждение сосуда, ввиду чего в мазках наблюдалось значительное число эритроцитов. В 2 случаях обнаружено несколько клеток измененного мезотелия в состоянии гиперплазии и пролиферации, характерных для злокачественного заболевания. В 2 случаях материал представлен детритом, в одном – фибрином.

Оценка диагностической результативности цитологического метода исследования представлена в таблице 2.

Результаты микробиологического исследования плевральной жидкости и данных ВАТС

Выполняли микробиологическое исследование всех образцов плевральной жидкости, полученных при ПП, исследовали биоптаты плевры.

Таблица 2. Сравнительная характеристика малоинвазивных методов диагностики

Метод/этиология ЭП	Чувствительность, %	Специфичность, %	Точность, %
Туберкулезный плеврит			
ПП (цитологическое исследование)	49	97,5	93
ВАТС (гистологическое исследование)	95,5	100	98,7
Опухолевой плеврит			
ПП (цитологическое исследование)	24,2	24,2%	60,4
ВАТС (гистологическое исследование)	96	96	97
Неспецифический плеврит			
ПП (цитологическое исследование)	80,5	42	53
ВАТС (гистологическое исследование)	93	96	95

В результате анализа полученных данных микробиологического посева у пациентов с неспецифическим или злокачественным плевритом рост микроорганизмов в плевральном экссудате не обнаружен. При микроскопическом исследовании плеврального экссудата только у 2 (2,3%) больных выявлены микобактерии туберкулеза. При исследовании экссудата культуральным методом МБТ выявлены у 8 (9,2%) пациентов. ДНК МБТ обнаружена у 33(37,9%) больных методом ПЦР диагностики экссудата. При бактериологическом исследовании биопсийного материала, полученного посредством ВАТС, культуральными методами у 25 (56,7%) больных выявлены МБТ. Бактериологическим исследованием биоптата плевры и фибрина у 4 больных неспецифическим плевритом обнаружена микробная флора. Результаты исследования антимикобактериальных антител в плевральной жидкости методом иммуноферментного анализа (ИФА) показали, что положительный результат удалось получить у 47 (55,2%) больных туберкулезным плевритом, что чаще, чем среди больных с неспецифическим плевритом, у которых положительный ответ установлен в 2 (8,7%) случаях. У всех пациентов с опухолевыми плевритами результат ИФА был отрицательным.

Результаты гистологического исследования биоптатов плевры, полученных ВАТС

В группе больных туберкулезным плевритом хирургическое вмешательство (ВАТС) выполнено у 28 (63,3%) – при длительности заболевания до 1 месяца; у 10 (23,3%) – от 1 до 2 месяцев и у 6 (13,4%) больных - при давности заболевания свыше 2 месяцев. Биопсия плевры при ВАТС с гистологическим исследованием биоптата была диагностически эффективной у 42 (95,5%) больных туберкулезным плевритом. В 2 (4,5%) случаях материал был неинформативным. При гистологическом исследовании ткани плевры среди жировой ткани и тонкого слоя волокнистой соединительной ткани визуализировались отграниченные друг от друга гранулемы из лимфоцитов, эпителиоидных клеток, редко встречающихся гигантских клеток Пирогова-Лангханса. Казеозные изменения выражены слабо, а иногда совсем не встречались. Гранулемы выбухали в просвет плевральной полости. Подобная картина наблюдалась у 28 (63,3%) больных при длительности заболевания 1 месяц до госпитализации в клинику. Стенка париетальной плевры была утолщена за счет разрастания волокнистой соединительной ткани, в которой выявлялись в большом количестве эпителиоидноклеточные гранулемы с большим количеством гигантских клеток Пирогова-Лангханса. Вокруг гранулем располагались лимфоидные клетки. Центральные отделы гранулем подвергались казеозному некрозу. Гранулемы сливались между собой, образуя обширные поля казеоза. Гранулемы без казеоза местами были окружены полями склерозированной соединительной ткани. Наряду со склеротическими изменениями в плевре на ее поверхности визуализировались обильные скопления фибрина. Подобная картина наблюдалась у 10 (23,3%) больных. Длительность заболевания у этих больных составила, в среднем, 2 месяца. До установления туберкулезной этиологии выпота пациенты получали эмпирическую неспецифическую терапию в общей лечебной сети. Хронизация процесса при гистологическом исследовании плевры сопровождалась развитием обширных полей склероза с фокусами гиалиноза. Гранулемы, иногда в небольшом количестве, располагались среди обширных полей склероза. Подобная эндоскопическая картина наблюдалась у 6 (13,4%) больных, неоднократно получавших неспецифическое лечение в различных лечебных учреждениях. Они, как правило, поступали в клинику, в среднем, спустя 2 месяца от начала заболевания.

Проведен анализ эффективности гистологической диагностики в зависимости от давности заболевания. Установлено, что у 38 больных со сроком заболевания до 2 месяцев эффективность составила 91,5%, а у 6 больных со сроком заболевания 2 и более месяцев эффективность резко уменьшалась, составляя 25%.

Среди 25 больных экссудативным плевритом (ЭП) злокачественной природы гистологический диагноз установлен по результатам ВАТС у 24 (96%). В 1 случае материал плевры оказался неинформативным в отношении истинной природы плеврита по причине скудного фрагмента с гистологическими признаками неспецифического воспаления. Точный диагноз установлен по наличию скопления опухолевых клеток на поверхности плевральных спаек. При гистологическом исследовании биоптатов плевры у 7 больных выявлены клетки железистого рака (аденокарцинома), в 7 случаях - мезотелиома плевры, в 1 случае – хорионкарцинома, в 9 случаях – метастазы в плевру. У 7 больных с гистологически верифицированной мезотелиомой плевры висцеральная плевра не поражена. На париетальной плевре определялись крупные узловые образования сливного характера.

При гистологическом исследовании биоптатов плевры в случае развития неспецифического плеврита правильный диагноз был установлен по результатам 14 из 15 случаев ВАТС. Среди 15 пациентов с неспецифическим плевритом у 14 (93,3%) процесс сопровождался частичным или полным осумкованием экссудата с образованием сращений между листками плевры, более выраженными изменениями в виде обширных отложений фибрина. Париетальный листок плевры поражался более интенсивно, чем висцеральный, как у больных туберкулезным плевритом. При гистологическом исследовании биопсийного материала выявлено хроническое неспецифическое воспаление. У одного (6,7%) пациента в группе с плевритом неспецифического генеза материал был неинформативен.

Сравнение чувствительности малоинвазивных методов диагностики этиологии ЭП в данном исследовании показало, что ВАТС с морфологическим исследованием биоптатов плевры и легкого характеризуется большей чувствительностью и специфичностью ($p<0,05$), чем пункция плевральной полости с цитологическим исследованием экссудата.

Выводы

1. Результаты лабораторных методов исследования плеврального экссудата малоспецифичны, за исключением случаев непосредственного нахождения этиологического фактора, например, атипичных клеток при цитологическом исследовании или же МБТ при бактериологическом.
2. Анализ цитологического, гистологического и микробиологического методов исследований выявил, что ВАТС характеризуется сравнительно высокой, сопоставимой с методом открытой биопсии плевры, диагностической эффективностью и чувствительностью в схеме диагностического алгоритма плевральных выпотов неясного генеза.
3. Результаты проведенных исследований могут быть использованы как дополнительный критерий в диагностически сложных случаях.

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SUMMARY

OPTIMIZATION OF DIAGNOSTICS OF EXUDATIVE PLEURITIS OF UNKNOWN ORIGIN

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The article describes 143 cases of exudative pleuritis of unknown origin in patients who were diagnosed and treated with any minimally invasive surgical procedures: pleural puncture (PP), video-assisted thoracoscopy (VATS) with biopsy of the pleura. A different diagnostic methods (cytological, microbiological, histological) used in various diagnostic surgical procedures are analyzed in detail and calculated diagnostic sensitivity, specificity, and accuracy of each method.

Based on the analysis of cytological, histological and microbiological studies in the performance of VATS concluded relatively high, comparable with the method of open pleural biopsy, diagnostic efficiency, the sensitivity of this method in the scheme of the diagnostic algorithm of EP of unknown origin.

Keywords: exudative pleuritis of unknown origin, video-assisted thoracoscopy.

РЕЗЮМЕ

ОПТИМИЗАЦИЯ ДИАГНОСТИКИ ПРИ СИНДРОМЕ ПЛЕВРАЛЬНОГО ВЫПОТА НЕЯСНОЙ ЭТИОЛОГИИ

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В статье описаны 143 случая экссудативных плевритов (ЭП) неясного генеза у пациентов, которым осуществляли диагностику и лечение с применением малоинвазивных хирургических процедур: плевральной пункцией (ПП), видеоассистированной торакоскопией (ВАТС) с биопсией плевры. Детально проанализированы различные методы диагностики (цитологические, микробиологические, гистологические), используемые при разных диагностических хирургических манипуляциях, рассчитана диагностическая чувствительность, специфичность и точность каждого из этих методов. На основании анализа результатов цитологического, гистологического и микробиологического исследований при выполнении ВАТС сделан вывод о сравнительно высокой, сопоставимой с методом открытой биопсии плевры, диагностической эффективности, чувствительности этого метода в схеме диагностического алгоритма ЭП неясного генеза.

რეზიუმე

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აზერბაიჯანის ჯანდაცვის სამინისტროს ფილტვის დაავადებათა სამეცნიერო-კვლევითი ინსტიტუტი, ბაქო, აზერბაიჯანი

სტატიაში აღწერილია უცნობი გენეზის ექსუდაციური პლევრიტის 143 შემთხვევა. პაციენტებს ჩაუტარდათ დაიგნოსტიკა და მკურნალობა მცირეინვაზიური ქირურგიული პროცედურების გამოყენებით (პლევრული პუნქცია,ვიდეოასისტირებული თორაკოსკოპია პლევრის ბიოფსიით). დეტალურად გაანალიზებულია დიაგნოსტიკის მეთოდები (ციტოლოგიური, მიკრობიოლოგიური, ჰისტოლოგიური), რომლებიც გამოიყენება სხვადასხვა სადიაგნოსტიკო ქირურგიული მანიპულაციის დროს; გამოთვლილია დიაგნოსტიკური მგრძნობელობა, სპეციფიკურობა და თითოეული მეთოდის სიზუსტე. ციტოლოგიური, მიკრობიოლოგიური და ჰისტოლოგიური კვლევის შედეგების ანალიზიდან გამომდინარე, დადგენილია ვიდეოასისტირებული თორაკოსკოპიის მეთოდის მაღალი, პლევრის ღია ბიოფსიის მსგავსი, ეფექტურობა და მგრძნობელობა უცნობი გენეზის ექსუდაციური პლევრიტის სადიაგნოსტიკო ალგორითმის სქემაში.

FACTORS AFFECTING SURVIVAL OF WOMEN DIAGNOSED WITH BREAST CANCER IN GEORGIA

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Breast cancer is the most frequently diagnosed cancer in women worldwide with nearly 2.4 million new cases diagnosed in 2015 [6]. Breast cancer incidence rates have been rising more rapidly in historically lower-risk areas, such as in many countries of Latin America, Africa, and Asia. These rising trends likely reflect changes in risk factors associated with economic development and urbanization, including obesity, physical inactivity, delayed childbearing and/or having fewer children, earlier age at menarche, and shorter duration of breastfeeding, as well as increases in breast cancer screening and awareness [1,4].

Cancer survival in a population are affected by a number of factors, mainly, the stages at which cancers are diagnosed, histological characteristics, and whether appropriate treatment is available. 5-year survival rates for breast cancer is varies from 85% or higher in the US, Canada, Australia, Israel and many Northern and Western European countries up to 60% or lower in many developing countries, such as South Africa, Mongolia, Algeria, and India. Differences in survival reflect variations in stage at diagnosis and access to appropriate treatment.

Survival from breast cancer in Georgia is lower than in many developing countries. However, it have not yet been examined in relation to tumor and patients' characteristics, treatment, screening history or other prognostic factors.

Material and methods. Data from population-based cancer registry of Georgia was used in order to estimate 1-year and 5-year relative survival rates for breast cancer. To identify predictors for low survival time, the

following factors were assessed: cancer stage at diagnosis, patient age at diagnosis, having mastectomy, having chemotherapy, histological grade, and participation in a screening program. For the statistical analysis survival time, less than 5-years was defined as a low survival, while 5-year and over was defined as a high survival. From the cancer registry database 195 breast cancer cases, whose diagnosis were conformed histologically and died in 2015 were included in a statistical analysis. All analyses were performed using Epi Info version 7. 95% of Confidence Interval (95% CI) was used to estimate significance of the results.

Results and their discussion. According to population-based cancer registry, breast cancer is the most distributed localization of cancer among women in Georgia. In 2015, 1838 breast cancer new cases were detected in the country, incidence rate composed 94.7 per 100000 population. Breast cancer age-specific incidence rate is given in the Fig. the highest rate was observed among the age group 60 to 69 yy.

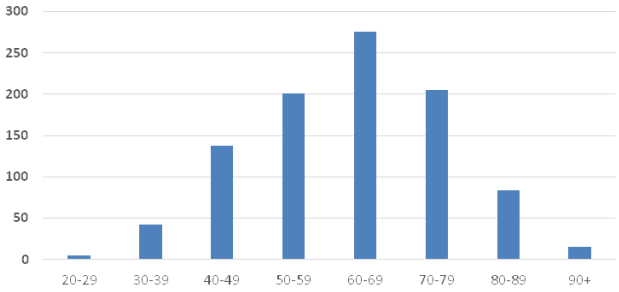

Fig. Breast-cancer age-standardize incidence rate, Georgia, 2015

Based on 195 Breast Cancer patients' data, one-year and 5-year survival rate composed 69% and 26% in accordance; Survival rates of breast cancer varies between regions of Georgia (Table 1).

The results of bivariate analysis, given in a Table 2, show that late stage at diagnosis, a young age of patients at diagnosis, highly differentiated histological grade is positively correlated with low survival time (less than 5 years), while having mastectomy, adjuvant chemotherapy and a radiotherapy have statistically significant negative association with low survival period.

Survival from breast cancer varies between countries even when the countries have the same development levels. One possible causal explanation is that the management of breast cancer differs between countries. However, these international differences should be examined in relation to tumor characteristics, treatment, screening history or other prognostic factors [5,11].

Our study revealed that there are big differences between regions of Georgia in terms of Breast Cancer survival, it could be related to different oncological alertness of population and PHC practitioners/family doctors in different localities of the country; as a result, in a majority districts high proportion of cancer cases were detected at late stages of disease (Table 1). Other reason of dissimilarity of survival periods could be correlated with treatment procedures. Additional investigation needs to be performed in order to identify whether it was reason of low accessibility to treatment because of lack of financial resources or inappropriate treatment was provided.

Table 1. One-year and 5-year survival rates for breast cancer according to selected regions of Georgia, 2015

Regions	Number of patients died in 2015	% detected at I and II stages	1-year survival rate	5-year Survival rate
Tbilisi	104	11.5%	71%	25%
Adjara	7	29%	86%	43%
Imereti	26	3.8%	59%	15%
Kacheti	16	12.5%	69%	31%
Racha-Lechkhumi	3	0%	0%	0%
Samegrelo	15	26.7%	93%	47%
Samtskhe-Javakheti	5	0%	25%	0%
Qvemo Qartli	11	27.3%	82%	27%

Table 2. Results of bivariate analysis of possible factors affecting survival of women diagnosed with breast cancer

Factors	OR	95% CI
stage at diagnosis	1.89	0.74 - 4.68
highly differentiated histological grade	1.21	0.44 - 3.54
cancer diagnosed under 49 vs. over 60 yy of age	1.42	0.64 – 3.12
cancer diagnosed under 40 vs. over 60 yy of age	1.89	0.50 – 7.17
having mastectomy	0.52	0.27 – 0.89
having adjuvant chemotherapy	0.38	0.20 – 0.74
having a radiotherapy	0.62	0.31 - 1.25
participation in a screening program	1.36	0.44 – 4.27

Our results are consistent with findings that reported Baghestani et al, in which age at diagnosis, disease stage at diagnosis, histological grade had a statistically significant effect on survival time [3].

This study results support the findings from other investigations showing that a young age at diagnosis is positively correlated with low survival time. A young age at diagnosis of breast cancer as a negative prognostic factor is a controversial issue. Some reports indicate that breast cancer in young women has different clinicopathological characteristics than in the elderly, while others found no correlation between prognosis and age. In the study, conducted by Aryandono T. et al breast cancer in young women showed a more aggressive phenotype than in elderly patients in the survey that involved thirty-seven operable breast cancer patients below 40 years of age. Prognostic factors were compared to those for breast cancer patients age 60 years and older [2]**.** In the study, conducted by Onega T. et al survaival time was lower among older women and for those with a higher stage of diagnosis [10]. In order to determine whether young breast cancer patients have poorer survival as compared with an older cohort was used the Surveillance, Epidemiology, and End Results cancer database in USA. Two age categories were analyzed: young group (<or=35 years old) and older group (50-55 years old). Overall, young patients had worse 5-year survival when compared with the older group (74.3% vs. 85.1%) [9]**.**

Unlike to other findings given above, age was not a significant prognostic factor in a cohort study, conducted by the University of Malaya Medical Centre (Malaysia), while late stage at diagnosis and highly differentiated histological grade status were correlated with poor prognosis, as in our research [8]**.**

Finally, our study revealed statistically significant correlation between high survival period and having mastectomy, chemotherapy and radiotherapy. In prior studies of survival predictors, prognosis was less favourable for women who received only palliative or symptomatic treatment, for women whose route to diagnosis was not the screening programme [**7]; ** but in our analysis participation in a screening programme was not positively correlated with early detection and high survival, because women do not participate on a regular base and attend to the program mainly after having a tumor or other symptoms.

Conclusions. A young age of patients at diagnosis, highly differentiated histological grade and late stage at diagnosis were possible predictors for low survival time (less than 5 years) in Georgia. Breast cancer survival can be extended by using complex methods of treatment and implementation of standardized approaches to management of diseases throughout the country.

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SUMMARY

FACTORS AFFECTING SURVIVAL OF WOMEN DIAGNOSED WITH BREAST CANCER IN GEORGIA

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Breast cancer is the most frequently diagnosed cancer in women worldwide with nearly 2.4 million new cases diagnosed in 2015, In Georgia survival from breast cancer is lower than in many developing countries. The goal of the study was to identify predictors for low survival of disease in the country.

Data from population-based cancer registry was used in order to estimate 1-year and 5-years relative survival rates for breast cancer. To identify predictors for low survival time, was performed bivariate analysis. Statistical analyses looked at correlations between possible predictors and survival period. From the cancer registry database 190 breast cancer cases, whose diagnosis were conformed histologically and died in 2015 were included in a statistical analysis. All analyses were performed using Epi Info version 7.

According to population-based cancer registry, breast cancer is the most common form of cancer among women in Georgia. In 2015 1838 breast cancer new cases were detected in the country, incidence rate composed 94.7 per 100000 population. Based on 190 breast cancer patients' data, that died during 2015, one-year and 5-year survival rate composed 69% and 26% in accordance. The results of bivariate analysis, show that late stage at diagnosis (OR=1.89, 95%CI=0.74-4.68), a young age of patients at diagnosis (OR=1.89, 95%CI=0.50–7.17), highly differentiated histological grade (OR=1.21, 95%CI= 0.44 - 3.54), is positively correlated with low survival period (less than 5 years), while having mastectomy (OR=0.52, 95%CI=0.27–0.89), adjuvant chemotherapy (OR=0.38, 95%CI=0.20–0.74), and a radiotherapy (OR=0.62, 95%CI=0.31–1.25), have statistically significant positive association with high (more than 5 years), survival period.

A young age of patients at diagnosis, highly differentiated histological grade and late stage at diagnosis were possible predictors for low survival time (less than 5 years) in Georgia. Breast cancer survival can be extended by using complex methods of treatment and implementation of standardized approaches to management of diseases throughout the country.

Keywords: breast cancer, cancer survival, in Georgia (country).

РЕЗЮМЕ

ФАКТОРЫ, ДЕЙСТВУЮЩИЕ НА ПЕРИОД ВЫЖИВАЕМОСТИ ЖЕНЩИН С ДИАГНОЗОМ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ В ГРУЗИИ

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Рак молочной железы (РМЖ) является самым распространенным онкологическим заболеванием среди женщин. В 2015 году в мире выявлено около 2,4 миллиона новых случаев заболевания. Согласно данным популяционного реестра, самым распространенным онкологическим заболеванием среди женщин в Грузии является РМЖ. В 2015 г. в Грузии выявлено 1838 новых случаев этого заболевания. Заболеваемость составила 94,7 на 100000 женщин. По имеющимся данным, в 2015 г. от РМЖ умерли 195 пациенток, показатель одно-и пятилетней выживаемости составил 69% и 26%, сответственно. Период выживаемости с диагнозом рака молочной железы в Грузии более низкий, чем во многих развивающихся странах.

Целью данного исследования явилось установление факторов, влияющих на выживаемость женщин с диагностированным раком молочной железы в Грузии.

Используя данные популяционного регистра рака, авторами оценены показатели одно- и пятилетней выживаемости женщин с РМЖ. С целью выявления определяющих факторов кратковременного периода выживания проведен бивариационный анализ. На основе статистического анализа оценена корреляция между возможными факторами и показателем низкого периода выживания. Статистически проанализированы данные умерших в 2015 г. 195 пациенток с гистологически подтвержденным диагнозом рака молочной железы. Все анализы выполнены с использованием VII версии Epi Info.

Результат бивариационного анализа показал, что выявление заболевания на поздней стадии (III и IV стадии) (OR=1.89, 95%CI=0.74-4.68), молодой возрасть пациенток (OR=1,89, 95%CI=0,50-7,17) и гистологически высокий степень дифференциации рака (OR=1.21, 95%CI=0.44-3.54) находятся в положительной корреляции с кратковременным периодом выживаемости (менее 5 лет); корреляция между проведением мастектомии (OR=0.52, 95%CI=0.27–0.89), химиотерапии (OR=0.38, 95%CI=0.20–0.74), радиотерапии (OR=0.62, 95%CI=0.31–1.25) и длительной выживаемостью (более 5 лет) является статистически достоверной.

К факторам, которые определяют кратковременный период выживаемости при РМЖ относятся молодой возраст пациенток, гистологически высокий степень дифференциации рака и несвоевремменое выявление болных в результате поздного обращения за медициской помощью. Увеличение периода выживаемости при РМЖ достигается путем осуществления комплексных методов лечения и стандартизированным подходом к управлению заболеванием в масштабах всей страны.

რეზიუმე

საქართველოში ძუძუს კიბოს გადარჩენის პერიოდზე მოქმედი ფაქტორები

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კვლევის მიზანს წარმოადგენდა ქვეყანაში დაავადების – ძუძუს კიბოს დაბალი გადარჩენის განსაზღვრელი ფაქტორების გამოვლენა.

კიბოს პოპულაციური რეგისტრის მონაცემების გამოყენებით შეფასდა ძუძუს კიბოს ერთწლიანი და ხუთწლიანი გადარჩენის მაჩვენებლები. გადარჩენის ხანმოკლე პერიოდის განმსაზღვრელი ფაქტორების გამოვლენის მიზნით ჩატარდა ბივარიაციული ანალიზი. სტატისტიკური ანალიზით შეფასდა კორელაცია შესაძლო ფაქტორებსა და დაბალი გადარჩენის პერიოდს შორის. სტატისტიკურ ანალიზში ჩართული იყო ჰისტოლოგიურად დადასტურებული ძუძუს კიბოს დიაგნოზით 195 პაციენტის შესახებ მონაცემები, რომლებიც 2015 წელს გარდაიცვალნენ. ყველა ანალიზი შესრულდა Epi Info მე-7 ვერსიის გამოყენებით.

პოპულაციური კიბოს რეგისტრის მონაცემების მიხედვით, საქართველოში ძუძუს კიბო ყველაზე გავრცელებული ონკოლოგიური დაავადებაა ქალებში. 2015 წელს ქვეყანაში ძუძუს კიბოს 1838 ახალი შემთხვევა გამოვლინდა. ინციდენტობის მაჩვენებელმა 100 000 ქალზე 94,7 შეადგინა. 2015 წელს ძუძუს კიბოს დიაგნოზით გარდაცვლილი 195 პაციენტის მონაცემების მიხედვით,დიაგნოზის დასმიდან ერთ- და ხუთწლიანმა გადარჩენის მაჩვენებელმა შეადგინა 69% და 26%, შესაბამისად. ბივარიაციული ანალიზის შედეგებმა აჩვენა, რომ დაავადების დაგვიანებული გამოვლენა (მესამე-მეოთხე სტადიაზე) (OR=1.89, 95%CI=0.74-4.68), პაციენტთა ახალგაზრდა ასაკი (OR=1.89, 95%CI=0.50–7.17) და კიბოს ჰისტოლოგიურად მაღალი დიფერენცირების ხარისხი (OR=1.21, 95%CI= 0.44-3.54) დადებით კორელაციაშია გადარჩენის ხანმოკლე (5 წელზე ნაკლები) პერიოდთან; მასტექტომიის (OR=0.52, 95%CI=0.27–0.89), ქიმიოთერაპიის (OR=0.38, 95%CI=0.20–0.74) და რადიოთერაპიის (OR=0.62, 95%CI=0.31–1.25) ჩატარება სტატისტიკურად სარწმუნო კორელაციაშია ხანგრძლივ გადარჩენასთან (5 წელზე მეტი).

საქართველოში ძუძუს კიბოს ხანმოკლე გადარჩენის პერიოდის განმსაზღვრელ ფაქტორებს მიეკუთვნება პაციენტთა ახალგაზრდა ასაკი,კიბოს ჰისტოლოგიურად მაღალი დიფერენცირების ხარისხი და დაავადების გვიან ეტაპზე გამოვლენა. ძუძუს კიბოს გადარჩენის პერიოდის გაზრდა შესაძლებელია მკურნალობის კომპლექსური მეთოდების გამოყენებით და დაავადების მართვის სტანდარტული მეთოდების დანერგვით ქვეყნის მასშტაბით.

PEMETREXED-INDUCED PSEUDOCELLULITIS – A RARE CUTANEOUS ADVERSE REACTION TO MULTI-TARGETED ANTIFOLATE THERAPY

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Pemetrexed is a folate antagonist which has been approved either as single agent or in combination with cisplatin for the treatment of pleural mesothelioma or non-small cell lung cancer (NSCLC) [1]. Because of the high frequency of cutaneous adverse effects, some studies recommend initial combination with dexamethasone [2].

Known cutaneous adverse reactions include skin rash, stomatitis, vasculitis, urticaria, pityriasis lichenoides-like dermatitis, cutaneous hyperpigmentation, toxic epidermal necrolysis, acute exanthematic pustulosis, scleroderma-like changes, eyelid edema, and pseudocellulitis [3-7].

Cellulitis (erysipelas) is an acute bacterial infection with massive edema leading to tenderness, pain, erythema, fever, warmth of affected area, and general malaise. The most common causative germ is *streptococcus pyogenes* [8].

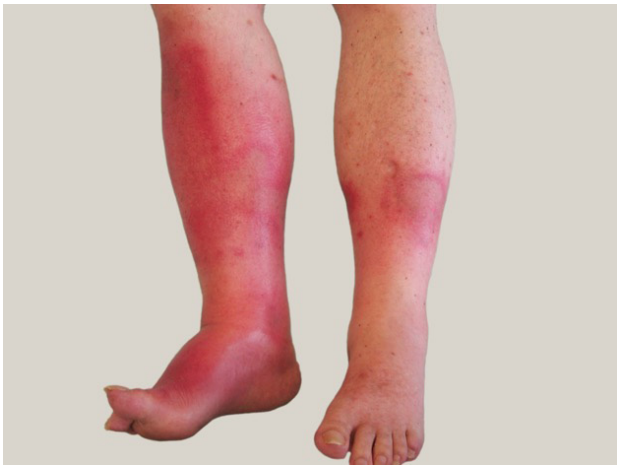
Case report. A 62-year-old male patient was referred to us due to painful erythema of the lower legs and feet. His medical history was remarkable for arterial hypertension, penicillin allergy, and nicotine use with 30 pack years.

He suffered from NSCLC since March 2016, cT2 cN3 pM1a – stage 4. Histologic examination of the tumor revealed an adenocarcinoma, G3. He developed a malignant pleural effusion on the right side and was treated by thoracoscopic talc pleurodesis in April 2016.

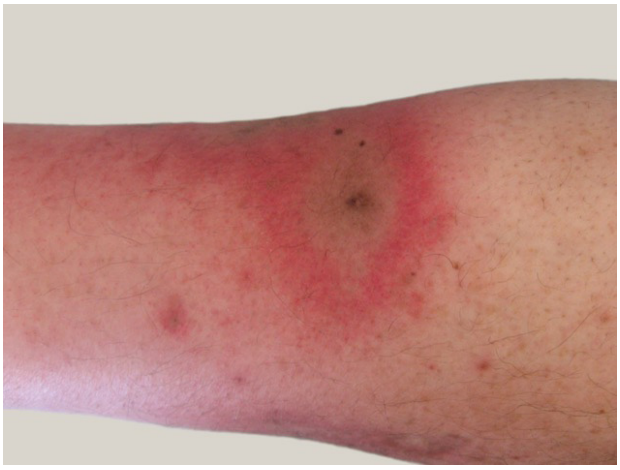
Palliative chemotherapy with cisplatin and pemetrexed (Alimta®) every three weeks was started in May 2016.

In September 2016, he developed an acute painful erythema of his right foot and lower leg about 2 weeks after the last chemotherapy. He had no general malaise, no fever, and no lymphadenopathy. Because of the suspicion of a cellulitis he was treated by oral erythromycin by his GP. The cutaneous lesions, however, progressed.

On examination, we observed ill-defined, dull, erythematous, edematous, warmth plaques on the right foot and both lower legs. The right side demonstrated the more inflammatory changes. These plaques imposed as targetoid or annular lesions (Fig 1a,b). The plaques were warm and tender to touch. Laboratory diagnostics found elevated C-reactive protein 190 mg/l and a blood sedimentation rate of 109 mm per hour but normal procalcitonin level.



A



B

Fig. 1. Pemetrexed-induced pseudocellulitis. (A) Overview with asymmetrical involvement of lower extremities. Erythema and edema. (B) Detail with a targetoid lesion

Neutrophil count was increased.

A skin biopsy found a superficial lymphocytic infiltrate (interface dermatitis) and edema.

The diagnosis of pemetrexed-induced pseudocellulitis could be confirmed. Antibiosis was stopped. The patient was treated by prednisolone; initially 80 mg/d and tapering down. Vitamin B and folate supplementation was continued, topical corticosteroid ointment was applied and

the feet and lower legs received a compression therapy by two-layered bandages. The patient achieved a complete remission with post-inflammatory hyperpigmentation after 10 days (Fig. 2).

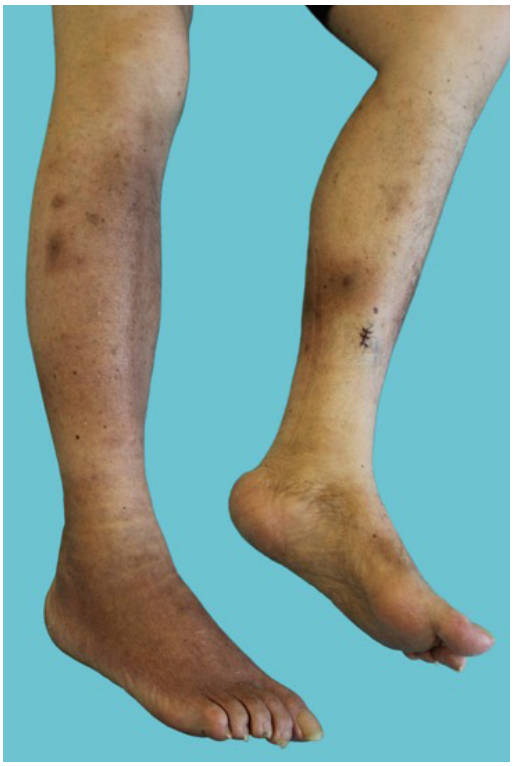


Fig. 2. Complete response after combined systemic and topical treatment with corticosteroids and compression therapy for lower legs. Mild post-inflammatory hyperpigmentation

In several trials with multi-targeted antifolate drug pemetrexed, adverse cutaneous reactions have been observed in 17% to 31% [8].

Pseudocellulitis is a rare adverse effect to folate antagonist pemetrexed observed in less than 3% of treated patients [3]. It can occur at any time during treatment. No clinical or laboratory predictors have yet been identified. Histology is variable. Eccrine squamous syringometaplasia has been previously reported in a 79-year-old Chinese NSCLC patients [3] while other authors observed a dense eosinophilic dermal infiltrate or an interface dermatitis [4].

Preventive measures include supplementation with folate and vitamin B and short cycle of dexamethasone. Treatment consists of non-steroidal anti-rheumatic drugs and corticosteroids. However, pseudocellulitis is not restricted to penetrexed use. It has also rarely been reported usually within 48h after gemcitabine infusion. Gemcitabine is an antimetabolite, deoxycitidine analogue used for advanced pancreatic cancer and other cancer types. In contrast to pemetrexed-induced pseudocellulitis, gemcitabine-induced pseudocellulitis disappears without treatment [10].

Oncologists and dermatologists should be aware of this adverse cutaneous reaction.

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SUMMARY

PEMETREXED-INDUCED PSEUDOCELLULITIS – A RARE CUTANEOUS ADVERSE REACTION TO MULTI-TARGETED ANTIFOLATE THERAPY

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Pemetrexed is a multi-targeted folate antagonists approved for non-small cell lung cancer and other malignancies. Adverse cutaneous reactions have been reported in up to 1/3 of patients treated. A rare cutaneous adverse reaction is pseudocellulitis.

We report about a 62-year-old male patient treated with a combination of cisplatin and pemetrexed for non-small cell lung cancer stage IV who developed about 4 months after initiation of treatment painful, non-febrile erythematous lesions on feet and lower legs. There was no lymphadenopathy and no general malaise. Laboratory investigations detected increased level of C-reactive protein but normal values of procalcitonin. A skin biopsy revealed a mild interface dermatitis. Antifolate treatment was stopped and he received oral and topical corticosteroids, compression therapy and supplementation with folate and vitamin B. A complete remission of skin eruptions was achieved.

Pemetrexed-induced pseudocellulitis is a possible, but rare complication of treatment that oncologists and dermatologists should know. Systemic antibiosis is unnecessary.

Keywords: Non-small cell lung cancer, chemotherapy, multitargeted antifolate treatment, pseudocellulitis.

РЕЗЮМЕ

ПСЕВДОЦЕЛЛЮЛИТ, ВЫЗВАННЫЙ ЛЕЧЕНИЕМ ПЕМЕТРЕКСЕДОМ - РЕДКАЯ ПОБОЧНАЯ РЕАКЦИЯ НА ПРОТИВОФОЛАТОВУЮ ТЕРАПИЮ

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Пеметрексед - это многоцелевой антагонист фолата, используемый при лечении немелкоклеточного рака легкого и других злокачественных новообразований. У одной трети пациентов, проходивших лечение пеметрекседом отмечалась неблагоприятная кожная реакция. Редкой кожной побочной реакцией является псевдоцеллюлит.

Авторы описывают клинический случай 62-летнего мужчины-пациента, проходившего комбинированное лечение цисплатином и пеметрекседом в связи с IV стадией немелкоклеточного рака легкого. Спустя 4 месяца после начала лечения развились болезненные, нефебрильные эритематозные поражения на обеих стопах и голенях. Лимфаденопатии и общего недомогания не отмечалось. Лабораторные исследования обнаружили повышенный уровень С-реактивного белка, однако нормальные значения прокальцитонина. Биопсия кожи выявила поверхностный дерматит лёгкой формы. Лечение антифолитом было прервано, и пациенту было назначено лечение пероральными и наружными кортикостероидами, компрессной терапией и пищевыми добавками фолата и витамина В. Достигнута была полная ремиссия.

Онкологам и дерматологам необходимо быть в курсе о возможности возникновения такого редкого осложнения лечения Пеметрекседом, как псевдоцеллюлит. Авторы не считают необходимым применение антибиотиков.

რეზიუმე

პემეტრექსედით მკურნალობით გამოწვეული ფსევდოცელულიტი – იშვიათი გვერდითი რეაქცია ანტიფოლატურ თერაპიაზე

[1]უ.ვოლინა, [1]გ. ჰანსელი, [2]ე. ცშუპპე, [3]დ. ჩერნევი

[1]დრეზდენ-ფრიდრიხშტატის აკადემიური კლინიკური ჰოსპიტალი, დერმატოლოგიისა და ალერგოლოგიის განყოფილება, დრეზდენი, გერმანია; [2]დრეზდენ-ფრიდრიხშტატის აკადემიური კლინიკური ჰოსპიტალი, IV სამედიცინო განყოფილება – ჰემატოლოგია-ონკოლოგია,დრეზდენი გერმანია; [3]შინაგან საქმეთა სამინისტროს სამედიცინო ინსტიტუტი,დერმატოლოგიისა და კანის ქირურგიის განყოფილება, სოფია, ბულგარეთი; ონკოდერმა – დერმატოლოგიისა და კანის ქირურგიის კერძო პოლიკლინიკა, სოფია, ბულგარეთი

პემეტრექსედი ფოლატის მრავალფუნქციური ანტაგონისტია, რომელიც გამოიყენება ფილტვის არაწვრილუჯრედოვანი კიბოს და სხვა ავთვისებიანი წარმონაქმნების სამკურნალოდ. პაციენტების ერთ მესამედს, ვინც მკურნალობდა პემეტრექსედით აღენიშნება კანის არაკეთილსაიმედო რეაქცია. იშვიათ კანისმიერ რეაქციას წარმოადგენს ფსევდოცელულიტი.

ავტორები აღწერენ კლინიკურ შემთხვევას 62 წლის მამაკაცი-პაციენტისა, რომელიც ფილტვის არაწვრილუჯრედოვანი კიბოს მეოთხე სტადიის დიაგნოზით გადიოდა კომბინირებულ მკურნალობას ცისპლატინით და პემეტრექსედით. მკურნალობის დაწყებიდან 4 თვის შემდეგ განვითარდა ტკივილი, ორივე ტერფის და წვივის ერითემატოზული არაფებრილური დაზიანებანი. ლიმფადენოპათია და საერთო სისუსტე არ

აღინიშნებოდა. ლაბორატორიული კვლევებით გამოვლინდა С-რეაქტიული ცილის მომატებული მაჩვენებელი, მაგრამ პროკალციტონინის დონე ნორმალური იყო. კანის ბიოფსიამ გამოავლინა მსუბუქი ფორმის ზედაპირული დერმატიტი. მკურნალობა ანტიფოლიტით შეწყდა; პაციენტს მიეცა პერორალური და გარეგანი კორტიკოსტეროიდებით კომპრესიული თერაპიის, ფოლატის და В ვიტამინის მიღების დანიშნულება. მიღწეული იქნა სრული რემისია.

ონკოლოგებისა და დერმატოლოგებისათვის აუცილებელია პემეტრექსედით მკურნალობის ისეთი იშვიათი გართულების განვითარების შესაძლებლობის ცოდნა,როგორიც ფსევდოცელულიტია. ავტორები ანტიბიოტიკების გამოყენებას არ მიიჩნევენ სავალდებულოდ.

ВАРИАБЕЛЬНОСТЬ РИТМА СЕРДЦА У ДЕТЕЙ С АНОМАЛЬНО РАСПОЛОЖЕННЫМИ ХОРДАМИ В ЛЕВОМ ЖЕЛУДОЧКЕ СЕРДЦА

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Дисплазия соединительной ткани по сей день занимает актуальное место среди сердечно-сосудистой патологии, в частности ее проявлений, среди которых значатся аномально-расположенные хорды (АРХ) в левом желудочке сердца [1]. АРХ – фибро-мышечные образования различной длины и толщины, которые расположены в полости левого желудочка сердца [2] от желудочковой перегородки к папиллярной мышце или свободной стенке ЛЖ, не связанные с митральным клапаном как обычная хорда [3]. Частота выявления АРХ составляет 2,5-95% [4]. В литературе указывается, что данные проявления дисплазии соединительной ткани (ДСТ) могут давать осложнения в виде нарушений ритма и проводимости сердца [5], указываются также нарушения процесса реполяризации желудочка на электрокардиограмме [2]. Кроме того, АРХ могут приводить к диастолической дисфункции левого желудочка, что может стать фактором риска развития инфекционного эндокардита и тромбоэмболического синдрома [6]. Согласно классификации, АРХ относятся к категории малых аномалий развития сердца [7]. Среди множества авторов доминирует мнение, что у пациентов с ДСТ нарушено равновесие между симпатической и парасимпатической регуляцией сердечного ритма, что, в свою очередь, влияет на поддержание вегетативного гомеостаза организма в целом [8].

Учитывая вышеизложенное, целью данного исследования явилось определение параметров вегетативной нервной системы у детей с аномально-расположенной хордой.

Материал и методы. Оценка состояния вегетативного гомеостаза проводилась с помощью метода кардиоинтервалографии (КИГ) с анализом показателей вариабельности ритма сердца (ВРС).

Обследованы дети с АРХ в левом желудочке сердца (n=64), из них 40 мальчиков и 24 девочки в возрасте 13-17 лет и 23 практически здоровых ребенка того же возраста. Исследование проводилось на клинической базе кафедры, в больнице “Центр Матери и Ребенка” города Винницы, Украина. Все дети клинически обследованы и проконсультированы узкими специалистами.

Оценка вегетативного гомеостаза проводилась при помощи КИГ с анализом показателей ВРС, используя режимы временного или статистического (time-domain) и частотного или спектрального (frequence-domain) анализов согласно Международным стандартам измерения, физиологической интерпретации и клинического использования, разработанными рабочей группой Европейского Кардиологического сообщества и Североамериканского сообщества кардиостимуляции и электрофизиологии [9].

При временном анализе использовались такие параметры: ЧСС, средний NN-интервал, SDNN, SDSD, rMSSD, pNN50%.

– SDNN (Standart deviation all NN intervals), мсек — стандартное отклонение всех NN-интервалов. Данный показатель является интегральным и характеризует ВРС в целом и зависит от влияния на синусный узел симпатического и парасимпатических отелов вегетативной нервной системы (ВНС). Уменьшение или увеличение данного показателя указывает на изменения баланса одного из отделов ВНС.

– SDSD (Standard deviation of successive differences), мсек – Стандартное отклонение разностей соседних RR-интервалов

– RMSSD (Square root mean sumsquares differences between adjacent NN intervals), мсек – квадратный корень среднего значения квадратов разниц продолжительности последовательных NN-интервалов

- pNN50% (Proportion derived dividing NN50 total numb

er NN intervals), % — % соседних NN-интервалов, разница между которыми не превышает 50 мсек.
Последние показатели используются для оценки коротковолновых колебаний и коррелируют с мощностью высоких частот, характеризуют состояние парасимпатического отдела ВНС.
- CVr – Коэффициент вариации.

При частотном анализе ВРС использовались такие показатели:
- VLF, very low frequence (0,003-0,04 Гц) – мощность колебаний очень низкой частоты, отображает низкочастотную составляющую ВРС. Отображает состояние гуморальной регуляции, активность центральный осцилляторов, колебаний метаболизма, системы терморегуляции.
- LF, low frequence (0,04-0,15 Гц) – мощность колебаний низкой частоты, на мощность в этом диапазоне влияют изменения как (преимущественно) симпатической активности, так и парасимпатической.
- HF, high frequence (0,15-0,40 Гц) – дыхательные волны сердечного ритма, отображают высокочастотную составляющую ВРС, характеризуют парасимпатический тонус ВНС
- LF/HF, симпато-вагальный индекс. Является отношением низкочастотных компонентов спектру к высокочастотным, характеризирует вегетативный баланс.
- TP – общая мощность спектра нейрогуморальных регуляций.

Отличия между результатами двух выборок оценивали параметрическим критерием Стьюдента (t). Все расчеты проводились специальной программой Microsoft Excel на компьютере IBM PC/AT.

Результаты и их обсуждение. Анализ временного домена ВРС у детей 13-17 лет с АРХ выявил различие в показателях в сравнении с нормативами. Так, у детей данной группы отмечается уменьшение SDNN у мальчиков относительно нормы (85,4±5,8 и 158,2 ±25,6, p<0,05), что указывает на доминирование симпатического отдела ВНС, а у девочек отмечена только тенденция к симпатикотонии. Одинаковая предрасположенность выявлены у мальчиков и девочек относительно показателя SDSD, а именно – недостоверное его уменьшение без статистической значимости в обеих подгруппах. Показатели, которые отвечают за парасимпатический отдел ВНС, достоверно не отличаются от таковых группы контроля. Так, rMSSD имеет незначительную тенденцию к уменьшению у мальчиков и к увеличению у девочек. Такая же картина вырисовывается касательно результатов средних значений показателя pNN50 в обеих подгруппах. Спектральный анализ полученных показателей показал, увеличение общего частотного спектра ТР в обеих подгруппах с достоверным результатом (4734,2±319,4 и 3520±381 – мальчики, p<0,05 относительно нормы; 4961,7±413,7 и 3520±381, p<0,05 – у девочек). Это указывает на активацию симпатического отдела ВНС у этих детей. При всем этом, частотные показатели характеризовались хорошо выраженными волнами всех частот. В частности, это касается средних значений очень низкочастотных волн, которые также достоверно увеличены относительно группы контроля (4188,4±413,1 и 1717±154, p<0,05 – мальчики; 3050,5±468,1 и 1433±811 – девочки, p<0,05, соответственно).

У подростков с АРХ высокочастотные волны имеют одинаковую зависимость от значений временного домена rMSSD и pNN50%. Отмечено, что HF у мальчиков как и другие показатели, имеет тенденцию к снижению, а у девочек - к повышению.

Недостоверное увеличение показателя LF/HF в обеих группах также указывает на тенденциозность к симпатикотонии (таблица).

Таблица. Показатели вариабельности ритма сердца у детей 13-17 лет с АРХ (M±m)

Показатель	Мальчики	Группа контроля	Девочки	Группа контроля
ЧСС	67,6±1,64	74±6,5	67,4±2,7	72±4,3
NN-интервал, мс	816±28	823,5±54,5	729,8±34,1	740,2±52,1
SDNN, мс	85,4±5,8*	158,2 ±25,6	143,5±32,5	163,5 ±11,6
SDSD, мс	58,2±3,7	67,25±42,28	60,3±6,6	67,25±42,28
rMSSD, мс	75,6±5	82,5±12,3	85,3±9,2	77,1±7,8
pNN50, %	40,7±3,5	42,7±6,8	43,4±4,2	39,9±6,8
CVr,ум.од	6,5±0,9	7,89±1,9	6,9±1,24	7,89±1,9
TP, мс	4734,2±319,4*	3520±381	4961,7±541,4*	3520±381
VLF, мс^2	4188,4±413,1*	1717±154	3050,5±468,1*	1433±811
LF, мс^2	2055,2±411,9	1386±1035	2064,8±407,3	1479±1420
HF, мс^2	1684,2±256,8	1952±1740	1844,5±246,6	1644±1462
LF/HF	1,33±0,24	1,23±0,90	1,9±0,048	1,4±1,7

примечание: звездочкой (*) обозначены достоверные отличия относительно нормативных показателей (p<0,05)

Таким образом, у детей с аномально расположенными хордами в левом желудочке сердца имеет место увеличение влияния симпатического отдела ВНС, что выражено сильнее у мальчиков, чем у девочек. Отмечается умеренная тенденция к напряжению парасимпатического отдела ВНС у девочек и его соответствующее снижение у мальчиков.

Анализируя результаты проведенного исследования, следует отметить, что вегетативная дисфункция (ВД) выражена как у мальчиков, так и у девочек. Следует подчеркнуть, что АРХ можно охарактеризовать как один из признаков изолированной дисплазии соединительной ткани, что затрагивает только сердечно-сосудистую систему и входит в группу малых аномалий развития сердца [8]. Учитывая, что признаки ВД всегда присутствуют при ДСТ [10], можно предположить, что присутствие АРХ может усугубить течение вегетативных нарушений у таких детей.

Литературные данные указывают [8], что аномальные хорды могут быть причиной болевых ощущений, ввиду наличия дисфункции вегетативной нервной системы, вследствие чего повышается порог болевой чувствительности и повышается эмоциональная готовность к восприятию болевых раздражений на фоне как физической, так и эмоциональной нагрузки. У обследованных нами детей это может выражаться в большей степени, учитывая присутствие такого предрасполагающего фактора как повышенная активность симпатического отдела ВНС, особенно у мальчиков, что впоследствии может привести к снижению и толерантности к физическим нагрузкам.

Кроме того, АРХ сами по себе могут быть причиной нарушений ритма серда [11], а усугубление дисфункции вегетативной регуляции сердечнососудистой системы, что, в свою очередь, также является предиктором их развития, может повысить вероятность появления более серьезных аритмий. Примером чего являются пароксизмальные нарушения сердечного ритма, возникающие на фоне преобладания парасимпатической нервной системы, представленные пароксизмальной желудочковой и наджелудочковой тахикардиями [12].

В предыдущей работе [13] также указывалось, что при наличии малых сердечных аномалий развития сердца, в частности при пролапсе митрального клапана, нарушение ритма и вегетативная дисфункция, очевидно, связанны между собой в патогенезе их развития. Учитывая эти данные, следует предположить, что нарушения сердечного ритма еще больше усугубляют вегетативное равновесие, тем самым образуя порочный круг.

Различие в результатах показателей временного домена ВРС у мальчиков и девочек указывает на изменения тонуса ВНС. Так, статистически значимое снижение SDNN у мальчиков и только тенденция к его снижению у девочек позволяет судить о преобладании симпатического влияния на ритм сердца именно у мальчиков. В тоже время, отмечается статистически незначимая тенденция к повышению rMSSD и pNN50 в обеих подгруппах детей. Парасимпатикотония, как компонент структуры ВРС согласуется с представлением об адаптационно-трофическом действии блуждающих нервов на сердце и является показателем индивидуальной устойчивости здорового организма к стрессовым факторам [14]. ЧТо касается обследуемых нами детей, утверждать об их устойчивости к стрессовым ситуациям невозможно, особенно у мальчиков, у которых отмечается выраженное напряжение симпатического отдела ВНС.

У всех обследованных детей частотный спектр ВРС характеризовался хорошо выраженными волнами высокой, низкой и очень низкой частот. При этом у большинства обследованных подростков суммарная мощность (TP) выше ($p<0,05$) контрольных данных, что указывает на преобладание симпатического регуляторного влияния на сердечнососудистую систему.

Выявленная тенденция к парасимпатическому влиянию на сердечный ритм, согласно повышению VLF ($p<0,05$) на фоне симпатикотонии, свидетельствует об умеренной устойчивости детей к стрессовым факторам как у мальчиков, так и у девочек.

Согласно литературным источникам [14], изменение отношения LF/HF говорит об изменении симпатической активности или отображает симпато-парасимпатический баланс. Данный показатель был использован для мониторинга симпато-парасимпатического равновесия. Увеличение его средних значений указывает на доминирование симпатикотонической регуляции сердечной деятельности. Дети с преобладанием симпатической активности в регуляции сердечного ритма характеризуются склонностью к снижению мощности высокочастотного компонента ВРС (HF). У детей с преобладанием симпатических влияний структура симпатико-парасимпатического воздействия на сердечный ритм характеризуется большим вкладом в регуляцию сердечного ритма центральных эрготропных и симпатических влияний. Показатели временного анализа ВРС у мальчиков характеризуются достоверно ($p<0,05$) более низкими значениями SDNN, чем у девочек, что позволяет судить о снижении вариабельности сердечного ритма. Кроме того, сниженные значения RMSSD указывают на низкую активность высокочастотных колебаний у этих детей.

Выводы. Подводя итоги исследования, можно резюмировать, что дети с малыми сердечными аномалиями, в частности с АРХ, имеют нарушение вегетативного гомеостаза в виде нарушения тонуса обеих звеньев ВНС с преобладанием симпатического отдела.

Полученные результаты свидетельствуют о том, что данные группы детей должны быть под постоянным наблюдением у педиатров и кардиологов. С целью предупреждения развития возможных осложнений следует с осторожностью подходить к выбору вида спортивных нагрузок для данных детей, принимая во внимание особенности тонуса ВНС.

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SUMMARY

HEART RATE VARIABILITY IN CHILDREN WITH FALSE CHORDS IN THE LEFT CARDIAC VENTRICULAR

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We examined 64 children with false tendons in the left cardiac ventricular. The research included evaluation of time and frequency domain parameters of the heart rhythm with cardiointervalography. The parameter changes were noted. Thus, sympathetic vegetative system (VS) part prevalence was present in boys and characterized by decreasing of SDNN when compared with control data (85,4±5,8 и 158,2 ±25,6, p<0,05). rMSSD and PNN50%, which are responsible for parasympathetic VS part have the tendency to increasing in girls. Nevertheless, frequency domain analysis showed an increasing of the total spectrum power (TP) in both subgroups with statistically significant result (4734,2±319,4 and 3520±381 – boys, p<0,05 when compared with control; 4961,7±413,7 and 3520±381, p<0,05 – girls, respectively). That was proved by other parameters. VLF were also increased when compared with control group (4188,4±413,1 and 1717±154, p<0,05 – boys; 3050,5±468,1 and 1433±811 – girls, p<0,05, respectively), which characterizes sympathetic VS part prevalence in both subgroups. Other frequency domain parameters statistically were not changed but they had tendency as to increasing as to decreasing. All previously noted shows the sympathicotonia in children with FT. These children should be under observation of pediatricians and child cardiologists.

Keywords: cardiointervalography, children, false tendons.

РЕЗЮМЕ

ВАРИАБЕЛЬНОСТЬ РИТМА СЕРДЦА У ДЕТЕЙ С АНОМАЛЬНО РАСПОЛОЖЕННЫМИ ХОРДАМИ В ЛЕВОМ ЖЕЛУДОЧКЕ СЕРДЦА

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Целью данного исследования явилось определение параметров вегетативной нервной системы у детей с аномально-расположенной хордой (АРХ).

Оценка состояния вегетативного гомеостаза проводилась с помощью метода кардиоинтервалографии с анализом показателей вариабельности ритма сердца, используя режимы временного или статистического (time-domain) и частотного или спектрального (frequence-domain) анализов согласно Международных стандартов измерения, физиологической интерпретации и клинического использования, разработанных рабочей группой Европейского кардиологического сообщества и Североамериканского сообщества кардиостимуляции и электрофизиологии.

Обследованы 64 детей с аномально расположенными хордами в левом желудочке сердца, из них 40 мальчиков и 24 девочки в возрасте 13-17 лет и 23 практически здоровых детей того же возраста. Исследование проводилось на клинической базе кафедры и в“Центре матери и ребенка” г. Винницы.

На основании результатов проведенного исследования следует заключить, что у детей с малыми сердечными аномалиями, в частности с АРХ, выявлены изменения вегетативного гомеостаза в виде нарушения тонуса обеих звеньев вегетативной нервной системы (ВНС) с преобладанием симпатического отдела, что требует постоянного наблюдения у педиатров и кардиологов. С целью предупреждения развития возможных осложнений следует с осторожностью подходить к выбору вида спортивных нагрузок для данных детей, принимая во внимание особенности тонуса ВНС.

რეზიუმე

გულის რითმის ვარიაბელობა ბავშვებში გულის მარცხენა პარკუჭში ანომალურად განლაგებული ქორდებით

ა კულეშოვი

ვინიცის ნ.ი. პიროგოვის სახ. ეროვნული სამედიცინო უნივერსიტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა ვეგეტატური ნერვული სისტემის (ვნს) პარამეტრების განსაზღვრა ბავშვებში ანომალურად განლაგებული ქორდებით (აგქ) გულის მარცხენა პარკუჭში.

გამოკვლეულია 13-17 წლის 64 ბავშვი აგქ-ით გულის მარცხენა პარკუჭში (40 ვაჟი, 24 გოგონა). საკონტროლო ჯგუფი შეადგინა 23-მა იმავე ასაკის პრაქტიკულად ჯანმრთელმა ბავშვმა. კვლევა ჩატარდა უნივერსიტეტის კათედრის კლინიკურ ბაზაზე და ქ. ვინიცის “დედათა და ბავშვთა ცენტრში”.

ვეგეტატური ჰომეოსტაზის შეფასება განხორციელდა კარდიოგრაფიულად, გულის რითმის ვარიაბელობის მაჩვენებლების შესწავლით საერთაშორისო სტანდარტების გამოყენებით, დროებითი, ანუ სტატისტიკური (time-domain) და ნაწილობრივი, ანუ სპექტრული (frequence-domain) ანალიზის რეჟიმში, ევროპული კარდიოლოგიური გაერთიანების და ჩრდილოეთ ამერიკის კარდიოლოგიისა და ელექტროფიზიოლოგიის საზოგადოებათა მიერ მოწოდებული ფიზიოლოგიური ინტერპრეტაციით და კლინიკური გამოყენებით.

ჩატარებული კვლევის შედეგად ავტორებს გამოტანილი აქვთ დასკვნა იმის შესახებ, რომ ბავშვებში მცირე გულ-სისხლძარღვოვანი ანომალიებით, კერძოდ - აგქ-ის პირობებში, ვლინდება ვეგეტატური ჰომეოსტაზის ცვლილებები ვნს-ის ორივე რგოლის ტონუსის დარღვევის სახით. ასეთი ბავშვების სპორტული დატვირთვის სახეობის შერჩევისას, შემდგომი გართულებების თავიდან აცილების მიზნით, აუცილებელია ვნს-ის ტონუსის გათვალისწინება.

CYTOKINES AS THE PREDICTORS OF SEVERE MYCOPLASMA PNEUMONIAE PNEUMONIA IN CHILDREN (REVIEW)

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Community-acquired pneumonia (CAP) is one of the most a common diseases in children. Annually, approximately 120–156 million cases of acute lower respiratory infections (ALRI) occur globally, with approximately 1.4 million resulting in death [31]. Of these, pneumonia kills an estimated 1 million children under the age of 5 every year and accounts for 15% of deaths in children <5 years of age with 90–95% of these deaths occurring in the developing world [26,36].

CAP refers to the acute infection of the lung parenchyma and is characterized by the development of fever and/or respiratory symptoms, as well as the presence of pulmonary infiltrates and consolidation on chest X-ray. Ideally, the definition should include the isolation of the causal microorganism. However, the pathogen is not identified in a great number of cases, thus not fulfilling the clinical definition. CAP is classically classified into three syndromes: typical or bacterial CAP, atypical (due to viruses or atypical bacteria) and indeterminate (cases that do not fulfill the criteria required to include them in the first two groups) [8]. Atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, are increasingly recognized as important causes of CAP worldwide [7,20].

In the last years, there is an increasing interest to understand these pathogens, since both have been identified as important causes of morbidity and mortality in children [4,26]. *Mycoplasma pneumoniae* pneumonia (MPP) occurs worldwide, and accounts for 10-40% of all cases of community-acquired pneumonia [11,19].

Mycoplasma pneumoniae can be found in all age groups, with higher prevalence in children aged 5±15 years old. Mycoplasma pneumonia infections occur both endemically and epidemically at 3-to-7-year intervals worldwide. Studies conducted in various countries have shown that Community acquired *Mycoplasma pneumonia* or *C. pneumoniae* infections affect mainly preschool, school-aged children and young adults. Although, few studies have reported the frequency of *M. pneumonia* and *C. pneumoniae* infections in infants [4,29].

Mycoplasma pneumoniae can cause mild, moderate, or severe acute respiratory infections. Clinical manifestations range from mild cases of tracheobronchitis to severe atypical pneumonia and can be followed by a broad spectrum of extra pulmonary complications [13, 28, 33].

The list of extrapulmonary manifestations due to *Mycoplasma pneumoniae* infection can be classified according to the following three possible mechanisms derived from the established biological activity of *M. pneumoniae*; (1) a direct type in which the bacterium is present at the site of inflammation and local inflammatory cytokines induced by the bacterium play an important role (2) an indirect type in which the bacterium is not present at the site of inflammation and immune modulations, such as autoimmunity or formation of immune complexes, play an important role, and (3) a vascular occlusion type in which obstruction of blood flow induced either directly or indirectly by the bacterium plays an important role [22].

Recent studies concerning extrapulmonary manifestations included: stroke, cardiac and aortic thrombi as cardiovascular manifestations; erythema nodosum, cutaneous leukocytoclastic vasculitis, and subcorneal pustular dermatosis as dermatological manifestations; renal artery embolism as a urogenital tract manifestation and also arthritis, pericarditis, hemolytic anemia, optic neuritis, acute psychosis. Continuing nosological confusion on *M. pneumoniae*–induced mucositis (without skin lesions), which may be called *M. pneumoniae*-associated mucositis or *M. pneumoniae*-induced rash and mucositis separately from Stevens-Johnson syndrome, is argued in the dermatological manifestations [2,10,14].

Several central nervous system complications have been reported with Mycoplasma infection. Cerebellar syndrome, polyradiculitis, cranial nerve palsies, aseptic meningitis, meningoencephalitis, acute disseminated encephalomyelitis, coma, optic neuritis, diplopia, mental confusion and, acute psychosis secondary to encephalitis, cranial nerve palsy, brachial plexus neuropathy, ataxia, choreoathetosis, and ascending paralysis are neurologic complications seen with *Mycoplasma pneumonia* infection. Encephalitis is most frequent extrapulmonary complication of *Mycoplasma pneumonia* manifested with fever, seizures, meningeal signs, ataxia, focal neurologic deficits, and altered behaviour, ranging from minor changes to lethargy in paediatric population. Twenty percent of patients or more with CNS findings have no preceding or concomitant diagnosis of respiratory infection [9, 34].

Youn et al have reported 5 patients with ocular myasthenia gravis; acute disseminated encephalomyelitis (ADEM), meningo-encephalitis, transverse myelitis, and left abduscens nerve palsy. They demonstrated acute Mycoplasma infection with positive IgM and IgG titer by indirect immunofluorescence test without *Mycoplasma pneumoniae* PCR. Patients with transverse myelitis may have acute motor disturbances tending to progress rapidly with leg pain, inability to walk, varying degrees of paralysis initially flaccid then evolving to spasticity when persistent; areflexia evolving to increased deep tendon reflexes, bilateral positive Babinski sign, bilateral segmental sensory changes that cannot be attributed to compression of spinal

cord or another systemic disease; loss of sphincter function and MRI may reveal scattered hyperintensities of spine [35].

Guillain-Barré syndrome (GBS) is defined as an acute, areflexic, flaccid paralysis, which is classified into four subgroups including acute inflammatory demyelinating polyneuropathy, acute motor-sensory axonal neuropathy, acute motor axonal neuropathy, and Miller-Fisher syndrome. GBS is usually due to multifocal inflammation of the spinal roots and peripheral nerves, especially, the myelin sheaths. The cause of GBS is poorly understood. The favored hypothesis is that it is due to an autoimmune response directed against antigens in the peripheral nerves that is triggered by a preceding bacterial or viral infection. Several cases of *Mycoplasma pneumoniae* related Guillain-Barre syndrome have been reported with no preceding respiratory tract infection [1].

Topcu et al [28] reported coexistence of myositis, transverse myelitis, and Guillain Barré syndrome following *Mycoplasma pneumoniae* infection in an adolescent. They described a 14-year-old female patient with transverse myelitis, myositis, and Guillain Barré syndrome following *Mycoplasma pneumoniae* infection. Patient presented with weakness and walking disability. Weakness progressed to involve all extremities and ultimately, she was unable to stand and sit. Based on the clinical findings, a presumptive diagnosis of myositis was made at an outside institution because of high serum creatine kinase level. Magnetic resonance imaging of spine revealed enhancing hyperintense lesions in the anterior cervicothoracic spinal cord. The electromyography revealed acute motor polyneuropathy. Serum *M. pneumoniae* IgM and IgG were positive indicating an acute infection. Repeated *M. pneumoniae* serology showed a significant increase in *Mycoplasma* IgG titer.

Central nervous system infections and inflammatory or autoimmune disorders may cause secondary central nervous system vasculitis. *Mycoplasma pneumoniae* may cause secondary central nervous system vasculitis in children. Neuropsychiatric symptoms, seizures, cerebral infarction or other focal neurologic deficits may be seen with CNS vasculitis secondary to infection by inflammation of the cerebral blood vessels by direct pathogen invasion or due to an immune-mediated response provoked by molecular mimicry, immune complex deposition, secretion of cytokines, and/or super antigen mediated responses [34].

Many studies showed that atypical pneumonia might have a higher incidence in patients with mild symptoms, and atypical pneumonia is not only considered to cause respiratory disease, but also severe diseases including neurological, dermatological, hematological, renal, gastrointestinal, and musculoskeletal diseases. Further reports showed that the clinical parameters of atypical pneumonia were different in patients without *M. pneumoniae* pneumonia, and symptoms include fevers, crackles, thrombocytosis, consolidation, sore throat, headache, skin rash, ear infection. Although the pathogenesis of mycoplasmal pneumonia is not clear at present, these manifestations may result from the immune response to infection and/or the ability of *Mycoplasma pneumoniae* to directly invade the ciliated airway epithelial cells in the respiratory tract [12,22].

Community acquired pneumonia is caused by bacteria, viruses, or a combination of these infectious agents. Moreover, the severity of the clinical manifestations of CAP significantly varies. Consequently, both the differentiation of viral from bacterial CAP cases and the accurate assessment and prediction of disease severity are critical to the effective management of individuals with CAP, including the decision to prescribe antibiotics and to admit patients to the hospital [24]. The limited possibility of obtaining lower respiratory tract secretions or sputum in young children, given their poor tussive force and inability to expectorate, are the most important barrier to obtaining adequate respiratory specimens for etiologic identification through microbiological methods in younger patients. Moreover, whereas in adults several well-established severity scores using clinical findings have facilitated treatment and disposition decisions, no validated clinical severity score is available in children [3].

Recently, three risk models that appear to accurately estimate risk for severe CAP in children have been proposed. However, these models do not include non-hospitalized children and require an external validation in an expanded population before they can be used in routine practice [32]. Finally, to solve questionable cases, several biomarkers capable of suggesting the etiology and severity of CAP have been studied and used in adult clinical practice and have provided further improvements toward solving CAP diagnostic and therapeutic problems [17,25]. Although, only a few studies have examined the roles of these biomarkers in pediatric practice, and in most cases, attempts to assess their role in CAP management have produced contrasting results, mainly because of the uncertainty regarding the true etiology of the studied diseases. The main aim of this paper was to describe the present knowledge regarding the use of biomarkers for diagnosing and treating CAP in children, analyzing the most recently published studies of relevance [24].

In very recent paper form China CAP patients with definite etiologies were studied. They were divided into three groups according to the causative pathogens: typical bacteria, *Mycoplasma pneumonia*e (MP), and viruses. Twenty-seven cytokines and bactericidal/permeability-increasing protein (BPI) levels of serum collected within 7 days onset in these groups were compared. Distinct inflammatory marker patterns were released by different pathogens: typical bacterial pneumonia patients had highest levels of IL-6, IL-8, IL-1rα; while patients caused by MP presented higher levels of IL-17A than those caused by viruses [18].

In other study from China Clinical features and changes in Th1/Th2 cytokines were analyzed in 67 children. Serum interleukin-4, interleukin-10 (IL-10), interferon-γ, and tumor necrosis factor-α (TNF-α) of segmental/lobar

Mycoplasma pneumoniae pneumonia were significantly higher than those of bronchial *Mycoplasma pneumoniae* pneumonia. Serum TNF-α and interleukin-6 of segmental/lobar MPP with pleural effusion were significantly higher than those of segmental/lobar MPP without pleural effusion [38].

In study of Xu et al [32] was evaluated the role of serum cytokines in discriminating *Mycoplasma pneumoniae* infection in children with CAP. Serum interleukin-2 (IL-2), IL-4, IL-6, IL-10, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) were detected by flow cytometry. It was found that in children younger than 5years, serum IL-6, TNF-α, and IFN-γ levels from MP group were significantly higher than those from control group. However in children 5-15years, serum IL-6, IL-10, and IFN-γ levels from MP group were significantly higher than those from control group. In the final multivariate logistic regression model for serum cytokine, moderately elevated IL-6, IL-10, and IFN-γ shows a higher prediction of development of *Mycoplasma pneumoniae* pneumonia among CAP patients.

Li et al [16] evaluated Th1/Th2 cytokine profile and its diagnostic value in *Mycoplasma pneumonia* pneumonia in children. A total of 13161 throat swab specimens were collected. The age of the 13161 patients ranged from 3 months to 10 years. All these children had been primarily diagnosed with pneumonia and had received no clinical treatment. *M. pneumonia* was detected using real-time PCR system. Specific tests were used to detect other pathogens, such as immunofluorescence to detect respiratory viruses including adenovirus, human metapneumovirus, respiratory syncytial virus, parainfluenza virus and influenza virus; blood and sputum culture for bacteria; and real-time PCR to detect human cytomegalovirus, Epstein-Barr virus, *Chlamydia pneumoniae*, *Ureaplasma urealyticum* and *Chlamydia trachomatis*. If any of these assays was positive, the patient was excluded from the study. IL-2, IL-4, IL-6, IL-10, TNF-α and IFN-γ were detected quantitatively. 2188 out of 13161 patients were tested positive for *M. pneumoniae*, with a positive rate of 16.62%. Among 2188 *M. pneumoniae* positive samples, 1277 were from boys and 911 from girls, giving positive rates of 15.80% in boys and 17.93% in girls. *M. pneumoniae* infection occurred all year round, the monthly positive rates for *M. pneumoniae* infection ranged from 7.65% to 27.35%, with a peak in June and August and steadily declined in the previous and the following months. Co-infections were found in 1662 (75.96%) *M. pneumoniae* positive children, which were higher than in mono-infection children. To evaluate the levels of these six cytokines in healthy children and children with *M. pneumoniae* pneumonia: 526 patients with single *M. pneumoniae* infection were used as *M. pneumoniae* pneumonia group and 30 healthy children acted as the control group. Comparisons between *M. pneumoniae* infection group and normal control group revealed no difference of inflammatory cytokine (IL-6 and TNF-α) levels between the two groups. The level of IL-2 was significantly lower in serum from *M. pneumoniae* pneumonia patients than in serum from normal controls, while the levels of IL-4, IL-10 and IFN-γ in *M. pneumoniae* pneumonia patients were significantly higher than in the normal controls. These result has a promising prospect in diagnosis of this disease in clinical practice.

Ding et al examined serum levels of interleukin (IL)-8, IL-10, and IL-18 in 34 patients with *Mycoplasma pneumonia* nfection (Group 1, 11 with severe mycoplasmal pneumonia; Group 2, 13 with mild mycoplasmal pneumonia; Group 3, 10 with asthma) and 32 age-matched, non-infected controls. The serum levels of IL-8, IL-10, and IL-18 increased significantly in patients with mycoplasmal pneumonia compared with those in controls. The serum levels of IL-10 decreased significantly in patients with severe pneumonia compared with those with mild disease. The serum levels of IL-18 increased significantly in in patients with severe pneumonia compared with those with mild disease. The serum levels of IL-10 and IL-18 decreased significantly in *Mycoplasma* pneumoniae-infected patients with asthma compared with those in *Mycoplasma* pneumoniae-infected patients without asthma [6].

Mycoplasma pneumoniae lysates may increase interleukin-8 (IL-8) levels in human airway epithelial cells, may contribute to neutrophilic asthma. It have been found that the cell-mediated immune response of the host plays an important role in the mechanism of mycoplasmal pathogenicity, specifically Th1-type cytokines. Lee et al investigated the interactions of signaling molecules regulating the release of IL-8 by the direct stimulation of *M. pneumoniae* lysate (MPL) in human airway epithelial cells. In human airway epithelial cells, MPL-induced IL-8 proteins were decreased by monoclonal anti-TLR2 antibody in a dose-dependent fashion, and significantly blocked by siRNA TLR2. The pharmacologic inhibitors of ERK, U0126 and PD98059, effectively reduced IL-8 expression and the active forms of ERK signaling molecules, as detected by anti-phosphorylated p44/42 antibody. After investigating transfections of the NF-κB and NF-IL6 reporter vectors, NF-IL6 activation was significantly induced by MPL stimulation, which was considerably decreased by U0126 and monoclonal anti-TLR2 antibody. These results indicate that MPL-induced IL-8 increase is transcriptionally regulated by NF-IL6 more than by NF-κB. Additionally, the activation of NF-IL6 is influenced by TLR2 and ERK signaling pathways in airway epithelial cells [15].

Oishi et al [23] examined serum levels of interleukin-18 (IL-18) using enzyme-linked immunosorbent assay in 23 pediatric patients (median age 6 years; 14 girls and 9 boys) with *M. pneumoniae* pneumonia. Serum levels of IL-18 ranged from 22 to 1808 pg/ml with a mean of 543 pg/ml. They started steroid therapy in two cases with IL-18 values greater than 1000 pg/ml without being aware of IL-18 levels. Examination of associations between IL-18 levels determined by enzyme-linked immunosorbent assay and a routine laboratory test showed that levels of lactate dehydrogenase (LDH) and IL-18 were significantly correlated. To determine the appropriateness of steroid administration in *M. pneumoniae* pneumonia patients, serum LDH should

be examined. Patients with elevated levels of LDH are likely to have significantly elevated IL-18 values (≥1000 pg/ml) and thus can be candidates for steroid therapy.

IL-18, a Th1-type cytokine, was originally designated interferon gamma (IFN-γ)-inducing factor. This cytokine was first reported to be produced by Kupffer cells and activated macrophages, and it was shown to be a critical factor in inducing liver injury in mice. Chung et al. studied 75 children with mycoplasmal pneumonia and divided them into asthmatic and non-asthmatic groups. They found that children with asthma exhibited a deficient IL-18 response and had more severe pneumonia. Plasma levels of IL-18 and the chemokines increased significantly in the patients with *Mycoplasma pneumonia* pneumonia compared to non-infected, age-matched controls. However, the asthmatic patients showed significantly reduced IL-18 and CXCL10 responses and had more severe pneumonia symptoms compared to non-asthmatic patients. IL-18 was significantly lower in severe pneumonia group than in non-severe group [5].

Matsuda et al [21] performed cytokine profile analysis of macrolide-resistant Mycoplasma pneumonia infection in Fukuoka, Japan. During an outbreak of *Mycoplasma pneumonia* infections in 2010–11, a total of 105 children with clinically suspected *Mycoplasma pneumonia* infection were enrolled. Sixty-five patients with PCR positive for *Mycoplasma pneumonia* were analyzed with regard to clinical symptoms, efficacy of several antimicrobial agents and several laboratory data. The resistance rate of *Mycoplasma pneumonia* was 89.2% in this general pediatric outpatient setting. Patients infected with MR-*Mycoplasma pneumonia* showed longer times to resolution of fever and required frequent changes of the initially prescribed macrolide to another antimicrobial agent. They observed three different genotypes of *Mycoplasma pneumonia* including the rarely reported A2063T mutation (A2063G: 31 strains, A2063T: 27 strains, no mutation: 7 strains). Drug susceptibility testing showed different antimicrobial susceptibility profiles for each genotype. Serum IFN-gamma, IL-6 and IP-10 levels were higher in patients with MR-genotypes than in those infected with no-mutation strains.

In retrospective study of Zhang [37] et al 634 patients with MPP were enrolled, 145 cases were diagnosed as refractory *Mycoplasma pneumoniae* pneumonia (RMPP), while 489 were general *Mycoplasma pneumoniae* pneumonia (GMPP). No distinctive differences of age, gender distribution, duration of symptom before admission and length before macrolide therapy were observed between the two groups, which meant the clinical course between the two groups were relatively consistent. However, longer duration of fever, longer length of stay, and higher incidence of extra-pulmonary complications were found in the RMPP group than those in the GMPP group, which indicated that to some extent children with RMPP had a more severe illness. Cell-mediated immunological response plays an important role in the progression of MPP. Meanwhile, the levels of IL-6, IL-10, and interferon gamma (IFN-γ) in RMPP group were significantly higher than those in GMPP group. In Receiver operating characteristic (ROC) curve analysis, the percentage of IL-6, IL-10 and IFN-γ were useful for differentiating patients with RMPP from those with GMPP. Multiple logistic regression analysis showed that the IL-6 >14.75pg/ml were significant predictors regarding to RMPP. The excessive inflammation reaction may lead to release of cytokines and immune disorder, which is might related to the severity of RMPP in children.

Conclusion

In spite of many attempts to differentiate bacterial from viral disease and predict severity and outcome, the etiologic diagnosis of paediatric community acquired pneumonia and the estimation of potential outcomes remain unsolved problems in most cases. *Mycoplasma pneumoniae* is one of the major pathogens causing CAP in children. Although MP infection was traditionally thought to be a self-limited process, more and more severe cases even fatal cases of MP infections were reported in recent years. So, it is essential for paediatricians to recognize severe or RMPP early, treat it promptly and prevent the progress of the disease.

In recent years, several new biomarkers have been tested in children with CAP. Some of the biomarkers used for etiologic diagnosis in children with CAP and they also have been used the MP infection severity. Among traditional biomarkers, several cytokines appears to be effective both in selection of bacterial cases and in evaluation of severity. However, a precise cut-off level able to separate bacterial from viral cases and mild from severe cases has not been defined. Further studies enrolled with a large number of children with *Mycoplasma pneumoniae* is needed to be carried out to identify the potential utility of different cytokines as the good predictors.

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SUMMARY

CYTOKINES AS THE PREDICTORS OF SEVERE MYCOPLASMA PNEUMONIAE PNEUMONIA IN CHILDREN (REVIEW)

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In spite of many attempts to differentiate bacterial from viral disease and predict severity and outcome, the etiologic diagnosis of paediatric community acquired pneumonia and the estimation of potential outcomes remain unsolved problems in most cases. Mycoplasma pneumoniae is one of the major pathogens causing CAP in children. Although MP infection was traditionally thought to be a self-limited process, more and more severe cases even fatal cases of MP infections were reported in recent years. So it is essential for pediatricians to recognize severe or refractory or severe MP early, treat it promptly and prevent the progress of the disease.

In recent years, several new biomarkers have been tested in children with CAP. Some of the biomarkers used for etiologic diagnosis in children with CAP and they also have been used the MP infection severity. Among traditional biomarkers, several cytokines appears to be effective both in selection of bacterial cases and in evaluation of severity. However, a precise cut-off level able to separate bacterial from viral cases and mild from severe cases has not been defined. Further studies enrolled with a large number of children with Mycoplasma pneumoniae is needed to be carried out to identify the potential utility of different cytokines as the good predictors.

Keywords: Mycoplasma pneumonia, bacterial disease, viral disease, cytokines, diagnosis.

РЕЗЮМЕ

ЦИТОКИНЫ, КАК ПРЕДИКТОРЫ ТЯЖЕЛОЙ ПНЕВМОНИИ, ВЫЗВАННОЙ MYCOPLASMA PNEUMONIAE, У ДЕТЕЙ (ОБЗОР)

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Несмотря на усилия клиницистов диагностика этиологии детской внебольничной пневмонии, прогнозирование тяжести и исхода заболевания в большинстве случаев остаются нерешенной проблемой. *Mycoplasma pneumoniae* является одним из частых возбудителей детской внебольничной пневмонии. Если раньше микоплазменная пневмония рассматривалась как легкое заболевание, на сегодняшний день зафиксированы тяжелые случаи, вплоть до летального исхода. Следовательно, ранняя диагностика и своевременное лечение микоплазменной пневмонии обеспечат предотвращение прогрессирования заболевания.

За последние годы у детей с внебольничной пневмонией тестированы несколько новых биологических маркеров, которые используются для установления этиологии заболевания и оценки его тяжести. Некоторые из традиционных биомаркеров оказались эффективными в установлении этиологии и тяжести заболевания. Несмотря на это, по сей день не определен точный показатель того уровня биомаркеров, который дифференцирует вирусную и бактериальную этиологию пневмонии и тяжесть заболевания. Требуются дальнейшие исследования на большем количестве больных для определения цитокинов, которые могут быть рекомендованы для уточнения этиологии и прогнозирования течения заболевания.

რეზიუმე

ციტოკინები - *Mycoplasma pneumoniae*-თი გამოწვეული მძიმე პნევმონიის პრედიქტორები ბავშვებში (მიმოხილვა)

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კლინიცისტების ძალისხმევის მიუხედავად, ბავშვთა გარეჰოსპიტალური პნევმონიის ეტიო-

ლოგია, დიაგნოსტიკა, დაავადების სიმძიმის და გამოსავლის პროგნოზი, უხშირეს შემთხვევებში, გადაუჭრელ პრობლემად რჩება. *Mycoplasma pneumoniae* ბავშვებში გარეჰოსპიტალური პნევმონიის გამომწვევი ერთ-ერთი უხშირესი პათოგენია. ტრადიციულად,მიკოპლაზმური პნევმონია მსუბუქ დაავადებად განიხილებოდა; უკანასკნელ წლებში დაფიქსირდა დაავადების უფრო მძიმე შემთხვევები, ლეტალური გამოსავლითაც კი. ამდენად, პედიატრების მიერ მიკოპლაზმური პნევმონიის მძიმე, ან რეზისტენტული ფორმების ადრეულმა დიაგნოსტიკამ და დროულმა მკურნალობამ ცხადია, რომ ხელს შეუშლის დაავადების პროგრესირებას.

ბოლო წლების განმავლობაში ბავშვებში გარეჰოსპიტალური პნევმონიით შესწავლილია რამდენიმე ახალი ბიომარკერი. მათი ნაწილი გამოიყენებოდა დაავადების ეტიოლოგიის დადგენისთვის, ნაწილი კი - დაავადების სიმძიმის პროგნოზირებისათვის. მიუხედავად ამისა,ჯერ-ჯერობით არ არის განსაზღვრული ბიომარკერების ის ზუსტი დონე, რომელიც იძლევა ვირუსული და ბაქტერიული ეტიოლოგიის დაავადების დიფერენცირების, ასევე, მისი სიმძიმის განსაზღვრის საშუალებას. დაავადების ეტიოლოგიის დაზუსტებისა და მიმდინარეობის პროგნოზისათვის მნიშვნელოვანი ციტოკინების განსაზღვრისათვის აუცილებელია შესაბამისი კვლევების ჩატარება პაციენტთა უფრო დიდ რაოდენობაზე.

ОСОБЕННОСТИ ВНЕБОЛЬНИЧНОЙ ПНЕВМОНИИ У ДЕТЕЙ С НЕВРОЛОГИЧЕСКОЙ ПАТОЛОГИЕЙ

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Пневмония относится к числу наиболее распространенных инфекционных заболеваний человека и является одной из главных причин детской смертности. Ежегодно она уносит жизни примерно 1,4 млн. детей в возрасте до пяти лет. Заболеваемость внебольничной пневмонией (ВП) в Европе у детей разного возраста колеблется в пределах от 2 до 15 случаев на 1000 человек в год [3,4,9].

Особенно актуальной является проблема развития пневмонии у детей с различными коморбидными состояниями, в частности с сопутствующей неврологической патологией (НП) [1,5,7]. Так, в настоящее время частота детского церебрального паралича (ДЦП) имеет тенденцию к росту, что объясняется большей выживаемостью детей с тяжелыми перинатальными поражениями ЦНС и значительным снижением смертности в последние годы среди недоношенных и детей с экстремально низкой массой тела [2,12,16]. ДЦП развивается по разным данным в 2-3,6 случаях на 1000 живых новорожденных и является основной причиной детской неврологической инвалидности. Среди недоношенных детей частота ДЦП составляет 1%. У новорожденных с массой тела менее 1500 г распространенность ДЦП увеличивается до 5-15%, а при экстремально низкой массе тела – до 25-30% [2,6,11,14].

Наиболее частыми являются спастические формы ДЦП, на долю которых приходится до 80-85% [6,13]. Известно, что неврологические нарушения у детей с ДЦП в большой степени влияют на течение многих соматических заболеваний, их исход и развитие возможных осложнений [6,11,15]. Следует отметить предрасположенность к развитию пневмоний, течение которых имеет затяжной и атипичный характер, что в свою очередь обуславливает тяжесть состояния и особенности терапевтической тактики [7,8,10]. Пневмония у детей с ДЦП является одной из причин развития тяжелой острой дыхательной недостаточности, что влечет за собой необходимость проведения искусственной вентиляции легких.

Цель исследования - выявление клинико-параклинических особенности при внебольничных пневмониях у детей раннего возраста с неврологической патологией в виде детского церебрального паралича.

Материал и методы. Под наблюдением находилось 37 детей в возрасте от 1 года до 3 лет с сопутствующей неврологической патологией (спастические формы ДЦП), которые перенесли внебольничную пневмонию (ВП на фоне НП). Группу сравнения составили 30 детей, в возрасте от 1 года до 3 лет с внебольничной пневмонией без неврологической патологии (ВП без НП).

Методы исследования: клинические (жалобы, анамнез заболевания и объективные данные), инструментальные (рентгенография ОГК, ЭКГ, ЭЭГ, пульсоксиметрия) и лабораторные (общеклинические и биохимические).

Полученные данные обрабатывались с помощью компьютерной программы Microsoft Excel 2010, отличия считались достоверными при $p<0,05$ [10].

Результаты и их обсуждение. В результате анализа анамнестических данных выявлено, что 17 (46±8,2%) детей с ВП на фоне НП относились к группе часто и длительно болеющих и переносили респираторные заболевания более 6 - 8 раз за год. В то время, как у детей с ВП без НП указания на наличие рекуррентных заболеваний респираторной системы отмечались у 5 (16,7±6,8%) детей (ОШ=2,55 (95ДИ 0,76-8,47). Аналогичные данные приводит Лучанинова В.Н. (2011), отмечая, что дети с ДЦП страдают заболеваниями органов дыхания в 1,45 раза чаще в сравнении с детьми без неврологической патологии.

Данные о перенесенной повторной внебольничной пневмонии в анамнезе у детей с ВП на фоне НП приведены у 11 (29,7±7,5%) детей. У детей с ВП без НП повторная пневмония была зарегистрирована всего в двух случаях, что составило (6,7±4,5%) (ОШ=5,92 (95ДИ 1,19 – 29,29).

Фебрильные судороги в анамнезе имели место у 10 (27±7,3%) детей с ВП на фоне НП и всего лишь у 2 (6,7±4,5%) детей с ВП без НП (ОШ = 5,18 (95ДИ 1,04 – 25,88).

Большинство детей с ВП на фоне НП поступали в стационар в ранние сроки от начала заболевания. Так, в период от 24 до 72 часов от появления первых симптомов ВП, поступило 28 (75,7±7,0%) детей. В то же время дети с ВП без НП в основном поступали в стационар позже 3 суток от начала заболевания, в среднем, на 4,58±1,62 день. Раннее обращение детей с НП за медицинской помощью обусловлено тяжестью состояния, быстрым нарастанием признаков интоксикации и дыхательной недостаточности. Необходимо отметить, что родители детей с ВП на фоне НП, имея опыт предыдущих респираторных эпизодов, уже имели определенную настороженность, что в большинстве случаев служило поводом к более раннему обращению за медицинской помощью.

При поступлении в стационар состояние 34 (91,9±4,5%) детей с ВП на фоне НП расценивалось как тяжелое. При этом, 13 (35,1±7,8%) детей поступили сразу в отделение интенсивной терапии. В группе детей с ВП без НП тяжелое состояние констатировано у 11 (36,6±8,8%) пациентов (ОШ = 19,57 (95ДИ 4,85 – 78,95).

Обращает на себя внимание наличие и степень выраженности интоксикации в дебюте заболевания, как одного из основных признаков пневмонии. Так, признаки интоксикации (слабость, сонливость, снижение аппетита, отказ от питья) были отмечены у 25 (67,6±7,7%) больных с ВП на фоне НП и у 12 (40,0 ±8,94%) детей с ВП без НП (ОШ=3,12 (95ДИ 1,14 – 8,52).

В раннем возрасте начало пневмонии часто манифистирует себя появлением таких симптомов как: катаральные явления, малопродуктивный кашель, фебрильная температура. Анализ данных анамнеза показал, что наличие кашля в группе детей с ВП на фоне НП, в первые дни заболевания отмечено лишь у 19 (51,4±8,2%) пациентов, что обусловлено в первую очередь неэффективностью кашлевого рефлекса, а также рядом патофизиологических факторов, связанных с основным неврологическим состоянием. Кашель в группе детей с ВП без НП имел место у 28 (93,3±4,5%) пациентов (ОШ = 13,26 (96ДИ 2,75 – 63,92).

Отмечены особенности температурной реакции у детей с ВП на фоне НП. Так, у 10 (27±7,3%) детей из этой группы отмечалась длительная (более 5-7 дней), стойкая, труднокупируемая лихорадка. В то время как у детей с ВП без НП температурная реакция практически во всех случаях, а именно у 28 (93,3±4,5%) детей имела классический вариант и купировалась к 2-3 дню от начала антибактериальной терапии.

В большинстве случаев при пневмониях у детей можно выявить типичные локальные физикальные данные: укорочение перкуторного звука, изменение характера дыхания, появление локальных крепитирующих и/или влажных мелкокалиберных хрипов. Однако, следует отметить, что при пневмониях у детей раннего возраста нередко сложно выявить аускультативную асимметрию в легких. Это связано с тем, что у детей первых лет жизни воспаление легочной паренхимы редко бывает изолированным и часто сочетается с поражением бронхов. В большей степени это относится и к детям с ДЦП, у которых ограничена способность самостоятельно передвигаться и эффективно эвакуировать имеющуюся мокроту с помощью кашля, что значительно быстрее приводит к генерализации процесса в легких, тяжелой дыхательной недостаточности. Согласно полученным данным, асимметрия хрипов имела место всего у 5 (13,5±5,6%) больных с ВП на фоне НП и у 20 (66,6 ±8,6)% детей с ВП без НП (ОШ = 12,8 (95 ДИ 3,8 – 42,9).

Наиболее значимым клиническим симптомом, позволяющим заподозрить пневмонию, является дыхательная недостаточность, которая проявляется одышкой, цианозом, снижением парциального давления кислорода. Частота и тяжесть дыхательной недостаточности во многом зависят от возраста детей и объема поражения легочной ткани. Однако этот признак значим только при отсутствии симптомов обструкции. Необходимо отметить, что у детей с ВП на фоне НП одышка при госпитализации была зарегистрирована у 34 (91,8±4,5%) детей. У детей с ВП без НП одышка также имела высокую частоту регистрации, и была отмечена у 25 (83,3±6,8%) больных (ОШ=2,27 (95 ДИ 0,49 – 10,38). Показатели сатурации кислорода ($Sat O_2$) при этом у детей с ВП на фоне НП составляли менее 92% (в диапазоне от 84 до 92%) у 11 (29,7±7,5%) детей, а у детей с ВП без НП колебались в пределах 92 – 95%. Наличие бронхообструкции с первых дней заболевания отмечено у 24 (64,9±5,9%) больных с ВП на фоне НП,

и у 11(36,6±8,8%) больных с ВП без НП (ОШ 3,19 (95 ДИ 1,17 – 8,69). Наличие сопутствующей бронхообструкции более чем у половины больных с ВП на фоне ДЦП можно объяснить поражением нервно – мышечного аппарата и обусловлено, как правило, снижением жизненной емкости легких ввиду мышечной слабости или спастического сколиоза, ослаблением кашлевого рефлекса и дисфагии и как следствие неспособностью произвести эффективный кашлевой толчок. Ослабление дренажной функции при этом приводит к более медленному регрессу бронхообструкции.

В последние годы нами была отмечена общая тенденция к увеличению в структуре ВП сегментарных форм. Так, в группе детей с ВП на фоне НП сегментарный процесс отмечен у 17 (45,9±8,2%) пациентов и у 12 (39,4±8,9%) детей с ВП без НП (ОШ=1,26 (95ДИ 0,48 – 3,38). Необходимо указать на то, что у детей с ВП на фоне ДЦП чаще имеет место поражение сегментов нижних отделов легких.

По данным литературы [3,4], с учетом анатомо-функциональных особенностей детей раннего возраста, в структуре ВП доминирует правосторонняя локализация воспалительного процесса. Так, правосторонний процесс имел место у 22 (73,3±8,0%) детей с ВП без НП. Интересно заметить, что у 32 (86±4,3%) детей с ВП на фоне НП, учитывая патофизиологические особенности ДЦП, сторона локализации воспалительного процесса в легких совпадала со стороной неврологически пораженной части тела.

Анализ частоты развития осложнений показал, что в группе детей с ВП на фоне НП плеврит отмечался у 9 (24,3±7,1%) пациентов. У детей с ВП без НП плеврит был диагностирован у одного ребенка, что составило (3,3±3,3)% случаев, (ОШ=9,32 (95ДИ 1,11 – 78,46).

Параклиническими симптомами ВП являются лейкоцитоз с нейтрофильным сдвигом и увеличение СОЭ. Однако, у детей с ВП на фоне НП в дебюте заболевания у 26 (70,3 ±7,5%) пациентов не отмечалось повышения уровня лейкоцитов выше возрастной нормы. Данный факт может служить косвенным признаком сниженной общей реактивности у детей на фоне ДЦП. В группе детей с ВП без НП классический высокий лейкоцитоз с нейтрофильным сдвигом имел место у 16 (54,6±4,0)% пациентов.

Увеличение СОЭ выше 20 мм/час было отмечено у 19 (51,6±3,6%) детей с ВП на фоне НП и у 13 (43,4±9,0%) детей с ВП без НП (ОШ = 1,38 (95 ДИ 0,52 – 3,63).

Данные биохимического исследования крови показали, что повышение уровня креатинина при госпитализации у детей с ВП на фоне НП отмечалось в 2,5 раза чаще, чем у детей с ВП без НП. Отмечено повышение (не более чем в 1,1 - 1,3 раза) активности трансаминаз у детей с ВП на фоне ДЦП: АЛТ в 4,9 раза и АСТ в 7,3 раза чаще, чем у детей с ВП без НП (рис.). Контроль данных показателей в динамике указывал на их нормализацию после купирования явлений интоксикации в процессе лечения.

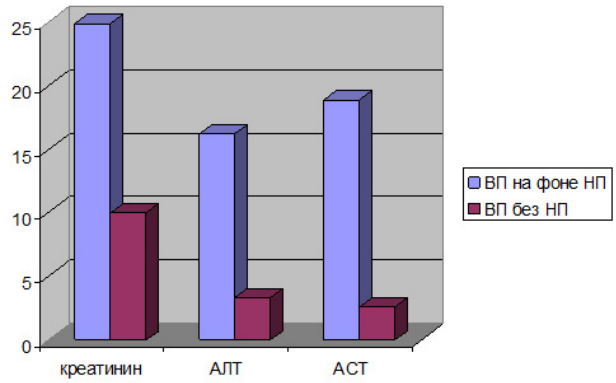

Рис. Биохимические показатели

Важно также отметить, что дети с ВП на фоне НП нуждались в более длительном лечении. Так, у 34 (91,9±4,5%) детей длительность пребывания в стационаре составила более 20 дней, а продолжительность приема антибиотика достигала порядка 30 дней. У 23 (76,7±7,7%) детей с ВП без НП длительность пребывания в стационаре составила не более 10 дней, а потребность в антибактериальной терапии ограничилась курсом в 10-12 дней.

Выводы. Наличие ДЦП позволяет отнести ребенка в группу риска по развитию респираторной патологии. Частота острых респираторных заболеваний у детей с ДЦП в 2,7 раза выше, чем у детей без сопутствующей неврологической патологии.

Течение внебольничной пневмонии у детей на фоне ДЦП отличается быстрым прогрессированием симптоматики и тяжестью состояния, при этом, такие признаки, как кашель и локальные физикальные данные регистрируются реже, а одышка и развитие бронхообструкции отмечаются, в среднем, в 2 раза чаще.

Пневмония у детей с ДЦП ввиду особенностей иммунного статуса и повышенной реактивности характеризуется затяжным течением, что определяет длительность пребывания в стационаре и объем антибиотикотерапии.

Риск возникновения пневмоний у детей с ДЦП необходимо учитывать на первичном этапе оказания медицинской помощи с учетом возможной необходимости ранней госпитализации и начала адекватной терапии, а также в дальнейшем для построения профилактических программ.

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SUMMARY

PECULIARITIES OF COMMUNITY-ACQUIRED PNEUMONIA IN CHILDREN WITH NEUROLOGICAL PATHOLOGY

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Neurological disorders in children highly affect the course of pneumonia, its outcome and the development of possible complications.

The aim of the study was to reveal clinical and paraclinical features of community-acquired pneumonia in younger children with neurologic pathology infantile cerebral palsy. Under observation were 37 children with community-acquired pneumonia aged 1 to 3 years that suffered from spastic forms of infantile cerebral palsy. The comparison group consisted of 30 children with community-acquired pneumonia without any concomitant neurological pathology. The age of the children in the comparison and study groups was the same.

The results of the study show that the presence of infantile cerebral palsy allow to relate the child to the risk group of respiratory pathology development. The course of community-acquired pneumonia in children affected by infantile cerebral palsy is characterized by rapid progression of symptoms and severity of the condition, and the clinical picture also has a number of characteristic features. Thus, cough, local physical data, classical laboratory signs of inflammation in the form of leukocytosis with neutrophil shift were noticed significantly less often in children with infantile cerebral palsy. The debut of the disease was often accompanied by bronchial obstruction, the inflammatory process was localized in the lower parts of the lungs and often matched the side of the neurologically affected part of the body. Children with cerebral palsy required a longer hospital-stay and a prolonged course of antibiotic therapy. Therefore, the risk of pneumonia in children with infantile cerebral palsy should be taken into account at the primary stage of medical care for the creation of preventive programs.

Keywords: community-acquired pneumonia, infantile cerebral palsy, children of early age, comorbid conditions.

РЕЗЮМЕ

ОСОБЕННОСТИ ВНЕБОЛЬНИЧНОЙ ПНЕВМОНИИ У ДЕТЕЙ С НЕВРОЛОГИЧЕСКОЙ ПАТОЛОГИЕЙ

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Неврологические нарушения у детей в большой степени влияют на течение пневмонии, ее исход и развитие возможных осложнений.

Цель исследования - выявление клинико-параклинических особенностей при внебольничных пневмониях у детей раннего возраста с неврологической патологией в виде детского церебрального паралича.

Под наблюдением находились 37 детей в возрасте от 1 года до 3 лет со спастическими формами детского церебрального паралича (ДЦП), которые перенесли внебольничную пневмонию. Группу сравнения составили 30 детей, той же возрастной категории, которые перенесли внебольничную пневмонию без какой-либо сопутствующей неврологической патологии.

Результаты проведенного исследования показали, что наличие ДЦП позволяет отнести детей в группу риска по развитию респираторной патологии. Течение внебольничной пневмонии у детей на фоне ДЦП отличается быстрым прогрессированием симптоматики и тяжестью состояния, а клиническая картина имеет ряд характерных особенностей: кашель, локальные физикальные данные, классические лабораторные признаки в виде лейкоцитоза с нейтрофильным сдвигом отмечались достоверно реже у детей с ДЦП. Дебют заболевания часто сопровождался явлениями бронхообструкции, а сам воспалительный процесс локализовался в нижних отделах легких, при этом сторона поражения часто совпадала со стороной неврологически пораженной части тела. Дети с ДЦП нуждались в более длительном нахождении в стационаре и пролонгированном курсе антибактериальной терапии.

Таким образом, риск возникновения пневмоний у детей с ДЦП необходимо учитывать на первичном этапе оказания медицинской помощи для построения профилактических программ.

რეზიუმე

გარეჯოსპიტალური პნევმონიის თავისებურებანი ნევროლოგიური პათოლოგიის მქონე ბავშვებში

ა. ზუბარენკო,ა. კოპეიკა,ტ. კრავჩენკო,ლ. კოვალი, ე. გურიენკო

ოდესის ეროვნული სამედიცინო უნივერსიტეტი, უკრაინა

ნევროლოგიური დარღვევები ბავშვებში მნიშვნელოვანწილად განსაზღვრავს პნევმონიის მიმდინარეობას, მის გამოსავალს და შესაძლო გართულებების განვითარებას.

კვლევის მიზანს წარმოადგენდა გარეჯოსპიტალური პნევმონიის კლინიკურ-პარაკლინიკური თავისებურებების გამოვლენა ბავშვთა ცერებრული დამბლის (ბცდ) მქონე ადრეული ასაკის ბავშვებში.

დაკვირვების ქვეშ იმყოფებოდა 1-3 წლის ასაკის 37 ბავშვი ბცდ-ის სპასტიკური ფორმით, რომელთაც გადაიტანეს გარეჯოსპიტალური პნევმონია. შედარების ჯგუფი წარმოდგენილი იყო იგივე ასაკობრივი ჯგუფის 30 ბავშვით თანმხლები ნევროლოგიური დარღვევების გარეშე,რომელთაც გადაიტანეს გარეჯოსპიტალური პნევმონია.

ჩატარებული კვლევის შედეგებმა აჩვენა, რომ ბცდ-ის არსებობა იძლევა ბავშვის მიკუთვნების საფუძველს რესპირაციული პათოლოგიის განვითარების რისკის ჯგუფისათვის. გარეჯოსპიტალური პნევმონიის მიმდინარეობა ბცდ-ის ფონზე გამოირჩევა სიმპტომატიკის სწრაფი პროგრესირებით და მიმდინარეობის სიმძიმით, კლინიკურ სურათს კი რიგი თავისებურებები ახასიათებს: ხველა, ლოკალური ფიზიკალური მონაცემები, კლასიკური ლაბორატორიული ნიშნები, ნეიტროფილური ლეიკოციტოზის სახით, სარწმუნოდ ნაკლებად აღინიშნება ბცდ-იან ბავშვებში. დაავადების დებიუტს ხშირად თან ერთვის ბრონქოობსტრუქცია, საკუთრივ ანთებითი პროცესი კი ლოკალიზებულია ფილტვის ქვედა წილებში; ამასთან, დაზიანების მხარე ხშირად თანხვედრილია ნევროლოგიური დაზიანების მხარესთან. ბცდ-იანი ბავშვები საჭიროებდნენ უფრო მეტ ხანს ყოფნას სტაციონარში და ანტიბაქტერიული მკურნალობის პროლონგირებულ კურსს.

ამრიგად, ბცდ-იან ბავშვებში პნევმონიის განვითარების რისკი აუცილებელად გასათვალისწინებელია პროფილაქტიკური პროგრამის შედგენისას სამედიცინო დახმარების პირველად ეტაპზე.

EXPANDED PHENOTYPE OF TMEM67 GENE MUTATION (CASE REPORT)

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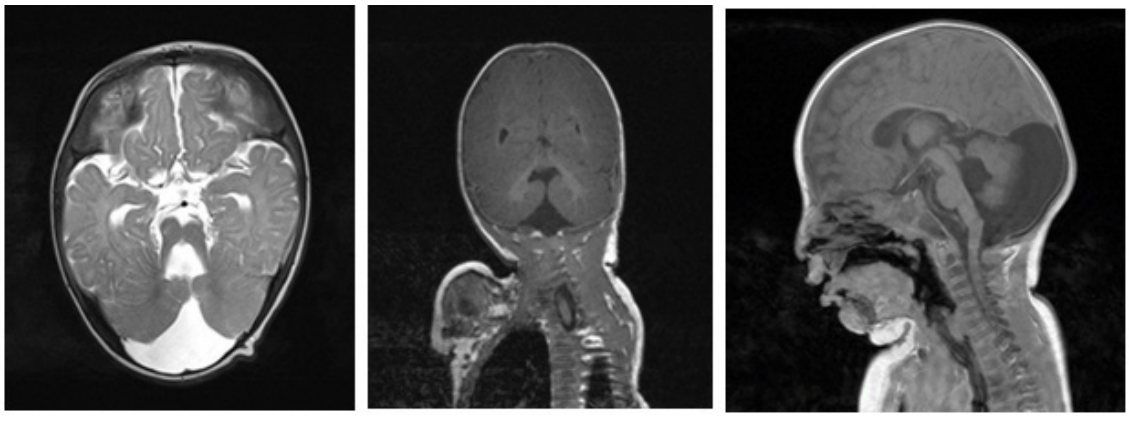
Human ciliopathies comprise a group of hereditary disorders caused by the abnormal formation or function of primary cilia, a highly conserved antenna-like organelle projecting from the surface of almost all cell types [8,9]. Recent findings have demonstrated the critical role of primary cilia in signal transduction, cell proliferation, developmental processes, and neuronal growth [13,14]. The ciliome is comprised of thousands of proteins, expressed at the primary cilia or its apparatus, which are essential for its assembly or function [1,14]. Therefore, ciliopathies can lead to a wide array of clinical phenotypes affecting almost every major part of the body, including the brain, eyes, liver, kidneys, skeleton, and limbs [1,7]. Of the more than 3000 genes that comprise the ciliome, approximately 50 mutant genes encoding defective proteins have been identified to date, causing a wide spectrum of conditions, often with overlapping phenotypes [9,14]. Thus, ciliopathies are a heterogeneous group of disorders in which a single gene may often be associated with multiple phenotypes. Furthermore, each specific syndrome may also be caused by different genes.

Here we present a patient with mutation in the *TMEM67* gene who has a combination of NPHP11, JBTS6 and microcephaly features. This case further broadens the phenotypic spectrum of the *TMEM67* gene mutation.

Material and methods. *Case report.* The patient is a 3-year-old boy, first child born to non-consanguineous parents at 38 weeks gestation with birth weight - 3500 g, height - 51 cm, head circumference (HC) - 34 cm, and Apgar scores - 7/7. Prenatal ultrasound revealed a cystic kidney disorder. At birth, he had acute respiratory insufficiency with tachypnea and anemia, and required ventilation for 2 months. Renal ultrasound revealed bilateral moderate renal enlargement, hyperechoic kidneys with poor corticomedullary differentiation, and multiple anechoic areas of varying size. Creatinine and BUN were elevated: 5.29 mg/dl (N <0.7); 22 mmol/l (N 4-19), respectively.

The patient was started on peritoneal dialysis on day 10. On day 14, hypotonia, tachycardia, bradypnea, and oculomotor apraxia appeared as well as severe growth retardation, profound developmental delay and slowing of head growth. A cranial MRI showed "molar tooth sign" (Fig. 1A, B, C). Ophthalmological examination revealed bilateral retinal colobomas.

Presently the patient is 3 years old, weighs 7.5 kg (below 3rd centile), height 77 cm (below 3rd centile), and HC 44 cm (below 3rd centile). Upon neurological examination, the patient presents with diffuse hypotonia, muscle atrophy, hyperextensibility of knee and elbow joints as well as contractures of ankle joints, nystagmus and oculomotor apraxia. He receives continuous ambulatory peritoneal dialysis on a regular basis. Complete blood count (CBC) shows anemia (HGB – 7.2 g/dl, RBC – 2.58 10^6/mm^3, and Hct – 22.4%). Ultrasound reveals hyperechoic shrunken kidneys (Fig. 2A, B) and hyperechoic liver, suggestive of diffuse fibrosis (Fig. 2C). Liver function tests show elevation of liver transaminases (ALT – 334 U/L (N <29), AST – 459 U/L (N <59) (Low Albumin due to liver or kidney). A liver biopsy was not performed. Denver screening revealed severe delay in all four areas of assessment: personal-social, 38%; fine motor-adaptive, 17%; language, 23%; and gross motor, 11%. Patient has mildly dysmorphic features with elongated face and bitemporal narrowing, high-arched eyebrows, high forehead, anverted nares, prominent nasal bridge, triangular shaped mouth with thin lips, and rhythmic tongue movements with tongue hypertrophy.



Fig, 1. MRI images of brain showing molar tooth sign, A - AX T2; B - COR T1; C - SAG T1

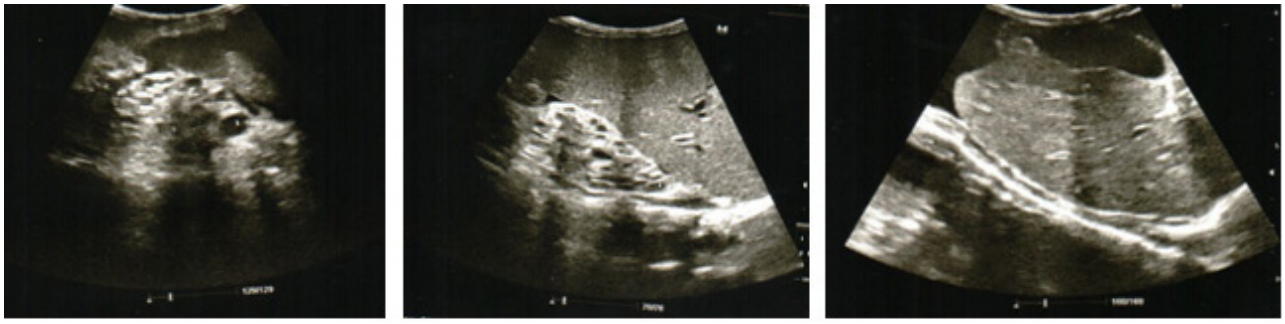


Fig. 2. Kidney and liver ultrasound at age 3 years. Kidney (A, B) showing poor corticomedullary differentiation and multiple polycystic dysplasia and liver ultrasound (C) showing hyperechoic liver suggesting fibrosis

Molecular-genetic investigations

Consenting and sampling was performed on both parents and was consistent with IRB guidelines approved by the ethical committee and according to the Declaration of Helsinki. General and neurological examination, clinical records, radiographs, photographs, videos documenting movement, and past history were reviewed and the patient was examined by one or more of the authors. Blood was collected on all consenting, potentially informative family members. DNA was extracted with the Qiagen AutoPure instrument, and was subjected to quality control measures for concentration/purity and to confirm inheritance for subsequent genetic investigation. WES (whole exome sequencing) was performed on the patient. All variants were prioritized by allele frequency, conservation, and predicted effect on protein function. After analyzing the exome data, we encountered a compound heterozygous mutation in a known Joubert syndrome gene, *TMEM67* (c.1646G>C, p.Arg549Pro; c.2720G>T, p.Gly907Val) which was compatible with the phenotype. Variants in *TMEM67* were analyzed by PCR reaction for segregation within family members and were confirmed by Sanger sequencing to both validate the variant and confirm that the mutation segregated according to a strictly recessive model with full penetrance. These variants were not seen in our in-house exome database containing more than 1800 individuals for whom whole-exome sequencing is available, nor was it evident in the NHLBI Exome Variant server or in any public SNP database.

Results and their discussion. Out of dozens of genes currently known to be responsible for human ciliopathies, the *TMEM67* mutation has received particular interest, as it can cause a wide array of syndromes: MKS3, NPHP, JBTS, COACH syndrome, and BBS — often with overlapping features [5,11]. The patient we present exhibits an unusual combination of NPHP and JBTS syndromes.

Nephronophthisis (NPHP) is an autosomal recessive disorder characterized by fibrosis and multiple cysts in the corticomedulary junction progressing to end-stage renal disease (ESRD) [3,4]. Despite a wide range of symptoms, the usual presentation includes polyuria, polydipsia, proteinuria, anemia, and ocular colobomas. NPHP is categorized into three types according to age of onset: infantile, juvenile, and adolescent. NPHP is a subtype of nephronophthisis caused by a mutation in *TMEM67*, specifically characterized by liver fibrosis [5]. Our patient exibits symptoms of NPHP, with very early (neonatal) onset renal failure.

Interestingly, the patient also presents with a full set of features belonging to another phenotype of *TMEM67*, JBTS, characterized by psychomotor delay, hypotonia, ataxia, oculomotor apraxia, and neonatal breathing abnormalities. Neuroradiologically, Joubert syndrome is characterized by peculiar malformation of the midbrain-hindbrain junction known as the 'molar tooth sign' (MTS) consisting of cerebellar vermis hypoplasia or aplasia, thick and maloriented superior cerebellar peduncles, and abnormally deep interpeduncular fossa [2,6,10,12]. Ocular colobomas are often seen as well.

Conclusion. To our knowledge, the combined phenotype of NPHP and JBTS, such an early onset of ESRD in nephronophthisis and acquired microcephalyhas not been reported thus far, so our case expands the phenotype of the *TMEM67* gene mutation. Although *TMEM67* missense mutations are usually associated with a less severe phenotype and truncating mutations cause more severe presentations, our patient with compound heterozygous missense mutation of *TMEM67* gene presents with extreme failure to thrive and ESRD at birth. Therefore, mutation in *TMEM67* can be associated with a multi-syndromic presentation in a single patient, highlighting the crucial role of primary cilia in developmental processes, neuronal growth, signal transduction, and cell proliferation.

Contributors. All authors equally contributed to the writing of this article.

Conflicts of interest. We declare that we have no conflicts of interest.

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SUMMARY

EXPANDED PHENOTYPE OF TMEM67 GENE MUTATION (CASE REPORT)

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Human ciliopathies are a class of multi-organ genetic disorders caused by defects of proteins expressed at the primary cilium, an organelle present on the cell surface of almost all cell types. Thus far, dozens of causative genes for ciliopathies have been identified and many of them are known to cause allelic disease. Of particular interest is the *TMEM67* gene, encoding the transmembrane protein meckelin. The involvement of the mutant *TMEM67* gene is known to be associated with a broad range of clinical presentations, namely Joubert syndrome 6 (JBTS6), nephronophthisis 11 (NPHP11), Bardet-Biedel syndrome (BBS), COACH syndrome, and lethal Meckel syndrome type 3 (MKS3). Here we present a case of a 3-year-old boy with compound heterozygous missense mutations in the *TMEM67* gene manifesting features of both JBTS and NPHP syndromes, with neonatal onset of end-stage renal disease **(**ESRD) and associated microcephaly. Such a phenotype has not been reported to date, thus highlighting the diversity of ciliopathies and expanding the phenotype of the *TMEM67* gene.

Keywords: Joubert syndrome, nephronoptisis, TMEM67, molar tooth, ciliopathy.

РЕЗЮМЕ

РАСШИРЕННЫЙ ФЕНОТИП МУТАЦИИ TMEM67 ГЕНА: ОПИСАНИЕ СЛУЧАЯ

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Человеческие цилиопатии представляют собой класс генетических мультиорганных нарушений, вызванных дефектами белков, которые экспрессируются на первичных ресничках органеллы, находящейся на поверхности почти всех типов клеток. На сегодняшний день идентифицированы десятки генов, вызывающие

цилиопатии, многие из них вызывают аллельные заболевания. Особый интерес представляет ген *TMEM67*, который кодирует трансмембранный белок мекелин. Как известно, мутация *TMEM67* гена связана с широким спектром клинических проявлений, а именно синдром Жубера 6 (JBTS6), нефронофтиз11 (NPHP11), синдром Барде-Бидля (BBS), синдром COACH и летальный синдром Меккеля тип 3 (MKS3).

В статье описан случай трехлетнего мальчика с компаунд гетерозиготной миссенс мутацией *TMEM67* гена, с характерными признаками синдрома Жубера и нефронофтиза, с неонатальным началом терминальной стадии почечной недостаточности (ТСПН) и ассоциированной микроцефалией. Этот фенотип по сей день не описан в литературе, что подчеркивает разнообразие цилиопатий и расширяет фенотип *TMEM67* гена.

რეზიუმე

TMEM67 გენის მუტაციის გაფართოებული ფენოტიპი: შემთხვევის აღწერა

[1,2]თ. ტყემალაძე, [1]გ. მელიქიშვილი, [1]ვ. ხერხეულიძე, [3]ა. მელიქიშვილი, [4]თ. დავითაია

[1]მედიქლაბჯორჯია სამედიცინო ცენტრი, პედიატრიული განყოფილება; [2]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, მოლეკულური და სამედიცინო გენეტიკის დეპარტამენტი; [3]წმ. ქრისტოფერის ბავშვთა საავადმყოფო, ფილადელფია, პენსილვანია, აშშ; [4]მ. იაშვილის სახ. ბავშვთა ცენტრალური საავადმყოფო, ურონეფროლოგიის დეპარტამენტი, თბილისი, საქართველო

ადამიანის ცილიოპათიები წაროადგენს მულტიორგანული გენეტიკური დაავადებების ჯგუფს, გამოწვეულს პირველად წამწამოვან აპარატში ექსპრესირებული ცილების დეფექტებით. წამწამოვანი აპარატი წარმოადგენს თითქმის ყველა უჯრედის ზედაპირზე არსებულ ორგანოიდს. დღემდე იდენტიფიცირებულია ცილიოპათიების გამომწვევი რამდენიმე ათეული გენი; მრავალი მათგანი იწვევს ალელურ დაავადებას. განსაკუთრებით საინტერესოა *TMEM67* გენი, რომელიც აკოდირებს ტრანსმემბრანულ ცილა მეკელინს. ცნობილია, რომ მუტანტური *TMEM67* გენი ასოცირებულია ფართო სპექტრის კლინიკურ გამოვლინებებთან, კერძოდ, ჟუბერის სინდრომი 6 (JBTS6), ნეფრონოფტიზი 11 (NPHP11), ბარდე-ბიდლის სინდრომი (BBS), COACH სინდრომი და ლეტალური მეკელის სინდრომი 3 (MKS3). სტატიაში აღწერილია 3 წლის ბიჭის შემთხვევა *TMEM67* გენის კომპაუნდ ჰეტეროზიგოტული მისენს მუტაციით, ჟუბერის სინდრომის და ნეფრონოფტიზისთვის დამახასიათებელი ნიშნებით, თირკმლის უკმარისობის ტერმინალური სტადიის ნეონატალური დასაწყისით და ასოცირებული მიკროცეფალიით. ეს ფენოტიპი ლიტერატურაში დღემდე არ არის აღწერილი, რაც ხაზს უსვამს ცილიოპათიების მრავალფეროვნებას და აფართოვებს *TMEM67* გენის ფენოტიპს.

РОЛЬ ДЕКОМПРЕССИИ ПИЩЕВАРИТЕЛЬНОГО ТРАКТА У БОЛЬНЫХ ОСТРОЙ НЕПРОХОДИМОСТЬЮ ТОНКОЙ КИШКИ. ОШИБКИ, ОСЛОЖНЕНИЯ И ИХ ПРЕДУПРЕЖДЕНИЕ

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Известно, что среди всех острых хирургических заболеваний органов брюшной полости острая непроходимость тонкой кишки (ОНТК) остается одной из сложных и актуальных проблем ургентной хирургии. Одной из основных причин неудовлетворительных результатов лечения больных с острой непроходимостью тонкой кишки является нарушение двигательной функции желудочно-кишечного тракта [5], что приводит к развитию у них синдрома полиорганной недостаточности. Освобождение тонкой кишки (ТК) от ее содержимого во время операции и создание беспрепятственного его оттока в послеоперационном периоде достигается интубацией этого органа кишечным зондом. Наши клинические наблюдения и

данные литературы свидетельствуют об отсутствии морфо-функционального обоснования использования интубации ТК у больных ОНТК.

В большинстве случаев хирурги или не выполняют интубацию ТК во время операции при наличии одного из показаний к ее применению, или используют только один из ее вариантов - назогастроинтестинальную интубацию (НГИИ), или недостаточно эффективно используют ее. Определение показаний к выполнению различных методов интубации ТК и усовершенствование известных ее способов остается актуальным в ургентной абдоминальной хирургии.

Целью исследования явилось улучшение результатов лечения больных острой непроходимостью тонкой кишки путем доказательного обоснования необходимости декомпрессии пищеварительного тракта у них и предложение различных целесообразных методов интубации тонкой кишки для эффективной эвакуации кишечного содержимого.

Материал и методы. Проведено экспериментальное обследование 53 белых половозрелых крыс - самцов массой 196-204 г, которые были разделены на 2 группы: контрольная группа (К) - 11 случаев практически здоровых интактных животных и 42 случая - крысы, которым моделировали механическую кишечную непроходимость путем перевязки лигатурой в безсосудистом участке брыжейки ТК на расстоянии 2 см от илеоцекального угла. Все оперативные вмешательства на экспериментальных животных проводили в условиях тиопенталового наркоза, путем введения раствора в брюшную полость. В конце эксперимента эвтаназию животных осуществляли путем быстрой декапитации. Исследовали морфологические и морфометрические изменения ТК [1]. 196 больным ОНТК проведено исследование степени выраженности интоксикационного синдрома с помощью определения лейкоцитарного индекса интоксикации (ЛИИ) [12], неспецифической резистентности организма [4] в сопоставлении со сроками восстановления моторно-эвакуаторной функции ТК. Кроме того, изучено 30 медицинских карт стационарных больных с летальным исходом лечения ОНТК.

Результаты и их обсуждение. У экспериментальных животных с явлениями динамической кишечной непроходимости вследствие ОНТК локальный кровоток в стенке ТК был почти в 1,5 раза меньше по сравнению с К.

Вследствие механического растяжения ТК, наблюдались существенные структурные изменения микроциркуляторного русла - артериол, прекапилляров, капилляров, посткапилляров, венул. При этом отмечалось расширение диаметров вышеперечисленных структур, а также тенденция к увеличению плотности капилляров на единицу площади слизистой оболочки. В этих экстремальных условиях диаметры артериол и прекапилляров увеличивались на 4-6%, капилляров - на 8-12%. В то же время аналогичные характеристики посткапилляров и венул увеличивались на 15-19%, плотность капиллярного русла повышалась на 5-8%.

Гистологически в микропрепаратах ТК отмечались расширение и полнокровие сосудистого русла, стазы в капиллярах и мелкоочаговые паравазальные кровоизлияния. Таким образом, при кишечной непроходимости возникает расширение всех звеньев микроциркуляторного русла с существенным преобладанием дилатации посткапилляров и венул, то есть венозных структур, вызывая затруднения венозного оттока.

Морфометрические исследования слоев стенки ТК при экспериментальной ОНТК подтвердили наличие истончения мышечного слоя стенки ТК в 2,15 раза, увеличение подслизистого слоя в 1,65 раза. Толщина слизистой оболочки составила 87,42% от нормы. Длина ворсинок уменьшилась в 1,41 раза по сравнению с интактными животными, а их толщина увеличилась до 68,3±3,9 мкм. Отмечалось существенное снижение высоты покровных эпителиальных клеток и увеличение диаметра их ядер, что приводило к нарушению ядерно-цитоплазматических соотношений в исследуемых структурах (увеличение их, более чем в 1,15 раза). Изменения последнего параметра свидетельствовало о напряжении и нестабильности структурного гомеостаза на клеточном уровне [17]. Такие изменения приводят к нарушению процессов всасывания и требуют эвакуации содержимого ТК.

Таким образом, приведенные данные экспериментальных исследований указывают на необходимость декомпрессии ТК у больных с ОНТК.

На необходимость использования декомпресии ТК указывает и проведенный нами ретроспективный анализ историй болезней умерших пациентов с ОНТК. Так, при выполнении первичной операции у умерших пациентов при наличии показаний к интубации ТК, последняя была выполнена в 60,71% случаев и в 50,0% случаев при релапаротомии. Причиной смерти в 80,0% случаев был синдром полиорганной недостаточности, который развивался в I-III сутки после операции за счет прогрессирования интоксикации вследствие функциональной непроходимости ТК, что приводило к появлению энтеральной недостаточности и развитию этого патологического симптомокомплекса.

Еще в 1989 году В.Т.Зайцев и соавт. [9] четко сформулировали требования к методам декомпрессии ТК, главным из которых является максимально полное освобождение кишки от ее содержимого.

Известно, что достаточно эффективным способом декомпрессии ТК является назогастроинтестинальная интубация (НГИИ) [8,15,16,19]. Некоторые авторы более категорично отмечают, что методом выбора декомпрессии желудочно-кишечного тракта при острой хирургической патологии органов брюшной полости является только НГИИ [6]. В тоже время, другие авторы указывают на то, что этот вид декомпрессии пищеварительного тракта способствует развитию пневмонии и дыхательной недостатности, приводит к увеличению времени пребывания больных в стационаре [20,21].

Проблемы, которые возникают при проведении

НГИИ могут быть во время операции и в послеоперационном периоде. В первом случае это - недостаточная длина интубационного зонда (ИЗ), что приводит к неполноценной декомпрессии ТК; спазмированный кишечник вызывает трудности при проведении ИЗ и увеличивает травматизацию этого органа; невозможность проведения ИЗ через желудок, двенадцатиперстную кишку и дуоденоеюнальный переход вследствие их анатомо-физиологических особенностей в конкретном случае или ввиду наличия спаечного процесса. После операции это - неэффективность декомпрессии ТК, нарушение функции внешнего дыхания, аспирация кишечного содержимого и возникновение явлений ринита, ларингита, эзофагита, пневмонии. Кроме этого, могут возникнуть трудности при удалении ИЗ из пищеварительного тракта. Неэффективность декомпрессии ТК в послеоперационном периоде приводит к неполной эвакуации кишечного содержимого, что поддерживает интоксикацию организма больного и усугубляет течение заболевания. Кроме того, при недостаточной длине ИЗ может возникнуть рецидив спаечной ОНТК.

Приводим рентгенограммы органов брюшной полости после хирургического лечения ОНТК и использования неэффективной интубации желудочно-кишечного тракта (рис. 1, 2).

Выполнение во время операции неэффективной НГИИ при ОНТК может быть одной из причин неудовлетворительных результатов лечения этих пациентов.

Клиническими исследованиями установлена целесообразная этапность в проведении операции с использованием интубации ТК. Так, у больных ОНТК I-II стадии заболевания порядок операции следующий: лапаротомия, интубация ТК, ликвидация непроходимости, промывание и дренирование брюшной полости (по показаниям), один из способов завершения операции. У пациентов с III стадией, которая сопровождается перитонитом - лапаротомия, ликвидация источника перитонита, интубация ТК, дренирование брюшной полости также один из способов завершения операции. Такая последовательность операции у больных ОНТК объясняется необходимостью защиты организма от возможного всасывания токсинов, микроорганизмов через стенку ТК в кровоток при устранении причины этой патологии и для уменьшения травматизации пищеварительной трубки во время устранения причины непроходимости.

Обязательным моментом перед выполнением интубации ТК является проведение блокады корня брыжейки ТК раствором новокаина или введение анестетика в катетер при наличии предварительной катетеризации эпидурального пространства, или предупреждения анестезиолога о начале интубации ТК для возможного углубления уровня наркоза. На необходимость выполнения этого мероприятия указывают полученные нами данные динамики гемодинамических показателей. При невыполнении указанных мероприятий величина систолического артериального давления снижалась в среднем на 20-25 мм рт. ст., а частота пульса увеличивалась на 10-15 ударов в минуту.

Нами экспериментально и клинически [3] подтверждена необходимость раздельной декомпрессии желудка и ТК. Установлено, что пассивная эвакуация кишечного содержимого проходит по типу каскада и при наличии отверстий в ИЗ на уровне полости желудка, часть кишечного содержимого попадает в последний, что отрицательно влияет не только на функциональное состояние желудка, но и на организм пациєнта в целом, вызывая различные осложнения (тошноту, рвоту), увеличивая уровень эндогенной интоксикации.

Для декомпрессии ТК использован ИЗ трех модификаций в зависимости от возложенных на его первоочередных функций.

Первый вариант (n=32) - при значительно раздутых и переполненных жидкостным содержимым

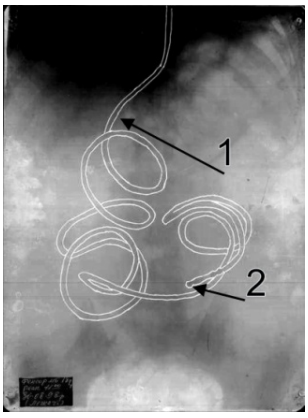

Рис. 1. Обзорная рентгенограмма органов брюшной полости. Тотальная интубация ТК назогастроинтестинальным зондом (1) у больного с ОНТК. Отхождение дистального конца интубационного зонда (2) от илеоцекального сегмента пищеварительного канала

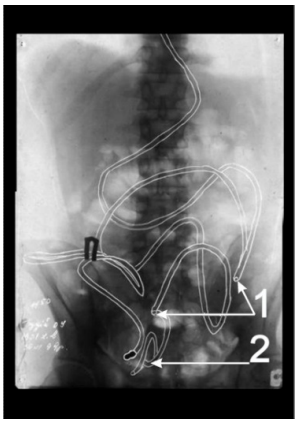

Рис. 2. Обзорная рентгенограмма органов брюшной полости у больного после тотальной назогастроинтестинальной интубации ТК. Наблюдается перегиб (1), узлообразование и перекручивание интубационной трубки (2)

петель ТК, что вызывает необходимость одновременного проведения эвакуации его и интубации ТК. Для этого использовали ИЗ и проводник для него. Последний представляет собой ПХВ трубку, диаметр которой больше интубационного зонда, в просвет которой вводится обычная декомпрессионная трубка. Проводник позволяет без труда проходить через пилорический сфинктер в двенадцатиперстную кишку и, в отдельных случаях, даже через дуоденоеюнальний переход, при проведении одновременной эвакуации кишечного содержимого. Попадание кишечного содержимого в трахеобронхиальное дерево во время выполнения интубации не наблюдалось.

Второй вариант (n=38). Петли ТК наполнены кишечным содержимым умеренно, что не вызывает срочной их эвакуации и выполнение интубации желудочно-кишечного тракта менее травматично. Для этого используется обычный, изготовленный в медицинской промышленности зонд с 2-3 баллончиками на дистальном его конце, которые наполняются воздухом при проведении ИЗ.

Третий вариант (n=28), когда петли ТК не переполнены кишечным содержимым и интубация ТК необходима в первую очередь для создания каркасного положения пищеварительного канала и ее фиксации в положении проходимости, что требует длительного нахождения ИЗ в просвете органа и в то же время, проведения декомпрессии ТК в послеоперационном периоде. В таких случаях нами предложен зонд для интубации кишки [11] (Рис.3).

Зонд выполнен из двух взаимоподвижных элементов, из которых внешний представлен эластической силиконовой трубкой (1) с боковыми отверстиями (2), дистальный конец которой заглушен оливкой (3). а внутренний - в виде стальной пружины (4), внутри которой проведен стальной тросик-стяжка (5).

Зонд для интубации кишки работает следующим образом: перед использованием взаемоподвижные элементы, а именно эластическую силиконовую трубку (1) и внутренний элемент - стальную пружину (4) со стальным тросиком-стяжкой (5) собирают в единую конструкцию. Во время хирургической операции при выполнении интубации кишки зонд с оливкой (3) на дистальном конце вводят через ротовую полость, глотку и пищевод в пилорический отдел желудка. Благодаря упругим свойствам составляющих элементов, а именно эластической силиконовой трубки (1) и стальной пружины (4) со стальным тросиком-стяжкой (5), свободно, без затруднений проходит пилорический отдел желудка, двенадцатиперстную кишку, дуоденоеюнальный переход. При этом заброса кишечного содержимого в глотку и пищевод не наблюдается благодаря тому, что внутренний элемент зонда - стальная пружина (4) перекрывает при интубации пищеварительной трубки просвет эластичной силиконовой трубки. После окончания интубации указанный внутренний элемент удаляется из просвета эластической трубки (1), что позволяет использовать зонд для эвакуации кишечного содержимого в послеоперационном периоде. Предложенный зонд для интубации ТК апробирован в клинике у 28 больных с ОНТК. Во всех случаях клинический эффект был положительным и осложнений не наблюдалось.

Для увеличения эффективности использования ИЗ, на наш взгляд, необходимо проводить дополнительные действия во время операции и после хирургического вмешательства. Во время операции проводили промывание полости пищеварительного канала растворами, энтеросорбентами с последующей их эвакуацией вместе с кишечным содержимым для предупреждения всасывания токсических веществ; вводили энтерально кислород, воздух для уменьшения травматизации стенки ТК и облегчения проведения ИЗ. В послеоперационном периоде промывали полость ТК растворами энтеросорбентов, вводили кислород или воздух в полость для предупреждения бактериальной транслокации и для стимуляции двигательной активности этого органа по предложенной нами методике [2], а также под прикрытием ИЗ проводили раннее энтеральное питание.

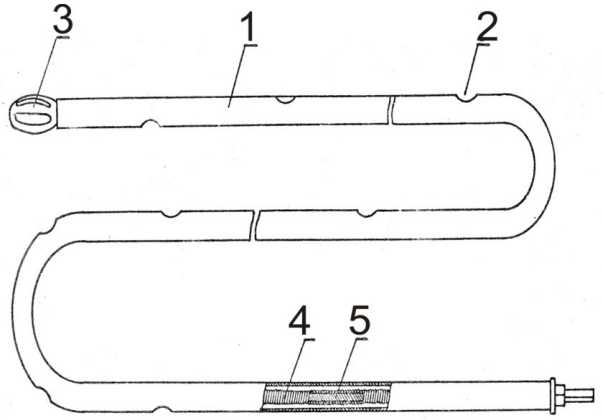

Рис. 3. Зонд для интубации кишки

Вышеописанное использование ИЗ при НГИИ позволяет более быстро нормализовать гомеостаз больного. Так, у пациентов с ОНТК, у которых проводилась только декомпрессия ТК, величина ЛИИ составляла 2,08±0,03 ед., креатинина - 108,52±1,79 мкмоль/л, мочевины - 7,82±0,14 ммоль/л, тогда как у больных с аналогичной патологией с использованием дополнительных мероприятий эти показатели были, соответственно, следующие: 0,74±0,01 ед., 85,12±1,38 мкмоль/л, 5,52±0,09 ммоль/л. При изучении показателей неспецифической резистентности организма выявлена стойкая тенденция к их улучшению, соответственно, с 1,78±0,11 ед. до 0,68±0,09 ед. Все это приводило к более быстрому восстановлению перистальтики ТК (почти в 1,5 раза), а также более раннему отхождению газов и появлению стула (в 1,3 раза), что позволяет уменьшить количество введений наркотических препаратов (почти в 2 раза) и сократить длительность применения ИЗ (в 1,4 раза) и уменьшить сроки стационарного лечения больных после операции на 3-4 сутки.

Таким образом, декомпрессия ТК является одним из значимых этапов оперативного вмешательства у больных с ОНТК. Выбор способа интубации желудочно-кишечного тракта зависит от конкретной хирургической ситуации, состояния больного, следует также отметить, что НГИИ не является абсолютно безупречным методом. Более эффективное использование ИЗ во время операции и в послеоперационном периоде улучшает результаты хирургического лечения пациентов с ОНТК.

Данные литературы [8] свидетельствуют о случаях неэффективного дренирования ТК этим методом в послеоперационном периоде, а результаты исследований группы авторов [13] указывают, что к использованию НГИИ следует относиться «... с осторожностью ... и строгих показаний к ее выполнению нет».

Мы согласны с мнением Г. Мондора [14] о том, что придерживаться одной клинической схемы, это значит обречь себя во многих случаях на ошибки и поэтому выбор способа интубации ТК должен быть с учетом не только диагноза и изменений в этом органе, но и с имеющейся конкретной интраоперационной ситуацией. Варианты способов декомпрессии желудочно-кишечного тракта больных ОНТК приведены на Рис. 4.

У 22 (11,22%) больных нами использована одномоментная декомпрессия пищеварительного тракта во время операции с помощью НГИИ, или через энтеротомическое отверстие в ТК. После эвакуации кишечного содержимого ИЗ было забрано.

Наличие декомпенсированной сопутствующей сердечно-легочной патологии у больных, неэффективность декомпрессии ТК и технические трудности в выполнении НГИИ, требуют от хирурга использование «открытых» методов декомпрессии желудочно-кишечного тракта.

Учитывая наш опыт лечения больных ОНТК мы предлагаем следующий алгоритм выбора способа интубации ТК при имеющихся абсолютных показаниях к ней (Рис. 4).

Особое значение приобретает декомпрессия ТК при релапаротомии и неэффективности НГИИ. В группе умерших больных у 3 пациентов во время релапаротомии для декомпрессии ТК была использована концевая энтеростома.

В 5 случаях при оперативном вмешательстве нами использован предложенный способ энтеростомии [17], с помощью которой проведена адекватная декомпрессия ТК (Рис. 5)

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Способ заключается в том, что дренирующую трубку вводят в петлю ТК через сформированный перед тем и подшитый к брюшной стенки анастомоз по Брауну. Способ энтеростомии осуществляют следующим образом. Необходимую петлю ТК соединяют между собой серозо-серозными швами на расстоянии 6-8 см в виде двустволки. Производят на них два параллельных разреза длиной до 4 см. В необходимом для декомпрессии направлении в ТК вводят дренирующую трубку на необходимое расстояние. Дистальный конец этой трубки погружают между анастомозирующими участками тонкой кишки с помощью серо-серозных

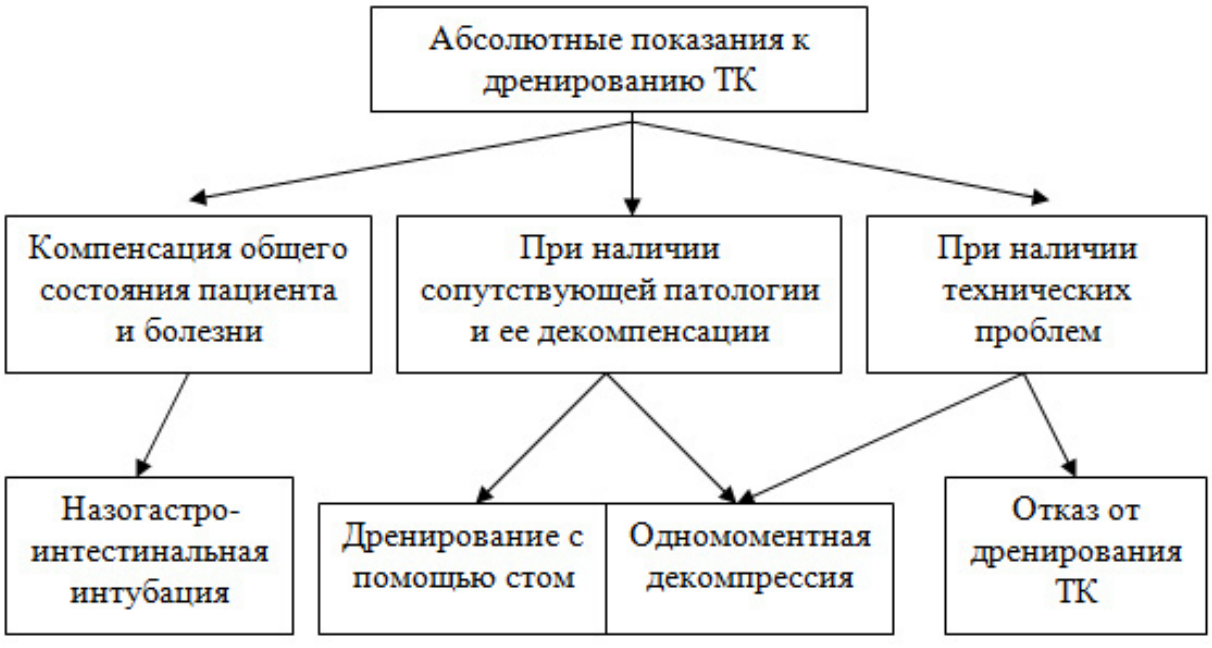
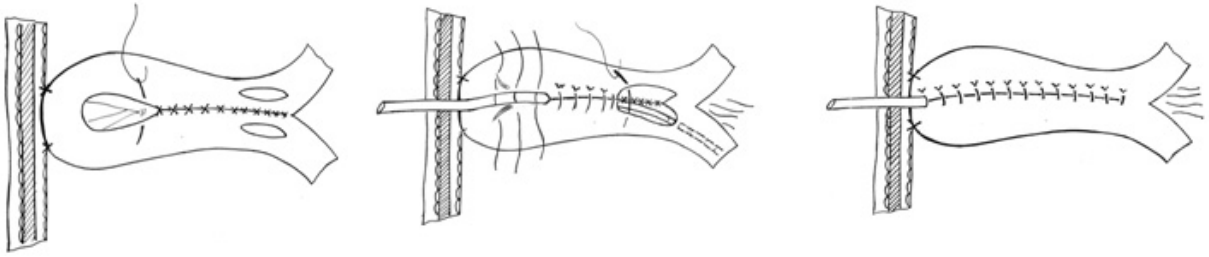


Рис. 4. Алгоритм выбора способа интубации ТК у больных с ОНТК



а б в

Рис. 5. Схематическое изображение предложенной энтеростомы

узловых швов (Рис. 5а,б), и в области энтеротомии накладывают энтеро-энтероанастомоз. «Слепой» конец этой петли подшивают к париетальной брюшине с помощью узловых швов (Рис. 5в). Подтеков кишечного содержимого не наблюдалось. Нарушений пассажа кишечного содержимого не обнаружено.

У одного больного во время релапаротомии выявлена недостаточность тонко-тонкокишечного анастомоза с развитием распространенного перитонита. Наложение кишечного анастомоза не представлялось возможным. На переднюю брюшную стенку выведены проксимальный и дистальный отрезки ТК с декомпрессией приводящей петли.

У больных ОНТК с благоприятным течением заболевания во время операции использованы следующие методы декомпрессии ТК: одномоментная декомпрессия с помощью НГИИ или через энтеротомическое отверстие в ТК с последующим ее ушиванием и длительная декомпрессия - с помощью НГИИ, конечной энтеростомы или с помощью энтеростомы по предложенной нами методике, или с помощью двудольной энтеростомы. Методы открытой декомпрессии ТК использовались нами у ослабленных больных во время релапаротомии в условиях глубокого пареза кишечника и перитоните, и при неэффективности НГИИ. Открытые способы декомпрессии ТК являются лечебными методами, которые показаны небольшому числу пациентов с ОНТК. Они относятся к «тяжелому вооружению» в арсенале хирурга, занимающегося лечением абдоминальных катастроф.

Выводы:

1. Интубация тонкой кишки является одним из значимых этапов оперативного вмешательства у больных острой абдоминальной патологией, особенно у больных острой непроходимостью тонкой кишки.
2. Выбор способа интубации желудочно-кишечного тракта зависит от конкретной хирургической ситуации, состояния больного следует учитывать, что и назогастроинтестинальная интубация не является абсолютно безупречным методом.
3. Использование декомпрессии тонкой кишки у больных с острой ее непроходимостью во время операции и в послеоперационном периоде улучшает результаты хирургического лечения таких пациентов.

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SUMMARY

ABOUT THE ROLE OF DIGESTIVE TRACT DECOMPRESSION IN PATIENTS WITH ACUTE BOWEL OBSTRUCTION. MISTAKES, COMPLICATIONS AND THEIR PREVENTION

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The purpose of the work is improvement in treatment of patients with acute small bowel obstruction by justification for gastrointestinal decompression and different methods of small intestine intubation for effective evacuation of itscontents.

We conducted morphological and morphometric study of the small intestine in 53 white rats. It was established that acute small bowel obstruction causes expansion of all parts of small bowel microvasculature with significant lesions of venous structures. We revealed thinning of intestinal muscular layer 2.15 timesand increase of submucosallayer 1.65 times. Changesin nuclear/cytoplasmic ratioof these structures showed tension and instability in structural homeostasis at cellular level. These changes lead to malabsorption and require evacuation of intestinal pathological contents.

We analyzed 30 medical records of patients who died from acute small bowel obstruction. Decompression was performed only in 60.71% ofall cases and in 50.0% of re-laparotomy cases. The cause of death in 80.0% was syndrome of multiple organ failure due to progressiveintoxication caused by functional obstruction of the small intestine.

196 patients were operated. In 50% of cases nasointestinal intubation was used for small bowel decompression, in 11.22% - intraoperative one-stage evacuation of intestinal contents and in 3.57% - “open” methods of intestinal drainage. We drew attention to problems and errorsin performingsmall bowel intubation. We offered some variants of intubation using different probes according to the operating situation and aim of intubation. Design of probe for intubation and method of enterostomy was suggested. We also offered an algorithm for selectionof small intestinal decompression method in patients with acute small bowel obstruction depending on the operating situation.

We emphasizethat intestinal decompression in patients with acute small bowel obstruction improves the results of surgery.

Keywords: acute bowel obstruction, decompression of the digestive tract.

РЕЗЮМЕ

РОЛЬ ДЕКОМПРЕССИИ ПИЩЕВАРИТЕЛЬНОГО ТРАКТА У БОЛЬНЫХ ОСТРОЙ НЕПРОХОДИМОСТЬЮ ТОНКОЙ КИШКИ. ОШИБКИ, ОСЛОЖНЕНИЯ И ИХ ПРЕДУПРЕЖДЕНИЕ

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Целью исследования явилось улучшение результатов лечения больных острой непроходимостью тонкой кишки путем обоснования необходимости декомпрессии пищеварительного тракта и сравнительная оценка эффективности использования различных методов интубации тонкой кишки.

Проведены морфологические и морфометрические исследования тонкоц кишки (ТК) на 53 белых крысах. Установлено, что острая непроходимость тонкой кишки (ОНТК) вызывает расширение всех звеньев микроциркуляторного русла ТК с существенным поражением венозных структур. Выявлено истончение мышечного слоя стенки ТК в 2,15 раза, увеличение

подслизистого слоя в 1,65 раза. Выявленные изменения ядерно-цитоплазматических соотношений в исследуемых структурах свидетельствуют о напряжении и нестабильности структурного гомеостаза на клеточном уровне, приводящие к нарушению процессов всасывания и требующие эвакуации патологического содержимого из ТК.

Параллельно проведен анализ 30 медицинских карт умерших пациентов с ОНТК. Декомпрессия была выполнена в 18 (60,71%) случаях при первичном хирургическом вмешательстве и в 15 (50,0%) - при релапаротомии. Причиной смерти 24 (80,0%) больных явился синдром полиорганной недостаточности ввиду прогрессирования интоксикации вследствие функциональной непроходимости ТК.

Операция выполнена 196 больным. В 98 (50%) случаях для декомпрессии ТК у них использована назогастроинтестинальная интубация, в 22 (11,22%) - интраоперационная одномоментная эвакуация кишечного содержимого, в 7 (3,57%) использованы «открытые» методы дренирования ТК. Заслуживают внимания ошибки, допущенные при выполнении интубации ТК. Предложены варианты использования различных зондов для интубации в зависимости от операционной ситуации и цели интубации. Описаны конструкция зонда для интубации и способ энтеростомы. Предложен алгоритм выбора декомпрессии ТК у больных ОНТК в зависимости от операционной ситуации.

Анализ полученных в результате исследования данных позволяет заключить, что использование декомпрессии ТК у больных ОНТК способствует улучшению результатов их хирургического лечения.

რეზიუმე

საჭმლის მომნელებელი ტრაქტის დეკომპრესიის როლი ავადმყოფებში ვრილი ნაწლავის მწვავე გაუვალობით: შეცდომები,გართულებები და მათი პრევენცია

ვ. ბენედიქტი

უკრაინის უმაღლესი სახელმწიფო საგანმანათლებლო დაწესებულება - უკრაინის ჯანდაცვის სამინისტროს ი. გორბაჩევსკის სახ. ტერნოპოლის სახელმწიფო სამედიცინო უნივერსტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა ვრილი ნაწლავის მწვავე გაუვალობით (ვნმგ) ავადმყოფების მკურნალობის შედეგების გაუმჯობესება საჭმლის მომნელებელი ტრაქტის დეკომპრესიის აუცილებლობის დასაბუთების გზით და ვრილი ნაწლავის (ვნ) ინტუბაციის სხვადასხვა მეთოდის გამოყენება ნაწლავის შიგთავსის ეფექტური ევაკუაციის მიღწევისათვის.

ჩატარდა 53 თეთრი ვირთაგვას ვნ-ის მორფოლოგიური და მორფომეტრიული კვლევა. დადგენილია, რომ ვნმგ იწვევს ვნ-ის მიკროცირკულაციური კალაპოტის ყველა რგოლის გაფართოებას, ვენური სტრუქტურების მნიშვნელოვანი დაზიანებით. გამოვლინდა ვნ-ის კედლის კუნთოვანი შრის გათხელება 2,15-ჯერ და ლორწოვანი გარსის მომატება 1,65-ჯერ. საკვლევ სტრუქტურებში ბირთვულ-ციტოპლაზმური თანაფარდობის გამოვლენილი ცვლილებები მოწმობს სტრუქტურული ჰომეოსტაზის დაძაბვასა და არასტაბილობას უჯრედულ დონეზე, რასაც შეწოვის დარღვევა მოსდევს და რაც მოითხოვს პათოლოგიური შიგთავსის ევაკუაციას ვნ-დან.

ზემოაღნიშნული ექსპერიმენტის პარალელურად, ჩატარდა ვნ-ის მწვავე გაუვალობით გარდაცვლილი 30 ავადმყოფის სამედიცინო ბარათების ანალიზი. დადგინდა, რომ დეკომპრესია პირველადი ქირურგიული ჩარევის დროს ჩატარებული ჰქონდა 18 (60,71%) პაციენტს, 15 (50%) კი – რელაპარატომიის დროს. 24 (80%) შემთხვევაში ავადმყოფის სიკვდილის მიზეზს წარმოადგენდა პოლიორგანული უკმარისობის სინდრომი, განვითარებული ინტოქსიკაციის პროგრესირებით გამოწვეული ვნ-ის ფუნქციური გაუვალობით.

ოპერაცია ჩაუტარდა 196 ავადმყოფს. 98 (50%) შემთხვევაში ვნ-ის დეკომპრესიისათვის გამოყენებული იყო ნაზოგასტროინტენსტინური ინტუბაცია, 22 (11,2%) შემთხვევაში - ნაწლავის შიგთავსის ინტრაოპერაციული ერთმომენტიანი ევაკუაცია, 7 (3,57%) შემთხვევაში - ვნ-ის დრენირების ღია მეთოდები. განსაკუთრებულ ყურადღებას იქცევს ვნ-ის ინტუბაციისას დაშვებული შეცდომები და პრობლემები. ოპერაციული სიტუაციისა და ინტუბაციის მიზნის შესაბამისად, მოწოდებულია საინტუბაციო ზონდების სხვადასხვა ვარიანტები. აღწერილია საინტუბაციო ზონდის კონსტრუქცია და ენტეროსტომის მეთოდი. ოპერაციული სიტუაციის გათვალისწინებით, შემოთავაზებულია ვნ-ის დეკომპრესიის შერჩევის ალგორითმი ვნმგ-ის დროს.

კვლევის შედეგად მიღებულ მონაცემებზე დაყრდნობით, სტატიის ავტორები დაასკვნიან, რომ ვნ-ის მწვავე გაუვალობით ავადმყოფებში ვნ-ის დეკომპრესიის გამოყენება აუმჯობესებს ქირურგიული მკურნალობის შედეგებს.

ПАТОМОРФОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ ПРИ ЛАТЕНТНОМ МАСТОИДИТЕ

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Многие заболевания, в том числе и острый мастоидит, претерпели патоморфоз, вследствие чего усложнилась его диагностика, изменилось течение. Четко выраженный характерный сиптомокомплекс острого мастоидита (боль в ухе, гиперемия заушной области, выпуклость, выделение гноя из уха, понижение слуха) в некоторых случаях отсутствуют, протекая в скрытой форме. В течение периода от нескольких месяцев до нескольких лет заболевание может протекать латентно, без видимой кинической картины, и, в итоге, проявиться в виде внутричерепных осложнений, таких, как: отогенный менингит, сепсис, необратимое ухудшение слуха, периферический парез лицевого нерва, а также тромбоз сигмовидного синуса и абсцесс головного мозга. Вышеизложенное обусловило необходимость систематизации и определения нового названия данного заболевания. В конце двадцатого и начале двадцать первого века в литературных источниках встречается термин латентного, т.е. замаскированного мастоидита, который, в отличие от классической (типичной) формы острого мастоидита, от нескольких месяцев до нескольких лет, протекает без явных клинических симптомов: заболевание проявляется в виде ухудшения слуха, головных болей, головокружения, что, в свою очередь, приводит к переадресации пациента в неврологическую клинику.

Латентный мастоидит является особой клинической формой осложненного острого мастоидита со спорной тактикой лечения; тактика лечения которого по сей день остается предметом дискуссии [2,6,9,11]. Считаем, что это положение вызвано отсутствием точных данных о сущности патологического процесса, его распространении и характером морфологических изменений у больных данного контингента [1,7,14].

Лечение латентного мастоидита - хирургическое, что обусловлено запоздалым обращением пациентов к оториноларингологу. Форма и объем хирургического вмешательства при данном заболевании является предметом дискуссии среди специалистов.

Исходя из вышеназванных обстоятельств, целью данного исследования явилось изучение структурных изменений в мягких, твердых и костных тканях различных полостей среднего уха, в частности адитоантральной и аттической областей у пациентов с латентным мастоидитом, которым проведено хирургическое лечение.

Материал и методы. Морфологическое исследование выполнено в Научно-практическом центре клинической патологии на базе департамента патологии медицинского факультета Тбилисского государственного университета им. И. Джавахишвили. Изучен материал, полученный в ходе хирургического вмешательства от 134 пациентов, которые проходили лечение в Университетской клинике им. С. Хечинашвили по поводу латентного мастоидита в период 2005-2016 гг. Операционный материал исследован методами гистологии.

Мягкие ткани после фиксации в 10% растворе формалина и соответствующей обработки заключали в парафин. Костную ткань подвергали декальцинации в 15-20% растворе азотной кислоты (HNO_3). Срезы мягких и костных тканей толщиной 5-6 мкм окрашивали гематоксилином и эозином (H&E).

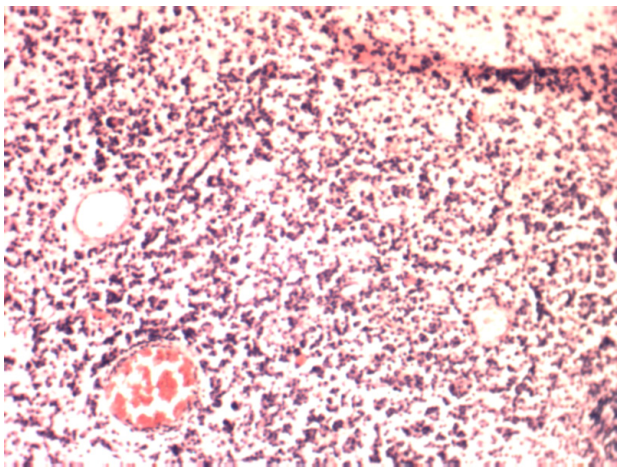

Рис. 1. Визуализируется воспалительный инфильтрат. Окр. гематоксилином и эозином. 200X

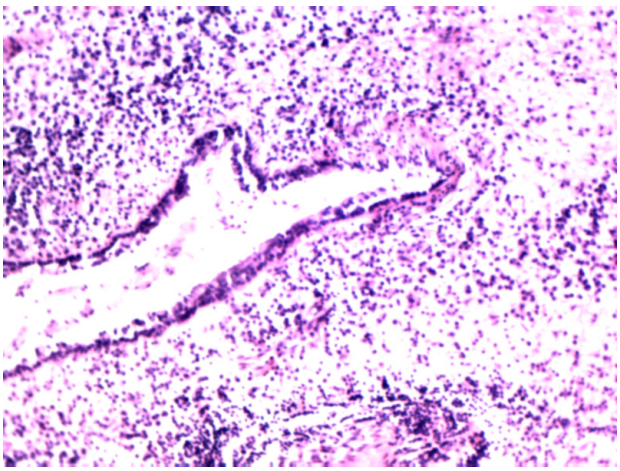

Рис. 2. Кистозная трансформация железы из той же области (рис 1). Окр. гематоксилином и эозином. 200Xt

Результаты и их обсуждение. По результатам микроскопического исследования как в слизистой, так и в костной ткани образцов обнаружены воспалительно-деструктивные изменения, серозно-фиброзное воспаление, значительный отек. Сдвиги особенно выражены в мукопериальной зоне, т.е. недалеко от антрума и костной ткани аддитуса. В воспалительном инфильтрате обнаружены клетки мононуклеарного ряда, прежде всего, лимфоциты, плазмоциты и макрофаги. Кроме того, встречаются сегментоядерные лейкоциты, расположенные вокруг кровеносных сосудов. Привлекают внимание узловатые образования разной формы и размеров, часть которых кистозно расширена (рис. 1,2).

Морфологические изменения костной ткани слизистой сосцевидного отростка и в адито-антральной и аттической областях среднего уха зависят от продолжительности и сложности протекания латентного мастоидита. Структурные изменения в костной ткани, по всей вероятности, являются результатом распространения воспалительного процесса со стороны слизистой оболочки. Эти изменения характеризуются полиморфизмом и кариесным характером. Костные трабекулы окружены остеокластами и воспалительным инфильтратом, т.е. представлена картина остита. Привлекает внимание деструкция костной ткани с неровными краями (рис. 3). В ряде случаев поражение костной ткани можно квалифицировать как изменения, характерные для остеомиелита.

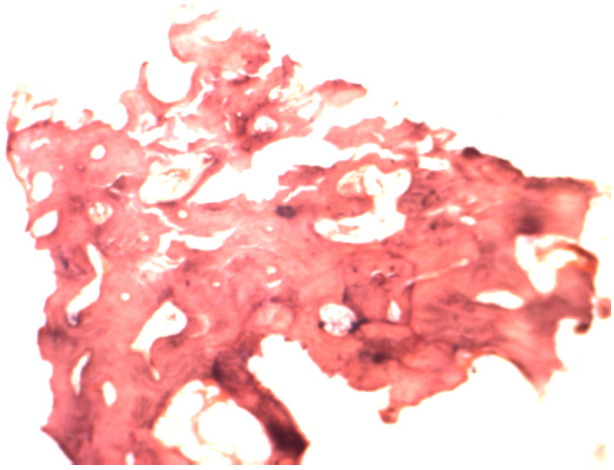

Рис. 3. Деструкция костной ткани сосцевидного отростка. Окр. гематоксилином и эозином. 200Х

Заключение. В настоящее время хирургическое лечение латентного мастоидита становиться более актуальным ввиду высокого риска внутричерепных осложнений [3,8,10,13,16]. Своевременная диагностика и целенаправленное вмешательство являются приоритетными задачами медицины [4,5,12,15,17], данные морфологического исследования могут быть основой для достижения оптимального результата.

Таким образом, данные, полученные в результате исследования хирургического материала, позволяют заключить, что радикальное лечение латентного мастоидита, как правило, должно быть хирургическим, необходимо полное иссечение не только грануляционных тканей, но и поврежденной костной массы. Хирургическая тактика, со своей стороны, зависит от распространения и характера узурпации ткани. В противном случае персистенция воспаления и деструкции послужат развитию необратимых последующих осложнений.

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SUMMARY

PATHOMORPHOLOGICAL CHANGES UNDER LATENT MASTOIDITIS

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In our opinion it is caused by incomplete awareness of the distribution of pathological process and the character of morphological changes in the patients. In this regard, we studied structural changes in the soft and bone tissue taken from various cavities of the middle ear system.

Operating material was formed in paraffin after the fixation and proper processing. We proceed with decalcification of bone tissues in 15-20% nitric acid. We painted 5-6 mm thick peels prepared on the rotating microtome with hematoxylin and eosin. The microscopic examination revealed inflammatory-destructive changes in the mucous membrane as well as in the bone tissues, also serous inflammation-fibrin inflammation, and well-expressed edema. The inflammatory infiltration demonstrated the presence of lymphocytes, macrophages, plasmocytes and also predominantly dislocated leukocytes. There were also revealed various amount of glandular structures. The bone tissues - along with the inflammatory infiltration - revealed destructive cells, which contained osteoclast, epithelial cells and fibroblasts. The mentioned structural changes should be assessed as demonstration of an osteitis and osteomyelitis.

Based on the above mentioned, we believe that treatment of latent mastoiditis requires surgical method and it is necessary the complete sanitization of not only the granulating tissue but the damaged bone masses. Otherwise, the remaining inflammatory nidus may cause a relapse. The correct treatment of latent mastoiditis in turn will reduce the mortality rate and the percentage of disability.

Keywords: Mastoiditis, masket mastoiditis, latent mastoiditis, meningitis, chronic suppurative inflammation of the middle ear, serous inflammation of the middle ear.

РЕЗЮМЕ

ПАТОМОРФОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ ПРИ ЛАТЕНТНОМ МАСТОИДИТЕ

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Целью данного исследования явилось изучение структурных изменений в мягких и костных тканях различных полостей среднего уха, в частности адитоантральной и аттической областей у пациентов с латентным мастоидитом, подвергшихся хирургическому лечению.

Морфологическое исследование выполнено в Научно-практическом центре клинической патологии на базе департамента патологии медицинского факультета Тбилисского государственного университета им. И. Джавахишвили. Исследованы тканевые образцы от 134 пациентов, которым проведено хирургическое лечение в Университетской клинике им. С. Хечинашвили по поводу латентного мастоидита в период 2005-2016 гг. После фиксации и соответствующей обработки материал заключали в парафин. Декальцинация костной ткани осуществлялась в 15-20% растворе азотной кислоты. Срезы толщиной 5-6 мкм, подготовленные на ротационном микротоме, окрашивали гематоксилином и эозином.

По результатам микроскопического исследования как в слизистой оболочке, так и в костных тканях, выявлены воспалительно-деструктивные изменения, серозно-фибринозное воспаление, хорошо выраженный отек. В воспалительном инфильтрате наблюдались лимфоциты, макрофаги, плазмоциты, а также преимущественно периваскулярно расположенные лейкоциты. Dыявлены железистые структуры в различных количествах. Наряду с воспалительным инфильтратом в костных тканях обнаружены деструктивные очаги с наличием в них остеокластов, эпителиоидных клеток и фибробластов. Вышеуказанные структурные изменения должны оцениваться как проявления отита и остеомиелита.

Исходя из вышеизложенного, считаем, что латентный мастоидит необходимо лечить хирургическим методом; при этом необходима полная санация не только грануляционной ткани, но и поврежденных костных масс. В противном случае, остаточный воспалительный очаг станет причиной рецидивов. Адекватное лечение латентного мастоидита обеспечивает снижение показателя смертности и процентного коэффициента инвалидности.

რეზიუმე

პათომორფოლოგიური ცვლილებები ლატენტური მასტოიდიტის დროს

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კვლევის მიზანს წარმოადგენდა სტრუქტურული ცვლილებების შეფასება შუა ყურის სისტემის სხვადასხვა ღრუდან აღებულ რბილ და ძვლის ქსოვილებში.

ოპერაციული მასალა, ფიქსაციისა და სათანადო დამუშავების შემდეგ, ყალიბდებოდა პარაფინში. ძვლოვანი ქსოვილის დეკალცინაცია ხორციელდებოდა 15-20%-ან აზოტმჟავაში; როტაციულ მიკროტომზე მომზადებული 5-6 მკმ სისქის ანათლების შეღებვა ხდებოდა ჰემატოქსილინითა და ეოზინით.

მიკროსკოპული კვლევით როგორც ლორწოვან გარსში,ისე ძვლის ქსოვილში გამოვლინდა ანთებით-დესტრუქციული ცვლილებები, სეროზულ-ფიბრინოზული ანთება,კარგად გამოხატული შეშუპება. ანთებით ინფილტრატში აღინიშნა ლიმფოციტები,მაკროფაგები,პლაზმოციტები,ასევე, უპირატესად პერივასკულურად განლაგებული ლეიკოციტები. გამოვლინდა,აგრეთვე,სხვადასხვა რაოდენობის ჯირკვლოვანი სტრუქტურები. ძვლის ქსოვილებში, ანთებით ინფილტრატთან ერთად, გამოვლინდა დესტრუქციული კერები, მასში ოსტეოკლასტების, ეპითელოიდური უჯრედების და ფიბრობლასტების არსებობით. აღნიშნული სტრუქტურული ცვლილებები შეფასდა როგორც ოტიტისა და ოსტეომიელიტის გამოვლინება.

სტატიის ავტორებს მიაჩნია,რომ ლატენტური მასტოიდიტის მკურნალობა აუცილებელია ქირურგიული მეთოდით; ამასთან, აუცილებელია არამარტო გრანულაციური ქსოვილის, არამედ დაზიანებული ძვლოვანი მასების სრული სანაცია. წინააღმდეგ შემთხვევაში, ნარჩენი ანთებითი კერა გახდება რეციდივის მიზეზი. ლატენტური მასტოიდიტის სწორი მკურნალობა უზრუნველყოფს სიკვდილობის და ინვალიდობის მაჩვენებელის შემცირებას.

CLINICAL AND GENETIC PECULIARITIES OF VASCULAR MANIFESTATIONS OF ANTIPHOSPHOLIPID SYNDROME (CASE REPORT)

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At the end of the last century a number of hereditary diseases were identified based on various hemostasis disorders. Exactly in relation to these states a relatively new term “thrombophilia” is being increasingly used lately [1]. According to the definition given by the British Committee on Hematology Standards in 1990, thrombophilia is a congenital or acquired hemostasis defect leading to a high degree of predisposition to thrombosis. Clinical guidelines for the detection of genetic forms of thrombophilia in the population as a whole are thromboses at a young age (up to 40-49 years), recurrent and causeless in nature, unusual localization of thromboses (mesenteric, cerebral vessels), the presence of a positive family thrombotic history, thrombosis after injury. Recent studies have shown that the presence of thrombophilia is associated with an increased risk of complications of pregnancy (habitual miscarriage, placental insufficiency, fetal growth delay, gestosis) [2-4].

In 1994, the international symposium on antiphospholipid disorders suggested using the term “Hughes syndrome” to describe a complex of symptoms including venous and / or arterial thromboses, various forms of obstetric pathology, thrombocytopenia, and a wide range of neurological, skin and cardiovascular disorders (named after English rheumatologist, who made the greatest contribution to the study of this problem). However, the abbreviation APS, which denotes the pathogenetic basis of this condition, is more popular all over the world. According to the definition, antiphospholipid syndrome (APS) is an autoimmune systemic disease with a wide range of predominantly thrombotic clinical manifestations against the background of increased production of antibodies to phospholipids. At present time, a number of scientists believe that APS is a model of acquired autoimmune disease and therefore refers to acquired thrombophilia [5,6], but is it so?

It has been stated that antiphospholipid antibodies (APL antibodies) are a heterogeneous group of antibodies to negatively charged phospholipids (including cardiolipin, phosphatidylserine, phosphatidylcholine, phosphatidylino-

sitol, phosphatidylethanolamine, phosphatidylglycerol), as well as to β2-glycoprotein-1 cofactor interacting with phospholipids and being a natural plasma anticoagulant and an inhibitor of thrombocytes' aggregation. It is believed that β2-glycoprotein-1 is the factor that mostly determines the pathogenicity of APL antibodies: the reaction of antibodies (the so-called «autoimmune» antibodies) to β2-glycoprotein-1 or the «β2-glycoprotein-1+ phospholipid» complex can lead to clinical (thrombotic) consequences. Due to the fact that recent scientific researches in the field of immunology have proved the fact of a genetic predisposition to the development of autoimmune disorders, APS, in the pathogenesis of which an infringement of the immune character plays an important role can be referred to a disease of genetic nature [7,10].

The basis of the pathogenesis of APS development is the persistent activation of the hemostatic system, caused by the intensification of thrombotic processes with simultaneous weakening of antithrombotic processes in the body, which inevitably leads to a relapse of thrombogenesis. Herewith, APL antibodies interacts with phospholipids forming the vascular and thrombocytes' endothelium, thereby provoking activation of thrombocytic cells, loss of antithrombogenic properties of the vascular endothelium and violation of fibrinolytic processes [16]. According to the pathogenetic theory [20], the symptoms of APS appear as a result of direct amplification of the processes of hypercoagulability under the influence of circulating APL antibodies («first stroke») with subsequent influence of local trigger mechanisms - factors of thrombogenesis inducing («second stroke»).

Depending on the method of detection, APL antibodies are conventionally divided into three groups: detectable with the help of immunoenzymatic methods using cardiolipin, less often than other phospholipids; antibodies detected by functional tests (lupus anticoagulant); antibodies that are not diagnosed by standard methods (antibodies to proteins C, S, thrombomodulin, heparin sulfate, endothelium, etc.). The clinical significance of APL-antibodies depends on whether their presence in blood serum is associated with the development of characteristic symptoms. Thus, APS manifestations are observed only in 30% of patients with positive lupus anticoagulant and in 30-50% of patients who have a moderate or high level of antibodies to cardiolipins. The disease develops mainly at young age, meanwhile APS can be diagnosed in children and even in newborns. Like other autoimmune rheumatic diseases, this complex of symptoms is more common for women than for men (5: 1 ratio) [11].

The true prevalence of APS in the population is still unknown. As the synthesis of APL antibodies is possible in the norm, a low level of antibodies is often found in the blood of healthy people. According to various data, the frequency of detection of antibodies to cardiolipins in the population varies from 0 to 14%, in average it is 2-4%, while high titers are found quite rarely (in about 0.2% of donors). APL antibodies are detected more often in the elderly, herewith the clinical significance of APL antibodies in «healthy» individuals (e.g., not having obvious symptoms of the disease) is not entirely clear. Often while repeating analyzes, the level of antibodies increased in previous determinations is normalized [17].

Fundamentally clinical and laboratory manifestations of APS are possible to represent as a result of the interaction of APL antibodies with antigens, on the basis of the patterns of distribution of negatively charged phospholipids in the body. The places of their maximum content are membranes of thrombocytes and endotheliocytes, phospholipids of prothrombin activating complex and β2-glycoprotein-1, cells of nervous tissue. Accordingly the main pathogenetic abnormalities at APS concern changes in the number (thrombocytopenia) and functional activity of thrombocytes (increasing of thromboxane A2 production and aggregation capacity), endothelial cells' properties (decreasing of prostacyclin synthesis, increasing production of thrombocytes activation and aggregation factors, endothelin-1, decreasing of antithrombogenic thrombomodulin protein activity, suppression of fibrinolytic factors), functions of responsible for hemostasis humoral agents (decreasing of protein C activation and protein S level, inhibition of β2-glycoprotein-1 and heparin activity and antithrombin III-heparin complex formation, inhibition of coagulation at the level of prothrombin activating complex), structural and functional disorders of the nervous tissue (direct damaging effect on neuronal and glial cells). The listed disorders are clinically realized in the form of the main APS complex of symptoms: recurrent arterial and venous thromboses, habitual miscarriages, skin livedo reticularis, central nervous system (CNS) lesion, thrombocytopenia [9].

The most severe and at the same time the most frequent clinical manifestations of antiphospholipid syndrome are vascular thromboses of different localization, the manifestations of which can be very different depending on the prevalence of the pathological process and the caliber of the affected vessel. In international surgical practice, there is an opinion that multiple vasculopathies of non-inflammatory nature develop at APS, accompanied by occlusion of the vessel's lumen [12].

As a rule the debut of thrombotic manifestations of APS is observed in the lesion of deep distal veins of the lower extremities, but in some cases there may be signs of the arterial bed lesion (loss of all types of sensitivities, skin cooling, skin and subcutaneous tissue trophic changes). When CNS structures are damaged due to ischemic disorders, neurologic manifestations of various degrees are observed - from transient ischemic attack to development of persistent neuropsychiatric symptoms of ischemic stroke; herewith thrombosis of the intracerebral arteries is the most frequent localization of arterial thrombosis at APS. It is considered that in women younger than 50 years the frequency of strokes associated with APL antibodies reaches 40% [14].

Venous thrombosis is the main manifestation of APS and occurs in 2 times more often than arterial. Thrombi

are usually localized in the deep veins of the lower extremities, but can also occur in the hepatic, axillary, subclavian, renal, superficial and others. Repeated embolisms from the deep veins of the lower extremities into the lungs are characterized, sometimes causing the development of pulmonary hypertension. It has been determined that APS is the second most frequent cause of development of the Budd-Chiari syndrome [18].

From the point of view of differential diagnosis, the presence of thrombotic complications can not be associated only with APS. Generally, only in 10% of patients with venous thrombosis in the population APL antibodies are revealed [15]. It is known that recurrent thromboses (venous mainly) can be caused by a hereditary deficiency of proteins C, S and antithrombin III. According to epidemiological studies, 12.9% of patients (of 2,132 examined) with venous thrombosis had different hereditary defects of natural anticoagulants (primarily protein S), and only in 4.1% APL antibodies were revealed. It is well known about the connection of recurrent thromboses with the presence of Leiden mutations in the of blood coagulation factor V gene and in the prothrombin gene [13].

Quite often several factors can play a role in the development of thrombotic complications in the same patient. For example, in patients with hereditary thrombophilias in half of the cases thrombotic complications are associated with such risk factors as obesity, surgical interventions, prolonged immobilization, pregnancy or oral contraceptives taking [21]. At the same time, it is necessary to note that the pathogenetic role of APL antibodies in thrombogenesis is mostly unclear. In particular, it is not clear which events trigger the thrombus formation, because the presence of APL antibodies alone can not induce clinically significant hemostasis disorders.

It is considered that APL antibodies create only a hypercoagulable background, and the thrombus formation occurs under the influence of other permissive procoagulation factors (obesity, smoking, pregnancy, etc.) [20]. It is very important to understand which genetic markers of thrombophilias are present in a particular patient with thrombosis as it reflects susceptibility of the estimated risk factor throughout the life of the patient better than the corresponding biochemical markers, whose rates may vary with time.

Despite the fact that nowadays due to numerous population studies the multifactoral character of thrombophilic conditions is shown, it is possible to allocate 3 groups of genetic disorders that determine the development of thrombosis and are included by the International Society for Thrombosis and Hemostasis in the panel of screening tests for hereditary thrombophilia: a deficiency of natural anticoagulants (protein C, protein S, antithrombin III), disorders in genes encoding blood coagulation factors (primarily factor V and prothrombin) and the enzymes of folate cycle participating in the processes of homocysteine remethylation and transsufurization (MTR, MTRR, MTHFR) [13,19]. But in practice, to determine the correct diagnosis of a specific nosological form of thrombophilia, it is often necessary to investigate other factors of hemostasis.

The increased risk of venous thromboembolism connected with the presence of a defective allele of the corresponding gene in the patient is proved for the hereditary deficiency of antithrombin III, protein C, protein S and factor V, which together are the reasons for more than 50% of cases of hereditary thrombophilias. Hereditary deficiencies of these proteins are revealed not only in people with thrombophilia as they can occur without clinical manifestations. These facts allow suggesting that a deficiency of only one protein is not always a sufficient condition for the development of thrombophilia and for the formation of the corresponding phenotype the involvement of other factors is necessary [19]. The combination of defects of listed factors is not uncommon, and usually such a compound is characterized by more severe clinical manifestations of thrombophilic conditions than single defects. In this case, the APL antibodies titers in the blood have the value.

According to the recommendations of the International Society of Thrombosis and Hemostasis [8], laboratory criteria for diagnosing APS are: 1) the presence of antibodies to cardiolipin IgG or IgM isotypes detecting in serum in medium or high titers at least 2 times for 12 weeks, with the help of a standardized enzyme-linked immunosorbent assay; 2) antibodies to β2-glycoprotein I IgG and / or IgM isotype, detecting in serum in medium or high titers, at least 2 times for 12 weeks, with the help of a standardized enzyme-linked immunosorbent assay; 3) lupus anticoagulant in plasma, in two or more cases of study with an interval of not less than 12 weeks.

Case report. We examined the patient P., born in 1987, who was observed in the department of acute vascular pathology of the Institute of General and Urgent Surgery of the NAMS of Ukraine named after V.T. Zaitsev" (SE "IGUS NAMSU") in connection with the carried unprovoked thrombosis of the deep veins of the lower extremities and pulmonary embolism of the pulmonary artery (PE). The patient was performed the thrombolytic therapy for PE with subsequent anticoagulant therapy. In order to clarify the pathogenetic cause of thrombosis, the patient underwent a complex examination for the presence of laboratory markers of thrombophilic conditions.

At a biochemical examination, moderate hyperhomocysteinemia was found - 16.01 μmol / L (at the age norm up to 15 μmol / L) and 3 laboratory APS markers: positive screening (126.2 sec at the norm 31.0-44.0) and confirming (48.2 seconds at the norm of 30.0-38.0) tests for lupus antibodies (LA-auto index 2.618 at the norm from 0.8 to 1.2), titers of IgG antibodies to cardiolipin and β2-glycoprotein I - more than 160 units / Ml (at the norm up to 20.0). To clarify the form of thrombophilia, a molecular PCR study was performed, which revealed heterozygous carriage of mutations in the F7 genes (blood clotting factor VII), serpine 1 (PAI-1), ITGB3-β-integrin and homozygous carriage of the A66G mutation in the MTRR gene (methionine-synthase reductase) of folate cycle.

To confirm the APS diagnosis in 12 weeks, the patient repeatedly underwent the biochemical examination, according to the results of which the homocysteine level was normalized to 14.77 μmol / l. However, the high titer of APL antibodies is preserved: screening (112.4 seconds at the norm 31.0-44.0) and confirming (42.5 seconds at the norm 30.0-38.0) tests for lupus antibodies (LA-auto index 2.645 at the norm from 0.8 to 1.2), titers of IgG antibodies to cardiolipin and β2-glycoprotein I - more than 160 U/ml (at the norm up to 20.0).

In the described clinical observation the presence of a genetic background in a male patient - the heterozygous carriage of mutations in the genes responsible for blood coagulation (F7, PAI-1 and ITGB3-β-integrin), as well as homozygous carriage of a mutation in the MTRR gene associated with a violation of homocysteine methylation, increased synthesis of APL antibodies led to the development of hypercoagulable syndrome and thrombosis processes at a young age. Timely diagnosis and individually developed pathogenetic therapy allowed avoiding life-threatening complications of APS, as well as improving the patient›s quality of life.

Conclusions:

1) APS is a model of an autoimmune thrombosis that occurs against the background of a particular primary disorder.
2) All patients of young age with unprovoked thrombosis of deep veins of lower extremities and PE are subjected to examination on APS and hereditary thrombophilias.

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SUMMARY

CLINICAL AND GENETIC PECULIARITIES OF VASCULAR MANIFESTATIONS OF ANTIPHOSPHOLIPID SYNDROME (CASE REPORT)

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Pathogenetic mechanisms of the development of antiphospholipid syndrome (APS) are considered in the article, which is the basis for the development of clinical manifestations and laboratory markers of APS. The modern literature data are analyzed, according to which the presence of antiphospholipid antibodies is a hypercoagulable background, and the formation of thrombi occurs under the influence of other allowing procoagulation factors. The classification of the main types of hereditary thrombophilia is given, which is the primary disorder, against the background of which an autoimmune thrombosis APS develops.

A clinical observation of a young age patient is given, whose heterozygous carriage of mutations in the genes responsible for blood coagulation (F7, PAI-1 and ITGB3-β-integrin), as well as homozygous carriage of a mutation in the MTRR gene associated with a violation of homocysteine methylation, APS was developed, which led to the processes of thrombosis. Timely diagnosis and individually developed pathogenetic therapy allow avoiding life-threatening complications of APS and improving the patients' quality of life. A conclusion about the need for APS and hereditary thrombophilias' examination to all patients of young age with unprovoked thrombosis of deep veins of lower extremities and PE was made.

Keywords: antiphospholipid syndrome, thrombogenesis, markers, diagnostics.

РЕЗЮМЕ

КЛИНИКО-ГЕНЕТИЧЕСКИЕ ОСОБЕННОСТИ СОСУДИСТЫХ ПРОЯВЛЕНИЙ АНТИФОСФОЛИПИДНОГО СИНДРОМА (СЛУЧАЙ ИЗ ПРАКТИКИ)

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В статье рассмотрены патогенетические механизмы развития антифосфолипидного синдрома (АФС), который является основой развития клинических проявлений и лабораторных маркеров АФС. Проанализированы современные данные литературы, согласно которым наличие антифосфолипидных антител является гиперкоагуляционным фоном, а формирование тромбов происходит под влиянием других разрешающих прокоагуляционных факторов. Приведена классификация основных видов наследственных тромбофилий, являющихся первичным нарушением, на фоне которых развивается аутоиммуннй тромбоз – АФС.

Описано клиническое наблюдение пациента молодого возраста, у которого на фоне гетерозиготного носительства мутаций в генах, отвечающих за свертывание крови (F7, PAI-1 и ITGB3-β-интегрин), а также гомозиготного носительства мутации в гене MTRR, ассоциированной с нарушением метилирования гомоцистеина, развился АФС, приведший к процессам тромбообразования. Своевременная постановка диагноза и индивидуально разработанная патогенетическая терапия позволяют избежать опасных для жизни осложнений АФС и улучшить качество жизни пациентов. Результаты исследования диктуют необходимость проведения обследования на наличие АФС и наследственные тромбофилии всем больным молодого возраста с неспровоцированным тромбозом глубоких вен нижних конечностей и тромбоэмболии легочной артерии.

რეზიუმე

ანტიფოსფოლიპიდური სინდრომის სისხლძარღვოვანი გამოვლინებების კლინიკური და გენეტიკური თავისებურებანი (შემთხვევა პრაქტიკიდან)

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სტატიაში განხილულია ანტიფოსფოლიპიდური სინდრომის (აფს) განვითარების პათოგენური მექანიზმები, რომლებიც წარმოადგენს კლინიკური გამოვლინებების და აფს-ის ლაბორატორიული მარკერების განვითარების საფუძველს. გაანალიზებულია თანამედროვე ლიტერატურის მონაცემები,რომლის თანახმადაც ანტიფოსფოლიპიდური ანტისხეულების არსებობა ჰიპოკოაგულაციური ფონითაა განპირობებული; თრომბების ფორმირება მიმდინარეობს სხვა გადამწყვეტი პროკოაგულაციური ფაქტორების ზეგავლენით. მოყვანილია მემკვიდრეობითი თრომბოფილიის ძირითადი სახეობების კლასიფიკაცია; იგი წარმოადგენს პირველად დარღვევას,რომლის ფონზეც ვითარდება აუტოიმუნური თრომბოზი - აფს. მოყვანილია საკუთარი კლინიკური დაკვირვება

ახალგაზრდა ასაკის პაციენტზე,რომელსაც სისხლის შედედებაზე პასუხისმგებელი (F7, RAI-1 და ITGB3-β-ინტეგრინი) გენის ჰეტეროზიგოტური მტარებლის მუტაციების და ჰომოცისტეინის მეთილირების დარღვევასთან ასოცირებული MTRR გენის ჰომოზიგოტური მტარებლის მუტაციის ფონზე, განუვითარდა აფს, რამაც გამოიწვია თრომბოზი. დროული დიაგნოსტიკა და ინდივიდუალურად შემუშავებული პათოგენური თერაპია იძლევა სიცოცხლისათვის საშიში აფს ის გართულებების თავიდან აცილების, აგრეთვე, პაციენტთა ცხოვრების ხარისხის გაუმჯობესების საშუალებას. ავტორების მიერ გამოტანილია დასკვნა აფს-ზე და მემკვიდრეობით თრომბოფილიაზე გამოკვლევის ჩატარების აუცილებლობის შესახებ ახალგაზრდა ასაკის ყველა პაციენტში,რომელთაც აღენიშნებათ ქვედა კიდურების თრომბოზი და ფილტვის არტერიის თრომბოემბოლია.

FORMULATION AND TECHNOLOGY DEVELOPMENT OF HERBAL PHENOLIC BIOPOLYMER-CONTAINING FILMS FOR BURN TREATMENT

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The development of rational remedies for burn healingis considered as one of the problems of dermatology and pharmacy. In particular, protection of the burned surface as the main task, proved to be necessary for effective fighting against shock, loss of plasma and preventing secondary infection.

The modern remedies, used currently for burn treatment are not effective enough, due to inability to maintain the drug concentration on the affected surface, short contact time and long-term treatment [1]. Application of phytofilms based on biosolublepolymers is considered as a prospectivemethod for burn treatment [4].

Herbal remedies contain biologically active substances, that are relatively less toxic, do not cause skin irritation or allergic reactions and, importantly, affectstrains of the microorganisms and viruses resistant to antibiotics and synthetic drugs [11].

Nowadays, the advantages are given to such burn healing drugs, which along with high specific efficacy, have analgesic, anti-inflammatory and antimicrobial effects, and don'tirritate the tissues. The mentioned peculiarities are characteristic fora new herbal phenolic biopolymer poly[3-(3,4-dihydroxyphenyl) glyceric acid](PDGA) /5,6,9,10/,isolated from the roots and stems of different comfrey species .

The aim of the study was the development of the formulation and technology of biosoluble films for burn treatment on the basis ofPDGA.

Material and methods. Several film–forming syntheticandnatural polymers such as: sodiumcarboxymethyl cellulose(NaCMC), gelatin, polyvinylpyrrolidone(PVP), sodium alginate, polyvinyl spirit (PVS) and ethylene-vinyl acetate(EVA), wereused.forthe development of the phytofilm,

The study was conducted using biopharmaceutical and technological methods [2,3,8]. Six sample films for the treatment of burns with different composition (Table 1) were formulated for the selection of most suitable one. Sample film-formers were prepared in different ways.

Sample 1: 3.5 g of sodium carboxy methylcellulose (Na-CMC) was weighed on the analytical scales,mixed with 40ml of distilled water, heated up to 55±5^{0}C, and left for 30 min for swelling; the remaining amount of cold

Table 1. Composition of Sample Films

Sample #	Composition of Sample Films (%)									
	PDGA	Na-CMC	Na alginate	gelatin	PVS	PVP	EVA	Chloroform	Water	Glycerol
1	10.0	3.5	-	-	-	-	-	-	84.0	2.5
2	10.0	-	-	3.5	-	-	-	-	84.0	2.5
3	10.0	-	-	-	3.5	-	-	-	84.0	2.5
4	10.0	-	-	-	-	3.5	-	-	84.0	2.5
5	10.0	-	3.5	–	–	–	-	-	84.0	2.5
6	10.0	-	-	-	-	-	3.5	84.0	–	2.5

Table 2. Impactof film-former on technological features of the phytofilm

Film-former sample #	**Composition**	**Average mass (g)**	**Thickness (mm)**	**pH**	**Humidity, (%)**	**Mechanical stability on destruction of phytofilm integrity ($Nx10^{-3}$)**
1	PDGA – 10.0 Na –CMC– 3.5 Glycerol – 2.5 Water– 85.0	17.6±0.002	0.82±0.002	6.2	8.81±0.23	89.23±0.02
2	PDGA – 10.0 Na-alginate – 3.5 Glycerol–2.5 water – 85.0	17.3±0.003	0.82±0.002	6.1	8.64±0.12	92.46±0.03
3	PDGA – 10.0 Gelatin – 3.5 Glycerol–2.5 water – 85.0	17.5±0.002	0.83±0.002	6.6	9.14±0.13	98.15±0.02
4	PDGA – 10.0 PVS – 3.5 Glycerol–2.5 water – 85.0	17.5±0,003	0.79±0.002	6.4	8.72±0.44	82.41±0.01
5	PDGA – 10.0 PVP – 3.5 Glycerol–2.5 water – 85.0	17.6±0.002	0.79±0.002	6.5	8.55±0.46	84.14±0.02
6	PDGA – 10.0 EVA– 3.5 Glycerol–2.5 Chloroform– 85.0	16.6±0.003	0.77±0.002	6.0	3. 06±0.39	168.98±0.04

water was added and mixed until an uniform solution was obtained. Then the solution was processed in accordance with general scheme.

Sample 2: 3.5 g of sodium alginate was weighed on the analytical scales, mixed with cold distilled water and left for 3 hours for swelling. After a while, solution was heated on the water bath, mixed with the residual water, and mixture was thoroughly stirred until a uniform solution was obtained.Then the solution was processed in accordance with general scheme.

Sample 3: 3.5 g of gelatin was weighed on the analytic scales, mixed with 40 ml of cold distilled water and left for 40 minutes for swelling. After a while, solution was heated on the water bath, mixed with the residual water, after which mixture was thoroughly stirred until a uniform solution was obtained.Then the solution was processed in accordance with general scheme.

Sample 4: 3.5 g of polyvinyl spirit (PVS) was weighed on the analytic scales, mixed with 40 ml of cold distilled water and the solution was heated on the water bath adding the residual water, after which mixture was thoroughly stirred until a uniform solution was obtained. Then the solution was processed in accordance with general scheme.

Sample 5: 3.5 g of polyvinylpyrrolidone (PVP) was weighed up on the analytic scales, mixed with 40 ml of cold distilled water and left for 30 minutes for swelling. After adding the residual water the obtained mixture was thoroughly stirred until a uniform solution was obtained.Then the solution was processed in accordance with general scheme.

Sample 6: 3.5 g of ethylene-vinyl acetate (EVA) granules was weighed on the analytic scales, mixed with 84 g of chloroform- and left for 4 hours until completely dissolved. Then, the film-formerwas processed differently from the general processing scheme.

A general processingscheme for the film-former samples 1-5: the film-former solution was filtered through glass filter and mixed with 2.5 g of pre-weighted plasticizer glycerol and 10g of PDGA. The obtained mixture was homogenized, placed on a glass plate (20 cm width, 25cm length) pretreated subsequently with ethanol and sunflower oil and dried at room temperature to 8-10% residual moisture. The final products were 0.80±0.002 mm thick brown, solid, elastic and homogeneous films.

Film-former sample 6 was processedas follows: 2.5 g of pre-weighted plasticizer glycerol and 10g of PDGA were added to the film-former. The obtained mixture was homogenized and placed on the ethanol-pretreated glass

surface (in fume hood).After the evaporation of the chloroform, a brown,homogenous, solid, elastic film remained on the surface of the glass.

The final selection of film-former was carried out according to the following functional features: appearance, thickness, pH, weight loss at drying, mechanical stability.

To determine the optimal composition of phytofilm, the release of PDGA from the phytofilms was studied *in vitro* using Franz diffusion cell followed by spectrophotometry [7].

Biosoluble wound healing films were obtained by placing the initial mixture on hydrophobic glass surface, followed by drying at 40-50^{0}C for 22-24 hours in drying oven. The final PDGA concentration in phytofilm was 10%.

For the standardization of phytofilm (which provides the desired quality and safety of the product) the following quality criteria were proposed: description (color, smell, size and shape of the film); identity of active substance, determination of average mass; solubility;pH of aqueous solution;weight loss at drying; quantitative determination of active ingredient; packaging; marking; transportation; shelf life. Besides this, technological parameters such as mechanical resistance against integrity and thickness of the film are considered as quality index of biosolublephytofilm. The quantitative determination of active ingredient content in PDGA film was performed by spectrophotometric method, modified according to the specificity of the study object (the film).

The stability of PDGA containing biosoluble film at storage process was determined according to physicochemical and technological indicators.

Results and their discussion. Impact of film-former on technological features of the phytofilm featureswas studied.The statistically processed results of the study are representedin Table 2.

Thus, according to the appearance of phytofilms, it can be concluded that the films prepared on the basis of Na-CMC (Sample 1), sodium alginate (Sample 2) and gelatin (Sample 3) have good physico-technological indicators.The quality of the of PVS-, PVP- and EVA-based films is not satisfactory.Consequently, the further studies were continued on sample films1, 2, and 3. The impact of film-former and residual moisture on the film adhesion was studied. Statistically processed results are presented in Table 3.

According to the data represented in the Table 3 the sample phytofilm2 showed the best adhesive features and consequently, the most optimal composition.In addition, the optimum humidity (30.4%) of phytofilm, ensuring its high adhesiveproperties was detected. The effect of film-formeron the ability of the therapeutic film to absorb moisture was detected as described in [2]. The results of the study were statistically processed and presented in Table 4.

As it is shown in Table 4, the sample phytofilm 3was not dissolved for the entire observation period and had the least ability of moisture absorption among tested phytofilms.

Sodium alginate-based phytofilm has better ability to absorb water than sample phytofilms 1 and 3. It was completely dissolved in 90 minutes after the experiment started. The film on the basis ofNaCMC was dissolved within the same period of time.

Table 3. Dependence of phytofilm adhesive properties on the nature of membrane-manufacturer and its humidity

Sample Film#	**Technological indicators**									
1	Humidity, %	51.6	43.4	35.2	31.9	28.7	25.7	16.2	10.5	6.2
	Peeling force Nx10^{-3}	152.5	189.6	236.5	247.,6	204.1	168.9	146.3	85.3	68.6
2	Humidity, %	50.6	47.2	45.1	37.5	30.4	27.65	22.8	10.2	66.4
	Peeling force Nx10^{-3}	156.9	168.7	164.1	194.7	263.6	207.4	173.6	88.2	72.2
3	Humidity, %	52.3	48.4	43.2	38.2	33.5	30.2	22.5	10.4	6.3
	Peeling force Nx10^{-3}	93.9	147.6	158.3	163.4	196.9	140.8	118.8	78.6	65.5

Table 4. Swelling of sample phytofilms

Sample Film#	**Technologicalindicators**									
Time (min)	10	20	30	40	50	60	70	80	90	100
Humidity, %										
1	1.87	1.87	2.23	2.89	2.65	2.38	2.12	1.23	Film -dissolved	–
2	1.92	2.41	2.77	2.94	3.37	2.82	2.12	1.44	Film -dissolved	–
3	1.15	1.53	1.61	2.28	2.66	3.09	3.34	3.64	3.87	4.11

Table 5. Physico-chemical and technologic features of bio-soluble PDGA film (n=5)

Name of the phyto-film	Ser #	Descrip-tion	Average mass, g	Thick-ness, mm	pH	Time taken for dissolu-tion, min	Weight lose, at drying, %	Mechani-cal stabil-ity against violation of PDGA film integ-rity N 10^{-3}	Quantita-tive content of PDGA (100cm^2) is not less than 2.005± 0.003 g
PDGA film	1	Brown, rectangu-lar	17.4±0.002	0.80±0.02	6.0	90.49±1.00	8.69±0.60	92.95±0.01	2.005± 0.003
	2	"-----"	17.2±0.003	0.78±0.02	5.8	89.36±0.17	8.60±0.10	93.28±0.03	2.005± 0.003
	3	"-----"	17.5±0.002	0.82±0.02	5.9	91.46±0.09	9.09±0.10	91.10±0.01	2.005± 0.003
	4	"-----"	17.5±0.002	0.79±0.01	5.8	90.86±0.13	8.93±0.50	92.08±0.01	2.005± 0.003
	5	"-----"	17.6±0.002	0.80±0.01	6.0	91.58±0.16	9.18±0.09	91.02±0.01	2.005± 0.003

From the results of the experimental study, it is clear, that sample phytofilm 3 was not dissolved over the entire period of time.Consequently, gelatin cannot be used as the basis of biosolublephytofilm.Taking into consideration the studied physical and technological indicators,it should be noted that, the sample film 2 might be considered as optimal one for development of biosolublephytofilm of prolonged action.

In vitro study of the PDGA release from phytofilms usingFranz diffusion cell revealed, that the hydrophilic bases such as sodium carboxymethyl-cellulose (69.2%) and sodium alginate (78,65%) appeared to be optimal among the others (Fig.).

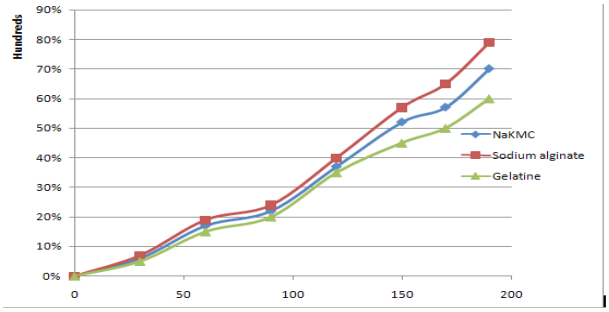

Fig. PDGA release from the phytofilm

The conducted study showed that rapid PDGA release was observed from the film, prepared on the basis of Na-CMC and/orNa-alginate(in 190 minutes – 69.2%and 78.6%, respectively), while PDGA release from the gelatin-based composition during the specified period of time was only 60%.

The final decision regarding the choice of the film-former was madebased on a preclinical evaluation of the treatment of burns.

The studyrevealed that the characteristics of two film-formers - Na-CMC and sodium alginate, are almost identical.It should also be noted that sodium alginate contributes to hemostasis that is especially important in the treatment of burns and wounds. In this regard, the preference was given to sodium alginate.

The quantitative content of PDGA in the finished dosage form(square100cm^{2}phytofilm) was 2.005±0.003 g.

It was established that all of above mentioned parameters remained stable for 2 years (Table 5).

Conclusions:

1. The optimal content ofphytofilm for burnhealing was selected on the basis of the biopharmaceutical study: PDGA – 10.0%; sodium alginate – 3.5%; glycerin – 2.5%; distilled water - 84.0%.
2. The optimal degree of the phytofilm moisture, determining its high adhesive properties, was established. The film prepared on the basis of sodium alginate, with 30.4% humidity, demonstrated the greatest adhesion strength.
3. Hydrophilic bases such as sodiumcarboxymethyl-celluloseand sodium alginate provided optimal PDGA release (69.2% and 78,65%, respectively). At the same time, taking into consideration the disadvantages of sodiumcarboxymethyl-cellulose(tautening effect on burnt surface, relatively low stability), a film based on sodium alginate has been chosen.
4. The manufacturing technology for obtaining PDGA-containing phytofilm by casting is proposed.
5. The shelf-life of proposed PDGA-containing phytofilm is 2 years.

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SUMMARY

FORMULATION AND TECHNOLOGY DEVELOPMENT OF HERBAL PHENOLIC BIOPOLYMER-CONTAINING FILMS FOR BURN TREATMENT

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Application of phytofilms based on biosolublepolymers is considered as a prospectivemethod for burn treatment .

Herbal remedies contain biologically active substances, that are relatively less toxic, do not cause skin irritation or allergic reactions and, importantly, affectstrains of the microorganisms and viruses resistant to antibiotics and synthetic drugs.

Nowadays, the advantages are given to such burn healing drugs, which along with high specific efficacy, have analgesic, anti-inflammatory and antimicrobial effects, and don't irritate the tissues. The mentioned peculiarities are characteristic for a new herbal phenolic biopolymer poly[3-(3,4-dihydroxyphenyl) glyceric acid](PDGA), isolated from the roots and stems of different comfrey species .

The aim of the study was the development of the formulation and technology of biosoluble films for burn treatment on the basis of PDGA. The optimal content of phytofilm for burn healing was selected on the basis of the biopharmaceutical study results. The impact of the film-former on the quality, adhesion and moisture absorption of the phytofilmhas been studied.

The optimal degree of the phytofilm moisture, determining its high adhesive properties,was established. The film prepared on the basis of sodium alginate, with 30.4% humidity, demonstrated the greatest adhesion strength. After investigation of the PDGA release it was found, that the hydrophilic bases such as: sodium carboxymethylcellulose (69.2%) andsodium alginate (78,65%) appeared to be optimal among the others. At the same time, taking into consideration the disadvantages of sodium carboxymethylcellulose (tautening effect on burnt surface, relatively low stability), a film based on sodium alginate has been chosen. The manufacturing technology for obtaining PDGA-containing phytofilm by casting is proposed. Theshelf-lifeofproposedPDGA-containingphytofilmis 2 years.

Keywords:phytophilms, burn treatment, biopolymer, PDGA, pharmaceutical technology.

РЕЗЮМЕ

ОПРЕДЕЛЕНИЕ СОСТАВА И РАЗРАБОТКА ТЕХНОЛОГИИ ПРОТИВООЖОГОВЫХ ПЛЕНОК НА ОСНОВЕ РАСТИТЕЛЬНОГО ФЕНОЛЬНОГО БИОПОЛИМЕРА

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Представлен новый метод лечения ожогов с применением лечебных пленок на основе водорастворимых полимеров.

Фитопрепараты содержат биологически активные вещества, которые во многих случаях нетоксичны, не оказывают раздражающего действия на кожу, не вызывают аллергических реакций, и, что особенно важно, действуют на штаммы микрооранизмов и вирусов, устойчивых к антибиотикам и синтетическим препаратам.

В настоящее время приоритет отдается ранозаживляющим и противоожоговым препаратам, которые, наряду с выраженным специфическим действием, обладают обезболивающим, противовоспалительным, антимикробным действием и при этом не раздражают окружающие ткани. Именно такими свойствами об-

ладает новый растительный фенольных биополимер – поли[3-(3,4-дигидроксифенил)глицериновая кислота] (ПДФГК), выделенная из некоторых видов рода окопник.

Целью исследования являлась разработка рецептуры и технологии биорастворимых пленок с поли[3-(3,4-дигидроксифенил)глицериновой кислотой для лечения ожогов.

На основании проведенных биофармацевтических исследований определен оптимальный состав противоожоговых фитопленок. Изучено влияние пленкообразующего компонента на качество фитопленки, адгезивные свойства и влагопоглощение. Установлена оптимальная степень влажности фитопленки, обеспечивающая наилучшую адгезионную способность.

При изучении высвобождения ПДФГК из различных носителей установлено, что оптимальными являются гидрофильных основы: натрий-карбоксиметицеллюлоза (69,2%) и альгинат натрия (78,65%). С учетом того, что натрий-КМЦ обладает недостатками: стягивает ожоговую поверхность и имеет относительно низкую стабильность, в качестве основы для пленок был выбран альгинат натрия. Разработана технология производства ПДФГК-содержащей пленки поливочным методом. Установлено, чтоПДФГК-содержащая пленка сохраняет стабильность в течение двух лет.

რეზიუმე

დამწვრობის სამკურნალო მცენარეული ფენოლური ბიოპოლიმერის შემცველი ფირფიტების შემადგენლობის განსაზღვრა და ტექნოლოგიის დამუშავება

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კვლევის მიზანს წარმოადგენდა დამწვრობის სამკურნალო პოლი[3-(3,4დიჰიდროქსიფენილ) გლიცერინისმჟავას (პდფგმ) ბიოხსნადი ფირფიტების რეცეპტურის და ტექნოლოგიის შემუშავება.

ჩატარებული ბიოფარმაცევტული კვლევის შედეგად შერჩეულია დამწვრობის სამკურნალო ფირფიტის ოპტიმალური შემადგენლობა; შესწავლილია აპკწარმომქმნელის გავლენა ფიტოფირფიტის ხარისხზე, ადჰეზიასა და ტენშთანთქმაზე. დადგენილია ფიტოფირფიტის ტენიანობის ოპტიმალური ხარისხი,რომელიც უზრუნველყოფს მის მაღალ ადჰეზიურ შესაძლებლობას.

პდფგმ-ის გამოთავისუფლების შესწავლისას სხვადასხვა ფუძე-მატარებელთა შორის ოპტიმალური აღმოჩნდა ჰიდროფილური ფუძეები ნატრიუმის კარბოქსიმეთილცელულოზას (69.2%) და ნატრიუმის ალგინატის (78.65%) ბაზაზე. ამასთან, ნატრიუმის კარბოქსიმეთილცელულოზას ფირფიტის ნაკლოვანი მხარეების გათვალისწინებით (მომჭიმავი ეფექტი დამწვრობის ზედაპირზე, შედარებით დაბალი სტაბილურობა) შერჩეულ იქნა ფირფიტა ნატრიუმის ალგინატის ფუძეზე.

მოწოდებულია პდფგმ-ის ფირფიტების მიღების ტექნოლოგია,ჩამოსხმის მეთოდი. პდფგმ-ის ფირფიტა სტაბილურობას ინარჩუნებს 2 წლის განმავლობაში.

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