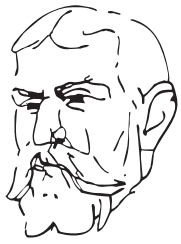
Wiadomości Lekarskie

Czasopismo Polskiego Towarzystwa Lekarskiego



Pamięci
dra Władysława
Biegańskiego

TOM LXXII, 2019, Nr1

Rok założenia 1928

Aluna Publishing

Wiadomości Lekarskie is abstracted and indexed in: PubMed/Medline, EBSCO, SCOPUS, Index Copernicus, Polish Medical Library (GBL), Polish Ministry of Science and Higher Education.

Zasady prenumeraty miesięcznika Wiadomości Lekarskie na rok 2019

Zamówienia na prenumeratę przyjmuje Wydawnictwo Aluna:

– e-mailem: prenumerata@wydawnictwo-aluna.pl
– listownie na adres:

Wydawnictwo Aluna
ul. Z.M. Przesmyckiego 29, 05-510 Konstancin-Jeziorna

Prosimy o dokonywanie wpłat na numer rachunku Wydawnictwa:
Credit Agricole Bank Polska S. A.: 82 1940 1076 3010 7407 0000 0000

Cena prenumeraty dwunastu kolejnych numerów: 240 zł/rok (w tym 5% VAT)

Cena prenumeraty zagranicznej: 120 euro/rok.
Cena pojedynczego numeru – 30 zł (w tym 5% VAT) + koszt przesyłki.
Przed dokonaniem wpłaty prosimy o złożenie zamówienia.

Wiadomości Lekarskie

Managing Editor:
Agnieszka Rosa amarosa@wp.pl

International Editor:
Lesia Rudenko l.rudenko@wydawnictwo-aluna.pl

Distribution and Subscriptions:
Bartosz Guterman prenumerata@wydawnictwo-aluna.pl

Graphic design / production:
Grzegorz Sztank www.red-studio.eu

Publisher:
ALUNA Publishing
ul. Przesmyckiego 29, 05-510 Konstancin – Jeziorna
www.aluna.waw.pl www.wiadomoscilekarskie.pl
www.medlist.org

REGULAMIN PRZYJMOWANIA I OGŁASZANIA PRAC W WIADOMOŚCIACH LEKARSKICH

1. Miesięcznik Wiadomości Lekarskie jest czasopismem Polskiego Towarzystwa Lekarskiego, ma charakter naukowo-edukacyjny. Zamieszczane są w nim prace oryginalne, kliniczne i doświadczalne oraz poglądowe w języku polskim lub angielskim oraz innych językach (za zgodą redakcji).
2. Publikacja pracy w Wiadomościach Lekarskich jest płatna. Od stycznia 2017 roku koszt opublikowania artykułu wynosi 1000 zł plus 23%VAT. Jeżeli pierwszym autorem pracy jest członek Rady Naukowej czasopisma lub zespołu recenzentów – za druk nie pracy nie pobieramy opłaty, jeśli zaś jest kolejnym współautorem – opłata wynosi 500 zł plus 23%VAT. Wydawca wystawia faktury. Opłatę należy uiścić po otrzymaniu pozytywnej recenzji, przed opublikowaniem pracy. Z opłaty za publikację zwolnieni są członkowie Polskiego Towarzystwa Lekarskiego z udokumentowaną opłatą za składki członkowskie za ostatnie 3 lata.
3. Prace zapisane w formacie DOC (z wyłączeniem rycin, które powinny stanowić osobne pliki) należy przesłać pocztą elektroniczną na adres redakcji: Agnieszka Rosa - amarosa@wp.pl.
4. Objętość prac oryginalnych – łącznie z rycinami i piśmiennictwem – nie może przekraczać 21 600 znaków (12 stron maszynopisu), prac poglądowych – do 36 000 znaków (20 stron).
5. Strona tytułowa powinna zawierać:
   – tytuł w języku angielskim i polskim,
   – pełne imiona i nazwiska autorów,
   – afiliację autorów,
6. Praca oryginalna powinna mieć następującą strukturę: wstęp, cel pracy, materiał i metody, wyniki, dyskusja i wnioski, które nie mogą być streszczeniem pracy. Przy zastosowaniu skrótów konieczne jest podanie pełnego brzmienia terminu przy pierwszym użyciu. W pracach doświadczalnych, w których wykonano badania na ludziach lub zwierzętach, a także w badaniach klinicznych, należy umieścić informację o uzyskaniu zgody komisji etyki badań naukowych.
7. Streszczenia zarówno w języku polskim, jak i angielskim powinny zawierać 200-250 słów. Streszczenia prac oryginalnych, klinicznych i doświadczalnych powinny posiadać następującą strukturę: cel, materiał i metody, wyniki wnioski. Nie należy używać skrótów w tytule ani w streszczeniu.
8. Słowa kluczowe (3-6) należy podawać w języku angielskim i polskim, zgodnie z katalogami MeSH (Medical Subject Headings Index Medicus http://www.nim.nih.gov.mesh/MBrower.html). Słowa kluczowe nie mogą być powtórzeniem tytułu pracy.
9. Materiał ilustracyjny - ryciny, wykresy, rysunki, fotografie, slajdy - powinien być opisany cyframi arabskimi i zapisany jako pliki JPG, TIFF lub EPS o rozdzielczości 300 DPI (nie w plikach tekstowych). Ich opisy należy przesłać w osobnym pliku. W tekście muszą znajdować się odniesienia do wszystkich rycin (w nawisach okrągłych).
10. Tabele – ich tytuły (nad tabelą) i treść - powinny być zapisane w programie Microsoft Word, ponumerowane cyframi rzymskimi. Wszystkie stopki dotyczące tabeli powinny znajdować się poniżej tekstu tabeli. W tekście pracy należy umieścić odniesienia do wszystkich tabel (w nawiasach okrągłych).
11. W wykazie piśmiennictwa ułożonym według kolejności cytowania należy uwzględnić wyłącznie te prace, na które autor powołuje się w tekście. W pracach oryginalnych nie powinno być więcej niż 30 pozycji, a w poglądowych nie więcej niż 40 pozycji. Każda pozycja powinna zawierać: nazwiska wszystkich autorów, pierwsze litery imion, tytuł pracy, skrót tytułu czasopisma (wg Index Medicus), rok, numer, stronę początkową i końcową. Przy pozycjach książkowych należy podać: nazwisko autora (autorów), pierwszą literę imienia, tytuł rozdziału, tytuł książki, wydawnictwo, miejsce i rok wydania. Dopuszcza się cytowanie stron internetowych z podaniem adresu URL i daty użycia artykułu oraz o ile to możliwe nazwisk autorów. Każda pozycja piśmiennictwa powinna mieć odwołanie w tekście pracy umieszczone w nawiasie kwadratowym, np. [1], [3–6]. Pozycje zapisuje się w sposób zaprezentowany w Załączniku nr 1 do niniejszego regulaminu.
12. Po piśmiennictwie należy podać adres do korespondencji, nazwisko i imię pierwszego autora, adres, numer telefonu oraz adres e-mail.
13. Do pracy należy dołączyć oświadczenie podpisane przez wszystkich autorów określające udział poszczególnych autorów w przygotowaniu pracy (np. koncepcja i projekt pracy, zbieranie danych i ich analiza, odpowiedzialność za analizę statystyczną, napisanie artykułu, krytyczna recenzja itd.), a także oświadczenie, że biorą oni odpowiedzialność za treść. Ponadto należy zaznaczyć, że praca nie była publikowana ani zgłaszana do druku w innym czasopiśmie.
14. Jednocześnie autorzy powinni podać do wiadomości wszelkie inne informacje mogące wskazywać na istnienie konfliktu interesów, takie jak:
   – zależności finansowe (zatrudnienie, płatna ekspertyza, doradztwo, posiadanie akcji, honoraria),
   – zależności osobiste,
   – współzawodnictwo akademickie i inne mogące mieć wpływ na stronę merytoryczną pracy,
   – sponsorowanie całości lub części badań na etapie projektowania, zbierania, analizy i interpretacji danych lub pisanie raportu.

   Konflikt interesów ma miejsce wtedy, gdy przynajmniej jeden z autorów ma powiązania lub zależności finansowe z przemysłem bezpośrednie lub za pośrednictwem najbliższej rodziny. Jeśli praca dotyczy badań nad produktami częściowo lub całkowicie sponsorowanymi przez firmy, autorzy mają obowiązek ujawnić ten fakt w załączonym oświadczeniu.
15. Każda praca podlega weryfikacji w systemie antyplagiatowym (zapora ghostwriting).
16. Redakcja przestrzega zasad zawartych w Deklaracji Helsińskiej, a także w Interdisciplinary and Guidlines for the Use of Animals In Research, Testing and Education, wydanych przez New York Academy nof Sciencees' Adhoc Resarch. Wszystkie prace odnoszące się do zwierząt lub ludzi muszą być zgodne z zasadami etyki określanymi przez Komisję Etyczną.
17. Czasopismo recenzowane jest w trybie podwójnej, ślepej recenzji. Nadesłane prace są oceniane przez dwóch niezależnych recenzentów, a następnie kwalifikowane do druku przez Redaktora Naczelnego. Recenzje mają charakter anonimowy. Krytyczne recenzje autorzy otrzymują wraz z prośbą o poprawienie pracy lub z decyzją o niezakwalifikowaniu jej do druku. Procedura recenzowania artykułów jest zgodna z zaleceniami Ministerstwa Nauki i Szkolnictwa Wyższego zawartymi w opracowaniu „Dobre praktyki w procedurach recenzyjnych w nauce" (Warszawa 2011) i szczegółowo została opisana na stronie http://www.nauka.gov.pl/g2/oryginal/2014_02/307f933b1a75d6705a4406d5452d6dbf.pdf
18. Redakcja zastrzega sobie prawo redagowania nadesłanych tekstów (dokonywania skrótów i poprawek). Prace są wysyłane do akceptacji autorów. Poprawki autorskie należy przesłać w terminie 3 dni od daty wysłania wiadomości e-mail (pocztą elektroniczną). Brak odpowiedzi w podanym terminie jest równoznaczny z akceptacją przez autora nadesłanego materiału.
19. Przyjęcie pracy do druku oznacza przejęcie praw autorskich przez Redakcję Wiadomości Lekarskich.
20. Autorzy otrzymują nieodpłatnie plik PDF wydania, w którym znajduje się ich praca, a na życzenie - egzemplarz drukowany. Plik elektroniczny przeznaczony jest do indywidualnego użytku autora, bez prawa do rozpowszechniania bez zgody redakcji.
21. Prace przygotowane niezgodnie z regulaminem zostaną zwrócone autorom do poprawienia.
22. Redakcja nie odpowiada za treść zamieszczanych reklam.

SPIS TREŚCI

ARTYKUŁ REDAKCYJNY / EDITORIAL ARTICLE
PRACA ORYGINALNA / ORIGINAL ARTICLE

DEVELOPMENT OF MOTIVATION TOWARDS EDUCATION IN MEDICAL STUDENTS

ROZWÓJ MOTYWACJI DO NAUKI U STUDENTÓW MEDYCYNY

Halyna Yu. Morokhovets[1], Olena V. Uvarkina[2], Olena M. Bieliaieva[3], Yuliia V. Lysanets[3], Hennadii A. Senkevych[4], Serhii A. Stetsenko[5]

[1]RESEARCH DEPARTMENT, UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY, POLTAVA, UKRAINE
[2]DEPARTMENT OF PEDAGOGICS, PSYCHOLOGY, MEDICAL AND PHARMACEUTICAL LAW, P.L. SHUPYK NATIONAL MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KYIV, UKRAINE
[3]DEPARTMENT OF FOREIGN LANGUAGES WITH LATIN AND MEDICAL TERMINOLOGY, UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY, POLTAVA, UKRAINE
[4]DEPARTMENT OF SOCIAL WORK, OLES HONCHAR DNIPRO NATIONAL UNIVERSITY, DNIPRO, UKRAINE
[5]DEPARTMENT OF MEDICAL INFORMATICS, MEDICAL AND BIOLOGICAL PHYSICS, UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY, POLTAVA, UKRAINE

ABSTRACT

Introduction: The quality of professional medical training is a relevant issue for clinical and educational setting due to modernization and reform processes at the present stage of the society's development. The formation of the future doctors' interest in professional activities mostly depends on the implementation of pedagogical conditions, aimed at developing the positive motivation towards education.

The aim: The authors aim to examine the concept of motivation and define its role in the process of professional training of future doctors.

Materials and methods. A questionnaire survey was conducted for students of the first year of study (medical and dental faculties) using the methods of studying the profession's attractiveness and its factors (by V. Yadov, modification by I. Kuzmina, A. Rean) and studying the orientation towards the acquisition of knowledge via the test by E. Ilyin and N. Kurdyakova.

Results: Based on the analysis of literary sources, the main factors that influence the interest of students in education were identified and the pedagogical conditions for the formation of positive motivation for training activity in the educational setting of a higher medical educational institution were highlighted. It was found that most students prefer social motives when choosing a profession, and almost 10% of the subjects show a low level of focus on learning in the process of education. The authors provided practical recommendations on the formation of positive motivation for students' training when studying humanities at a medical university with the help of multimedia teaching materials, inclusion of students in the self-directed research activity, etc.

Conclusions: On the basis of generalized experience of educators and psychologists, as well as our own studies, we consider that the following pedagogical conditions form the positive motivation towards education in medical students of the first year of study: effective use of modern multimedia specialized tools (electronic journals, specialized web-sites); students' engagement in the self-directed research activity; use of modern specialized software for solving professional tasks. Such techniques enable the integration of knowledge, skills and abilities in several subjects, prepare students for academic subjects in the second year of study and maximally approximate the training objectives to future professional activities.

KEY WORDS: motivation, motive, future doctors, professional training, higher medical education

Wiad Lek 2019, 72, 1, 7-11

INTRODUCTION

Care for the health of population is a priority task of the state, which envisages the improvement of the quality of training, along with comprehensive development of medical sector. This process is provided by reviewing the existing methods, forms and means of teaching at a medical university, which is closely linked to the implementation of the person-oriented approach in the educational process. The quality of professional medical training is a topical issue for clinical and educational setting, due to modernization and reform processes at the present stage of the society's development. The process of professional training of medical students should now be advanced to a qualitatively new level, the content of the educational process should be directed towards the formation of the future doctor's self-awareness, initiative, and professional maturity. The main source of professionalization of future doctors is the educational process in which they act as active subjects of learning [1]. Pedagogical conditions act as a combination of factors providing regulation, interaction of objects and phenomena of the pedagogical process to achieve the objectives, improve the interpersonal relations of participants in the pedagogical process to solve specific didactic

tasks, promote the activization of educational and cognitive activity of future specialists, their autonomy, initiative and professional interest. The formation of the future doctors' interest in professional activities mostly depends on the implementation of a pedagogical condition, aimed at forming a positive motivation to study. In our previous studies, we have already discussed the ways of improving the learning content and methods for teaching humanities at a medical university [2; 3; 4; 5; 6]. The present paper aims to analyze the concept of motivation in psychology and education, and to define its role in the process of professional training of future doctors.

LITERATURE REVIEW

The analysis of scientific sources on the above-mentioned problem shows that motivation to study at a higher medical institution is one of the most important problems of doctors' professional training, but it is not sufficiently studied today. Priority bases for considering this problem may be the concepts of O.O. Yakovleva, K.V. Pivtorak and I.V. Fedzhaha [7; 8], who distinguish the main problems in forming the future doctor's personality. The study delineates determinants for personal growth of a future professional at the medical university: conceptual unity and continuity of the content, forms and methods of teaching; problem-oriented, developing character of teaching, connection between theory and practice; openness of educational process and content of educational material to innovations; individualization and differentiation of the educational process; teachers' cooperation with students in the educational process. V.B. Drindak, N.D. Yakovychuk, A.O. Mikheev [9] note that the greatest interest in the subject of study is not stimulated by forceful compulsion or fear due to poor assessments, but a decent example of a professional and the desire to follow the best features of the chosen "ideal". V.V. Minukhin and co-authors [10] state that the process of development of abilities, qualities and skills takes place in the educational space of higher educational institutions systematically and consistently, by involving students in research work and participation in the scientific, practical and theoretical conferences.

Taking into account the considerable number of scientists' points of view, on the basis of practical expediency and theoretical generalization of the above-mentioned aspects, we consider that motivation to study at a higher medical institution is determined by a number of factors specific to this activity. The formation of future doctors' interest in professional activities depends mostly on the implementation of the following conditions: unity of content, forms and methods of learning, openness of teaching material to innovation, involvement of students in research activities, cooperation of students with teachers, unity of theory and practice.

THE AIM

The authors aim to examine the concept of motivation and define its role in the process of professional training of future doctors.

MATERIALS AND METHODS

We analyzed the academic performance of 109 students of the first year of study (medical and dental faculties of Ukrainian Medical Stomatological Academy) at the Department of Medical Informatics, Medical and Biological Physics when studying medical and biological physics. The peculiarity of the Department of Medical Informatics, Medical and Biological Physics consists in the fact that the subject is the basis for the formation of the future doctor's professional competence; it is the initial stage in the study of medical and biological subjects, in particular physiology. During the research, we conducted a questionnaire survey via the methodology for studying the profession's attractiveness [11] (by V. Yadov, modification by I. Kuzmina, A. Rean). The attractiveness of a profession is determined by 11 factors placed in columns A and B. Respondents mark the factors that attract and do not attract them in the chosen profession. The processing of the survey results to study the profession's attractiveness involves calculation of the coefficient of significance (Cs) and the ratio of the number of respondents who chose this factor in column A (n) to the number of respondents who selected this factor in column B (m). Consideration of both coefficients is a necessary methodological aspect in interpreting the results. A high coefficient of significance (close to 1) indicates high significance of this factor in the sample. We also conducted research on the orientation to gaining knowledge using the test by E. Ilyin, N. Kurdyakova. The purpose of the test is to identify the level of expressiveness of students' motivation for acquiring knowledge. On the basis of generalization of the obtained results and their qualitative analysis, a conclusion is made about the degree of expressiveness of students' motivation to acquire knowledge and the peculiarities of its manifestation in the process of learning. Consequently, recommendations were given to ensure the conditions for the development of internal motivation to study. The test provides answers to 12 questions, for each of which respondents will receive 1 point. Statistical analysis of the results of the study (determination of the Spearman rank correlation coefficient) was performed using the Microsoft Office MS Excel table editor.

RESULTS

The distribution of research results by the method of studying the factors of the profession's attractiveness is given in Table I.

As can be seen from Table 1, 75.2% of respondents consider the profession of a doctor as one of the most important in the society, 58.7% of students chose the profession of a doctor as an opportunity for self-improvement, and 85.3% – for the opportunity to achieve social recognition and respect. High salary attracts 46.8% of respondents, 19.3% of students who participated in the study stated that a short working day is the attraction factor of the chosen profession.

As can be seen from the results of the study via the method of studying the profession's attractiveness, students are motivated predominantly by social factors (answers

Table I. Distribution of research results by the method of studying the factors of the profession's attractiveness (by V. Yadov, modification by I. Kuzmina, A. Rean)

Indicators	Factors										
	1	2	3	4	5	6	7	8	9	10	11
p	16	30	26	43	23	36	27	19	36	31	13
n	82	6	56	48	51	9	80	85	52	6	93
m	11	73	27	18	35	64	2	5	21	72	3
Cs	0.651	-0.615	0.266	0.275	0.147	-0.505	0.716	0.734	0.284	-0.606	0.826

Table II. Distribution of research results on orientation to acquiring knowledge (by E. Ilyin, N. Kurdyakova)

The amount of points	Distribution of subjects	
	Number	% of the total number
0-3	10	9.18
4-6	13	11.93
7-9	58	53.21
10-12	28	25.68
Total	109	100

To exclude random answers to test questions, the nonparametric Spearman correlation coefficient was used. As a result of the study on knowledge acquisition (by E. Ilyin, N. Kurdyakova's test), we observed a close correlation between the students' answers to questions that indicate the motivation for acquiring knowledge ("a" to questions 1-6, 8-11, and "b" to question 7, 12) (0.7, 0.95).

in column A to question 11 and answers in column B to questions 6, 10). This group of motives reflects the social significance of learning, in particular, self-affirmation in the team, self-improvement, self-education, competition for the depth of knowledge on the subject, social prestige and identification, communication, etc. Professional motives reflecting the significance of learning activities for occupation prevail in 75.2% of respondents (answers in column A to the first question of the test).

According to the research methodology on orientation to acquiring knowledge (test by E. Ilyin, N. Kurdyakova), we have the following distribution of results (Table II). From the table, one can observe that only 25.68% of respondents have a high level of motivation to acquire knowledge, while 9.18% of students present with low motivation.

DISCUSSION

In our opinion, it is highly important to form the positive motivation for learning activities to ensure successful professional training of future doctors. For the holistic formation of motivation in future doctors, this process should have a systematic character [1]. Interest is an important element in the development of motivation (Fig. 1), and it is divided by the scholars into emotional, intellectual and professionally-cognitive components. Emotional interest arises when particular attention is drawn to something that causes positive emotions and is pleasant. Intellectual interest is associated with knowledge of the surrounding world and intellectual activity of a person.

Professionally-cognitive interest is defined as an integrated form of personality, which is expressed in the constant desire for comprehension of new knowledge in the future profession and as a manifestation of cognitive needs that ensure professional orientation of the individual. Consequently, the essence of professionally-cognitive interest consists in self-directed acquisition of the necessary knowledge and their use for solving professionally significant tasks.

In our opinion, the formation of professionally-cognitive interest in learning takes place due to diversification of educational activities, involvement of future doctors in self-directed research projects, and solving the professional problems [12]. Thus, during practical sessions at medical universities it is recommended using online resources, such as *PubMed Central Database* (https://www.ncbi.nlm.nih.gov/pubmed/) [13; 14; 15], etc. The use of these resources makes it possible to expand the field of opportunities to form motivation for learning through new activities and new opportunities for implementation of one's own competencies, which ensures their transition to the new quality (practical direction). The feasibility to use the abovementioned resources is conditioned by the need to find information when preparing for practical classes, work on individual tasks. While studying the topic "Medical equipment. Devices for taking the readings of biomedical information", we recommend to demonstrate multimedia images and videos of clinical case on cardiac catheterization (online journal *The New England Journal of Medicine* by Dr. Enrico Serratto of Infermi Rivoli and

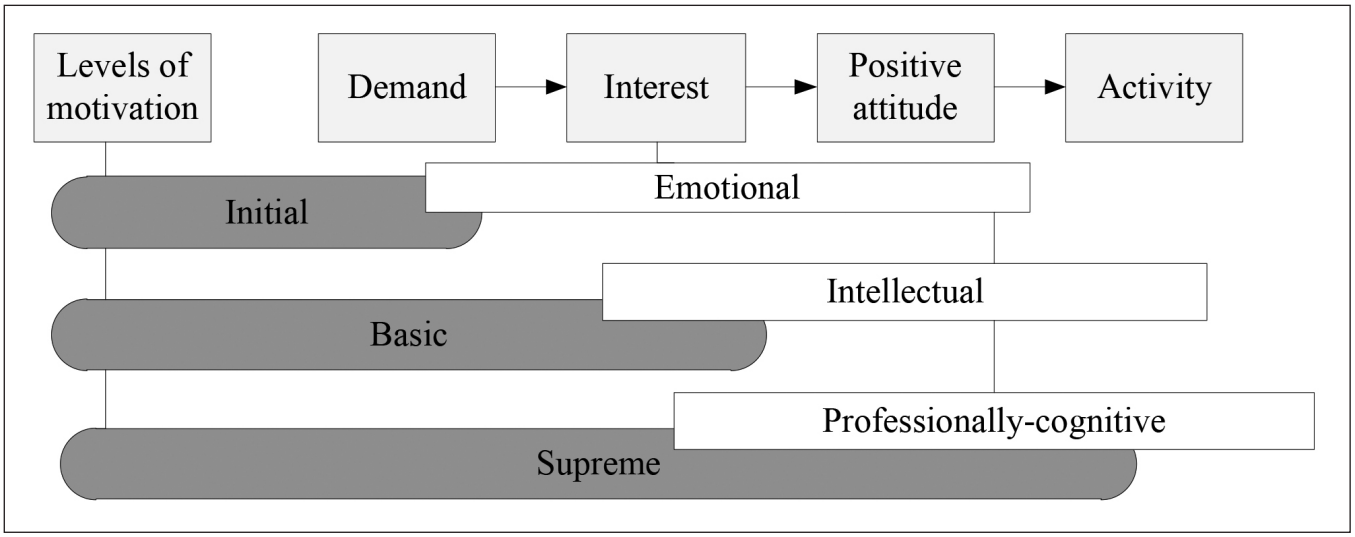


Fig. 1. Schematic representation of the process of motivation development.

San Luigi Gonzaga University Hospital). Such materials help to elucidate the complex teaching material, to orientate students in the modern diagnostic and therapeutic techniques, to prepare for the study of clinical subjects [16; 17]. When studying the topic "X-rays", in our opinion, it is appropriate to draw students' attention to the modern method of diagnostics – computed tomography and its capacity as exemplified by multimedia images and videos, including the detection of mobile aortic blood clots in patients (described in detail by Dr. Willy Sallinenom, Helsinki University Hospital at *New England Journal of Medicine* website).

An important aspect of students' learning in the context of studying a particular discipline is individual work with educational material [18]. In addition to preparing reports and abstracts, we offer students the opportunity to prepare educational demonstration materials. Under the teacher's supervision, students work on the creation of posters with structural and logical schemes, tables, images that briefly reflect the key points of the topic. Hence, for dental students when studying the topic "X-rays", it is necessary to combine the basic theoretical information on the application of thermography in dentistry and clinical interpretation of the results of this study. Thus, students independently search for relevant information, organize the search results, illustrate this material with images from research articles, report on their work, explaining the nature of physical phenomena in their clinical use [19; 20].

Studying the topic "Fundamentals of Higher Mathematics and Biological Physics", students should master the methodology of finding the function areas, the rules of differentiation, integration, solving differential equations, and find the probability of events in medical problems. At practical sessions on this topic we suggest students to get acquainted with the main features of Maple 10 computing environment. The software allows students to optimize the process of mathematical calculations during the preparation for practical classes and self-directed work [21; 22; 23].

CONCLUSIONS

After analyzing the problem of motivation to study during practical classes in medical and biological physics, we observed that there are numerous opportunities for increasing the students' motivation to study. They are not universal and require consideration of the content, means and methods of presenting the educational material. On the basis of generalized experience of educators and psychologists, as well as our own studies, we consider that the following pedagogical conditions form the positive motivation towards education in medical students of the first year of study: effective use of modern multimedia specialized tools (electronic journals, specialized web-sites); students' engagement in the self-directed research activity; use of modern specialized software for solving professional tasks. Such techniques enable the integration of knowledge, skills and abilities in several subjects, prepare students for academic subjects in the second year of study and maximally approximate the training objectives to future professional activities.

REFERENCES

1. Morokhovets H. Y., Lysanets Y. V. Developing the professional competence of future doctors in the instructional setting of higher medical educational institutions. Wiad Lek. 70(1). 2017: 101-104.
2. Bieliaieva O., Synytsia V., Lysanets Yu. Pharmaceutical Terms with Onomastic Component: Quantitative, Structural and Lexico-Semantic Analysis. Wiadomości Lekarskie. Vol. 71. Nr.1. cz.II. 2018: 217-221.
3. Melaschenko M., Bieliaieva O., Lysanets Yu. Lexical Borrowings from Classical Languages in the English and French Medical Terminologies: A Comparative Study. Wiadomości Lekarskie. Vol. 71. Nr.5. 2018: 1080-1083.
4. Bieliaieva O., Lysanets Yu., Havrylieva K., Znamenska I., Rozhenko I., Nikolaieva N. Paronymy in the Sublanguage of Medicine (Linguistic and Linguo-Didactic Aspects). Georgian Medical News. No.10 (271). 2017: 144-149.
5. Bieliaieva O.M., Lysanets Yu.V., Znamenska I.V., Rozhenko I.V., Nikolaieva N.M. Terminological Collocations in Medical Latin and English: A Comparative Study. Wiadomości Lekarskie. Tom LXX. Nr 1. 2017: 139-143.

6. Bieliaieva O., Lysanets Yu., Melaschenko M. Latin as a Language of International Communicative Status: Medicine of the 16th-17th Centuries. Georgian Medical News. No 1(262). 2017: 120-124.
7. Yakovleva O. O. Sotsialno-ekonomichni peredumovy formuvannya osobystosti spetsialistiv u medytsyni. Aktualni problemy formuvannya osobystosti likarya u studentiv medykiv: materialy KHI mizhnarodnoyi naukovo-praktychnoyi konferentsiyi (Kyiv, 23.03.2011). K.; 2011: 124.
8. Pivtorak K. V., Fedzhaha I. V. Formuvannya osobystosti ta motyvatsiyi do navchannya u studentiv medychnoho universytetu. Medychna osvita. 4. 2013: 28-31.
9. Mikhyeyev A. O., Mikhyeyeva H. V. Navchalna motyvatsiya shkolyariv ta studentiv yak skladova rozvytku maybutnikh fakhivtsiv. Sovremennyy nauchnyy vestnyk. 7(2). 2013: 30-34.
10. Minukhin V. V., Habysheva L. S., Tkachenko V. L. et al. Formuvannya profesiynoyi kompetentnosti studentiv-medykiv. Realizatsiya zakonu Ukrayiny "Pro vyshchu osvitu" u vyshchiy medychniy ta farmatsevtychniy osvity Ukrayiny: materialy Vseukrayins'koyi navchal'no-naukovoyi konferentsiyi z mizhnarodnoyu uchastyu, Ternopil, 21-22 travnya 2015 r. Ternopil; 2015: 108-110
11. Bordovskaya N. V., Rean A. A. Pedagogika. Uchebnyk dlya vuzov. SPb.; 2000: 304 s.
12. Morokhovets H. Yu. Formuvannya informatsiynoho osvitnoho seredovyshcha vyshchoho medychnoho zakladu osvity. Visnyk Chernihivskoho natsionalnoho pedahohichnoho universytetu. Seriya: Pedahohichni nauky. Fizychne vykhovannya ta sport. (136). 2016: 132-134.
13. Kaidashev I.P. NF-kB activation as a molecular basis of pathological process by metabolic syndrome. Fiziol Zh. 58(1). 2012: 93-101.
14. Lysanets Y., Morokhovets H., Bieliaieva O. Stylistic features of case reports as a genre of medical discourse. Journal of medical case reports. 11(1). 83. 2017: http://10.1186/s13256-017-1247-x
15. Lysanets Yu., Bieliaieva O. The Use of Latin Terminology in Medical Case Reports: Quantitative, Structural, and Thematic Analysis. Journal of Medical Case Reports. Vol. 12 (45). 2018: https://10.1186/s13256-018-1562-x
16. Morokhovets H. Yu. Metodyka formuvannya informatsiyno-komunikatsiynoyi kompetentsiyi maybutnikh likariv u osvitnomu seredovyshchi vyshchoho medychnoho navchalnoho zakladu. Osvita ta rozvytok obdarovanoyi osobystosti. (3). 2016: 32-34.
17. Morokhovets H., Mishchenko S. Efektyvnist zastosuvannya informatsiyno-komunikatsiynykh tekhnolohiy pry vykladanni medychnoyi i biolohichnoyi fizyky u konteksti kompetentnistnoho pidkhodu v osviti. Naukova diyal'nist' yak shlyakh formuvannya profesiynykh kompetentnostey maybutn'oho fakhivtsya (NPK-2015): materialy Vseukrayins'koyi naukovo-praktychnoyi konferentsiyi 2-3 hrudnya 2015 r., m. Sumy u 2-kh tomakh. Sumy, 2015: 49-53.
18. Morokhovets H. Yu. Metodyka formuvannya informatsiyno-komunikatsiynoyi kompetentsiyi maybutnikh likariv u osvitnomu seredovyshchi vyshchoho medychnoho navchalnoho zakladu. Osvita ta rozvytok obdarovanoyi osobystosti. 3. 2016: 32-34.
19. Lyenkova O. O., Morokhovets H. Yu., Mishchenko S. V. Formuvannya informatsiyno-komunikatsiynykh kompetentsiy maybutnikh likariv na zasadakh vykorystannya kompyuternykh tekhnolohiy u navchalnomu protsesi. Aktualni problemy suchasnoyi medytsyny: Visnyk ukrayinskoyi medychnoyi stomatolohichnoyi akademiyi. T.15. Vyp. 3(51). 2015: 264-269.
20. Morokhovets H. Informatsiyno-komunikatsiyni kompetentsiyi v systemi profesiynoyi pidhotovky maybutnikh likariv. Problemy ta perspektyvy rozvytku nauky na pochatku tretoho tysyacholittya u krayinakh Yevropy ta Aziyi. Pereyaslav Khmel'nyts'kyy; 2011: 68.
21. Tron N. V., Lobach N. V., Tkachenko Yu. P. et al. Dydaktychni umovy vprovadzhennya informatsiyno-komunikatsiynykh tekhnolohiy v protses navchannya medychnoyi ta biolohichnoyi fizyky inozemnykh studentiv. Svit medytsyny ta byolohyy. 2. 2013: 182-183.
22. Morokhovets H. Yu. Pedahohichni umovy formuvannya informatsiyno-komunikatsiynykh kompetentsiy u maybutnikh likariv. Visnyk Cherkaskoho universytetu: Pedahohichni nauky. 3. 2016: 13-16.
23. Lysanets Yu., Morokhovets H., Ostrovska L., Purdenko T. Methodological Feasibility of Test Technologies in Assessing Medical Students' Proficiency. Problemy ekolohii ta medytsyny. 21(3-4). 2017: 55-58.

Authors' contributions:
According to the order of the Authorship.
Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Halyna Yu. Morokhovets
Ukrainian Medical Stomatological Academy
23 Shevchenko Str., 36011 Poltava, Ukraine
e-mail: polstomumsa@gmail.com

Received: 10.08.2018
Accepted: 20.12.2018

PRACA ORYGINALNA
ORIGINAL ARTICLE

HEALTH-RELATED BEHAVIOUR IN ADOLESCENTS WHO HAVE RECEIVED BASIC INSTRUCTION IN HEALTH PROMOTION

ZACHOWANIA ZDROWOTNE U MŁODZIEŻY, KTÓRA OTRZYMAŁA PODSTAWOWY INSTRUKTAŻ W ZAKRESIE PROMOCJI ZDROWIA

Ruslan V. Tekliuk, Ihor V. Serheta, Oksana A. Serebrennikova
DEPARTMENT OF GENERAL HYGIENE AND ECOLOGY, NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSYA, UKRAINE

ABSTRACT

Introduction: Both positive and risky health behaviours among adolescents are of paramount importance as they often pathway further lifestyles and determine future health outcomes. The paper focuses on the trends of health promotion activities and health risks among adolescents who have been instructed on these topics at secondary schools.
The aim: to detect trends in pro-active health behaviour and risk taking activities of Ukrainian adolescents in the last 14 years.
Materials and methods: males and females, aged 15-17, who studied in secondary schools of the urban area of Vinnytsia city, Ukraine, in the years 2003, 2013, 2017, anonymously filled in the 118-item questionnaire. Descriptive statistics, Cochran Q test, Spearman correlation analysis, Kendall's tau coefficient were used to analyze the data.
Results: Overall, the data about health related issues obtained in the year 2003 vary significantly from the years 2013 and 2017, which indicates some beneficial influence that has taken place since 2003. Much fewer differences were spotted between the years 2013 and 2017. Health related behaviours in females showed less significant dynamics and some changes indicate regression, while males reported multiple improved results. Meanwhile actual numbers of males who opted for risky behaviours were higher than those of females. Significant relationships were found between some socio-economic factors, positive health behaviours (sufficient sleep, physical activity, daily regime, and life satisfaction) and proactive health choices.
Conclusions: The available data suggests that there was a beneficial health-related influence on the schoolchildren over the years 2003-2017. Our findings also support the view that certain assets may protect the youth from risk-taking behaviours.

KEY WORDS: adolescents, health risks, proactive health behaviour, health promotion

Wiad Lek 2019, 72, 1, 12-16

INTRODUCTION

The European child and adolescent health strategy 2015-2020 points out promotion of health literacy from childhood through adolescence as a strategic aim that can improve skills of informed decision making in European citizens. This strategy falls in line with the understanding of multiple determinants of adolescent health, which include risk and protection factors, as well as controversial influence of social norms of peer groups, family and school, which 'may expose adolescents to risk, as well as protect them' [1, p. 8-9].

Modern health promotion interventions are becoming more patient-centered, as the problem-oriented approach to health care is no longer sufficient. By complementing the deficit model with 'assets' models, the researchers and policy makers are investing more effort and means into promoting the self-management, empowerment and coping abilities of individuals and communities, eventually leading to less dependency on health care professional services [2; 3; 4]. Numerous publications display health assets' contribution to improved health behaviour and outcomes [5]. However, we can also hear warnings against blind focusing only on psychosocial factors, abstracted from socio-economic issues and their relationship to the distribution of health [6].

In general, protective factors, the so-called 'health assets', are considered to be a combination of internal qualities and personal potentials, as well as positive external factors that promote positive health behaviour and optimal health outcomes [7]. These protective factors operate at different levels: 1) an individual or group level (e.g. social competence, commitment to learning, positive values, a sense of purpose); 2) community level (e.g. family and friendship support, mutual aid, religious tolerance and harmony); 3) institutional level (environmental resources necessary for promoting physical, mental and social health, employment security, safe housing, social justice, etc.) [2].

Major concerns about risky behaviour among adolescents are connected with use of alcohol, tobacco and other substances, unprotected sex and early start of sexual behaviour, sedentary lifestyle, harmful eating habits, etc., because such actions lead to long-term negative effects [1; 8]. Addressing these and other health risks means introduction of health promotion strategies, for instance,

strengthening protective factors in schools, homes and local communities and improving the quality of health care for children and adolescents, as well as enhancing their knowledge of health related issues [9].

Numerous researches estimate significant positive relationships between various assets and health risks. Roy F. Oman et al. (2004) study supports the view that links risk reduction with simultaneous efforts to increase protective factors [10]. Non-use of alcohol is positively connected with peer role models, positive family communication, physical exercise, proper nutrition, and adolescents' aspirations for the future [10].

Social capital (such as sense of family belonging and involvement in the neighbourhood) appears to offer a protective influence on health and certain health-related outcomes, despite the fact that teenagers from high affluence families are more likely to drink alcohol compared with peers from the least wealthy families [11]. Parental expectations, positive peer influence and future aspirations are also found to be protective against adolescent substance use and sexual behaviour [12]. Feeling connected to family or school is associated with lower odds of having engaged in risky sexual behaviours, too [13]. Even the frequency of family dinners may serve as a protective factor that reduces high-risk behaviours among youth [14].

Leisure-time physical activity in adolescence has a long-term beneficial psychological effect [15]. Participation in school sports is associated with less likelihood of cigarette smoking and illegal drug use [16].

Intensive use of each ICT form (computer, digital gaming and mobile phone), especially of mobile phones, was associated with health problems. However, high social background and success at school signify better health, independently of the ways of using ICT [17]. Interestingly, the research by Iannotti et al. (2009) found regional differences in positive influence of adolescent physical activity and negative influence of screen-based sedentary behaviours on psychological and social health, which suggests the idea that cultural, regional and social factors may modify the influence of protective and risk factors [18]. According to Springer et al (2006), protective factors may also work differently with males and females [19].

Combined risk prevention and assets-based approach, supported by systematic school instruction on health care can stimulate adolescents to 'transition from mere recipients of health promotion and risk prevention efforts into proactive, informed individuals who consciously make healthy choices for themselves' [20].

The issues of positive and risky health behaviours among adolescents are carefully monitored within the frames of the collaborative cross-national study Health Behaviour in School-aged Children (HBSC) [21]. However, we think it is important to overcome one of the limitations of the survey – too varied social and regional contexts, which makes it difficult to spot any changes in a particular location.

We will outline our findings, obtained from the surveys of the pupils of the same schools, made at different periods. Though the interviewees are probably not acquainted with each other, it is important to discover some changes in the same adolescent "subculture": the teenagers, who attended the same schools in different years, mostly live in the same neighbourhood, are of the similar social status, are instructed by the same teachers, hear the same urban legends, etc. Thus, any changes, which are spotted, will not be explained by regional or acute social discrepancies, but should be viewed from some other perspectives.

THE AIM

The following study was aimed at detecting changes in pro-active health behaviour and risk taking activities of adolescents over the period of 14 years, with particular reference to outcomes of formal instruction on health promotion. We hypothesized that there should be some difference in health-related behaviours between the adolescents who have received systematic schooling on health related issues and those who have not.

MATERIALS AND METHODS

We explored positive and risky health behaviour in groups of adolescents, aged 15–17, via the surveys conducted in the years 2003, 2013, 2017. The data were obtained from adolescents who went to secondary comprehensive schools №4 and №29 in the urban area of Vinnytsia, Ukraine. The participation was voluntary. The general numbers of the participants were the following: year 2003 – 133 females and 116 males; year 2013 – 118 females and 97 males; year 2017 – 124 females and 115 males.

The participants filled in questionnaires (developed at the Department of General Hygiene and Ecology of VNMU), which cover about 165 variables. The questionnaires were filled in anonymously. All incomplete questionnaires (no more than 1% of all papers) were excluded from further analysis.

In the initial year of our study, 2003, the participants of our survey had not received systematised schooling in health issues, whereas teenagers in the years 2013 and 2017 had 9 years of full health promoting course, introduced by the Ministry of Education and Science of Ukraine. Yet, the difference between the last two groups is that the survey of 2013 was conducted just before the start of the armed conflict in the East of Ukraine, and the 2017 survey was done after four years of the military actions in Ukraine. This unfavourable change may have influenced the outcomes of some interventions, including the one we take into consideration. We looked at the differences between the groups, which might be prompted by the educational intervention.

The statistical analyses were performed by STATISTICA 6.1 software (license number AXX910A374605FA). First, the standard descriptive and frequency analyses of each variable were conducted. The significance of changes in health-related issues through years was measured by Cochran Q test. Spearman rank order correlation analysis and Kendall's tau coefficient were used to explore associations between key risk and protective factors. We considered p-value less than 0,05 as statistically significant.

Data included demographic and socioeconomic information, issues related to perceived health status, various risk exposures and health-related behaviours (exercise, nutrition, fresh air, daily routines), as well as protective factors, such as psychological wellbeing, family, school, use of time (entertainment, religious activities), aspirations for the future and responsible choices. Some questions have been added or omitted in subsequent surveys to respond to emerging issues. However, the core questions have remained the same.

RESULTS

This study documented several trends in health-related behaviours among adolescents, aged 15-17, over the last 14 years.

RISK PRONE BEHAVIOUR

From 2003 to 2017, the percentage of the youth, who admit that they smoke, decreased significantly for both males (35,34% to 15,65%, p< 0,05) and females (24,06% to 6,45%, p< 0,01). Interestingly, the results were generally more positive in the survey of 2013 both in terms of any experience of smoking and continuous smoking, which makes us wonder whether some political or social factors (e.g. military conflict, economic crises) had additional influence on the teenagers' attitudes and behaviour. So far we must point out much more optimistic decline in the number of males who have ever tried smoking from 78,45% in 2003 to 42,27% in 2013 and 40,87% in 2017. The difference is statistically significant at p<0,001 for the years 2003 and 2013, as well as 2003 and 2017. Among females the situation is considerably less clear: 56,39% in 2003, then 23,73% (p< 0,001) in 2013 and staggering 46,77% in 2017. Our findings fall in line with the HBSC results which stated the decline of weekly smoking among 15-year old Ukrainian males and females in 2013 [21] compared to 2009-2010 [22].

Drug addiction does not seem have a clear pattern. The numbers in males and females who took up illegal drugs 2003 and 2017 were not significantly different: among females 4,51% and 4,84% respectively, and among males 9,48% and 8,7%. As well as with smoking, year 2013 showed considerably lower numbers – 0% among girls and 5,6% among boys. We cannot account for the factors that have prompted such results. The only positive tendency we have found was the stable decrease in the number of males who have ever tried drugs from 22,41% in 2003 to 14,43% in 2013 and 13,91% in 2017.

Reduction of alcohol consumption faces some cultural and social obstacles, as adolescent alcohol consumption is not always condemned, especially when it occurs in the presence of the parents. Fortunately, we may state eventual shift in the age groups when first alcohol consumption occurs. Far less males reported alcohol consumption before the age of 10: compare 25,22% in 2003 and 2,61% in 2017, which means children are now limited in their access to such beverages and are probably better controlled by their parents, or are not offered a swig by elder children in the yard. Reduction in the number of females who have tried alcohol before the age of 10 was significant, but not so steep – from 26,32% in 2003 to 7,63% in 2013 and 8,07% in 2017. In 2013-2017 years, there appeared groups of male and female teenagers who claimed they had never tried alcohol. Interestingly, among males more than a half claimed absence of such experience (58,76%-53,05%), but only every fifth girl stated the same (21,17%-20,16%). These encouraging results may be related in part to the changed attitude to being regularly drunk. We may see that the number of males who had been drunk more than 4 times fell from 22,61% in 2003 to 9,09% in 2013 (p<0,05) and 10,43% in 2007. The numbers of girls with the same experience decreased from 9,78% in 2003 to 0,85% in 2013 (p<0,01), then rose to 5,65% in 2017.

Lack of sufficient sleep seems to be an emerging problem that may lead to negative outcomes. The change in daily routines and accessibility of gadgets made it easy for teenagers to shift their going to bed to very early hours of the morning, but sleeping hours are becoming shorter as they still have to get up soon to go to school. 54, 03% females interviewed in 2017 were severely deprived of sleep – slept less than 6 hours a day (compared with 16,95% in 2013 and 8,97% in 2003, p <0,05). The increase in sleep-deprived males was not so steep, but significant: 4,84% in 2003; 16,49% in 2013, and 33,91% in 2017 (p<0,05). The Ukrainian society has recently become extremely concerned with the cases when sleep-deprived children got psychologically involved in deadly dangerous online groups who promoted suicidal actions. As we can see, the figures of sleep-deprived children make it an urgent issue.

Both males and females' personal assessments of probability of developing numerous health risks did not show any clear tendencies, apart from one – over the years fewer teenagers admitted the likelihood of some problems that might arise due to their sexual relationships (such as sexually transmitted diseases, unwanted pregnancy). The numbers of the females who were predicting, to some degree, health problems connected with sexual relations fell from 27,72% in 2003 to 9,32% in 2013 (p < 0,01) and 16,13% in 2017. More males than females predicted such problems, and their number fell insignificantly from 34,48% in 2003 to 31,96% in 2013 and 28,7% in 2017.

PRO-ACTIVE HEALTH-RELATED BEHAVIOUR

Popularity of daily physical exercise over 2 hours has risen among both males and females, compare: 48,82% in 2003 and 60,48% in 2017 among females; 54,84% in 2003 and 76,09% in 2017 among males. These numbers support the findings of HBSC surveys of 2002/2006 [23] and 2013/2014 [21], which also state the increase of moderate-to-vigorous physical activity among Ukrainian teenagers.

Significant improvement in the amount of time, spent in the fresh air, was found in the year 2017 for females – 54,02% (as compared to 25,42% in 2013 and 26,92% in 2003) and in 2013-1017 years for males – 45,35% and 64,35% respectively (compared to 35,48% in 2003). This tendency can be partly explained by the fact that teenagers can easily take their gadgets with them and entertain themselves outdoors, without being controlled by their parents.

On the basis of 2017 survey, we explored the associations between some protective factors (family, school adaptation,

extracurricular community activities, healthy habits, etc.) and key risk/health choices.

Full family served as a protective factor for females, as a significant negative association was found between full family membership and friendship with people who suffered from sexually transmitted diseases (STD) (r_s=-0,28, τ=-0,27, p<0,05), and first cases of taking illegal drugs (r_s=-0,33, τ=-0,32, p<0,05). Among males full family membership was associated with having breakfast (r_s=0,21, p<0,05) and brushing teeth (r_s=0,24, p<0,05), negatively related to frequency of wine consumption (r_s=-0,22, p<0,05).

Family affluence has a controversial relationship to health-related issues among girls: positive associations were found with daily routine (r_s=0,26, τ=0,25, p<0,05), school adaptation (r_s=0,25, τ=0,23, p<0,05), plans for the future (r_s=0,20, τ=0,19, p<0,05), life satisfaction (r_s=0,39, τ=0,36, p<0,05), good perceived health (r_s=0,30, τ=0,28, p<0,05), less days on sick leave (r_s=0,25, τ=0,20, p<0,05). Yet, higher economic status of female teenagers' families turned out to be associated with earlier age of alcohol consumption (r_s=0,29, τ=0,25, p<0,05) and friendship with people who suffered from STD (r_s=0,29, τ=0,25, p<0,05). Among males, family economic status was related to daily routine (r_s=0,21, p<0,05), knowledge of HIV transmission (r_s=0,23, p<0,05), cleaning teeth (r_s=0,25, p<0,05) and eating breakfast (r_s=0,20, p<0,05), but also with smoking habits (r_s=0,20, p<0,05).

High academic achievements of males at school are positively associated with psychological school adaptation (r_s=0,25, p<0,05), dental care (r_s=0,23, p<0,05) and rational dieting (r_s=0,20, p<0,05), but negatively related with perceived health (r_s=-0,21, p<0,05). Successful studies of females at school are negatively associated with friendship with people who suffered from STD (r_s=-0,20, p<0,05) and perceived problems connected with sexual relationships (r_s=-0,20, p<0,05). It is positively related to having breakfast (r_s=0,30, p<0,05), daily routine (r_s=0,25, p<0,05), non-smoking beliefs (r_s=0,25, p<0,05), school adaptation (r_s=0,31, p<0,05), and, sadly, with more days on sick leave (r_s=0,24, p<0,05).

Going in for sports and clubs also show some preventive influence. Among females, sport is positively associated with rational eating routine (r_s=0,22, p<0,05), other hobbies (r_s=0,24, p<0,05), ability to count calories in the daily ration (r_s=0,25, p<0,05), and beliefs about later start of sexual relationships for girls (r_s=0,21, p<0,05) and boys (r_s=0,26, p<0,05). Going to extracurricular clubs is positively related to psychological readiness for school activities (r_s=0,24, p<0,05), and negatively related to experience of smoking (r_s=-0,23, p<0,05), being ever drunk (r_s=-0,20, p<0,05) and friendship with drug addicts (r_s=-0,22, p<0,05). Among males, going in for sports was not associated with any particular health-related issues, except for using less computer (r_s=-0,21, p<0,05) and watching more TV (r_s=0,23, p<0,05). Attending clubs showed no significant influence on health-related choices of teenaged boys.

Sufficient night sleep was associated among the girls with healthy eating routine (r_s=0,28, p<0,05), frequency of meals (r_s=0,30, p<0,05), and negatively associated with bad mood (r_s=-0,27, p<0,05) and daily use of computer (r_s=-0,18, p<0,05). Enough sleep among the boys was related to daily routine (r_s=0,26, p<0,05), better perceived health (r_s=0,21, p<0,05), and less computer work (r_s=-0,31, p<0,05).

Adhering to daily routine was associated among females with absence of friends who are drug addicts (r_s=0,27, p<0,05), good perceived health (r_s=0,22, p<0,05), perceived importance of health (r_s=0,23, p<0,05), psychological readiness for school (r_s=0,24, p<0,05), school adaptation (r_s=0,25, p<0,05), life satisfaction (r_s=0,42, p<0,05), ability to decline an unpleasant offer (r_s=0,26, p<0,05).

Males who carried out daily routines showed multiple proactive behaviours: they often slept longer (τ=-0,23, p<0,05), had daily breakfast (r_s=0,39, p<0,05), felt better after weekend (r_s=0,27, p<0,05), missed fewer classes because of illness (r_s=-0,23, p<0,05), didn't drink beer (r_s=-0,37, p<0,05) or wine (r_s=-0,24, p<0,05), didn't take drugs (r_s=-0,29, p<0,05), didn't have friends who were drug addicts (r_s=-0,42, p<0,05), had positive perception of their health (r_s=0,36, p<0,05), felt physically fit (r_s=-0,28, p<0,05), etc.

Length of daily physical activity is positively related to length of time spent outdoors both among males (r_s=-0,31, p<0,05) and females (r_s=0,26, p<0,05). Among females it was also associated with ability to decline an unpleasant offer (r_s=0,24, p<0,05), knowledge about ways of transmitting HIV (r_s=0,29, p<0,05), ability to count one's pulse (r_s=0,24, p<0,05), and was negatively connected with eating daily lunch (r_s=0,21, p<0,05) and friendship with people who suffered from STD (r_s=-0,29, p<0,05). Among males physical activity was related to perceived importance of health (r_s=0,32, p<0,05), negative alcohol-related beliefs (r_s=-0,27, p<0,05), physical and psychological adaptation to school (r_s=0,23 and r_s=0,22, p<0,05), with absences of breakfast (r_s=-0,24, p<0,05).

DISCUSSION

The data about health-related issues obtained in the year 2003 vary significantly from the years 2013 and 2017, which indicates some beneficial influence that has taken place since 2003. Much fewer differences were spotted between the years 2013 and 2017. Health related behaviours in females showed less significant dynamics and some changes indicate regression, while males reported multiple improved results. Meanwhile actual numbers of males who opted for risky behaviours were higher than those of females. Yet, we cannot claim that only educational intervention prompted significant positive dynamics in the adolescents' health related behaviours.

Some surprising negative changes that appeared in 2017 might be explained by aggravated socio-economic crises and armed conflict in the country, but need some additional research into this issue.

We tried to look into the relations between protective and risk factors that might prompt the changes in the survey 2017. Significant relationships were found between some socio-economic factors, positive health behaviours (sufficient sleep, physical activity, daily regime, and life satisfaction) and proactive health choices, as well as lower

prevalence of youth alcohol, smoking and drug abuse. The factors mostly had different significance for males and females. These findings, as well as the analysis of the overall tendencies, suggest that teenagers of different sex may respond differently to health promoting interventions.

CONCLUSIONS

The available data suggests that there was a beneficial health-related influence on the schoolchildren over the years 2003-2017. Our findings also support the view that certain assets may protect the youth from risk-taking behaviours. Additional research is needed to document the effectiveness of population-level educational intervention, which was introduced by the Ministry of Education and Science of Ukraine in 2001.

REFERENCES

1. Investing in children: the European child and adolescent health strategy 2015-2020// Regional Committee for Europe 64th Session. Copenhagen, Denmark, 15–18 September 2014. [accessed 6.06.2018]. http://www.euro.who.int/en/health-topics/Life-stages/child-and-adolescent-health/policy/investing-in-children-the-european-child-and-adolescent-health-strategy-20152020 .
2. Morgan A, Ziglio E. Revitalising the evidence base for public health: an assets model. Promotion & Education. 2007, Supplement (2): 17-22.
3. Rotegård AK, Moore SM, Fagermoen MS, Ruland CM. Health assets: A concept analysis. Int J Nurs Stud. 2010; 47(4):513-25. doi: doi.org/10.1016/j.ijnurstu.2009.09.005
4. Scales PC. Reducing risks and building developmental assets: essential actions for promoting adolescent health. 2009; 69 (3):113-119. https://doi.org/10.1111/j.1746-1561.1999.tb07219.x .
5. Alvarez-Dardet C, Morgan A, Ruiz Cantero MT, Hernán M. Improving the evidence base on public health assets—the way ahead: a proposed research agenda. J Epidemiol Community Health. 2015; 69(8):721-3. http://dx.doi.org/10.1136/jech-2014-205096 .
6. Friedli L. 'What we've tried, hasn't worked': the politics of assets based public health. Critical Public Health. 2012; 23 (2): 131-145. https://doi.org/10.1080/09581596.2012.748882
7. Rotegaard AK, Ruland CM. Patient centeredness in terminologies: Coverage of health assets concepts in the International Classification of Nursing Practice. Journal of Biomedical Informatics. 2010; 43: 805–811.
8. Serheta IV, Bratkova O.Yu, Mostova OP, Panchuk OYu, Dudarenko OB. Naukovi pryntsypy psykhohihiyenichnoyi diagnostyky stanu zdorovia ditey, pidlitkiv ta molodi. Dovkillia ta zdorovia. 2012; 4(64): 21-25.
9. Serheta IV, Tekliuk RV, Bratkova OYu. Zdoroviazberihayuchi kompetentsii shkoliariv ta osoblyvosti yikh zmin v dymanitsi ostannikh desiatylit. Materialy naukovo-praktychnoyi konferentsii "Dovkillia ta zdorovia". Ternopil, Ukrmedknyha. 2018: 105-107.
10. Oman RF, Vesely S, Aspy CB, McLeroy KR, Rodine S, Marshall LaD. The potential protective effect of youth assets on adolescent alcohol and drug use. Am J Public Health. 2004; 94:1425-1430.
11. Morgan A, Haglund JA. Social capital does matter for adolescent health: evidence from the English HBSC study. Health Promotion International. 2009; Vol. 24; No. 4: 363-372. doi:10.1093/heapro/dap028 .
12. Dunn MS, Kitts C, Lewis S, Goodrow B. Effects of youth assets on adolescent alcohol, tobacco, marijuana use, and sexual behavior. Journal of Alcohol and Drug Education. 2011; 55 (3): 23-40.
13. Saewyc EM, Taylor D, Homma Y, Ogilvie G. Trends in sexual health and risk behaviours among adolescent students in British Columbia. Can J Hum Sex. 2008; 17(1-2): 1–13.
14. Fulkerson JA, Story M, Mellin A, Leffert N, Neumark-Sztainer D, French SA. Family dinner meal frequency and adolescent development: relationships with developmental assets and high-risk behaviors. Journal of Adolescent Health. 2006; 39: 337-345.
15. Sacker A, Cable N. Do adolescent leisure-time physical activities foster health and well-being in adulthood? Evidence from two British birth cohorts. European Journal of Public Health. 2005; Vol. 16; No. 3: 331–335. doi:10.1093/eurpub/cki189 .
16. Page RM, Hammermeister J, Scanlan A, Gilbert L. Is School Sports Participation a Protective Factor against Adolescent Health Risk Behaviors? 2013; 29 (3): 186-193. https://doi.org/10.1080/10556699.1998.10603332 .
17. Koivusilta LK, Lintonen TP, Rimpela AH. Orientations in adolescent use of information and communication technology: A digital divide by sociodemographic background, educational career, and health. Scandinavian Journal of Public Health. 2007; 35(1): 95-103.
18. Iannotti RJ, Janssen I, Haug E, Kololo H, Annaheim B, Borraccino A. Interrelationships of adolescent physical activity, screen-based sedentary behaviour, and social and psychological health. International Journal of Public Health. 2009; 54 (Supplement 2): 191-198.
19. Springer A, Parcel G, Baumler E, Ross M. Supportive social relationships and adolescent health risk behavior among secondary school students in El Salvador. Social Science & Medicine. 2006; 62: 1628-1640. https://doi.org/10.1016/j.socscimed.2005.08.018
20. Duncan PM, Garcia AC, Frankowski BL, et al. Inspiring healthy adolescent choices: a rationale for and guide to strength promotion in primary care. Journal of Adolescent Health. 2007; 41: 525-535.
21. Growing up unequal: gender and socioeconomic differences in young people's health and well-being. Health behaviour in school-aged children (HBSC) study: international report from the 2013/2014 survey. World Health Organization, 2016.
22. Currie C et al., eds. Social determinants of health and well-being among young people. Health Behaviour in School-aged Children (HBSC) study: international report from the 2009/2010 survey. Copenhagen, WHO Regional Office for Europe, 2012.
23. Health Policy for Children and Adolescents, No. 5. World Health Organization / Eds. Candace Currie, Saoirse Nic Gabhainn et al. Edinburgh: University of Edinburgh, 2008. 208p.

Authors' contributions:
According to the order of the Authorship.
Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Ruslan V. Tekliuk
42/ 83 Lytvynenko-Volgemut street, 21018, Vinnytsia, Ukraine
tel: +380972821314
e-mail: teklyukru@gmail.com

Received: 20.07.2018
Accepted: 12.12.2018

PRACA ORYGINALNA
ORIGINAL ARTICLE

TREATMENT OF LACTASE DEFICIENCY IN CHILDREN'S OBESITY WITH GENOTYPE C/C 13910 OF LACTASE GENE

LECZENIE NIEDOBORU LAKTOZY U OTYŁYCH DZIECI Z GENOTYPEM C/C 13910 DLA GENU LAKTAZY

Alexandr Ye. Abaturov, Yuri M. Stepanov, Anna A. Nikulina
STATE INSTITUTION "DNEPROPETROVSK MEDICAL ACADEMY OF THE MINISTRY OF HEALTH OF UKRAINE", DNIPRO, UKRAINE

ABSTRACT

Introduction: Excess lactose in the diet of modern man causes the development of not only lactase deficiency, but it can be a factor that contributes to obesity.

The aim: To study associations between obesity and genotype C/C 13910 of lactase gene (*LCT*) in children, to investigate the effectiveness of treatment using drug exogenous lactase and a low-lactose diet.

Materials and methods: genotyping of lactase gene by real-time polymerase chain reaction, determining the level of lactose maldigestion by hydrogen breath test (HBT), estimating the insulin resistance with the HOMA-IR index in 70 obese children and 40 healthy children 6 - 18 years. Obese children with genotype C/C 13910 and lactose maldigestion (n=40) were randomized in two groups: children from group I (n=20) received an exogenous lactase preparation, and children from group II (n=20) - low-lactose diet.

Results: in obese children, the genotype C/C 13910 is 2 times more often than in healthy children. Obese children with genotype C/C 13910 have a significantly higher value of HBT (32.8–39.8 ppm) compared to healthy children ($p<0.05$), and an increased value of the HOMA-IR index. After treatment, there was a significant decrease in HBT and the HOMA-IR index in the two comparison groups.

Conclusions: signs of insulin resistance are observed in children with obesity, genotype C/C 13910 and lactose maldigestion. The use of exogenous lactase in the therapy or the administration of a low-lactose diet cause approximately the same decrease in the HOMA-IR index.

KEY WORDS: hydrogen breath test, genotype C/C 13910, lactose maldigestion, obesity

Wiad Lek 2019, 72, 1, 17-21

INTRODUCTION

The leading cause of the disorder of lactose digestion is the discrepancy between the level of lactose load and the activity of lactase production. Single nucleotide polymorphisms (SNP) of the lactase gene (*LCT*) affect the characteristics of the production of this enzyme during human ontogenesis. According to modern concepts, at position 13910 of the *LCT* gene sequence, the majority of representatives of the human population have cytosine (C). This cytosine base is located approximately 14 kb upstream of the *LCT* transcription site, in the regulatory region of the lactase gene - *MCM6* (minichromosome maintenance complex 6). The gradual age-related decrease in the level of lactase production, most often manifested from the second year of life, is characteristic of the individual's homozygous state (C/C). The homozygous state of C/C 13910 is recorded in, more than 32% of Caucasians, 99% of East Asians, 74% of South Asians and 59% of individuals of other or mixed ethnic groups [1]. The loss of the lactase activity of the lactase and the ability to synthesize lactase at a sufficiently high level throughout life is characteristic of individuals with the SNP of the *LCT* gene, which are characterized by replacement of the cytosine by the thymine base (T) at position 13910. The SNP data of the *LCT* gene lead to the appearance two variants of genotypes: heterozygous (C/T) and homozygous (T/T). Taking into account, that allele T is dominant; both these genotypes are accompanied by lactase persistence (LP) [2; 3; 4; 5].

The maximum level of LCT expression is noted in the duodenum (121.7 RPKM (reads per kilobase per million), and the jejunum (73.8 RPKM) and provides hydrolysis of lactose disaccharide to two monosaccharides - glucose and galactose, capable of being absorbed by intestinal enterocytes [6]. Galactose is metabolized in the liver, where epimerization to glucose occurs upon accession to uridine-5'-diphosphate (UDP), with the formation of UDP-glucose. UDP-glucose is a direct precursor of glycogen synthesis and can not be reversed through UDP-glucose pyrophosphorylase (EC 2.7.7.9) to glucose-1-phosphate in vivo [7]. Due to this pathway, which is perhaps one of the evolutionary advantages of galactose as a lactose, almost 100% of the dietary galactose absorbed from the gastrointestinal tract, is converted into hepatic glycogen. While with lactase deficiency (LD), it becomes impossible.

Most often clinical manifestations of LD begin to be registered from 10 to 16 years of age, which coincides with

the critical period of risk of obesity and the formation of insulin resistance in the pubertal period. It is in adolescents 12-19 years, the incidence of obesity has the highest level - 20.5%, while in the children's population as a whole, this figure is about 17% [8, 9, 10].

It is also interesting that the occurrence of LP in the geographical regions of Europe has a negative feedback from the prevalence of obesity. Thus, the maximum frequency of occurrence of LP, more than 90%, is observed among the population of the Nordic countries of Scandinavia and the Netherlands, and the minimum among the population of southern Europe (Italy and Spain). The lowest prevalence of overweight and obesity in the European Region is registered in Norway and is 15% among children aged 7- 8 years (13.5% for boys and 17.8% for girls), the highest level is in Italy and is 36% (among boys – 37.2% and among girls – 34.7%) [11]. Therefore, we believe that the genotype C/C 13910, associated with adult-type LD, is targeted for the emergence of a systemic inflammatory response and the formation of insulin-resistant obesity [12].

The occurrence of obesity and its complicated course in recent years, especially among children living in large cities, is increasing at an epidemic rate, but the causes of this pathomorphosis remain poorly understood. In particular, the role of lactose in the formation of insulin resistance associated with obesity in children is not reflected.

THE AIM

Objective: to study associations between obesity and genotype C/C 13910 of the lactase gene (*LCT*) in children, to investigate the effectiveness of treatment using drug exogenous lactase and a low-lactose diet.

MATERIALS AND METHODS

We inform that patients gave their informed consent to participate in the study. The study was carried out according to the ethical principles of the Medical Study conducted with the participation of people set forth in the Helsinki Declaration. The study was with the permission of the local bioethics commission in accordance with the requirements of the bioethical committee (protocol No. 2 of the bioethical examination of the State Institution "DMA of Ministry of Health of Ukraine" dated 10.02.2016. Head of the Commission: MD, Professor V.V. Koldunov).

Genotyping was carried out at the polymorphic locus of the *LCT* gene by real-time polymerase chain reaction (RT-PCR) in 70 obese children and 40 healthy children from 6 to 18 years of age. The SNP *LCT* study was carried out in a certified Synevo laboratory, as the analyzer used the detector "CFX96 (BioRad)", USA. The material for the study was venous blood.

To determine insulin resistance, the Homeostasis Model Assessment was calculated, before and after treatment, based on basal insulinemia and blood glucose in venous blood, using the Immunochemical Test Method with Electrochemiluminescent Detection (ECLIA) in the Synevo laboratory. The presence of insulin resistance was recorded with the index HOMA-IR>95th percentile, respectively, with the percentile curves recommended by the IDEFICS consortium for the European population according to the age and sex of the child [13].

A hydrogen breath test with lactose load (at a rate of 1 g/kg but not more than 25 g of lactose in the form of a 10% aqueous solution) was performed at the "Gastro+ Gastrolyser" Gas Analyzer of the British company "Bedfont Scientific Ltd" at the Institute of Gastroenterology of the National Academy of Medical Sciences of Ukraine. The hydrogen concentration in the patient's exhaled air was determined in parts per million (ppm). The test was considered positive when the level of hydrogen concentration in the exhaled air increased by more than 20 ppm (0.002%) after 60 minutes compared to the basal level and the appearance of clinical symptoms of LD during the next three hours of observation [14]. An increase of H2 in air samples without the appearance of characteristic symptoms indicated the lactose maldigestion, with the appearance of characteristic symptoms - of lactose intolerance [15].

Children with obesity, with genotype C/C 13910 and lactose maldigestion (n=40), to study the effectiveness of various treatments, were randomized in two comparison groups. Patients from group I (n=20) received an exogenous lactase preparation "Mamalac" (National Enzyme Company Inc., USA, Distributor in Ukraine: Pharmunion BSV Development Ltd.), 30 mg (3000 ALU Aspergillus orizae) three times a day for 1 month, and patients in group II (n=20) had a low-lactose diet, according to the computer program „Low- lactose diet" [16]. In addition, all patients and their parents received counseling on lifestyle modification, psychologist's recommendations, in the case of insulin resistance; children over 12 years of age were prescribed metformin at the age-appropriate dosage.

Criteria for the effectiveness of treatment were the normalization of the HOMA-IR index and HBT indices.

Statistical processing of the results of the study used the methods of variation statistics using the STATISTICA software package (version 6.1) StatSoftInc. serial number AGAR 909E415822FA, adapted for biomedical research with the False Discovery Rate control (FDR) to compare the effectiveness of various methods of treatment ($p<0.05$).

RESULTS

Insert the text of the results here. In children with obesity of 6-18 years (n=70), the genotype C/C 13910 was registered in 57.1% (n=40), the genotype of C/T 13910 - in 28.6% (n=20), and the genotype T/T 13910 - in 14.3% of cases (n=10). Of 40 healthy children 6-18 years old, the genotype C/C 13910 was registered in 37.5% (n=15), the genotype of C/T 13910 was 55% (n=22), and the genotype T/T 13910 - in 7.5% of cases (n=3).

The level of hydrogen concentration in the exhaled air, determined using the HBT in obese children and with genotype C/C 13910 was 36.03±3.71 ppm; in children with genotype T/T 13910 – 1.35±0.83 ppm; and in healthy children with genotype C/C 13910 – 14.21±3.54 ppm, $p<0.05$. It is interesting

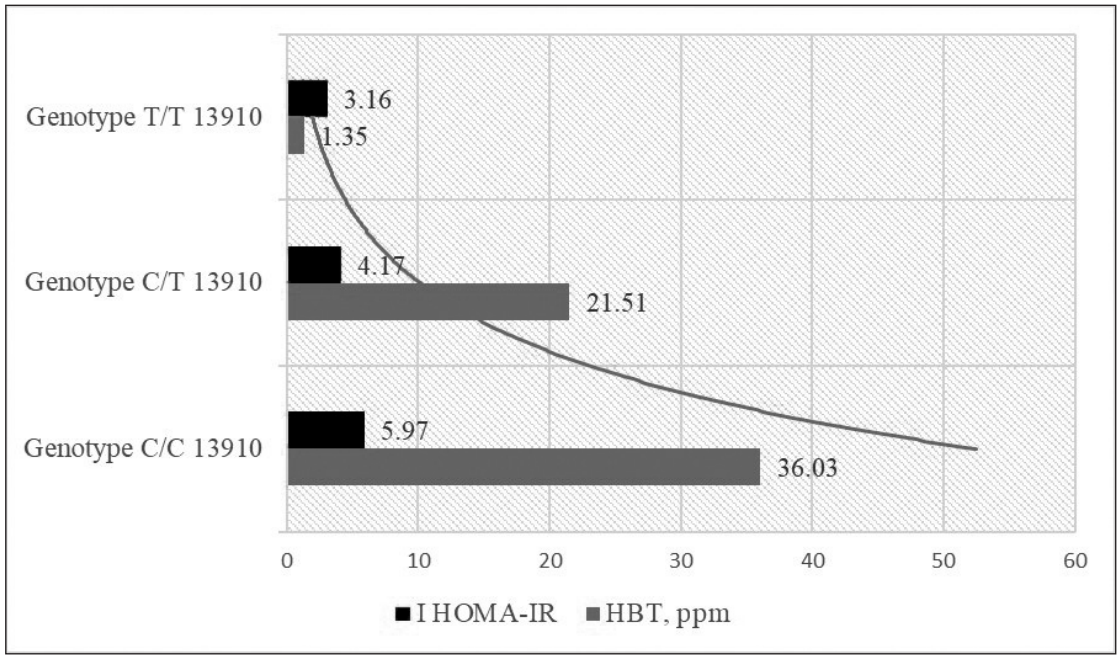


Figure 1. Association figures hydrogen concentration in exhaled air in a HBT and insulin resistance in obese children with genotypes LCT

that the level of hydrogen concentration in the exhaled air with HBT in healthy children with genotype C/C 13910 did not have a statistical difference compared to obese children with the genotype C/T 13910– 21.51±3.1 ppm ($p>0.05$).

It was identified that a high level of HOMA-IR index of 5.97±0.86 was recorded in children with obesity and genotype C/C 13910. With the C/T 13910 genotype, the HOMA-IR index level was 4.17±0.21 and was lower than in genotype C/C 13910 ($p<0.05$). The lowest HOMA-IR index was characteristic of children with obesity and genotype T/T 13910 – 3.16±0.66 ($p<0.05$), figure 1.

The fact that the level of HOMA-IR index in children with obesity and genotype T/T 13910 was comparable to that of healthy children (HOMA-IR index=2.24±0.51, p>0.05) is of great interest. Probably, this circumstance emphasizes the special role of lactase deficiency in the development of insulin resistance in children's obesity.

The study of the effect of diet and pharmacological therapy on insulin resistance in obese children showed that both methods of treatment are quite effective. Thus, in children of group I, before the prescription of the drug for exogenous lactase, the value of the HOMA-IR index was 7.36±0.34, and after one month of treatment they had a significant decrease in 1.85 times, up to 3.97±0.6 ($p<0.05$). In children of group II, the HOMA-IR index before treatment was 5.55±0.68, and after the administration of the low-lactose diet for one month its value decreased by 1.75 times and was 3.16±0.35 ($p<0.05$).

DISCUSSION

Insert the text of the discussion here. The genotype of C/C 13910 in children with obesity aged from 6 to 18 years is 2 times more common than in children with physiological body weight. According to HBT data, the highest frequency of lactose maldigestion is registered among children with genotype C/C 13910, which coincides with the results of other studies [9]. According to the literature, the value of the correlation coefficient between the determination of genotype C/C 13910 by genotyping SNP *LCT* and the probability of a positive HBT is 0.74 [17]. Concetta Santonocito et al. [18] demonstrated that in persons with positive HBT genotype C/C 13910 was determined in 97% of cases. Our study showed that the ratio between the levels of the hydrogen breath test in 70 children with obesity and different genotypes of T/T, C/T, C/C 13910 corresponds to 1:16:27. It follows that in children with obesity and genotype C/C 13910, the risk of lactose maldigestion is 27 times higher than in T/T 13910 genotype. Changes in the results of HBT, which occurred as the consequence of treatment, indicate that the use of exogenous lactase "Mamalac" (National Enzyme Company Inc., USA, Distributor in Ukraine: Pharmunion BSV Development Ltd.) and a low-lactose diet according to our computer program "Low-lactose diet" significantly ($p<0.05$) contribute to lactose digestion in patients with genotype C/C 13910.

Excess lactose in the diet of modern man causes clinical manifestations of lactase deficiency. Food interviewing conducted by Lucyna Ostrowska et al. [19] showed that clinical lactase persistence in adult males correlates with a low HOMA-IR index. Studies Priska Stahel et al. [20] have shown that in male Sprague-Dawley rats, eating a diet that contains 15% galactose increases insulin sensitivity, and the use of higher doses of galactose promotes the formation of type 2 diabetes.

In our study, the level of insulin resistance studied by calculating the HOMA-IR index was directly correlated

with the level of lactose maldigestion in obese children and was the highest in the genotype of C/C 13910, which is identical to the data of other authors [21].

The ratio of HOMA-IR index in children with T/T, C/T, C/C 13910 genotypes was 1:1,3:2. It is likely that the risk of insulin resistance in children with obesity and genotype C/C 13910 is 2 times higher than in genotype T/T 13910. It is possible that the deficiency of lactase is accompanied by the interaction of excess lactose with galectin 9 (Gal-9), which blocks it binding to the Tim-3 receptor and prevents the activation of signaling pathways that activate Treg - cells. Inhibition of the Gal-9/Tim-3 signaling pathway leads to the development of a low-level inflammatory response and, as a consequence, to the formation of insulin resistance [11].

The use of an exogenous lactose drug or a low-lactose diet in treating children with genotype C/C 13910 and obesity, approximately, equally contributes to a decrease in the level of insulin resistance. It should be noted that the administration of exogenous lactase preparations preserves the possibility of taking dairy products, so necessary in the childhood period.

CONCLUSIONS

In this study, we demonstrated for the first time the significance of lactose maldigestion associated with genotype C/C 13910 *LCT*, when insulin resistance is formed in obese children. The genotype of C/C 13910 is 2 times more often detected in obese children than in healthy children and is associated with lactose maldigestion, causing an increase in insulin resistance ($p<0.05$). The use of the drug exogenous lactase or low-lactose diet prevents the formation of insulin resistance in children with obesity and genotype C/C 13910 *LCT*. However, being aware of the fact, that dairy products are the source of other nutrients, we recommend prescribing exogenous lactase preparations especially for young children.

In the future, it is planned to study the effect of lactose maldigestion on the level of expression of the main ligand of the T-cell apoptosis receptor (Tim-3) of galectin 9 in children with obesity and genotype C/C 13910.

REFERENCES

1. Alharbi O, El-Sohemy A. Lactose Intolerance (LCT-13910 C>T) Genotype Is Associated with Plasma 25-Hydroxyvitamin D Concentrations in Caucasians: A Mendelian Randomization Study. J Nutr 2017 Jun; 147 (6):1063-1069. doi: 10.3945/jn.116.246108. Epub 2017 Apr 26.
2. Brasen CL, Frischknecht L, Ornskov D, Andreasen L, Madsen JS. Combination of real-time PCR and sequencing to detect multiple clinically relevant genetic variations in the lactase gene. Scand J Clin Lab Invest 2017 Feb; 77 (1): 60-65. doi: 10.1080/00365513.2016.1261408.
3. Enattah NS, Sahi T, Savilahti E, Terwilliger JD, Peltonen L, Järvelä I. Identification of a variant associated with adult-type hypolactasia. Nat Genet 2002 Feb; 30 (2):233-7. doi: 10.1038/ng826
4. Fang L, Ahn JK, Wodziak D, Sibley E. The human lactase persistence-associated SNP -13910*T enables in vivo functional persistence of lactase promoter-reporter transgene expression. Hum Genet 2012 Jul; 131 (7):1153-9. doi: 10.1007/s00439-012-1140-z. Epub 2012 Jan 19.
5. Labrie V, Buske OJ, Oh E, Jeremian R, Ptak C, Gasiūnas G et al. Lactase nonpersistence is directed by DNA-variation-dependent epigenetic aging. Nature Structural & Molecular Biology 2016; 23: 566–573. doi:10.1038/nsmb.3227.
6. Fagerberg L, Hallström BM, Oksvold P, Kampf C, Djureinovic D, Odeberg J et al. Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. Mol Cell Proteomics. 2014; 13(2):397-406. doi: 10.1074/mcp.M113.035600. Epub 2013 Dec 5.
7. Barosa C, Silva C, Fagulha A, Barros L, Caldeira MM, Carvalheiro M et al. Sources of hepatic glycogen synthesis following a milk-containing breakfast meal in healthy subjects. Metabolism 2012; 61: 250–254. doi: 10.1016/j.metabol.2011.06.022.
8. Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH et al. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2017 Mar 1; 102(3):709-757. doi: 10.1210/jc.2016-2573.
9. Storhaug ChL, Fosse SK., Fadnes LT. Country, regional, and global estimates for lactose malabsorption in adults: a systematic review and meta-analysis. The Lancet Gastroenterology & Hepatology. Available online 7 July 2017 doi.org/10.1016/S2468-1253 (17)30154-1.
10. Bayless TM, Brown E, Paige DM. Lactase Non-persistence and Lactose Intolerance. Curr Gastroenterol Rep 2017 May; 19(5):23. doi: 10.1007/s11894-017-0558-9.
11. Wijnhoven TM, van Raaij JM, Spinelli A, Rito AI, Hovengen R, Kunesova M et al. WHO European Childhood Obesity Surveillance Initiative 2008: weight, height and body mass index in 6-9-year-old children. Pediatr Obes. 2013; 8:79-97.
12. Paasela M, Kolho K-L, Vaarala O, Honkanen J. Lactose inhibits regulatory T-cell-mediated suppression of effector T-cell interferon-γ and IL-17 production. British Journal of Nutrients 2014; 112(11): 1819–1825. doi:10.1017/S0007114514001998.
13. Peplies J, Börnhorst C, Günther K, Fraterman A, Russo P, Veidebaum T et al. IDEFICS consortium. Longitudinal associations of lifestyle factors and weight status with insulin resistance (HOMA-IR) in preadolescent children: the large prospective cohort study IDEFICS. Int J Behav Nutr Phys Act 2016 Sep 2; 13(1):97. doi: 10.1186/s12966-016-0424-4.
14. Gasbarrini A, Corazza GR, Gasbarrini G et al. Methodology and indications of H2-breath testing in gastrointestinal diseases: the Rome Consensus Conference. Aliment Pharmacol Ther 2009 Mar 30; 29 (1): 1-49. doi: 10.1111/j.1365-2036.2009.03951.x.
15. Misselwitz B., Fox M. What is normal and abnormal in lactose digestion? The Lancet Gastroenterology & Hepatology, Available online 7 July 2017. doi.org/10.1016/ S2468-1253(17)30180-2.
16. Abaturov OE, Nikulina AO, Logvinov DV, Colbasin PO. Diet therapy for obesity in children associated with adult lactase deficiency. Child Health 2017; 12 (6): 657-662; do: 10.22141 / 2224-0551.12.6.2017.1128335. [Ukrainian].
17. Di Stefano M, Terulla V, Tana P, Mazzocchi S, Romero E, Corazza GR. Genetic test for lactase non-persistence and hydrogen breath test: Is genotype better than phenotype to diagnose lactose malabsorption? Digestive and Liver Disease 2009; 41 (7): 474-479. doi.org/10.1016/j.dld.2008.09.020.
18. Santonocito C, Scapaticci M, Guarino D, Annicchiarico EB, Lisci R, Penitente R et al. Lactose intolerance genetic testing: is it useful as routine screening? Results on 1426 south-central Italy patients. Clin Chim Acta 2015 Jan 15; 439:14-17. doi: 10.1016/j.cca.2014.09.026.
19. Ostrowska L, Witczak K, Adamska E. Effect of nutrition and atherogenic index on the occurrence and intensity of insulin resistance. Pol Arch Med Wewn 2013; 123(6):289-96. doi.org/10.20452/pamw.1774.

20. Stahel P, Kim JJ, Xiao Ch, Cant JP. Of the milk sugars, galactose, but not prebiotic galacto-oligosaccharide, improves insulin sensitivity in male Sprague-Dawley rats. PLoS One 2017; 12(2): e0172260. doi: 10.1371/journal.pone.0172260.
21. de Campos Mazo DF, Mattar R, Stefano JT, da Silva-Etto JM, Diniz MA, Duarte SM et al. Hypolactasia is associated with insulin resistance in nonalcoholic steatohepatitis. World J Hepatol 2016 Aug 28;8 (24):1019-27. doi: 10.4254/wjh.v8.i24.1019.

Authors' contributions:
AA analyzed the results of the study, interpreted the research data and drafted the paper. YuS designed the written above study, was in charge of HBT. AN was responsible for data collection in patients from randomized groups. All authors contributed to revisions into the paper. All authors read and approved the final manuscript.

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Anna A. Nikulina
Department of Pediatrics 1 and Medical Genetics
State Institution "Dnepropetrovsk Medical Academy of the Ministry of Health of Ukraine"
Street 9, V. Vernadskogo, 49044, Dnipro, Ukraine.
e-mail: anna.nikulina.201381@gmail.com

Received: 30.08.2018
Accepted: 22.12.2018

PRACA ORYGINALNA
ORIGINAL ARTICLE

ORGANIZATION OF UROLOGICAL CARE FOR PATIENTS WITH IATROGENIC URETERAL INJURY

ORGANIZACJA OPIEKI UROLOGICZNEJ DLA PACJENTÓW Z JATROGENNYM USZKODZENIEM MOCZOWODU

Dmytro V. Shchukin[1,2], Vladislav M. Demchenko[1,2], Ganna V. Lisova[2], Iana S. Bielievtsova[2]
[1]KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE
[2]V.I. SHAPOVAL REGIONAL CLINICAL CENTER OF UROLOGY AND NEPHROLOGY, KHARKIV, UKRAINE

ABSTRACT

Introduction: We conducted a retrospective assessment of diagnostic and therapeutic approaches in patients with iatrogenic ureteral injury, who were treated in a specialized medical center.

The aim: The aim of the research was to determine the optimal treatment method for correction of iatrogenic ureteral defects.

Materials and methods: The study included 73 patients with iatrogenic ureteral injury. In 70 cases ureteral reconstruction was carried out with the help of Boari bladder flap. The effectiveness of this approach was assessed retrospectively by analysis of the complications and long-term results of the treatment.

Results: The length of the bladder flap varied from 3 to 21 cm and averaged 9.8 ± 1.4 cm. In 6 (8.2%) cases a successful reconstructive surgery of the ureter up to the level of its upper third was performed. The overall frequency of intraoperative complications did not exceed 12.9%. The total frequency of early postoperative complications was high (75.8%), however, they were not severe and required surgical correction only in one (1.4%) case. The total number of positive long-term results (good + satisfactory) amounted to 91.5%. Nephrectomy was required only in 2 (2.3%) cases.

Conclusions: The Boari bladder flap operation should be considered as the basis of the algorithm for providing medical care to patients with iatrogenic ureteral injury. This type of surgery makes it possible to completely replace the damaged or having doubtful blood supply portion of the ureter even with the defects extending to its upper third. The main advantages of this surgery technique are good blood supply of tubularized bladder flap and a high level of positive long-term results.

KEY WORDS: Boari bladder flap, reconstructive surgery of the ureter, trauma of the ureter

Wiad Lek 2019, 72, 1, 22-25

INTRODUCTION

Damage to the ureters is a very serious medical problem, since it is often associated with iatrogenic injury, can be difficult to diagnose and cause serious complications, including peritonitis, massive urinomas, renal failure and formation of ureterovaginal fistulas. The most common cause of ureteral damages is considered to be gynecological surgery. There is indication in the literature that those are the surgeries which approximately in 75% of cases are associated with the ureteral injury [1]. In particular, hysterectomy is accompanied by the urinary tract damages in 4.8% of cases, 2.2% of them are ureteral injuries [2]. After the surgical correction of prolapse this number increases up to 7.3%. Among the other causes of iatrogenic ureteral trauma are surgeries on the rectum and sigmoid colon, ureteroscopy, as well as reconstructive surgery of the aorta and iliac vessels [3].

Complexity of surgical correction of the ureteral defects directly depends on their length and location. For instance, minor defects of the lower third of the affected organ require various modifications of simple ureterocystoneostomy. However, in case of extensive damage reaching the middle and upper third of the ureter, a surgeon finds himself in a difficult situation, which may require the use of psoas hitch, as well as complicated options for reconstruction of the upper urinary tract including transuretero-ureteral anastomosis, Boari flap ureteroneocystostomy, intestinoplasty of the ureter or kidney autotransplantation [4-6]. Each of these methods has obvious disadvantages. In particular, it is necessary to take into account the high risk of damage to the contralateral ureter in cases of ureteroureterostomy, intestinal complications in cases of ileal ureter replacement, and loss of the kidney in cases of autotransplantation due to problems with vascular anastomosis or prolonged ischemia [7-9]. Boari bladder flap technique was first performed more than 100 years ago, but so far in the literature there are only few reports about this surgical technique in small series of patients [10-13]. In recent years Boari-flap technique has begun to be used for correction of long defects of the ureter, including reconstruction up to the level of its middle and upper third [14]. However, the objective results of this approach are not clear yet. At

Table I. Range of iatrogenic ureteral pathology

Ureteral pathology	N (%)
Obstetric-gynecologic trauma	63 (86.3%)
Ureteroscopic trauma	3 (4.1%)
Trauma after rectal extirpation or resection	5 (6.8%)
Trauma after aorto-femoral bypass	2 (2.8%)

present, the choice of one or another technique is individual and depends primarily on surgical experience and capability of a medical institution.

THE AIM

We conducted a retrospective assessment of diagnostic and therapeutic approaches for patients with iatrogenic ureteral injury, who were treated in a specialized medical center.

MATERIALS AND METHODS

The study included 73 patients (69 females and 4 males). Their average age was 46.8 ± 5.6 years old (22 to 78). The range of iatrogenic ureteral pathology in these patients is presented in Table I. The right-side damage occurred in 32 (43.9%) cases, the left-side - in 35 (47.9%) cases, bilateral - in 6 (8.2%). Preliminary radiation therapy for gynecological tumors was carried out in 6 (8.2%) patients. Ureteral trauma of a solitary kidney was observed in 2 (2.8%) patients. Ureterovaginal fistulas were found in 23 (33.3%) out of 69 females, as well as vesicoureterovaginal fistulas - in 3 (4.3%) females. In 5 (6.8%) patients massive retroperitoneal urinomas were identified, in the other 2 (2.8%) - urinary peritonitis. In 5 (6.8%) cases trauma of the duplicated ureters was detected. Defects of the ureter were limited to the level below its crossover with the iliac vessels in 33 (45.2%) patients, to the level 3 cm above its crossover with the iliac vessels in 34 (46.6%) patients and extended up to the level of its upper third in the other 6 (8.2%) patients. Bladder capacity in the whole population averaged 250±38.8 ml.

Diagnostic algorithm included examination of complaints and medical history of patients, urinalysis and hematology tests, biochemistry (glucose, total protein, creatinine, electrolytes), ultrasonography, contrast-enhanced multi-detector computed tomography (MDCT), cystoscopy and gynecological examination. In 20 (27.4%) cases urodynamics was performed.

Treatment approaches included ureteroscopy with ureteral stenting attempt. In 28 (38.4%) patients with ureteral obstruction and acute pyelonephritis, the percutaneous nephrostomy was performed at hospital admission. Retroperitoneal space urinomas were also drained with the use of puncture drainage. 70 patients undergone Boari bladder flap procedure for reconstruction of the ureter. In 2 (2.8%) cases of bilateral injury synchronous reconstruction was performed, in the other 4 (5.7%) cases surgery was carried out in two stages.

Due to severe fibrosis of the retroperitoneal space, anastomosis between the ureter and tubular bladder flap was carried out through the abdominal cavity in 4 (5.7%) cases. For correction of the vesicoureterovaginal fistulas reimplantation of the ureter via Boari-flap procedure was combined with suturing of the vesicovaginal fistula via O´Connor technique. One female patient underwent a two-stage total reconstruction of the upper third of the ureter using the renal pelvis tubular flap and reconstruction of the lower and middle third of the ureter with the use of the bladder tubular flap. Another female patient with the solitary kidney had Boari-flap procedure following colpocleisis due to a giant vesicovaginal fistula.

The performed surgical techniques were quite different from the classical Boari bladder flap operation due to the use of the least number of sutures to connect the ureter with the vesical flap and lack of its fastening to the lumbar muscle. The procedure included infusion of 250-300 ml of normal saline solution into the bladder, as well as mobilization of its apex and lateral surfaces. The bladder mobilization range depended on the length of the flap. For dissecting a flap longer than 5 cm the contralateral and rear part of the bladder was exposed. The flap distal part width was at least 2.0 cm, its base width was at least 4.0 cm long. The psoas hitch was performed only in 2 (2.9%) cases. In most of the cases (67 patients, 95.7%) a submucosal tunnel at least 10 mm long was created in the flap distal part. The ureter and stent were passed through the tunnel and secured to the bladder mucosa with one interrupted stitch. Afterwords, the flap was tubularized and fixed to the ureteral adventitia with four interrupted sutures. In 3 (4.3%) cases simple anastomosis was used between the flap and a ureter without formation of a submucosal tunnel. Kidney mobilization was carried out in 26 (37.1%) patients. The urethral catheter was removed at 2 weeks, and the ureteral stent at 2 months after surgery. The average follow-up period was 24.6 ± 3.4 months. The results were evaluated at three, six and twelve months postoperatively, based on the analysis of patient complaints, clinical evidence, ultrasound data, MDCT or excretory urography.

Functional results were divided into three types: good (absence of complaints and obstructive changes on visual investigation, good renal function), satisfactory (absence of complaints, good renal function, moderate obstructive changes) and bad (obstructive changes, deterioration of renal function, frequent exacerbation of pyelonephritis, kidney pain complaints, severe dysuria symptoms). Statistical analysis was carried out using standard descriptive statistics methods by means of "Statistica 8.0" software.

Table II. Main results in patients with Boari bladder flap

	Total (n = 70)
Preliminary radiation therapy, n (%)	8 (11.4%)
Flap length, cm	9.8 ± 1.4
Intraoperative complications	
- iliac vessels injury	1 (1.4%)
- IVC injury	1 (1.4%)
- > 500 ml blood loss	7 (10%)
Early postoperative complications	
- urine leakage from PO wound	8 (11.4%)
- pyelonephritis exacerbation	23 (32.9%)
- persistent bowel paresis	13 (18.6%)
- severe dysuria	7 (10%)
- chronic urinary retention	2 (2.9%)
Long-term functional result	
- good	58 (82.9%)
- satisfactory	6 (8.6%)
- bad	6 (8.5%)
Bladder capacity reduction with persistent hyperactivity	2 (2.3%)
Boari flap re-operation	3 (4.3%)
Nephrectomy	2 (2.3%)

RESULTS AND DISCUSSION

The interval between the ureter damage and iatrogenic injury diagnosis ranged from 0 to 36 days (on average, 6.8 ± 2.6 days). The proportion of intraoperative diagnosis did not exceed 8.2% (6 patients). The most informative diagnostic method was MDCT, which allowed us to correctly visualize the presence and localization of ureteral injuries, obstructive changes in the upper urinary tract, the presence of urinomas in the retroperitoneal space, as well as ureterovaginal and vesicovaginal fistulas in all cases.

Ureteral stenting was successful only in 3 (4.1%) cases. In two of these female patients ligature transection was performed. In one patient stenting helped to eliminate a ureterovaginal fistula, which had developed two days before the procedure.

The main results of the study are presented in Table II. The vesical flap length varied from 3 to 21 cm and averaged 9.8 ± 1.4 cm. The overall intraoperative complication rate did not exceed 12.9%. In most cases, the complications were associated with severe cicatricial and inflammatory changes in the retroperitoneal space after radiotherapy or previous surgeries, and were serious.

One complication such as injury to the common iliac artery, was recorded in a patient who had undergone two ureterocystoneostomies. This injury was accompanied by a massive bleeding (around 1500 ml) and required iliac artery prosthetic reconstruction.

Although the total level of early postoperative complications was high enough (75.8%), they were not severe, recovered conservatively and required surgical correction only in one (1.4%) case (cystostomy because of prolonged urinary retention). The most common problem was acute pyelonephritis, which with the same frequency was observed in patients both with short and long vesical flaps. Among specific complications dysuria should be pointed out, which was severe only in patients with flaps extending to the upper third of the ureter. Urine leakage from the wound occurred in 11.4% of patients and reversed at 10 days on average.

The total number of positive long-term results (good + satisfactory result) amounted to 91.5%. Nephrectomy was required only in 2 (2.3%) cases. Boari flap re-operation was successful 2 out of 3 (66.7%) cases.

The persistent decrease of bladder capacity was observed only in 2 out of 70 (2.3%) patients. In our opinion, it was not associated with flap surgery, but rather with radiation therapy in one case, and prolonged inflammatory changes in the urinary bladder in the other case.

Considering diagnostic methods of the iatrogenic injury to the ureter, it should be noted that its intraoperative damage, according to our data, is observed very rarely (8.2%). In vast majority of cases it is diagnosed within one week after surgery. Based on this data, we recommend performing MDCT in all patients after surgeries on pelvic organs or great vessels of the retroperitoneal space, reporting complaints resembling renal colic, acute pyelonephritis or urinary fistula in the early postoperative period.

Our results demonstrate that the attempts of ureteral stenting are undoubtedly justified in most patients with iatrogenic ureteral injury. However, the effectiveness of this method is not great (4.3%).

The management algorithm of ureteral injury correction is quite broad and may comprise various modifications of simple ureterocystoneostomy, psoas hitch, transuretero-ureteral anastomosis, Boari flap uretero-

neocystostomy, intestinoplasty of the ureter or kidney autotransplantation. Based on our experience in Boari flap operation, we believe it has the highest priority among the reconstructive methods for the lower and middle third of the ureter due to its iatrogenic injury. At present we completely discontinued the ligature removal from the ureter and its isolation from infiltrates and cicatricial conglomerates. From our point of view, there is no need to preserve the maximal length of the ureter at the expense of the blood supply of its distal part. The damaged part of the organ or the organ portion with doubtful blood supply, should be completely replaced. Ureteral reconstruction with the use of bladder tubular flap completely meets these requirements.

Among the early specific complications severe dysuria syndrome should be pointed out, which is more frequent in patients with reconstruction of the ureter up to the level of its upper third. In our opinion, this can be caused by significant reduction of bladder capacity due to creation of a flap with the maximum length. However, in most cases, dysuria events disappeared within one week after surgery, and the bladder capacity was restored within two months. Persistent reduction of the bladder capacity after one year was registered only in 2 out of 70 (2.9%) patients.

Assessment of the long-term results with an average follow-up period of 24.6 ± 3.4 months suggests that total number of positive results (good + satisfactory result) was very high and amounted to 91.5%.

CONCLUSIONS

The basis of the algorithm for providing medical care to patients with iatrogenic ureteral injury should be considered Boari bladder flap operation. This type of surgery makes it possible to completely replace the damaged or having doubtful blood supply portion of the ureter even with the defects extending to its upper third. The main advantages of this surgery technique are good blood supply of tubularized bladder flap and a high level of positive long-term results.

REFERENCES

1. Dowling RA, Corriere JN, Sandler CM. Iatrogenic ureteral injury. J Urol. 1986; 135: 912-5.
2. Vakili B, Chesson RR, Kyle BL, Shobeiri A, Echols KT, Gist R. et al. The incidence of urinary tract injury during hysterectomy: A prospective analysis based on universal cystoscopy. Am J Obstet Gynecol. 2005; 192: 1599-604.
3. Best CD, Petrone P, Buscarini M, Demiray S, Kuncir E, Kimbrell B. et al. Traumatic ureteral injuries: a single institution experience validating the American Association for the Surgery of Trauma-Organ Injury Scale grading scale. J Urol. 2005; 173(4): 1202-5.
4. Pereira BMT, Ogilvie MP, Gomez-Rodriguez JC, Ryan ML, Peña D, Marttos AC. et al. A review of ureteral injuries after external trauma. Scand J Trauma Resusc Emerg Med. 2010; 18: 6.
5. Benoit L, Spie R, Favoulet P, Cheynel N, Kretz B, Gouy S. et al. Management of ureteral injuries. Ann Chir. 2005; 130(8): 451-7
6. Ordorica R, Wiegand LR, Webster JC, Lockhart JL. Ureteral replacement and onlay repair with reconfigured intestinal segments. J Urol. 2014, 191(5): 1301-6.
7. Ehrlich RM, Skinner DG. Complications of transureteroureterostomy. J Urol. 1975; 113: 467-73.
8. Bodie B, Novick AC, Rose M, Straffon RA. Long-term results with renal autotransplantation for ureteral replacement. J Urol. 1986; 136: 1187-9.
9. Armatys SA, Mellon MJ, Beck SD, Koch MO, Foster RS, Bihrle R. Use of ileum as ureteral replacement in urological reconstruction. J Urol. 2009; 181: 177-81.
10. Boari A. Contribute speremental alla plastica delle uretere. Atti Accad Med Ferrara. 1894; 14: 444.
11. Bowsher WG, Shah PJ, Costello AJ, Tiptaft RC, Paris AM, Blandy JP. A critical appraisal of the Boari flap. BJU Int. 1982; 54: 682-5.
12. Sutherland RS, Pfister RR, Koyle MA. Endopyelotomy associated ureteral necrosis: complete ureteral replacement using the Boari flap. J Urol. 1992; 148: 1490-2.
13. Thompson IM, Ross G Jr. Long-term results of bladder flap repair of ureteral injuries. J Urol. 1974; 111: 483-7.
14. Mauck RJ, Hudak SJ, Terlecki RP, Morey AF. Central role of Boari bladder flap and downward nephropexy in upper ureteral reconstruction. J Urol. 2011; 186: 1345-49.

Authors' contributions:
According to the order of the Authorship.
Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Dmytro V. Shchukin
V.I. Shapoval Regional Clinical Center of Urology and Nephrology,
Moskovsky ave. 195, Kharkiv, Ukraine
tel: +380675859206
e-mail: shukindv@gmail.com

Received: 02.08.2018
Accepted: 10.12.2018

PRACA ORYGINALNA
ORIGINAL ARTICLE

ANALIZA MEDYCZNYCH CZYNNOŚCI RATUNKOWYCH WYKONYWANYCH PRZEZ ZESPOŁY RATOWNICTWA MEDYCZNEGO Z CAŁEJ POLSKI U PACJENTÓW Z RANAMI OPARZENIOWYMI

ANALYSIS OF MEDICAL RESCUE OPERATIONS PERFORMED BY MEDICAL RESCUE TEAMS FROM ALL OVER POLAND IN PATIENTS WITH BURN WOUNDS

Klaudiusz Nadolny[1, 2], Jerzy Robert Ładny[1], Daniel Ślęzak[3], Mateusz Komza[4,5], Robert Gałązkowski[5, 6]

[1]KLINIKA MEDYCYNY RATUNKOWEJ, WYDZIAŁ NAUK O ZDROWIU, UNIWERSYTET MEDYCZNY W BIAŁYMSTOKU, BIAŁYSTOK, POLSKA
[2]KATEDRA RATOWNICTWA MEDYCZNEGO, WYDZIAŁ MEDYCZNO-SPOŁECZNY, WYŻSZA SZKOŁA PLANOWANIA STRATEGICZNEGO W DĄBROWIE GÓRNICZEJ, DĄBROWA GÓRNICZA, POLSKA
[3]PRACOWNIA RATOWNICTWA MEDYCZNEGO, KATEDRA I KLINIKA MEDYCYNY RATUNKOWEJ, WYDZIAŁ NAUK O ZDROWIU, GDAŃSKI UNIWERSYTET MEDYCZNY, GDAŃSK, POLSKA
[4]KRAJOWE CENTRUM MONITOROWANIA RATOWNICTWA MEDYCZNEGO, WARSZAWA, POLSKA
[5]LOTNICZE POGOTOWIE RATUNKOWE, WARSZAWA, POLSKA
[6]ZAKŁAD RATOWNICTWA MEDYCZNEGO, WYDZIAŁ NAUK O ZDROWIU, WARSZAWSKI UNIWERSYTET MEDYCZNY, WARSZAWA, POLSKA

STRESZCZENIE

Wstęp: Oparzenie to powierzchowne lub głębokie uszkodzenie tkanek spowodowane działaniem: ciepła (wysokiej temperatury), substancji chemicznych, prądu elektrycznego, promieni słonecznych i promieni jonizujących.

Cel pracy: Analiza wyjazdów zespołów ratownictwa medycznego w okresie od 1 listopada 2017 roku do 30 kwietnia 2018 roku do pacjentów z rozpoznaniem oparzenia na terenie całego kraju.

Materiał i metody: Analiza obejmuje cała Polskę, wszystkie zespoły ratownictwa medycznego. Uzyskane dane pochodzą z Systemu Wspomagania Dowodzenia Państwowego Ratownictwa Medycznego. Analiza obejmuje charakterystykę badanej populacji oraz zastosowane leki. Do badania włączono te wyjazdy, które kończyły się rozpoznaniem oparzenia (T-20 do T-32). Z uwzględnieniem powyższych kryteriów uzyskano 547 przypadków.

Wyniki: W 321 przypadkach interwencje dotyczyły mężczyzn, a w 226 przypadkach kobiet (58,68% *vs.* 41,32%, p<0,001). Częściej dotyczyły pacjentów powyżej 18. roku życia (317 przypadków *vs.* 193 poniżej 18. roku życia, p<0,001), w 37 przypadkach brak danych. Najwięcej zdarzeń odnotowano w województwach mazowieckim i śląskim (12,97 % i 11,33%), a najmniej w podlaskim (2,92%). W 20,47% przypadkach było zastosowane leczenie przeciwbólowe, z czego w grupie dorosłych w 25,23% *vs*. 16,58% u dzieci, p<0,001.

Wnioski: Powyższe wyniki działań zespołów ratownictwa medycznego wskazują niedostateczne wdrożenie postępowania farmakologicznego, co wymaga szybkiej poprawy.

SŁOWA KLUCZOWE: oparzenie, zespół ratownictwa medycznego, leczenie przeciwbólowe

ABSTRACT

Introduction: A burn is a superficial or deep tissue damage caused by the action of: heat (high temperature), chemicals, electric current, solar rays and ionizing radiation.

The aim: To analyze the trips of emergency medical teams in the period from November 1, 2017 to April 30, 2018 to patients diagnosed with burns throughout the country.

Materials and methods: The analysis covers the whole of Poland, all medical rescue teams. The obtained data comes from the System of Supporting the State Medical Rescue System. The analysis includes the characteristics of the population studied and the medicines used. The study included those that ended with the diagnosis of burns (T-20 to T-32). Taking into account the above criteria, 547 cases were obtained.

Results: In 321 cases, there were women and 226 cases of men (58.68% vs 41.32%, p <0.001). More often, it referred to patients over 18 (317 cases vs. 193 below 18 years of age, p <0.001) in 37 cases no data. Most events were recorded in the Masovian and Silesian voivodships (12.97% and 11.33%) and the least in Podlasin (2.92%). In 20.47% of cases, pain treatment was applied, of which in the group of adults in 25.23% vs. 1658% in children, p <0.001.

Conclusions: The above results of medical emergency teams' activities indicate insufficient pharmacological treatment, which requires rapid improvement.

KEY WORDS: burn, medical rescue team, analgesic treatment

WSTĘP

Oparzenia stanowią bardzo poważny problem kliniczny, ekonomiczny i społeczny. W ciągu jednego roku około 1% populacji ulega różnego typu oparzeń, najczęściej niewymagających pilnej interwencji systemu ratownictwa medycznego, ale w tej grupie około 50–70% przypadków stanowią dzieci [1]. Temperatura od 55°C jest uważana jako graniczna, powyżej której dochodzi do nieodwracalnego uszkodzenia białka tkankowego. Wystarczą 3 minuty jej działania, aby doszło do martwicy naskórka. Przy temperaturze 70°C jest to jedynie sekunda. W zależności od wysokości temperatury działającej na organizm człowieka oraz czasu jej działania dochodzi do uszkodzenia miejscowego tkanek lub uszkodzenia ogólnoustrojowego [2]. Wstrząs pojawia się zazwyczaj przy oparzeniu powyżej 10% powierzchni ciała u dzieci, natomiast u dorosłych przy powierzchni powyżej 15% [3]. Ponadto następuje zakażenie tkanek. W miejscach najbardziej narażonych dochodzi do koagulacji, a tym samym do niedokrwienia tkanek oparzonych. Właściwe działanie ratunkowe powinno polegać na natlenowaniu i ukrwieniu oparzonych miejsc [4, 5]. Dużym zagrożeniem i niebezpieczeństwem dla pacjenta jest oparzenie górnych dróg oddechowych. Stanowi ono około 20–30% wszystkich urazów termicznych [6, 7]

W zależności od głębokości uszkodzenia tkanek oparzenia dzielimy na cztery stopnie:

- **oparzenie I°** – uszkodzenie naskórka; objawy to: rumień, silna bolesność, zbielenie skóry pod naciskiem, oparzenia I° ustępują po kilku dniach bez pozostawienia blizn [8];
- **oparzenie II°** – uszkodzenie naskórka i powierzchownej warstwy skóry właściwej lub jej pełnej grubości; objawy to: często występujące pęcherze z substancją surowiczą, bolesność, obrzęk, oparzenie II° goi się w ciągu 10–21 dni – bez blizn lub do kilku tygodni – z bliznami [9];
- **oparzenie III°** – uszkodzenie pełnej grubości skóry właściwej; objawy to: zaczerwienienie lub zbielenie, znieczulenie, skóra nie blednie pod naciskiem, oparzenie III° pozostawia widoczne blizny [10];
- **oparzenie IV°** – martwica sięga tkanek głębiej położonych, takich jak: mięśnie, ścięgna, kości itp. W najcięższych przypadkach tego typu oparzeń' cechą charakterystyczną jest zwęglenie oparzonej części ciała. Czasami nie wyróżnia się odrębnego IV° i wszystkie oparzenia tego typu zalicza się do oparzeń III° [11].

Do obliczenia prawidłowej powierzchni oparzonej stosuje się różne reguły, są to:

- **reguła dłoni** – dłoń pacjenta łącznie z palcami (zwartymi) stanowi około 1% powierzchni ciała [12];
- **reguła piątek** (reguła wielokrotności 5%), która znalazła zastosowanie w przypadku oparzeń niemowląt. Mówi ona, iż na każdą z kończyn przypada wartość 10% powierzchni ciała, natomiast na głowę, przód i tył tułowia po 20% całkowitej powierzchni ciała [13];
- **reguła „dziewiątek" Wallace'a**, stosowana u pacjentów dorosłych oraz dzieci powyżej 15. roku życia, która zakłada, iż odpowiednie części ciała stanowią 9% lub wielokrotność 9% całości [14].

CEL PRACY

Celem pracy jest analiza wyjazdów i działań zespołów ratownictwa medycznego na terenie całego kraju w okresie od 1 listopada 2017 roku do 30 kwietnia 2018 roku, do pacjentów z rozpoznaniem oparzenia.

MATERIAŁ I METODY

Analizie retrospektywnej poddano karty zlecenia wyjazdu (KZW) i karty medycznych czynności ratunkowych (KMCR) ze wszystkich zespołów ratownictwa medycznego (ZRM) w Polsce, w okresie od 1 listopada 2017 roku do 30 kwietnia 2018 roku (obserwacja 6-miesięczna). Dane zostały przygotowane na prośbę Konsultanta Krajowego w dziedzinie Medycyny Ratunkowej, dzięki Systemowi Wspomagania Dowodzenia Państwowego Ratownictwa Medycznego (SWD PRM) przy udziale Ministerstwa Zdrowia. SWD PRM jest systemem teleinformatycznym, obejmujący cały teren naszego kraju. Głównym celem jest realizacja zadań określonych w ustawie o Państwowym Ratownictwie Medycznym przez dyspozytorów medycznych, członków ZRM, lekarzy koordynatorów ratownictwa medycznego z wykorzystaniem jednolitego w skali kraju systemu – SWD PRM.

Liczba wszystkich interwencji ZRM w badanym okresie wyniosła około 1,6 mln wizyt.

Do badania włączone te, które kończyły się odpowiednim rozpoznaniem zgodnie z Międzynarodową Statystyczną Klasyfikacją Chorób i Problemów Zdrowotnych ICD-10 (T20-T32). Po uwzględnieniu powyższych kryteriów pozostało 547 przypadków.

ANALIZA STATYSTYCZNA

Obliczenia wykonano w programie IBM SPSS 24.0. W celu oceny zależności między zmiennymi jakościowymi (nominalnymi) wykonywano tabele porównawcze (z zastosowaniem testu chi-kwadrat (χ^2). Jako istotne statystycznie przyjęto $p<0,05$.

WYNIKI

W 321 przypadków dotyczyło mężczyzn i 226 przypadków kobiet (58,68% *vs.* 41,32%, $p<0,001$). Częściej dotyczyło pacjentów powyżej 18. roku życia (317 przypadków *vs.* 193 poniżej 18 roku życia, $p<0,001$), w 37 przypadkach brak danych (Tab. I).

W Polsce obowiązują zasady tworzenia identyfikacyjnych oznaczeń w systemie Państwowe Ratownictwo Medyczne i przydzielania nazw technicznych w SWD PRM (wydane przez Ministra Zdrowia), co oznacza, że każdy ZRM, posiada swój unikatowy numer identyfikacyjny. Związku z powyższym dokonano analizy z podziałem na województwa. Najwięcej zdarzeń odnotowano w województwach Mazowieckim i Śląskim (12,97 % i 11,33 %) a najmniej w Podlaskim (2,92 %) (Tab.II).

Analiza również obejmowała rodzaj podanych środków farmakologicznych. Wzięto pod uwagę środki

Tabela. I. Podział grupy badanej ze względu na wiek.

Wiek	Liczba [N]	Odsetek [%]
<1. roku życia	23	4,2
1.–6. rok życia	136	24,87
7.–12. rok życia	18	3,29
12.–18. rok życia	16	2,92
>18. roku życia	317	57,96
Brak danych	37	6,76

Tabela. II. Podział interwencji ZRM ze względu na województwo.

Województwo - ZRM	Liczba interwencji [N]	Odsetek [%]
Z – zachodniopomorskie	37	6,76
W – mazowieckie	71	12,97
T – świętokrzyskie	24	4,38
S – śląskie	62	11,33
R – podkarpackie	23	4,2
P – wielkopolskie	34	6,21
O – opolskie	25	4,58
N – warmińsko-mazurskie	35	6,39
L – lubelskie	31	5,67
K – małopolskie	30	5,49
G – pomorskie	32	5,86
F – lubuskie	21	3,84
E – łódzkie	22	4,03
D – dolnośląskie	52	9,51
C – kujawsko-pomorskie	32	5,86
B – podlaskie	16	2,92

przeciwbólowe, sedacyjne oraz zastosowanie płynoterapii. Szczegóły przedstawia tabela III.

W 20,47% przypadkach było zastosowane leczenie przeciwbólowe, z czego w grupie dorosłych w 25,23% *vs*. 16,58% u dzieci, p<0,001 (Tab. IV).

DYSKUSJA

Rany oparzeniowe to najczęściej niegroźny, ale bolesny stan. Stosunkowo rzadko oparzenie jest na tyle poważne, że konieczna jest interwencja ZRM i leczenie szpitalne. W obserwacji 6-miesięcznej z całego kraju niewielka liczba interwencji dotyczyła oparzeń, bo tylko 547, co stanowiło bardzo mały odsetek wszystkich interwencji ZRM realizowanych w badanym okresie czasu. Dzięki systemowi SWD PRM po raz pierwszy w historii można tak szczegółowo analizować wyjazdy ZRM i oceniać jakość udzielanych przez nich medycznych czynności ratunkowych [15].

Rozległy uraz termiczny lub oparzenie miejsc wstrząsorodnych będzie powodować stan zagrożenia życia w postaci wstrząsu. Głównym postępowaniem na miejscu zdarzenia jest zabezpieczenie podstawowych parametrów życiowych, zastosowanie u pacjenta leczenia przeciwbólowego, zabezpieczenie ran oparzeniowych i uzupełnienie płynów, na przykład poprzez implementację formuły Parkland (zakłada, że w ciągu 24 h od oparzenia przetoczy się mleczanowy płyn Ringera w objętości: kg m.c. x powierzchnia oparzenia x 4ml), która jest rekomendowana w opiece przedszpitalnej [2, 4, 11]. Dlatego bardzo istotnym elementem w udzielaniu pomocy jest kompetencja członków ZRM. Niestety, w wielu przypadkach jest ona niewystarczająca [16].

Do oparzeń częściej dochodzi u mężczyzn niż u kobiet, niezależenie od wieku. Bardzo duży odsetek przypadków dotyczy pacjentów poniżej 18. roku życia (193 *vs*. 317), a w szczególności w przedziale pomiędzy 1. a 6. rokiem życia dziecka. Najczęstszą przyczyną (85%) oparzeń u dzieci są gorące płyny, wrzątek [17]. W Polsce do większości oparzeń u dzieci dochodzi przypadkowo, lecz należy również pamiętać na przykład o przypadkach zespołu dziecka maltretowanego [18].

Najczęściej do przypadków oparzeń dochodziło w dużych województwach, gdzie odsetek wszystkich realizowanych interwenci w badanym okresie jest największy, dlatego najwyższy wskaźnik odnotowany został w województwie śląskim i mazowieckim, a najniższy w podlaskim. Należy

Tabela. III. Rodzaj poddawanych środków farmakologicznych z podziałem dorośli *vs.* dzieci.

Lek	Dorośli N=317	Dzieci (do 18 r.ż) N=193
Paracetamolum	2	15
Morphini sulfas	39	10
Fentanylum	10	2
Metamizolum	7	0
Ketoprofenum	19	0
Iburofenum	0	5
Dolcontral	2	0
Tramadol	1	0
Midazolamum, Diazepamum	4	3
Thiopental	2	0
PWE, Plasmatyle	9	1
0,9% NaCl	33	3

Tabela.IV. Podział zastosowanego leczenia farmakologicznego *vs.* całość grupy.

Leczenie	Dorośli N=317	Dzieci N=193	Liczba % (całość)
Płynoterapia	42	4	8,4
Przeciwbólowe	80	32	20,47
Sedacja	6	3	1,8

jednak pamiętać, że często w mniejszych województwach czas dojazdu na miejsce zdarzenia może być zwiększony, to po pierwsze, a po drugie z powodu odległości czas dojazdu z miejsca zdarzenia do ośrodka o najwyższej referencyjności (ośrodek leczenia oparzeń) może często wynieś ponad godzinę, dlatego bardzo ważnym aspektem już na poziomie dyspozytora medycznego jest dysponowanie lotniczego pogotowia ratunkowego na miejsce zdarzenia.

Jednym z głównych celów działań medycznych jest zastosowanie farmakoterapii przeciwbólowej, również pod kątem wystąpienia wstrząsu neurogennego (bólowego). Do maja 2016 roku walka ta była ograniczona z powodu trzech leków o działaniu przeciwbólowym (kwas acetylosalicylowy, ketoprofen lub morfina) dopuszczonych do stosowania przez ratowników. Obecnie kierownik zespołu podstawowego (bez lekarza) ma większe możliwości walki z bólem w postaci: fentanylu, pyralginy, ibuprofenu czy paracetamolu. Niestety wnioski dotyczące braku leczenia przeciwbólowego zawarte we wcześniejszych publikacjach pod redakcją prof. Basińskiego z Gdańskiego Uniwersytetu Medycznego potwierdzają się w naszym badaniu [19, 20]. 20,47% ze wszystkich pacjentów otrzymało jakiekolwiek leczenie przeciwbólowe, u dorosłych najczęściej morfina i ketoprofen, a u dzieci paracetamol i morfina. Wydaje się, że ze względu na skórę dziecka, która jest bardziej wrażliwa niż u dorosłego, więc urazy tego narządu mają poważniejsze konsekwencje [21], w tej grupie odsetek leczenia przeciwbólowego powinien być dużo wyższy. Niestety wynik naszego badania jest odwrotny, u dorosłych wynosi 25,23%, a u dzieci tylko 16,57%. Można wytłumaczyć taki stan rzeczy jedynie tym, że większość członków ZRM nigdy nie pracowała z dziećmi i nawet założenie wkłucia dożylnego często jest dla nich trudne lub niemożliwe. Ponieważ w ciężkich i rozległych oparzeniach dochodzi do wstrząsu hipowolemicznego bezwzględnego polegającego na utracie płynów (osocza), jednym z priorytetów jest uzupełnienie łożyska naczyniowego. Lecz tylko u 8,4% pacjentów była zastosowana płynoterapia. Jakby tego było mało, głównym stosownym płynem był 0,9% NaCl.

WNIOSKI

Przedstawione wyniki działań członków ZRM wskazują na niedostateczne postępowanie farmakologiczne dotyczące zarówno leków przeciwbólowych, jak i stosowania płynoterapii. Istnieje więc potrzeba wprowadzenia mechanizmów, których celem będzie zwiększenie jakości świadczeń medycznych udzielanych przez ratowników. Wydaje się, że cykliczne szkolenia w ramach kształcenia podyplomowego powinny przynieść oczekiwany skutek.

PIŚMIENNICTWO

1. Topczewska-Cabanek A, Pernach A, Nitsch-Osuch A et al. Oparzenia jako przyczyna hospitalizacji dzieci w jednym z warszawskich szpitali w latach 2008-2012. Fam Med. Prim Care Rev. 2014;16(3):297-299.
2. Kucap M, Nadolny K, Ładny JR, Borowicz A. Analiza interwencji ZRM do urazów termicznych (oparzeń) w latach 2014-2016 na przykładzie WPR w Katowicach. Na Ratunek 2017;06:22-29.
3. Roczniak W, Babuśka-Roczniak M, Zachaczewski K et al. Postępowanie przedszpitalne w ciężkich oparzeniach ciała. Opis przypadku. Med Ogoln

Nauki Zdr. 2017;23:68-72.
4. Kopta A, Mierzejewski J, Kołodziej G. Kwalifikowana pierwsza pomoc. Warszawa: Wydawnictwo Lekarskie PZWL, 2016.
5. Strużyna J. Wczesne leczenie oparzeń. Warszawa: Wydawnictwo Lekarskie PZWL, 2006.
6. Kimla J, Glik A, Nowak-Wróżyna M, Jarosławiecka M, Nowak M, Kawecki M. Physioterapy in patients with inhalation injury in burns. J Orthop Trauma Surg Rel Res. 2008;1:68-77.
7. Hassan Z, Wong JK, Bush J, Bayat A, Dunn KW. Assessing the severity of inhalation injuries in adults. Burns 2010;36:212-216.
8. Buchfelder MA. Podręcznik pierwszej pomocy. Warszawa: Wydawnictwo Lekarskie PZWL, 2011.
9. Gregory P, Mursell I. Diagnostyka i postępowanie w ratownictwie medycznym. Wrocław: Wydawnictwo Medyczne, 2013.
10. Cenajek-Musiał D, Okulicz-Kozaryn I, Grześkowiak M. Stany zagrożenia życia: postępowanie lecznicze i leki stosowane w ratownictwie medycznym. Poznań: Wydawnictwo Naukowe Uniwersytetu Medycznego im. Karola Marcinkowskiego w Poznaniu, 2009.
11. Nadolny K. Rekomendacje postępowania w ratownictwie medycznym. Elamed 2015.
12. Briggs SM (przekład Rowiński W, Domienik J). Wczesne postępowanie medyczne w katastrofach. Warszawa: Wydawnictwo Lekarskie PZWL, 2007.
13. Keim SM, Kokot F. Medycyna na dyżurze. Warszawa: Wydawnictwo Lekarskie PWN, 2011.
14. Stoy WA, Platt TE, Lejeune DA. Ratownik medyczny. Wrocław: Wydawnictwo Elsevier Urban & Partner, 2013.
15. Nadolny K, Kozłowski R, Wardyn T. System Wspomagania Dowodzenia Państwowego Ratownictwa Medycznego – przyszłość systemu ratownictwa medycznego w Polsce. Ogolnopol Przegl Med. 2017;4:61-67.
16. Nichols DG, Yester M, Schleien ChL, Paidas CN. Złota godzina. Wydawnictwo Wrocław: Elsevier Urban & Partner, 2013.
17. Kaźmierski M. Oparzenia u dzieci. In: Jankowski A (edn.). Zarys chirurgii dziecięcej. Poznan': Wydawnictwo Naukowe Uniwersytetu Medycznego; 2008, 129-135.
18. Drabik-Danis E, Pokorna-Kałwak D. Dziecko maltretowane – co musi wiedzieć lekarz pierwszego kontaktu, aby nie przeoczyć i właściwie zareagować' w zetknięciu z tym problemem. Fam Med Prim Care Rev 2005;7(2):497-502.
19. Żuratyński P, Ślęzak D, Krzyżanowski K. Porównanie farmakologicznych metod leczenia bólu przez ratowników medycznych na podstawie obowiązującego stanu prawnego w Polsce. Ból 2017;18(1):34-36.
20. Krzyżanowski K, Ślęzak D, Basiński A, Żuratyński P, Buca P. Uśmierzanie bólu po urazie na etapie przedszpitalnym. Ból 2017;18(1):37-43.
21. Smereka J. ABC oparzeń'. Wrocław: Wydawnictwo Medyczne Górnicki; 2007, 5-40.

Konflikt interesów:
Autorzy deklarują brak konfliktu interesów

AUTOR KORESPONDUJĄCY
Klaudiusz Nadolny
Klinika Medycyny Ratunkowej,
Uniwersytet Medyczny w Białymstoku,
ul. Szpitalna 37, 15-295 Białystok, Polska
tel. 513 082 398
e-mail: knadolny@wpr.pl

Nadesłano: 28.12.2018
Zaakceptowano: 15.01.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

INFLUENCE OF AUTOLEUKOCYTE VACCINATION ON ACTIVITY LEVEL OF TUMOR NECROSIS FACTOR ALPHA IN PATIENTS WITH CHRONIC HEPATITIS B

WPŁYW AUTOLOGICZNEJ SZCZEPIONKI LEUKOCYTARNEJ NA AKTYWNOŚĆ CZYNNIKA MARTWICY NOWOTWORU ALFA U PACJENTÓW Z PRZEWLEKŁYM ZAPALENIEM WĄTROBY TYPU B

Alexandr Zinchuk, Oleksandr Herasun, Andrij Zadorozhnyi, Olga Vorozhbyt, Borys Gerasun
DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

ABSTRACT

Introduction: data about influence of intradermal vaccination with native autoleukocytes on activity level of pro-inflammatory cytokine tumor necrosis factor alpha in patients with chronic hepatitis B have been presented in the article.

The aim: Based on positive results, obtained from autoleukocyte immunization in patients with psoriasis [14], the aim of our research was to use and study such therapy for reducing the synthesis of pro-inflammatory cytokine TNF-α in patients with chronic hepatitis B (chronic hepatitis B).

Materials and methods: Patients with chronic hepatitis B with high level of tumor necrosis factor alpha (≥30pg/ml) were vaccinated with native autoleukocytes (23); simultaneously, the same procedure was performed to patients (11) with low level of this cytokine (5pg/ml). Leukocytes were isolated from heparinized peripheral venous blood of a patient with hepatitis B by centrifuging plasma, obtained after blood precipitation for 140-160 minutes at temperature 37^0 C. The suspension was resuspended in 1-1.5 ml of a patient's blood serum and injected into the skin of the back in the dose 0.1 ml.

Results: in 30 days after immunization, reduction of tumor necrosis factor alpha was observed in all patients with its high level (100%), in 65.25% of individuals – to 5 pg/ml; in some patients, who had low or average level of pro-inflammatory cytokine, the level individually increased (41.67%).

Conclusions: The elaborated method of influence on activity of tumor necrosis factor alpha in patients with chronic hepatitis B is effective and worth implementing into clinical practice.

KEY WORDS: tumor necrosis factor alpha, vaccination with autoleukocytes, chronic hepatitis B

Wiad Lek 2019, 72, 1, 31-34

INTRODUCTION

Current treatment strategy of a number of inflammatory processes implies inhibition of synthesis of pro-inflammatory cytokines, especially TNF-alpha with the medications, which are blockers of this cytokine or inhibit proliferation of Th1-lymphocytes, producing TNF [1-4].

Recently, drugs, action of which is aimed at inhibition and blockage of TNF-α biological activity (for example, infliximab, etanercept and adalimubab), are more often used for the treatment of immune-mediated diseases, such as rheumatoid arthritis, inflammatory diseases of the intestines and psoriasis [2, 3 ,5]. Although clinical efficacy of these drugs is proved, however, inhibition of cytokine synthesis by means of antibodies to certain determinants of immunocompetent cells has a negative influence on immune system status. Long-term use of TNF-α inhibitors increases susceptibility to infectious diseases (or leads to exacerbation of the existing ones). Taking into account these side effects, it is obvious that such methods of influence on TNF-α are unfavorable in infectious diseases [1, 6, 7].

In chronic viral hepatitis, excessive synthesis of TNF-α intensifies an inflammatory process with impairment of liver metabolism, playing a significant role in fibrosis pathogenesis and formation of liver cirrhosis [6, 7]. Thus, patients with chronic viral hepatitis with high level of TNF-α are administered medicines, which inhibit TNF-α content. However, it should be considered that biological inhibitors of TNF-α are foreign proteins and this may accelerate their excretion and lead to allergic reactions [8]. Concerning antibodies to certain determinants of immunocompetent cells (for example, chimeric monoclonal antibodies to CD20 antigen to B-lymphocytes), their long-term administration may lead to weakening of the immune response [4, 7]. Though viral hepatitis B may be referred to the diseases that negatively influence powerful immune processes, nevertheless, inhibition of immunity is undesirable, since it promotes intensification of virus

Table I. Influence of single autoleukocyte immunization on high TNF-α level (over 30 pg/ml) in blood serum of patients with chronic hepatitis B

TNF-α level before autoleukocyte immunization (pg/ml)	Number of patients	TNF-α level in 30 days after autoleukocyte immunization (pg/ml)[1]		
		0-5	10-15	20-30
		Number of patients		
30-50	15	11	4	
51-70	6	4	2	
71- 90	1	0	0	1
100-180	1	0	1	
Total	23	15 (65.22%)	7 (30.43%)	1 (4.35%)

[1]Influence of vaccination on TNF-α activity was manifested already in 10-12 days, however in some patients maximal indices were revealed later, thus, the results presented were obtained in 30 days.

reproduction and reactivation of the process, which is manifested by intensification of inflammatory process activity and acceleration of fibrosis development. After such therapy, there is a need for intensification (or renewal) of antiviral therapy [1, 6]. The risk for reactivation of chronic hepatitis B infection during therapy with TNF-α inhibitors is confirmed by data of many investigations, where authors emphasize that inhibitors of TNF-α may increase chronic hepatitis B replication and reactivate chronic hepatitis not only during, but also after cessation of treatment. It should be mentioned that a number of patients, who received TNF-α inhibitors before or simultaneously with the treatment, were treated with other immunosuppressants, sometimes for a long time, that significantly increases the risk for chronic hepatitis B reactivation and can be manifested by the appearance of fulminant hepatitis and even need in liver transplantation [8-11].

Thus, in the treatment of inflammatory processes (for example, in patients with rheumatoid arthritis, psoriasis, etc.) with inhibitors of pro-inflammatory cytokine, it is expedient to prescribe lamivudin to the patients, who have at least anti-HBc, for prevention of possible exacerbation of hidden hepatitis B [12, 13].

In our prior investigations, it was established that the method of cell therapy as intradermal vaccination with native autoleukocytes significantly inhibits high level of TNF-α in patients with psoriasis, having a positive impact on the disease course [14].

THE AIM

Based on positive results, obtained from autoleukocyte immunization in patients with psoriasis [14], the aim of our research was to use and study such therapy for reducing the synthesis of pro-inflammatory cytokine TNF-α in patients with chronic hepatitis B (chronic hepatitis B).

MATERIALS AND METHODS

To study influence of intradermal autoleukocyte immunization on TNF-α synthesis in patients with chronic hepatitis B, a group of patients with high level of this cytokine (≥30 pg/ml) was chosen. The investigation involved patients who did not take any medicines that influence the level of cytokines.

The group of patients with chronic hepatitis B included 23 patients aged 20-60 years (13-females, 10 – males). An obligatory condition was monoinfection (hepatitis C and AIDS were excluded in patients). Test-system "Corbett Research" (Australia) was used for quantitative determination of HBV DNA by PCR method. Hepatitis C was excluded determining HCV RNA by qualitative PCR method (real-time), using test-system "Corbett Research" (Australia); the patients were examined for HIV-infection by ELISA method with test system of the fourth generation Genscreen Ultra HIV Ag–Ab (Bio-Rad, France).

Simultaneously, patients with chronic hepatitis B (12), in whom TNF-α could not be detected or its level in blood serum did not exceed 5 pg/ml, were vaccinated.

TNF-α in blood serum was detected by the method, which is based on "sandwich" variation of ELISA test using mono- and polyclonal antibodies to TNF-α (manufacturer "Vector Best", Russia).

The method of reducing activity of pro-inflammatory cytokine by means of autoleukocyte vaccination was performed in two stages: isolation of leukocytes from peripheral blood and their intradermal injection to a patient. The method of immunization and mechanism of its action was described earlier [14].

In 10-12, 30, 60 and 180 days after immunization, the content of TNF-α in blood serum was investigated. Further, cytokine level was monitored, if necessary, the immunization was repeated (individually, considering peculiarities of response to the procedure). The research was performed analogously to the previous one [14].

Patient consent: The health, privacy, and confidentiality of personal information and rights of patients, involved in medical research, were taken into consideration according to Helsinki declaration. The study was approved by the local Ethical Committee of Danylo Halytsky Lviv National Medical University.

RESULTS AND DISCUSSION

The influence of autoleukocyte immunization on intensive TNF-α synthesis in blood serum of patients with chronic hepatitis B is confirmed by the results of monitoring its content before and after immunization (table I).

From the data given in table 1, it is seen that reduction of TNF-α in blood serum was observed in all patients with chronic hepatitis B due to autoleukocyte immunization. At the same time, their general condition improved, which was manifested by the reduction of fatigue and positive influence on extrahepatic manifestations: skin vasculitis; the level of creatinine in blood serum returned to norm or decreased in patients with various forms of liver damage (6).

It is impossible to explain the improvement of clinical manifestation only by the influence on TNF-α, because autoleukocyte vaccination has a positive impact on different autoimmune processes that are present in many patients with chronic viral hepatitis. However, in our investigation the most important is the proof that this method of treatment inhibits TNF-α production. In addition, in all patients with high level of ALT, it decreased (or returned to norm), which in fact indicates weakening of an inflammatory process in hepatocytes.

As a result of immunization of patients with chronic hepatitis B, in whom TNF-α level in blood serum could not be detected or did not exceed 5 pg/ml (12), its level did not change in 7 individuals, however in 5 (41.67%) it increased: in four patients to 10 pg/ml, and in one – to 175 pg/ml). It is important that in the patient, whose level of cytokine significantly increased, general condition improved and concentration of HBV DNA decreased almost twice. In 2 weeks, reduction of TNF-α level to 35 pg/ml was recorded. This patient was repeatedly immunized, and in 10 days after immunization, the level of pro-inflammatory cytokine was already 6 pg/ml. In fact, intensification of cytokine production in patients with chronic hepatitis B and low TNF-α level indicates that autoleukocyte immunization may intensify the activity of CD8+ T-cells, which produce different cytokines, in particular TNF-α. It should positively influence the efficacy of chronic hepatitis B treatment, since CD8+ T-cells are thought to control HBV replication via non-cytolytic route and this effect is initiated through interferon-gamma and TNF-α [15].

Thus, the results of investigation indicate the expediency of implementing this method into complex therapy of chronic hepatitis B with high TNF-α activity and intensive inflammatory process in the liver. Moreover, a significantly wider range of a positive influence of this procedure results in reduction of the content of precipitating cold-shock proteins – cryoglobulins [16-19], and unlike antibodies-inhibitors of TNF-α, may promote improvement of antiviral immunity [20].

CONCLUSIONS

It has been established that immune cell therapy in the form of intradermal autoleukocyte vaccination has a regulatory effect on TNF-α synthesis in patients with chronic hepatitis B. Thus, it will be expedient to use this method for the treatment of patients with high level of this cytokine. In addition, this method, according to previously obtained results, positively influences different extrahepatic manifestations in patients with chronic viral hepatitis.

REFERENCES

1. Maurizio Pompili, Marco Biolato, Luca Miele, Antonio Grieco. Tumor necrosis factor-α inhibitors and chronic hepatitis C: A comprehensive literature review World J Gastroenterol. 2013; Nov 28; 19(44): 7867–7873.
2. Nielsen OH, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. N Engl J Med. 2013; 369:754–762.
3. Brimhall AK, King LN, Licciardone JC, Jacobe H, Menter A. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. Br J Dermatol. 2008; 159: 274–85.
4. Gupta S., Gollapudi S. Molecular mechanisms of TNF-alpha-induced apoptosis in aging human T cell subsets. Int. J Biochem Cell Biol. 2005; 37 (5): 1034-1042.
5. Paul J. Anderson. Tumor necrosis factor inhibitors: Clinical implications of their different immunogenicity profiles. Semin Arthritis Rheum. 2005; 34: 19–22.
6. Nathan DM, Angus PW, Gibson PR. Hepatitis B and C virus infections and anti-tumor necrosis factor-alpha therapy: guidelines for clinical approach. J Gastroenterol Hepatol. 2006; 21:1366–1371.
7. Viganò M, Degasperi E, Aghemo A, Lampertico P, Colombo M. Anti-TNF drugs in patients with hepatitis B or C virus infection: safety and clinical management. Expert Opin Biol Ther. 2012; 12: 193–207.
8. Boris LC, Steinke JW. Cytokines and chemokines. Journal of Allergy and Clinical Immunology 2003; 111 (2): 460–475.
9. Fernando Bessone, Melisa Dirchwolf. Management of hepatitis B reactivation in immunosuppressed patients: An update on current recommendations. World J Hepatol. 2016; 18 (8): 385–394.
10. Lorenzo Nobili, Lisa Albani, Armando Gabrielli, Gianluca Moroncini. Reactivation of Hepatitis B Virus Infection Associated with Anti-Tumor Necrosis Factor-α Therapy. J Antivir Antiretrovir. 2014; 6: 3.
11. Cannizzaro MV, Franceschini C, Esposito M, Bianchi L, Giunta A. Hepatitis B reactivation in psoriasis patients treated with anti-TNF agents: prevention and management Psoriasis. Targets and Therapy 2017; 7: 35–40.
12. European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B. J Hepatol. 2009; 50:227–242.
13. Lok AS, McMahon BJ. Chronic hepatitis B: update. 2009; Hepatology. 50: 661–662.
14. Gerasun BA. New Method of Inhibition of Activity of tumor Necrosis Factor Alpha in Patients with psoriasis. Recent Patents on Endocrine, Metabolic & Immune Drug Discovery 2016; 10, 63-66.
15. Fhillips S., Chokshi S., Riva A. et all (2010). CD8+ T Cell Kontrol of Hepatitis B Virus Replikation: Direct Comprasion between Cytolytic and Noncitolytic Funstions. Th e Journal of Immunol 2010; 184:287-295.
16. Gerasun BA, Kopets RA. Patent of Ukraine for invention No 97461. Application of method of autoleukocytes vaccination as oligo- and astenozoospermia method of treatment; published 10.02.2012.
17. Gerasun BA, Chopiak VV, Vorozhbyt OB. Treatment of autoimmune disorders caused by chronic hepatitis B and C with the help of autoleukocyte immunization. Mir Virusnykh Hepatitov (Moscow) 2006; 1: 13–8.

18. Gerasun BA, Holubovska OA, Hrytsko RY, Zinchuk ON, Shkurba AV. Reduction of Hyperproduction of Thyroid Autoantibodies in Patients without Disturbance of the Thyroid Function: New Patents. Recent Patents on Endocrine, Metabolic & Immune Drug Discovery 2014; 8 (2):140-145.
19. Gerasun B, Kopets R, Hrytsko R, Gerasun O. Correction of fertility disorders in patients with cryoglobulinemia. Central European Journal of urology. 2013; 66: 316.
20. Herasun O.B. Investigation of influence of intradermal immunization with inactivated autoleukocytes on the condition of antiviral immunity in patients with chronic hepatitis B. Gepatologia 2016; 2: 24-30.

Authors' contributions:
According to the order of the Authorship.
Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Borys Gerasun
Department of Infectious Diseases
Danylo Halytsky National Medical University
54, Pekarska Street 79010, Lviv, Ukraine
tel:+38 066 90827 59
e-mail: gerab@3g.ua

Received: 27.07.2018
Accepted: 11.12.2018

PRACA ORYGINALNA
ORIGINAL ARTICLE

MEDICAL AND SOCIAL ISSUES OF CARDIOVASCULAR DISEASES AND THEIR SOLUTION BASED ON THE EXPERIMENTAL STUDY OF MYOCARDIAL FIBROSIS

KWESTIE MEDYCZNE I SPOŁECZNE CHORÓB UKŁADU SERCOWO-NACZYNIOWEGO I ICH ROZWIĄZYWANIE W OPARCIU O EKSPERYMENTALNE BADANIE WŁÓKNIENIA MIOKARDIUM

Hanna Saturska, Arkadii Shulhai, Rostyslav Levchuk, Nataliya Potikha, Ruslan Usynskyi
I. YA. HORBACHEVSKY TERNOPIL STATE MEDICAL UNIVERSITY, TERNOPIL, UKRAINE

ABSTRACT

Introduction: The prevalence and incidence of cardiovascular diseases have been attracting considerable attention in recent decades. This is partly due to the fact that myocardial fibrosis is the major consequence of the most nosological units of cardiovascular diseases. We believe that early pathogenic therapy of myocardial fibrosis should be taken into consideration as a solution to this issue. The change of the connective tissue metabolism in myocardium is the central chain in pathogenesis of diffuse ischemic necrotic cardiosclerosis (DINC) occurs after repeated epinephrine injury of myocardial tissues.

The aim: The present study establishes that use of metabolic therapy by trimetazidine (TM) has a protective effect on myocardium repeatedly damaged by epinephrine in hight concentration during the development of DINC in rats with different resistance to hypoxia.

Materials and methods: Using the method of hypobaric hypoxia, male albino rats were divided into three groups due to their different resistance to hypoxia. Each group was divided into four equal subgroups: control group, DINC group (2 times repeated injections of epinephrine hydrotartrate (0,5 mg/kg body weight) and calcium gluconate (5 mg/kg body weight), control group introdused with trimetazidine dihydrochloride (10 mg/kg body weight), DINC treated with TM group (2 times repeated injections of epinephrine hydrotartrate (0,5 mg/kg body weight) and calcium gluconate (5 mg/kg body weight) group introduced with TM (10 mg/kg body weight) for all period of observation. The concentration of protein-bound oxyproline in homogenate of myocardium was determined at 7, 14 and 30 days after the modelling pathology and the histological examination of Masson trichrome staining of myocardium was performed.

Results: Experimental modeling of DINC increased the concentration of protein-bound oxyproline in homogenate of myocardium at 7, 14 and 30 days after the modelling pathology, as well as accompanied by metabolic imbalances in diffuse connective tissue elements, which are rich in collagens. Experimental modeling of DINC+TM increased the concentration of protein-bound oxyproline in blood serum significantly less intensive.

Conclusions: The intensity of metabolic imbalances in diffuse connective tissue elements of myocardium is the highest in the low resistant animals to hypoxia. Those results are confirmed by histological examination of the myocardium of rats with different resistance to hypoxia. Fibrotic regions in myocardium are rich in collagens. It has been revealed that the most pronounced therapeutic effect of TM is observed in animals with low resistance to hypoxia, slightly less – in animals with medium resistance to hypoxia, and the lowest – in animals with high resistance to hypoxia.

KEY WORDS: hypoxia, heart, myocardial fibrosis, trimetazidine, oxyproline

Wiad Lek 2019, 72, 1, 35-39

INTRODUCTION

The pathology of the cardiovascular system is the major health and social problem, because it takes the first place in the structure of morbidity and mortality [1-2]. The prevalence and incidence of cardiovascular diseases have been attracting considerable attention in recent decades. This is partly due to the fact that myocardial fibrosis is the major consequence of the most nosological units of cardiovascular diseases. The special attention is focused on the research of diagnostic markers of degradation and reparation of myocardial tissue [3-5], which would reflect the dynamic changes in the myocardium and were predictors of prognosis the diffuse cardiosclerosis [2-3]. The purpose of this investigation was to determine the changes of the content of protein-bound oxyproline in blood as a diagnostic marker of metabolic activity of collagen at the experimental diffuse ischemic necrotic cardiosclerosis in the rats of different resistance to hypoxia.

We believe that early pathogenic therapy of myocardial fibrosis should be taken into consideration as a solution to this issue as at the recent study we have demonstrated that the use of trimetazidine as inducer of endogenous cardioprotection in the development of diffuse ischemic necrotic cardiosclerosis is manifested via decreased manifestations

Table I. Protein-bound oxyproline concentration in homogenate of myocardium at the experimental diffuse ischemic necrotic cardiosclerosis (DINC) due to innate resistance of rats to hypoxia

Resistance of animals to hypoxia	Control (n=8)	The stages of observation DINC		
		7 days (n=8)	14 days (n=8)	30 days (n=8)
Low	49,55±0,59 p<0,05	57,45±1,78 p<0,01 p*<0,01	79,15±2,66 p<0,01 p*<0,01	104,84±3,42 p<0,01 p*<0,01
Middle	42,07±1,10	47,92±0,62 p*<0,01	58,24±1,00 p*<0,01	73,38±3,30 p*<0,01
High	34,52±0,92 p<0,05	38,53±0,55 p<0,01 p*<0,05	42,65±1,19 p<0,01 p*<0,01	56,43±2,84 p<0,01 p*<0,01

Notes: p<0.05 – significantly different from middle resistant animals to hypoxia at all times of observation; *p<0.05 – significantly different from control at all times of observation.

of oxidative and nitrooxidative stress, optimization of immune and cytokine response, stabilization of humoral immune responsiveness [6].

THE AIM

The current work carried out to study the effects of TM on the improvement of metabolism of connective tissue elements in myocardium, indicating inhibition of cardiosclerotic process.

MATERIALS AND METHODS

ANIMALS AND TREATMENT

Experiments were done on 192 male albino rats (190-250 g) (Ternopil State Medical University vivarium, Ukraine). All animals received care in compliance with the "Guide for the Care and Use of Laboratory Animals" (National Institute of Health Publication № 85-23, revised 1985). The studies were carried out according to the National Institute of Health Guide for the Care and Use of Laboratory Animals and were approved by the local animal protection committee.

The experimental animals were divided into 3 groups according to their different resistance to hypoxia using the method of hypobaric hypoxia [6] [Berezovskyi, 1975; Markova, 1998]. Each group was divided into four equal subgroups: control group, diffuse ischemic necrotic cardiosclerosis group (2 times repeated injections of epinephrine hydrotartrate (0,5 mg/kg body weight) and calcium gluconate (5 mg/kg body weight), control group introdused with trimetazidine dihydrochloride (10 mg/kg body weight) [6], diffuse ischemic necrotic cardiosclerosis treated with trimetazidine dihydrochloride group (2 times repeated injections of epinephrine hydrotartrate (0,5 mg/kg body weight) and calcium gluconate (5 mg/kg body weight) group introdused with trimetazidine dihydrochloride (10 mg/kg body weight) for all period of observation (n=8 each group).

MEASUREMENT OF PROTEIN-BOUND OXYPROLINE IN BLOOD SERUM

Concentration of protein-bound oxyproline in homogenate of myocardium was determined biochemically [7] at 7, 14 and 30 days after the modelling pathology.

HISTOPATHOLOGY STUDY

A portion of the tissue from the ventricles of myocardium was taken at 30 days after the modelling pathology, then fixed in 10 % neutral-buffered formalin solution for 5 days, embedded in paraffin, and sectioned. Histological examination of Masson trichrome staining of myocardium was performed [8].

STATISTICAL ANALYSIS

Statistical analysis was carried out by OriginPro Program. Results are expressed as mean±standard deviation. The results were statistically analyzed using non-parametric indexes in the Excel software (Microsoft, USA) and STATISTICA 10.0 (StatSoft, USA). The reliability of the differences in values between independent quantitative values was determined with a normal distribution according to the Mann–Whitney U criterion [9]. Values p<0.05 are considered as statistically significant.

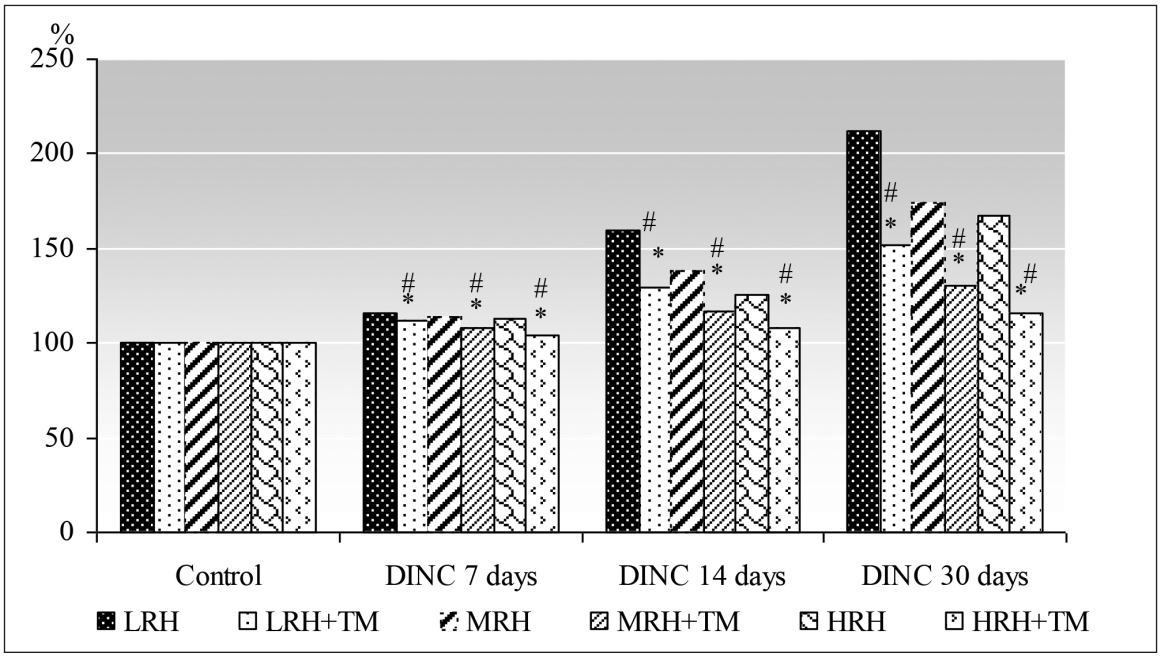
RESULTS

Before the modeling DINC results determine the protein-bound oxyproline concentration in homogenate of myocardium of rats with low resistance to hypoxia was 17.8 % (p<0.05) higher than in serum of rats with middle resistance to hypoxia (Table I), while the high resistant to hypoxia animals' oxyproline concentration in homogenate of myocardium was 21.9 % lower (p<0.05) than in homogenate of myocardium of rats with middle resistance to hypoxia. In the simulation DINC the protein-bound oxyproline concentration in homogenate of myocardium of rats gradually increases at all groups.

Table II. Influence of trimetazidine on protein-bound oxyproline concentration in homogenate of myocardium at the experimental diffuse ischemic necrotic cardiosclerosis (DINC) due to innate resistance of rats to hypoxia

Resistance of animals to hypoxia	Control TM (n=8)	The stages of observation DINC+TM		
		7 days (n=8)	14 days (n=8)	30 days (n=8)
Low	45,58±1,51	51,15±1,36 p*<0,05 p<0,001	59,09±1,85 p*<0,001 p<0,001	69,32±1,86 p*<0,001 p<0,001
Middle	40,58±1,83	43,97±1,34	40,58±1,83 p*<0,05	52,72±3,15 p*<0,05
High	34,90±0,96 p<0,05	36,33±0,91 p<0,001	37,72±1,52 p<0,001	34,90±0,96 p*<0,05 p<0,01

Notes: p<0.05 – significantly different from middle resistant animals to hypoxia at all times of observation; *p<0.05 – significantly different from control at all times of observation.



Notes: indicators of control groups expressed in 100 %; * – significantly different from control at all times of observation, p<0.05; # – significantly different from untreated rats at all times of observation, p<0.05.

Fig. 1. Influence of trimetazidine on protein-bound oxyproline concentration in homogenate of myocardium at the experimental diffuse ischemic necrotic cardiosclerosis (DINC) due to innate resistance of rats to hypoxia.

Under the influence of metabolic therapy by trimetazidine changes of protein-bound oxyproline concentrations in homogenate of myocardium of animals with low resistance to hypoxia were less pronounced (Table II), but significantly the concentration of this metabolite collagen within 7 days after modeling pathology was reduced by 11.0 % (p<0.05) (Figure 1) than in the group of untreated animals at this stage of observation. By stage 14 days DINC protein-bound oxyproline concentration in homogenate of myocardium of rats with low resistance to hypoxia was 25.3 % lower (p<0.001) than in untreated animals, and during 30 days of observation DINC – by 33.9 % (p<0.001) lower than in untreated animals with low resistance to hypoxia in a similar stage of cardiosclerotic process development without correction.

In the serum of rats with middle resistance to hypoxia the protein-bound oxyproline concentration after 7 days DINC and trimetazidine correction was lower by 8.3 % (p<0.05) (Fig. 1) than in the group of untreated animals at this stage of observation. In the next stage of observation, 14 days DINC, protein-bound oxyproline concentration in homogenate of myocardium was 18.6 % lower (p<0.001) than in untreated animals, and during 30 days of observation DINC – by 28.2 % (p<0.001) lower than in untreated rats.

There was no significantly difference between treated and untreated animals with high resistance to hypoxia at the stage of observation 7 days DINC. After 14 days of modeling pathology index was lower by 11.6 % (p<0.05) than in the group of untreated animals at this stage of observation

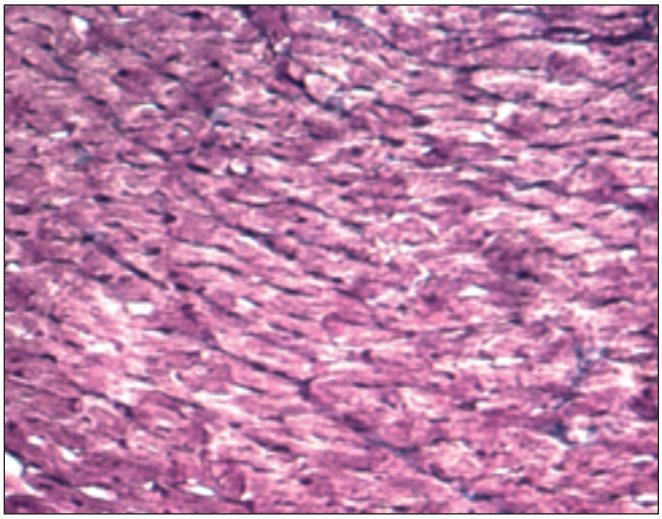


Fig. 2. Myocardium of control rat. Masson trichrome staining of myocardium. x 400.

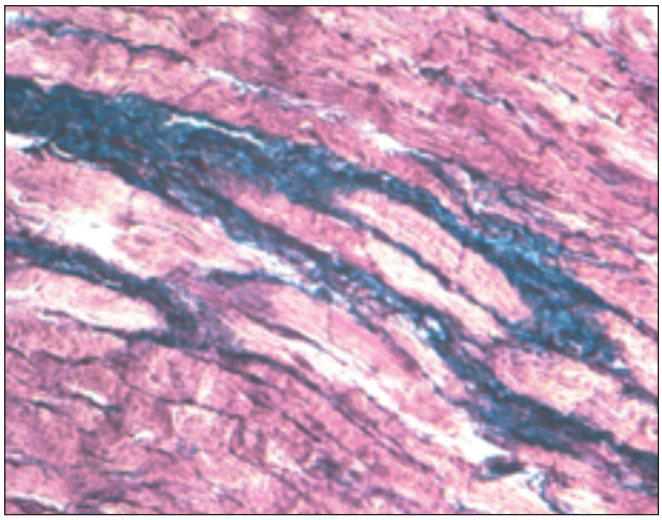


Fig. 3. Myocardium of low resistant to hypoxia rat with DINC. Fibrotic regions in myocardium are rich in collagens and therefore appear in blue upon Masson trichrome staining. In addition, centralized nuclei as well as the shape and the size distribution of the myofibers are visualized and show expressed hypertrophy of cardiomyocytes. 30 days DINC. Masson trichrome staining of myocardium. x 400.

and after 30 days of observation and correction DINC by metabolic therapy the concentration of protein-bound oxyproline in serum was 28.4 % ($p<0.001$) lower than in untreated animals with high resistance to hypoxia without correction.

Histological examination of the myocardium during 30 days of DINC showed that the of micropreparations hearts healthy animals, irrespective of the resistance to hypoxia, connective tissue provided very little in the form of thin collagen fibers (Figure 2), whereas in micropreparations of hearts in the development of DINC (Figure 3) revealed the presence of focal cardiosclerosis, perivascular sclerosis hyperelasticity of the inner membrane of vessels, cardiomyocyte hypertrophy, diffuse proliferation of connective tissue. Fibrotic regions in myocardium are rich in collagens and therefore appear in blue upon Masson trichrome staining. In addition, centralized nuclei as well as the shape and the size distribution of the myofibers are visualized and show expressed hypertrophy of cardiomyocytes.

All the above-mentioned symptoms are the highest in the low resistant animals to hypoxia, indicating the intense development of diffuse cardiosclerosis in animals with low resistance to hypoxia and confirm the results obtained in determining the concentration of protein-bound oxyproline serum of rats with different resistance to hypoxia.

DISCUSSION

Using the determination of protein-bound oxyproline concentrations in homogenate of myocardium in modeling DINC with and without trimetazidine correction and given that hydroxyproline contained mainly composed of collagen and is the product of its metabolism [4-5], it can be used as a biological marker of the intensity of the synthesis of collagen in tissue infarction can draw the following conclusion: the intensity of the metabolic imbalance of connective elements with diffuse ischemic necrotic cardiosclerosis and trimetazidine correction depends on the resistance of animals to hypoxia. In animals with low resistance to hypoxia manifested maximum effect of trimetazidine correction, however, given the more pronounced changes in the concentration oxyproline them in modeling DINC without correction, this effect was not enough for leveling differences between animals with different resistance to hypoxia. This pattern is similar for the group of animals with middle resistance to hypoxia, but the changes were less pronounced. Animals with high resistance to hypoxia were characterized by lower concentrations oxyproline changes in modeling DINC, so the effect of the use manifested to a lesser extent, but in general, they are characterized by minimal metabolic disorders of connective tissue elements in the development of DINC and correction by trimetazidine [10-16]. The activity of the connective tissue metabolism was studied in experimental diffuse ischemic necrotic cardiosclerosis due to different resistance of the organisms to hypoxia. The investigations were based on the changes of concentration of protein-bound oxyproline in homogenate of myocardium that reflect adequacy metabolic changes of collagen [4-5].

CONCLUSIONS

The development of the experimental diffuse ischemic necrotic cardiosclerosis at all times of observation is accompanied by metabolic imbalance in the connective tissue of the heart, and argumented by the increasing of oxyproline level in homogenate of myocardium of animals with different resistance to hypoxia. The intensity of metabolic imbalances in diffuse connective tissue elements is the highest in the low resistant animals to hypoxia. Those results are confirmed by histological examination of the myocardium of rats with different

resistance to hypoxia. Fibrotic regions in myocardium are rich in collagens. It has been revealed that the most pronounced therapeutic effect of TM is observed in animals with low resistance to hypoxia, slightly less – in animals with medium resistance to hypoxia, and the lowest – in animals with high resistance to hypoxia. This pattern was observed at all stages of observation, but it was most expressed in the early period of cardiosclerotic process, indicating the feasibility of early use of metabolic therapy. It explains the absence of cardioprotective effect of trimetazidine in the later stages of cardiosclerosis, when the myocardial fibrosis is already formed.

REFERENCES

1. Lopez AD, Mathers CD. Measuring the global burden of disease and epidemiological transitions: 2002 – 2030. Ann Trop Med Parasitol. 2006; 100(5–6): 481–99.
2. Salemi VM, Leite JJ, Picard MH et al. Echocardiographic predictors of functional capacity in endomyocardial fibrosis patients. Eur J Echocardiogr 2009; 10(3): 400–5.
3. Iglezias SD, Benvenuti LA, Calabrese F. et al. Endomyocardial fibrosis: pathological and molecular findings of surgically resected ventricular endomyocardium. Virchows Arch 2008; 453(3); 233–41.
4. Ito A, Yamagiwa H, Sasaki RJ. Effects of aging on hydroxyproline in human heart muscle. Am Geriatr Soc. 1980; 28(9): 398–404.
5. Hoerstrup SP, Zünd G, Ye Q, et al. Tissue engineering of a bioprosthetic heart valve: stimulation of extracellular matrix assessed byhydroxyproline assay. ASAIO J. 1999; 45(5): 397–402.
6. Saturska HS. Peculiarities of cardioprotective effect of trimetazidine at experimental cardiosclerosis in rats with different sensitivity to hypoxia. Vestnik of Vitebsk State Medical University 2015; 14(1): 34–40. (in Russian).
7. Sharaev PN. Method for determination of free and bound hydroxyproline in serum. Lab business 1981; 5: 283–5. (in Russian).
8. Merkulov GA. Course of histological techniques. – L .: Medicine, 1969; 422 p. (in Russian).
9. Orlov AI. Mathematics cases: probability and statistics – the basic facts: a tutorial. M. : M-Press, 2004; 100 p. (in Russian).
10. Detry JM, Sellier P, Pennaforte S, et al. Trimetazidine: a new concept in the treatment of angina: comparison with propranolol in patients with stable angina. Trimetazidine European Multicenter Study Group. Br J Clin Pharmacol 1994; 37: 279-88.
11. Gupta R, Sawhney JP, Narain VS. Treatment of stable angina pectoris with trimetazidine modified release in Indian primary-care practice. Am J Cardiovasc Drugs. 2005; 5(5): 325–9.
12. Marzilli M, Klein WW. Efficacy and tolerability of trimetazidine in stable angina: a metaanalysis of randomized, double-blind, controlled trials. Coron Artery Dis 2003; 14: 171-9.
13. Sellier P, Broustet JP. Assessment of anti-ischemic and antianginal effect at trough plasma concentration and safety of trimetazidine MR 35mg in patients with stable angina pectoris: a multicenter, double-blind, placebo-controlled study. Am J Cardiovasc Drugs 2003; 3: 361-9.
14. Szwed H, Sadowski Z, Pachocki R, et al. Anti-ischaemic efficacy and tolerability of trimetazidine in elderly patients with angina. Clin Drug Invest 2000; 19: 1-8.
15. Szwed H, Sadowski Z, Pachocki R, et al. Combination treatment in stable effort angina using trimetazidine and metoprolol: results of a randomized, double-blind, multicentre study (TRIMPOL II). TRIMetazidine in POLand. Eur Heart J 2001; 22: 2267-74.
16. Szwed H, Sadowski Z, Pachocki R, et al. The antiischemic effects and tolerability of trimetazidine in coronary diabetic patients: a substudy from TRIMPOL 1. Cardiovasc Drugs Ther 1999; 13: 217-22.

Authors' contributions:
According to the order of the Authorship.
Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Hanna Saturska
Department of Social Medicine,
Organization and Economics of Health Care,
and Medical Statistics,
I. Horbachevsky Ternopil State Medical University
st. Slovatskoho, 2, 46000, Ternopil, Ukraine
tel: +380 980651672
e-mail: saturska.gs@gmail.com

Received: 10.10.2018
Accepted: 27.12.2018

PRACA ORYGINALNA
ORIGINAL ARTICLE

ZMIANY OSOCZOWEGO STĘŻENIA PARATHORMONU U PACJENTÓW KRYTYCZNIE CHORYCH: BADANIE PROSPEKTYWNE, OBSERWACYJNE

TRENDS IN PARATHYROID HORMONE PLASMA CONCENTRATION IN CRITICALLY ILL PATIENTS: PROSPECTIVE OBSERVATIONAL STUDY

Aneta Czarnik[1], Tomasz Czarnik[2], Robert Kapłon[3], Marek Bolanowski[4]
[1]ODDZIAŁ ENDOKRYNOLOGII, SZPITAL WOJEWÓDZKI W OPOLU, OPOLE, POLSKA
[2]ODDZIAŁ ANESTEZJOLOGII I INTENSYWNEJ TERAPII, UNIWERSYTECKI SZPITAL KLINICZNY W OPOLU, OPOLE, POLSKA
[3]WYDZIAŁ INFORMATYKI I ZARZĄDZANIA, POLITECHNIKA WROCŁAWSKA, WROCŁAW, POLSKA
[4]KATEDRA I KLINIKA ENDOKRYNOLOGII, DIABETOLOGII I LECZENIA IZOTOPAMI, UNIWERSYTET MEDYCZNY WE WROCŁAWIU, WROCŁAW, POLSKA

STRESZCZENIE

Wstęp: W piśmiennictwie brak jest danych dotyczących oceny zmian stężenia osoczowego parathormonu u pacjentów krytycznie chorych.
Cel pracy: Ocena stężeń osoczowych oraz kinetyki parathormonu w reprezentatywnej populacji pacjentów krytycznie chorych, z niewydolnością wielonarządową, leczonych na oddziale intensywnej terapii.
Materiał i metody: Do badania włączono 30 pacjentów z niewydolnością wielonarządową, obejmującą co najmniej układ oddechowy i krążenia. Kryteriami wyłączenia były: ostra niewydolność wątroby, hiperkalcemia, choroba przytarczyc w wywiadzie, schyłkowa niewydolność nerek, znaczny niedobór witaminy D, leczenie na innym oddziale intensywnej terapii bezpośrednio przed przyjęciem, wiek poniżej 18 lat, brak zgody rodziny pacjenta. Pomiary osoczowego stężenia parathormonu wykonywano w odstępach 12-godzinnych.
Wyniki: Rozkład osoczowych stężeń parathormonu dla wszystkich 30 pacjentów włączonych do badania pokazuje, że wyniki pierwszych pomiarów są bardzo zróżnicowane, a mediany przekraczają górną granicę referencyjnej normy laboratoryjnej. Szczególnie jest to widoczne w grupie pacjentów z ostrym uszkodzeniem nerek leczonych za pomocą ciągłych technik nerkozastępczych. Dla niej wyjściowe stężenia osoczowe parathormonu powyżej normy laboratoryjnej zaobserwowano u 8 pacjentów, co stanowiło 80% tej grupy. Sama wartość tych stężeń była bardzo wysoka. Grupa pacjentów z ostrym uszkodzeniem nerek wykazuje tendencję do bardzo szybkiego spadku stężenia osoczowego parathormonu, który następuje między pomiarem drugim a trzecim. Również zróżnicowanie wyników w tej grupie dla pierwszych dwóch pomiarów jest bardzo duże.
Wnioski: Osoczowe stężenia parathormonu u pacjentów krytycznie chorych leczonych na oddziale intensywnej terapii podlegają większym lub mniejszym fluktuacjom. W grupie pacjentów z ostrym uszkodzeniem nerek leczonych ciągłą terapią nerkozastępczą obserwowano u większości chorych bardzo wysokie wyjściowe stężenia osoczowe parathormonu z następczym dynamicznym spadkiem.

SŁOWA KLUCZOWE: parathormon; niewydolność wielonarządowa; intensywna terapia; ostre uszkodzenie nerek; ciągła terapia nerkozastępcza

ABSTRACT

Introduction: There is no data in the literature regarding trends in parathormone serum concentration assessment in critically ill patients.
The aim: To assess the parathyroid hormone plasma concentrations and kinetics in critically ill patients admitted to the intensive care unit due to multiorgan failure.
Materials and methods: Thirty multiorgan failure (at least circulatory and respiratory failure) patients were included. Patients who met any of the following criteria were excluded: acute liver failure, end stage renal disease, hypercalcemia, parathyroid gland disease, severe vitamin D deficiency, admission from another ICU or readmission, age younger than 18 years, or lack of consent from relatives. We performed the parathyroid hormone plasma measurements in 12-hour time intervals.
Results: The initial parathyroid hormone plasma concentration levels in the study group were rather variable and medians exceeded laboratory reference values. Especially in the acute kidney injury subpopulation treated with continuous renal replacement therapy these trends were emphasized. The initial parathyroid hormone plasma concentration levels in this group significantly exceeded laboratory reference values in 80% of patients. After initial spike we observed subsequent drop between second and third measurement. The distribution of plasma levels was rather variable between second and third measurement in this group of patients.
Conclusions: The parathyroid hormone plasma concentration levels in the critically ill patients are variable. In the acute kidney injury subpopulation treated with continuous renal replacement therapy after initial significant spike we observed subsequent drop between second and third measurement.

KEY WORDS: parathyroid hormone, multiorgan failure, intensive therapy, acute kidney injury, continuous renal replacement therapy

Wiad Lek 2019, 72, 1, 40-46

WSTĘP

Parathormon (PTH) to polipeptyd powstający w przytarczycach, który razem z witaminą D pełni fundamentalną rolę w regulacji procesów odpowiedzialnych za gospodarkę wapniowo-fosforową organizmu ludzkiego. Wydzielanie PTH przez przytarczyce zależy od stężenia wapnia zjonizowanego w surowicy (hipokalcemia pobudza, a hiperkalcemia hamuje jego wydzielanie na zasadzie sprzężenia zwrotnego) oraz stężenia 1,25 dihydroksywitaminy D3, która hamuje jego wydzielanie. Za regulację wydzielania PTH przez przytarczyce odpowiada receptor wapniowy (CaSR) działający poprzez kaskadę białka G i wykrywający zmiany osoczowego stężenia wapnia. Pobudzenie receptora CaSR w warunkach hiperkalcemii zmniejsza wydzielanie PTH, sytuacja odwrotna ma miejsce w warunkach hipokalcemii [1–3].

Biologicznym efektem działania PTH jest zwiększenie stężenia osoczowego wapnia poprzez nasilenie jego reabsorpcji z kości, zwiększenie wchłaniania z przewodu pokarmowego oraz zmniejszenie utraty z moczem. Dodatkowo PTH zmniejsza stężenie osoczowe fosforanów. PTH stymuluje nerkową hydroksylację 25-hydroksywitaminy D3 w pozycji 1-alfa przy udziale enzymu 1-alfa hydroksylazy czego efektem jest powstanie kalcitriolu czyli 1,25-dihydroksywitaminy D3 – formy witaminy D najbardziej aktywnej biologicznie, odpowiedzialnej za stymulację wchłaniania jelitowego wapnia. Reakcja ta nasila się przy niskim poziomie wapnia we krwi. PTH działa na swoiste receptory w nerkach zwiększając reabsorpcję wapnia, fosforanów, dwuwęglanów w kanalikach krętych, dystalnych, zaś w kanalikach proksymalnych hamuje reabsorpcję fosforanów. Parathormon pobudza różnicowanie, tworzenie i aktywność dojrzałych osteoklastów oraz jest podstawowym hormonem regulującym czynność osteoblastów [1–3].

W piśmiennictwie medycznym brak jest danych dotyczących oceny zmian stężeń osoczowych parathormonu u pacjentów krytycznie chorych leczonych na oddziale intensywnej terapii z powodu niewydolności wielonarządowej. Brak jest także danych dotyczących stężeń PTH u pacjentów krytycznie chorych poddanych zabiegom ciągłej terapii nerkozastępczej z powodu ostrego uszkodzenia nerek.

Celem niniejszej pracy była ocena zmian stężenia osoczowego PTH w czasie, w początkowym okresie choroby krytycznej, u pacjentów leczonych na oddziale intensywnej terapii z powodu niewydolności wielonarządowej.

MATERIAŁ I METODY

Badanie jednoośrodkowe, prospektywne, obserwacyjne prowadzono od września 2015 roku do stycznia 2017 roku w wieloprofilowym, jedenastołóżkowym oddziale intensywnej terapii (Oddział Anestezjologii i Intensywnej Terapii, Uniwersytecki Szpital Kliniczny w Opolu). Pisemna zgoda na włączenie do badania uzyskiwana była od członków najbliższej rodziny pacjenta. Projekt badawczy został zaaprobowany przez Komisję Bioetyczną przy Okręgowej Izbie Lekarskiej w Opolu (numer protokołu: 214/2015 z dnia 25/03/2015 roku), zarejestrowany przed rozpoczęciem procesu rekrutacji pacjentów w rejestrze badań klinicznych clinicaltrials.gov (NCT02414386) oraz prowadzony zgodnie z założeniami Deklaracji Helsińskiej. Prezentowana praca jest częścią większego projektu badawczego oceniającego kinetykę stężeń witaminy D u pacjentów krytycznie chorych z ostrym uszkodzeniem nerek, poddanych zabiegowi ciągłej terapii nerkozastępczej z regionalną antykoagulacją cytrynianową. Celem prowadzonych badań była ocena zmian stężeń osoczowych PTH w czasie w reprezentatywnej populacji pacjentów krytycznie chorych, z niewydolnością wielonarządową, leczonych na oddziale intensywnej terapii.

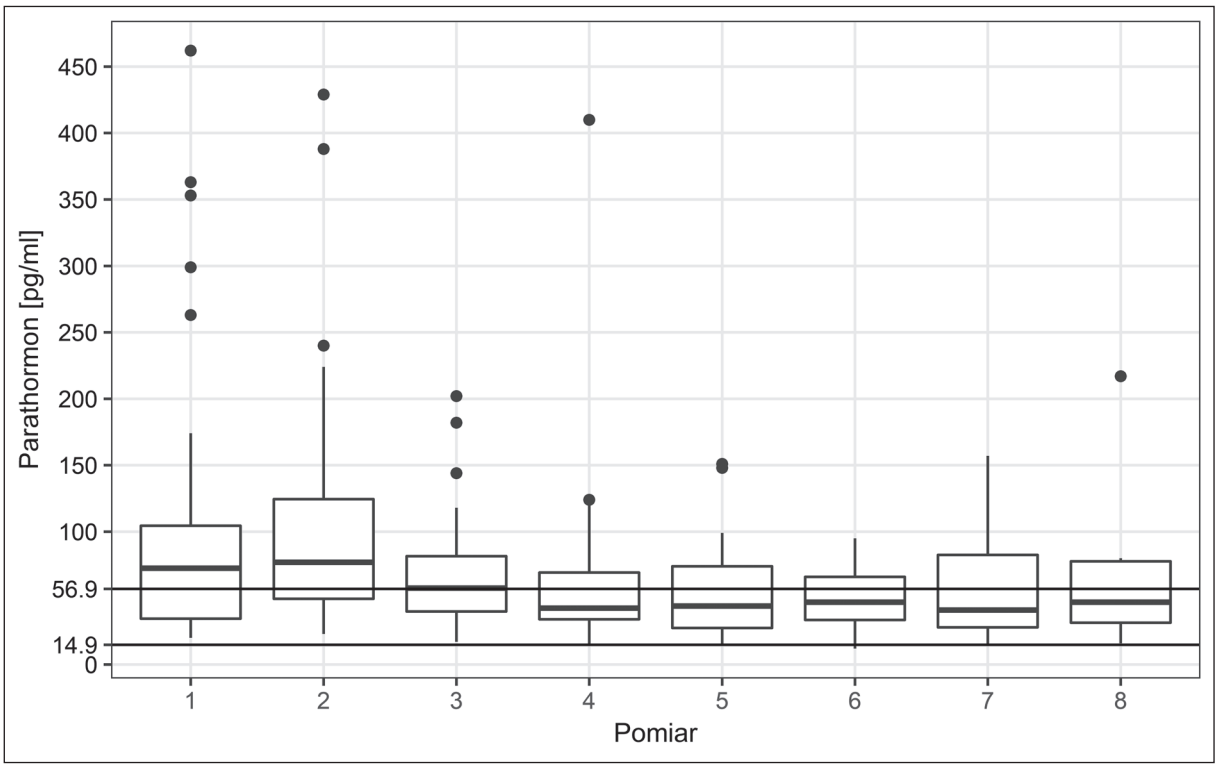
Do badania włączeni zostali pacjenci, u których wyjściowe stężenie witaminy D w osoczu wyniosło minimum 10 ng/ml oraz współistniała niewydolność wielonarządowa obejmująca co najmniej układ oddechowy i krążenia. Osoczowe stężenie witaminy D na poziomie 10 ng/ml i mniejszym definiowane jest w piśmiennictwie jako ciężki niedobór i wiązane jest ze zwiększoną śmiertelnością w grupie pacjentów krytycznie chorych [4, 5]. Niewydolność oddechową zdefiniowano jako stan jednoznaczny z koniecznością wdrożenia inwazyjnej wentylacji mechanicznej dowolnym trybem, a niewydolność krążenia jako stan jednoznaczny z koniecznością wdrożenia dożylnego leczenia lekiem inotropowym i/lub wazopresyjnym. Kryteriami wyłączenia były: ostra niewydolność wątroby, hiperkalcemia (stężenie wapnia całkowitego w osoczu >10,6 mg/dL, stężenie wapnia zjonizowanego w osoczu >1,35 mmol/L), choroba przytarczyc w wywiadzie, schyłkowa niewydolność nerek, leczenie na innym oddziale intensywnej terapii bezpośrednio przed przyjęciem, wiek poniżej 18 lat, brak zgody rodziny pacjenta.

Procedura pomiarów osoczowego stężenia PTH była zgodna ze standardem wypracowanym przez Centralne Laboratorium Uniwersyteckiego Szpitala Klinicznego w Opolu. Krew na badanie pobierano z linii tętniczej, żylnej centralnej lub drogą bezpośredniej punkcji żyły obwodowej wprowadzając ją bezpośrednio do monowet EDTA. Monowety chroniono przed dostępem światła i dostarczano do laboratorium analitycznego w czasie do 30 minut od pobrania, następnie wirowano przez 10 minut (3500 rpm), a następnie poddawane były obróbce przez techników laboratoryjnych. Pomiar osoczowego stężenia parathormonu prowadzono metodą elektrochemiluminescencyjną ECLIA z użyciem apartów Cobas e411 lub Cobas 6000 (Roche Diagnostics GmbH, Mannheim, Niemcy).

Kolejni pacjenci przyjmowani na Oddział Anestezjologii i Intensywnej Terapii, Uniwersyteckiego Szpitala Klinicznego w Opolu byli oceniani pod kątem kryteriów włączenia i wyłączenia. W przypadku włączenia pacjenta do badania pierwsze próbki krwi pobierano nie później niż po 12 godzinach. Kolejne próbki krwi pobierano w odstępach 12-godzinnych (dwa razy na dobę, o godzinie 6:00 i 18:00). Minimalna, akceptowana liczba pobranych próbek u jednego pacjenta wynosiła 4, maksymalna – 8. Wszystkie niezbędne dane demograficzne pacjentów oraz wyniki badań laboratoryjnych były zapisywane i archiwi-

Tabela I. Podstawowa statystyka opisowa pacjentów grupy badanej.

	n	Średnia	Mediana	IQR	Zakres
Charakterystyka pacjentów	30				
Punktacja SOFA przy przyjęciu		13,2	13	3	8–16
Stężenie PTH przy przyjęciu		112,2	72.5	70	20–462
Główna diagnoza przy przyjęciu	30				
Zatrzymanie krążenia	15				
Ostra niewydolność oddechowa	5				
Wstrząs kardiogenny	3				
Wstrząs septyczny	4				
Uraz mnogi	2				
Wstrząs krwotoczny	1				



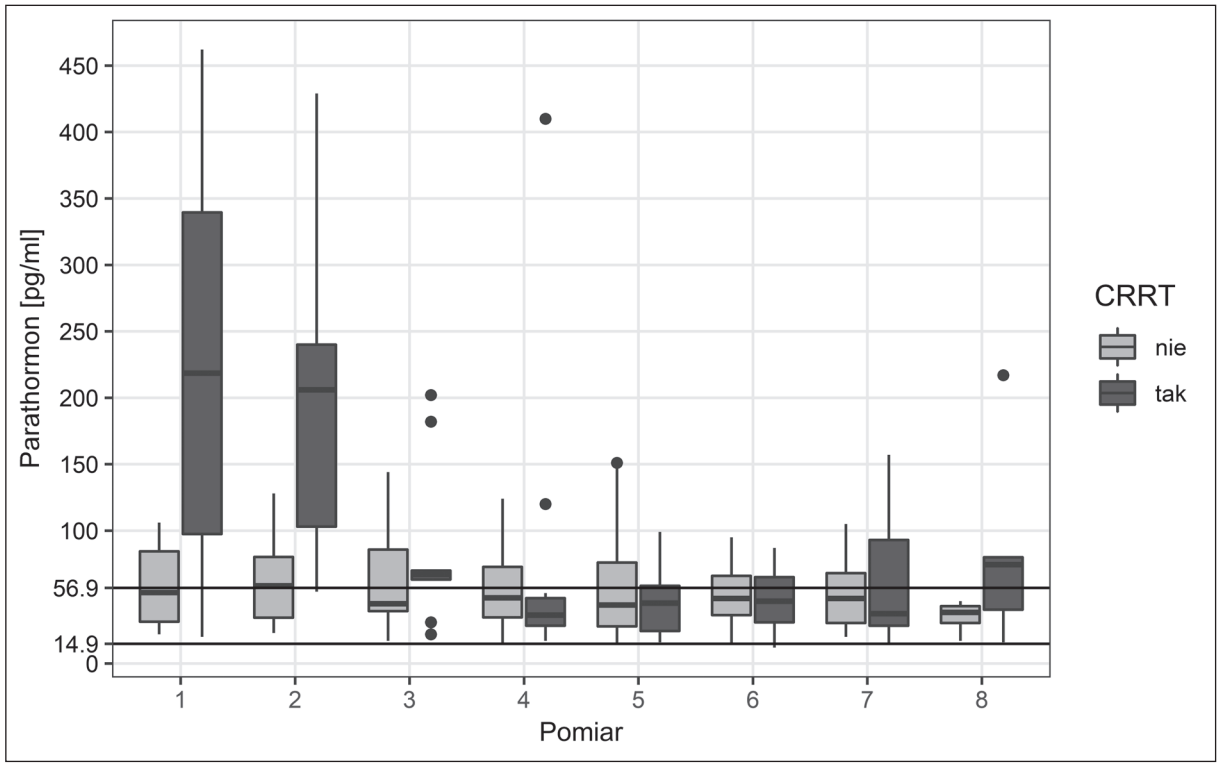
Ryc. 1. Wykres zbiorczy stężenia osoczowego parathormonu dla wszystkich pacjentów grupy badanej.
Linią pogrubioną zaznaczono wartość mediany stężenia PTH, kropkami wartości odstające. Norma laboratoryjna stężenia PTH: 14,9–56,9 pg/ml.

zowane w formie elektronicznej w szpitalnym systemie informatycznym. Po zakończonym procesie rekrutacji wszystkie dane elektroniczne pacjentów odczytywano, dane mogące posłużyć przypadkowej identyfikacji pacjenta zaślepiano oraz przesyłano profesjonalnemu statystykowi w celu przeprowadzenia analizy. Statystykę opisową przedstawiono w formie mediany, rozstępu kwartylowego (IQR), zakresów.

WYNIKI

Oceniono łącznie 388 pacjentów pod kątem włączenia do badania. Po wstępnej ocenie 358 pacjentów nie zostało zakwalifikowanych. Przyczynami wyłączenia były: brak niewydolności oddechowej, brak niewydolności krążenia, niewykonanie oznaczeń osoczowych stężeń witaminy D i PTH, schyłkowa niewydolność nerek, przyjęcie pacjenta z innego oddziału intensywnej terapii, ostra niewydolność wątroby, wiek poniżej 18 lat.

Ostatecznie 30 pacjentów spełniło kryteria włączenia i zostało zakwalifikowanych do oceny zmian osoczowych stężeń PTH w czasie. Podstawowe dane demograficzne pacjentów zawarto w tabeli I. U 20 pacjentów w grupie badanej współistniała niewydolność oddechowa i krążenia w momencie przyjęcia na oddział intensywnej terapii, zaś u pozostałych 10 pacjentów istniały dodatkowo cechy ostrego uszkodzenia nerek z koniecznością wdrożenia ciągłego leczenia nerko-



Ryc. 2. Wykres zbiorczy stężenia osoczowego parathormonu dla wszystkich pacjentów grupy badanej z rozróżnieniem na pacjentów poddanych ciągłej terapii nerkozastępczej (CRRT) lub niepoddanych tej terapii.
Linią pogrubioną zaznaczono wartość mediany stężenia PTH, kropkami wartości odstające. Norma laboratoryjna stężenia PTH: 14,9–56,9 pg/ml.

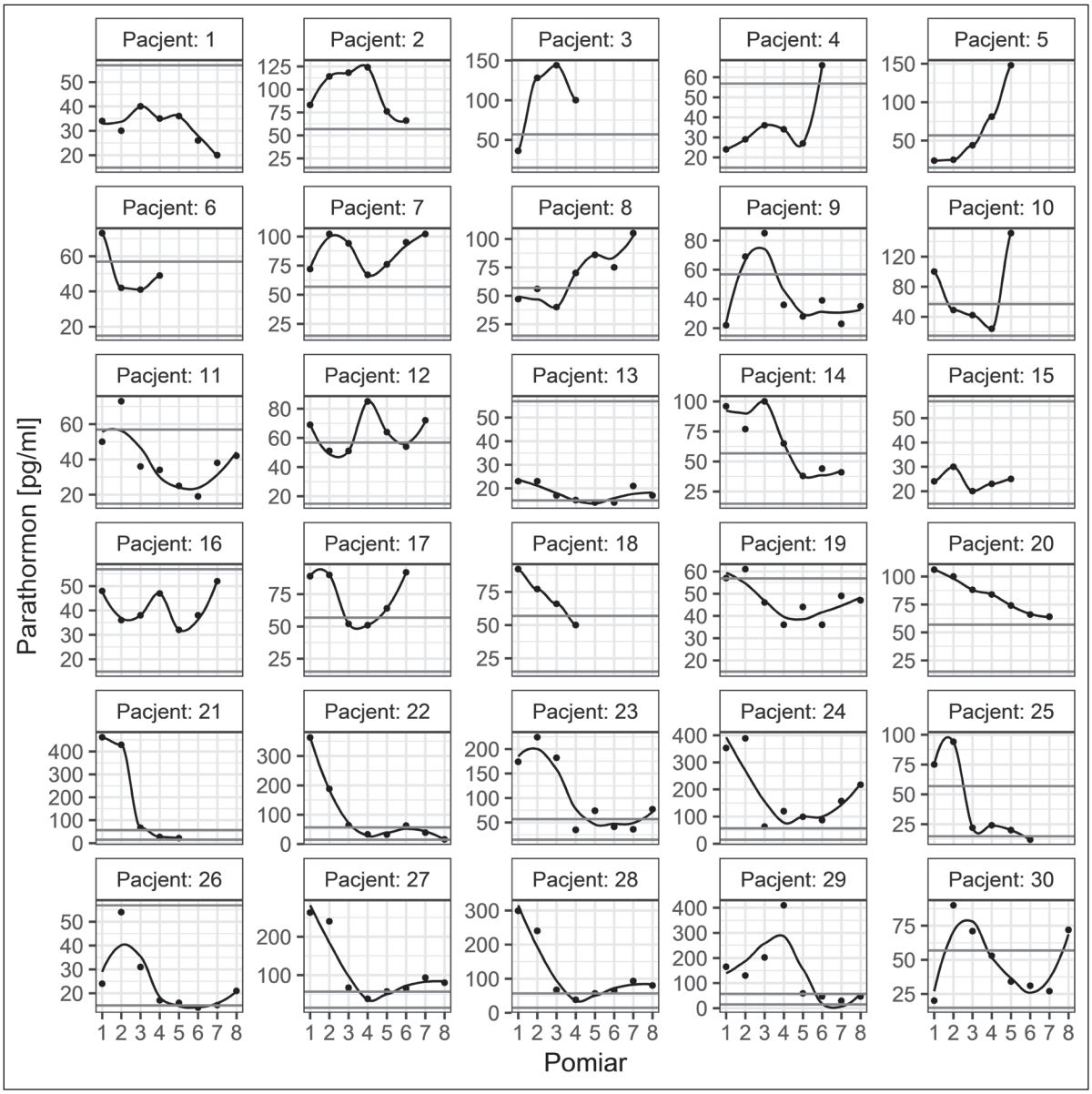
zastępczego. U wszystkich pacjentów początkowe stężenia osoczowe PTH (pierwsze pomiary) wynosiły od 20 do 462 pg/ml przy normie laboratoryjnej przyjętej przez Centralne Laboratorium Uniwersyteckiego Szpitala Klinicznego w Opolu wynoszącej 14,9 do 56,9 pg/ml. Nie stwierdzono wyjściowych stężeń osoczowych PTH poniżej referencyjnej normy laboratoryjnej, jednakże u 18 pacjentów początkowe stężenia PTH przekraczały normę laboratoryjną (zakres od 57 do 462 pg/ml), co stanowiło 60% badanej grupy.

U wszystkich pacjentów zanotowano wyjściowe stężenia osoczowe witaminy D w zakresie od 10,6 do 39 ng/ml. U 29 pacjentów stężenia witaminy D wyniosły od 10 do 30 ng/ml, co jest jednoznaczne z obniżonym jej stężeniem lub niedoborem, zaś tylko u 1 pacjenta zanotowano normalny osoczowy poziom witaminy D (39 ng/ml).

Rozkład osoczowych stężeń PTH dla wszystkich pacjentów przedstawiono na rycinie 1. Jego analiza pokazuje, że wyniki pierwszych pomiarów są bardzo zróżnicowane (duża dyspersja, obserwacje odstające), a mediany przekraczają górną granicę referencyjnej normy laboratoryjnej. W grupie pacjentów z ostrym uszkodzeniem nerek wyjściowe stężenia osoczowe PTH powyżej normy laboratoryjnej zaobserwowano u 8 pacjentów, co stanowiło 80% tej grupy. Sama wartość tych stężeń była bardzo wysoka (zakres od 75 do 462 pg/ml). Dla porównania w grupie bez ostrego uszkodzenia nerek wyjściowa wartość osoczowego stężenia PTH nie przekroczyła 106 pg/ml.

W kontekście powyższych ustaleń dokonano analizy trendów pomiarowych osoczowych stężeń PTH z uwzględnieniem ostrego uszkodzenia nerek. Rozkład stężeń PTH w kolejnych pomiarach przedstawiono na rycinie 2. Grupa z ostrym uszkodzeniem nerek wykazuje tendencję do bardzo szybkiego spadku stężenia osoczowego PTH, który następuje między pomiarem drugim a trzecim. Również zróżnicowanie wyników w tej grupie, dla pierwszych dwóch pomiarów, jest bardzo duże (duży rozstęp międzykwartylowy).

Rycina 3 dostarcza bardziej szczegółowych wyjaśnień, gdyż przedstawiono na niej zmiany stężeń PTH dla każdego pacjenta. Naniesiono również krzywą tendencji tychże zmian. W grupie pacjentów z ostrym uszkodzeniem nerek (pacjenci: 21–30) widoczna jest tendencja do dynamicznego spadku stężenia osoczowego PTH w kolejnych pomiarach – odnosi się to do 7 pacjentów. U pozostałych 3 pacjentów tej grupy stężenia PTH pozostawały stabilne lub fluktuacje były stosunkowo niewielkie. U 2 pacjentów tej grupy z początkowym, wysokim stężeniem PTH, po wstępnym spadku stężenia zaobserwowano ponowny dynamiczny wzrost poziomu PTH. Tylko u jednego pacjenta tej grupy osoczowe stężenie PTH pozostawało w granicach normy w kolejnych 8 pomiarach. W grupie pacjentów bez niewydolności nerek (pacjenci: 1–20) dynamika zmian osoczowego stężenia PTH nie była tak wyraźnie zaznaczona. U większości pacjentów tej grupy poziomy stężeń PTH można określić jako stabilne przez cały okres monitorowania (14 pacjentów). Jedynie u 6 pacjentów tej grupy obserwowano nieco bardziej zaznaczone zmiany stężeń PTH, jednakże nie tak dynamiczne, jak w grupie z ostrą niewydolnością nerek oraz o charakterze raczej nieuporządkowanym.



Ryc. 3. Wykresy zmian stężenia osoczowego parathormonu dla wszystkich pacjentów grupy badanej.
Linią pogrubioną zaznaczono wartość mediany stężenia PTH, kropkami wartości odstające. Norma laboratoryjna stężenia PTH: 14,9–56,9 pg/ml.

DYSKUSJA

Prezentowane badanie pokazało, że u pacjentów krytycznie chorych leczonych na oddziale intensywnej terapii osoczowe stężenia parathormonu podlegają większym lub mniejszym fluktuacjom. W głównej mierze fluktuacje te polegają na wzrostach stężeń osoczowych PTH z następczym spadkiem. W grupie pacjentów bez ostrego uszkodzenia nerek wzrosty wartości stężeń osoczowych PTH nie są ekstremalnie wysokie, a fluktuacje charakteryzują się stosunkowo niewielką dynamiką i są mniej przewidywalne. Zupełnie inną tendencję obserwowano w grupie pacjentów z ostrym uszkodzeniem nerek leczonych ciągłą terapią nerkozastępczą. Obserwowano tam u większości pacjentów bardzo wysokie wyjściowe stężenia osoczowe PTH. Co charakterystyczne, w kolejnych pomiarach obserwowano tendencję do dynamicznego spadku stężenia PTH u większości pacjentów z tej grupy. Nigdy nie obserwowano wyjściowych stężeń osoczowych PTH poniżej referencyjnej normy laboratoryjnej.

Wyniki prezentowanego badania są niemożliwe do oceny z perspektywy innych badań o podobnym charakterze, gdyż takowe nie istnieją. Analiza wyników badania rodzi pytanie o przyczynę wzrostów i fluktuacji stężenia osoczowego PTH u pacjentów krytycznie chorych. Jedną z hipotez jest potencjalny związek ciężkiego zaburzenia homeostazy organizmu, jakim jest niewątpliwie choroba krytyczna z dysregulacją wydzielania PTH przez przytarczyce. Należy podkreślić, że fluktuacjom stężenia osoczowego PTH nie towarzyszyły zmiany stężenia osoczowego witaminy D (25 hydroksywitaminy D3) i wapnia zjonizowanego – głównych regulatorów jego wydzielania. Jednakże stężenia osoczowe 1,25 dihydroksywitaminy D3 nie były oznaczane,

gdyż nie jest to standard laboratoryjny (duża labilność tego związku). Poczynione obserwacje rodzą pytanie, czy podwyższone stężenia osoczowe PTH nie są markerem nasilenia (ciężkości) choroby, a stopniowy spadek stężenia PTH odbiciem procesu stabilizacji (zdrowienia). Należy się także zastanowić, czy istnieje jakiś specyficzny czynnik wpływający na wyrzut PTH z przytarczyc w warunkach choroby krytycznej.

Przyczyny przetrwałych, wysokich stężeń osoczowych PTH u pacjentów ze schyłkową niewydolnością nerek są powszechnie znane (hipokalcemia, hipowitaminoza D oraz hiperfosfatemia) z następczą zwiększoną ekspresją genów PTH oraz proliferacją komórek przytarczyc [6]. W przypadku pacjentów z ostrym uszkodzeniem nerek przyczyny nie są tak jasne [7–11]. W grupie badanych pacjentów z ostrym uszkodzeniem nerek obserwowano wyjściowo normalne stężenia osoczowe wapnia całkowitego i zjonizowanego oraz hiperfosfatemię. Osoczowe stężenia witaminy D3 były obniżone, ale jest to regułą dla całej populacji pacjentów intensywnej terapii, także tych bez ostrego uszkodzenia nerek [12]. Podwyższone stężenia osoczowe PTH u pacjentów z ostrym uszkodzeniem nerek mogą więc być związane z hiperfosfatemią lub upośledzonym klirensem nerkowym tej substancji. Należy jednak pamiętać, że główny szlak metaboliczny PTH wiedzie przez wątrobę, a testy laboratoryjne mogą hipotetycznie wykrywać także metabolity PTH krążące we krwi. Następcze, dynamiczne spadki stężenia osoczowego PTH związane mogą być z wdrożeniem ciągłej terapii nerkozastępczej i eliminacją tego związku oraz jego metabolitów drogą układu pozaustrojowego [13]. Nie należy wykluczać również związku dysregulacji wydzielania PTH z chorobą krytyczną, gdyż nie zbadano funkcjonowania przytarczyc w warunkach wstrząsu, hipoperfuzji narządowej, uogólnionej odpowiedzi zapalnej itd. Niewątpliwie temat związku osoczowych stężeń PTH z chorobą krytyczną pozostawia wiele niewiadomych i wymaga dalszych badań klinicznych.

Prezentowane badanie ma kilka ograniczeń. Pierwszym jest brak użycia wnioskowania statystycznego ze względu na niewielką grupę badanych pacjentów. Trudno jest więc jednoznacznie stwierdzić, czy nasze obserwacje można uogólnić na całą populację pacjentów leczonych na oddziale intensywnej terapii. Drugim ograniczeniem badania pozostaje jego obserwacyjny charakter. Nie można wobec tego stwierdzić, czy istotnie zaznaczone fluktuacje stężenia osoczowego PTH w grupie pacjentów z niewydolnością nerek mają związek z charakterem choroby, prowadzoną terapią nerkozastępczą oraz czy ma to znaczenie rokownicze. Ostatnim ograniczeniem pozostaje fakt, że tylko 7,7 % pacjentów leczonych w tym czasie na oddziale intensywnej terapii włączono do badania. Związane jest to ze zróżnicowanym przekrojem pacjentów przyjmowanych do wieloprofilowego oddziału intensywnej terapii oraz zastosowaniem kryterium minimalnego stężenia witaminy D (ekstremalnie niskie stężenia D są niemal regułą u pacjentów krytycznie chorych). Naszą intencją było włączenie do badania pacjentów w stanie zagrożenia życia będących grupą reprezentacyjną dla ogólnej populacji intensywnej terapii stąd współistniejąca niewydolność układu oddechowego i krążenia stanowiły minimalne warunki włączenia do badania (typowe cechy choroby krytycznej).

WNIOSKI

Osoczowe stężenia parathormonu u pacjentów krytycznie chorych leczonych w oddziale intensywnej terapii podlegają większym lub mniejszym fluktuacjom. W głównej mierze fluktuacje te polegają na wzrostach stężeń z następczym spadkiem. W grupie pacjentów bez ostrego uszkodzenia nerek wzrosty wartości stężeń osoczowych PTH nie są ekstremalnie wysokie, a fluktuacje charakteryzują się stosunkowo niewielką dynamiką i są mniej przewidywalne. W grupie pacjentów z ostrym uszkodzeniem nerek leczonych ciągłą terapią nerkozastępczą obserwowano u większości pacjentów bardzo wysokie wyjściowe stężenia osoczowe PTH z następczym dynamicznym spadkiem w kolejnych pomiarach. Związek osoczowych stężeń PTH z chorobą krytyczną pozostaje niejasny i wymaga dalszych badań klinicznych.

PIŚMIENNICTWO

1. Bolanowski M. Regulacja hormonalna metabolizmu mineralnego i kostnego. In: Zgliczyński W (ed). Endokrynologia. 1st edn. Warszawa: Medical Tribune Polska, 2012.
2. Goltzman D. Physiology of Parathyroid Hormone. Endocrinol Metab Clin North Am 2018;47(4):743-758.
3. Insogna KL. Primary Hyperparathyroidism. N Engl J Med 2018;379(11):1050-1059.
4. Amrein K, Schnedl C, Holl A et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. JAMA 2014;312(15):1520-1530.
5. Brook K, Camargo CA, Christopher KB, Quraishi SA. Admission vitamin D status is associated with discharge destination in critically ill surgical patients. Ann Intensive Care 2015;5(1):23.
6. Guillaume J, Souberbielle JC, Zaoui E et al. Analysis of the kinetics of the parathyroid hormone, and of associated patient outcomes, in a cohort of haemodialysis patients. BMC Nephrology 2016;17:153.
7. Akmal M, Goldstein DA, Kletzky OA, Massry SG. Hyperparathyroidism and hypotestosteronemia of acute renal failure. Am J Nephrol 1988;8:166-169.
8. Fuss M, Bagon J, Dupont E, Manderlier T, Brauman H, Corvilain J. Parathyroid hormone and calcium blood levels in acute renal failure. Nephron 1978;20:196-202.
9. Ozmen S, Danis R, Akin D. Parathyroid hormone as a marker for the differential diagnosis of acute and chronic failure. Ren Fail 2007;29:509-512.
10. Pietrek J, Kokot F, Kuska J. Serum 25-hydroxyvitamin D and parathyroid hormone in patients with acute renal failure. Kidney Int 1978;13:178-185.
11. Kokot F, Mleczko Z, Pazera A. Parathyroid hormone, prolactin, and function of the pituitary-gonadal axis in male patients with acute renal failure. Kidney Int 1982;21:84-89.
12. Czarnik T, Czarnik A, Gawda R et al. Vitamin D kinetics in the acute phase of critical illness – a prospective observational study. J Crit Care 2018;43:294-299.

13. Bellomo R, McGrath B, Boyce N. Effect of continuous venovenous hemofiltration with dialysis on hormone and catecholamine clearance in critically ill patients with acute renal failure. Crit Care Med 1994;22:833-837.

Konflikt interesów:
Autorzy deklarują brak konfliktu interesów.

AUTOR KORESPONDUJĄCY
Tomasz Czarnik
Oddział Anestezjologii i Intensywnej Terapii,
Uniwersytecki Szpital Kliniczny w Opolu,
Al. Witosa 26, 45-401 Opole, Polska.
tel. 669906333
e-mail: tczarnik@mac.com

Nadesłano: 11.12.2018
Zaakceptowano: 21.01.2019

PRACA ORYGINALNA
ORIGINAL ARTICLE

IMPROVED QUALITY OF LIFE OF PATIENTS WITH RHEUMATOID ARTHRITIS AND NONPSYCHOTIC MENTAL DISORDERS

POPRAWA JAKOŚCI ŻYCIA U CHORYCH Z REUMATOIDALNYM ZAPALENIEM STAWÓW I NIEPSYCHOTYCZNYMI ZABURZENIAMI PSYCHICZNYMI

Svitlana Savka
THE HIGHER STATE EDUCATIONAL ESTABLISHMENT OF UKRAINE, "BUKOVINA STATE MEDICAL UNIVERSITY", CHERNIVTSI, UKRAINE

ABSTRACT

Introduction: Somatic pathology of patients with rheumatoid arthritis (RA) combined with nonpsychotic mental disorders (NMD) leads to deterioration in the quality of life.
The aim: We aimed to examine the quality of life of patients with rheumatoid arthritis and nonpsychotic mental disorders.
Materials and methods: We formed two clinical groups of observation of the patients with rheumatoid arthritis and nonpsychotic mental disorders. First group (GA) included participants with duration of RA for 1-5 years, second group (GB) included those with duration of RA for 5-10 years. For assessment we used the Hamilton Rating Scale for Depression (HRSD), Hamilton Rating Scale for Anxiety (HRSA) and the Quality of Life Index developed by J.E. Mezzich (QLI). All patients received basic treatment, as well as antidepressants, anxiolytics, vitamin therapy and psychotherapy, depending on the form of nonpsychotic mental disorders.
Results: Study of the life quality showed that for the examined patients the quality of life was significantly lower in comparison with the control group. Mainly, for GA partners the overall assessment of life quality after treatment improved by 12,1% and the positive effect was probable. The greatest positive changes for the first group included increasing of physical well-being points by 2,5 and psychological/emotional well-being – by 2,1 points($p<0,05$). Mainly, for GB patients overall quality of life improved by 14,9%. Major positive changes were identified in psychological/emotional well-being - 2,93 points, physical well-being by 2,47 points, self-care and independent functioning by 2,09 points, and disability which increased by 2,06 points ($p <0,05$)
Conclusions: The patients with rheumatoid arthritis and nonpsychotic mental disorders have a significant decline in quality of life based on all indicators. The general assessment of the life quality of the first basic clinical group surveyed was $62,2 \pm 1,33$, while for the second basic clinical group surveyed – $57,0 \pm 1,47$. The increase in the duration of the RA disease significantly weakens the general working capacity by 0,83 points $p<0,05$, self-service and independence of the patients by 0,80 points, $p<0,05$, psychological and emotional well-being by 0,75 points, $p<0,05$, interpersonal interaction at 0,91 points, $p<0,05$.The overall quality of life of the patients with duration of RA for 1-5 years and NMD after treatment was $74,1\% \pm 0,93$, for the patients with duration of RA for 5-10 years and NMD after treatment was $71,9\% \pm 1,20$ ($p <0,05$).

KEY WORDS: Nonpsychotic mental disorders, rheumatoid arthritis, quality of life

Wiad Lek 2019, 72, 1, 47-51

INTRODUCTION

Rheumatoid arthritis is a chronic autoimmune disease with a worldwide adult prevalence of 0.2-1.2 % [1]. This disease is painful and progressive, leading to increasing levels of disability and systemic complications [2]. Rheumatoid arthritis is in 2-3 times more common among middle-aged women than among men. Incidence of rheumatoid arthritis among women over 65 years old is about 5%. The problem of the interaction between rheumatoid arthritis and mental disorders is an issue of interest according to current research [3-5]. Measurement and evaluation of health-related the Quality of Life Index provides valuable and relevant data for patients, clinicians and researchers. The health-related QLI can be used to monitor population's health with a particular connection to the emerging concept of positive health; to evaluate the effects of social- and health-related policies for the distribution of resources according to necessity, for the diagnosis of the nature, severity, and prognosis of a disease, and for the evaluation of treatment outcomes [6].

THE AIM

We aimed to study the quality of life of patients with rheumatoid arthritis and nonpsychotic mental disorders.

MATERIALS AND METHODS

One hundred and twenty patients with a diagnosis of Rheumatoid arthritis, who attended clinics for follow-up visits between June 2011 and November 2016, were examined in the course of this study. The study was approved by the ethics committee of the hospital and written consents were obtained from the patients.

Patients with a diagnosis of RA and aged between 20 and 60 years were subject of the study. Exclusion criteria

Table I. Demographic features of patients

Parameters	Group A (n=55)	%	Group B (n=65)	%	Control group (n=40)	%
Age (year)	37.9 ± 1.82		37.9 ± 1.82		36.5 ± 1.70	
Sex						
male	9	16,4	13	20,0	7	17,5
female	46	83,6	52	80,0	33	82,5
Marital status						
Married	34	61,8	38	58,4	26	65
Single	11	20,0	7	10,8	12	30,0
Divorced	10	18,2	20	30,8	2	5,0
Educational status						
Primary school graduates	35	63,6	48	73,8	25	62,5
College graduates	5	9,1	4	6,2	12	30,0
University graduates	15	27,3	13	20,0	3	7,5
Place of residence						
City	24	43,6	25	38,5	24	60,0
Village	25	45,5	38	58,5	14	35,0
Urban village	6	10,9	2	3,1	2	5,0

Table II. Nonpsychotic mental disorders of patients with rheumatoid arthritis

Parameters	Group A (n=55)	%	Group B Z(n=65)	%
Anxiety-depressive disorders (F- 41.2)	13	23,6	31	47,7
Disorders of adaptation (F- 43.2)	26	47,3	14	21,5
Somatoform disorder (F- 45)	5	9,1	17	26,2
Anxiety-phobic disorders (F- 40.8)	11	20,0	3	4,6

were as follows: age less than 20 years and over 60 years, trauma and/or history of a severe heart failure, malignancy, additional connective tissue disease, previously diagnosed peripheral nervous system involvement.

The patients of first basic clinical group (GA) included participants with duration of RA for 1-5 years; the second basic clinical group included those with duration of RA for 5-10 years. The third control group of comparison included 40 healthy people. The remaining demographic variables, age, sex, education, relationship status, place of residence were comparable among these three groups. The results of the survey were compared with the data of 40 persons in the control group.

The patients with a diagnosis of rheumatoid arthritis and nonpsychotic mental disorders were examined using Hamilton Rating Scale for Depression (HRSD) and Hamilton Rating Scale for Anxiety (HRSA) and the Quality of Life Index (QLI). HRSD and HRSA are both 35-questioned multiple-choice self-report inventories. For depression, 21 points and over are significant; for anxiety, 14 points and over are significant. The Quality of Life Index (QLI). QLI developed by Mezzich et al. was also used (it is a self-reporting questionnaire). Its purpose is to measure health-related QLI and it includes the following 10 items or domains: physical well-being, psychological/emotional well-being, self-care and independent functioning, occupational functioning, interpersonal functioning, social-emotional support, community and services support, personal fulfillment, spiritual fulfillment, and overall QLI [7].

Patients were compared based on the presence of the nonpsychotic mental disorders associated with duration of RA for 1-5 years, and with duration of RA for 5-10 years. Correction of NMD was carried out using medical treatment and psychotherapy. All patients received basic treatment, as well as antidepressants (venlafaxine – 75mg/day), anxiolytics (buspirone – 15 mg/day), vitamin therapy (magnesium lactate, pyridoxine hydrochloride) and psychotherapy, depending on the form of nonpsychotic mental disorders. Psychotherapy was conducted along with psychopharmacological treatment, which included sessions of rational psychotherapy with gestalt therapy elements. The course of treatment consisted of 20 sessions of psychotherapy, using the technique of gestalt therapy for duration of 40 minutes.

Primary data of scientific research were transferred to the electronic database. Statistical analysis was performed in SPSS for Windows 17.0 and STATISTICA for Windows 5.1. In the course of statistical processing results corresponded to the normal (Gaussian) distribution. Assessment of the type of distribution was carried out with the definition of the degree

Table III. Indicators of quality of life in the surveyed groups (by method of Mezzich J.E., Cohen N., Ruiperez M. 1999)

№	Parameters	Group (n=160) / indexes					
		Group A (n=55)		Group B (n=65)		Control group(n=40)	
		M	m	M	M	M	M
1	Physical well-being	4,69*	0,14	4,40*	0,18	8,90	0,10
2	Psychological/emotional well-being	5,78*	0,25	5,03*,**	0,23	8,27	0,17
3	Self-care and independent functioning	7,80*	0,18	7,0*,**	0,19	9,60	0,10
4	Occupational functioning	5,89*	0,21	5,06*,**	0,22	9,15	0,10
5	Interpersonal functioning	6,98*	0,22	6,07*,**	0,19	8,07	0,20
6	Social-emotional support	6,34*	0,24	5,28*	0,18	7,55	0,16
7	Community and services support	4,67*	0,25	4,43*	0,19	7,12	0,22
8	Personal fulfillment	6,78*	0,19	6,86*	0,19	8,12	0,14
9	Spiritual fulfillment	6,90*	0,21	7,16*	0,18	7,25	0,26
10	The general perception of the quality of life	6,38*	0,15	6,07*	0,17	8,37	0,11
11	Overall assessment of quality of life	62,2*	1,33	57,0*	1,47	82,4	1,04

Note: * - the probable difference (p <0,05) with in the control group, ** - between the GA and the GB patients.

Table IV. Dynamics of quality of life indicators for patients of the main group A in the process of treatment

№	Parameters	Period of examination			
		Before treatment		After treatment	
		M	m	M	m
1	Physical well-being	4,69	0,14	7,14*	0,12
2	Psychological/emotional well-being	5,78	0,25	7,87*	0,17
3	Self-care and independent functioning	7,80	0,18	8,47*	0,14
4	Occupational functioning	5,89	0,21	7,58*	0,17
5	Interpersonal functioning	6,98	0,22	7,65*	0,17
6	Social-emotional support	6,34	0,24	7,00*	0,18
7	Community and services support	4,67	0,25	5,40*	0,23
8	Personal fulfillment	6,78	0,19	7,49*	0,16
9	Spiritual fulfillment	6,90	0,21	7,32*	0,17
10	The general perception of the quality of life	6,38	0,15	7,74*	0,11
11	Overall assessment of quality of life	62,2	1,33	74,1*	0,93

Note: * - probable difference (p <0,05)

of central tendency. When calculating the statistical variables, we calculated the arithmetic mean sample (M) and the standard error of the arithmetic mean (m). When estimating the probability of the difference between the average values, the coefficient t was calculated using the Student method. For the assessment of the likelihood of difference, account taken was of the generally accepted level in the medical-biological studies the level of probability (p) - p <0,05.

RESULTS AND DISCUSSION

The first clinical group included 55 patients with a duration of rheumatoid arthritis up to 5 years old (mean age 37,9 ± 1,82), among which women predominated (46 persons – 83,6%). The second main group consisted of 65 patients with a duration of rheumatoid arthritis from 5 to 10 years old (mean age 37,9 ± 1,82), among whom females dominated (52 persons – 80,0%) [8]. Control group included 40 person (mean age 36,5 ± 1,70), among whom females also dominated as well (33 persons – 82,5%). The demographic features of the patients are shown in Table I.

Nonpsychotic mental disorders including anxiety-depressive disorders were diagnosed for 44 patients (36,7%), disorders of adaptation – 40 patients (33,3%), somatoform disorder – 22 patients (18,3%), anxiety-phobic disorders – 14 patients (11,7%). The mental disorders characteristics in group A and B are presented in Table II.

Table V. Dynamics of quality of life indicators of patients of the main group B in the process of treatment

№	Parameters	Period of examination			
		Before treatment		Before treatment	
		M	m	M	m
1	Physical well-being	4,40	0,18	6,87*	0,13
2	Psychological/emotional well-being	5,03	0,23	7,96*	0,16
3	Self-care and independent functioning	7,00	0,19	9,09*	1,07
4	Occupational functioning	5,06*	0,22	7,00*	0,17
5	Interpersonal functioning	6,07	0,19	7,47*	0,17
6	Social-emotional support	5,28	0,18	6,55*	0,16
7	Community and services support	4,43	0,19	5,13*	0,18
8	Personal fulfillment	6,86	0,19	7,67*	0,15
9	Spiritual fulfillment	7,16	0,18	7,63*	0,16
10	The general perception of the quality of life	6,07	0,17	7,55*	0,12
11	Overall assessment of quality of life	57,0	1,47	71,9*	1,20

Note: * - probable difference (p <0,05)

The quality of life means system of indicators that characterize the peculiarities of realization and satisfaction of human needs. World Health Organization defines quality of life as a perception of physical, psychological and social well-being, independence, satisfaction with a specific level of life and other components of psychological comfort. The quality of life of a sick person is considered as an integral characteristic of his condition consisting of physical, psychological, social components. Each of the components in turn includes a number of components, such as physical component includes the symptoms of the disease, the ability to perform physical work, the ability to self-service; psychological - anxiety, depression, hostile behavior; social - social support, work, public relations. Comprehensive study of these components makes it possible to determine the level of the life quality and influence of the components on the life quality as well as to answer the question what should affected in order to improve it (adjusting treatment, providing social support).

Study of the life quality showed that for the examined patients the quality of life was significantly lower in comparison with the control group. In particular, patients had significant complications in the performance of daily activities due to both physical and mental well-being, reduced performance and low level of public and official support (table III).

GA patients had low level of physical well-being (4,69 ± 0,14), public and official support (4,67 ± 0,25), psychological and emotional well-being (5,78 ± 0,25). Examining the GB patients, minimum number of points was given for physical well-being (4,40 ± 0,18), community and services support (4,43 ± 0,19), occupational functioning (5,06 ± 0,22), psychological and emotional well-being (5,03 ± 0,23) and social and emotional support (5,28 ± 0,18). At the same time, the indicators of spiritual fulfillment, self-care and independent functioning named above, namely, the spiritual fulfillment of GA patients (6,90 ± 0,21), GB patients (7,16 ± 0,18), self-care and independent functioning of GA patients (7,80 ± 0,18), of GB patients (7,00 ± 0,19).

Somatic pathology of patients with rheumatoid arthritis is accompanied by a number of negative sensory and psychological phenomena, which in general leads to deterioration in the quality of life [9, 10]. NMD have a negative impact on patients' quality of life assessment. The increase in the duration of RA disease impairs the most general occupational functioning and self-care and independent functioning of the patients, psychological and emotional well-being, and interpersonal functioning. All other components of the quality of life in both groups are significantly lower than in the control group.

As a result of analyzing the dynamics of the life quality indicators for patients with RA and NMD under the influence of complex treatment, the following features were identified. In the main group A, the overall assessment of quality of life improved by 12,1% and the positive effect was probable. The greatest positive changes in the first group were related to the aspect of physical well-being, namely, increasing the feeling of energy, lack of pain and physical problems by 2,5 points and psychological/emotional well-being (good feeling, coherence with oneself) – by 2,1 points (p<0,05). Minor positive changes were identified in the sphere of spiritual fulfillment (feeling of faith, religiousness and going beyond the ordinary material life) – increasing by 0,4 points (table IV).

In the main group B, overall quality of life improved by 14.9% (table V). The dynamics of improvement of the life quality according to various indicators in this group had characteristics similar to patients in the first group and major positive changes were identified in the following aspects: psychological/emotional well-being – increasing by 2,93 points, physical well-being – by 2,47 points, self-care and independent functioning (implementation of daily

tasks, adoption their own decisions) - by 2,09 points, and disability which increased by 2,06 points (p <0,05).

Minor positive changes in the second group were noted by the indicator of spiritual fulfillment (increased by 0,47 points) and public and official support (by 0,70 points), social and emotional support (by 1,27 points), namely, the ability of people surveyed to believe and offer help and emotional support (p <0,05). The insignificant dynamics of the results on the point of socio-emotional support for patients with prolonged course of the disease may be occurred due to the fact that in 83,0% of the families studied psychological comfort was unfavorable and they had the highest level of negative communicative installation.

The management of symptoms of NMD in routine care is recommended by the National Institute for Health and Care Excellence (NICE) [12], and NMD is treatable within the context of long-term physical health conditions [13-15].

In general, the positive dynamics of the overall quality of life indicator after the treatment of nonpsychotic mental disorders in both main groups was noted. In the first group, the overall quality of life before treatment was higher by 5,0%, and after treatment by 2,0% compared to the second group (p <0,05).

CONCLUSIONS

1. The patients with rheumatoid arthritis and nonpsychotic mental disorders have a significant decline in quality of life based on all indicators. The general assessment of the quality of life of the examined patients in the first basic clinical group is 62,2 ± 1,33, while in the second basic clinical group examined – 57,0 ± 1,47. Longer duration of the RA disease significantly weakens the general working capacity by 0,83 points p<0,05, self-service and independence of the patients by 0,80 points, p<0,05, psychological and emotional well-being by 0,75 points, p<0,05, interpersonal interaction at 0,91 points, p<0,05.
2. The overall quality of life of the patients with duration of RA for 1-5 years and NMD after treatment was 74,1% ± 0,93, patients with duration of RA for 5-10 years and NMD after treatment was 71,9% ± 1,20 (p <0,05).

REFERENCES

1. Singh J.A., Saag K.G., Bridges Jr.S.L., Akl E.A., Bannuru R.R., Sullivan M.C., et al. American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68:1-26.
2. Aletaha D., Neogi T., Silman A.J.. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69:1580-8.
3. Matcham F., Rayner L., Steer S., Hotopf M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatology. 2013;52:2136-48.
4. Aker D.A., Kose S., Solmaz M., Bal Z.E., Akin E. Temperament and Character Dimensions of Personality in Patients with Chronic Pain Disorders. J of Mood Disord. 2017;7:1-9.
5. Volkan Yılmaz, Ebru Umay, İbrahim Gündoğdu, Zeliha Özgür Karaahmet, Arif Erhan Öztürk. Rheumatoid Arthritis: Are psychological factors effective in disease flare? Eur J Rheumatol 2017; 4: 127-32
6. Kurt I Schwartz, María I Zapata-Vega, Juan E. Mezzich, Guido Mazzotti. Validation study of the Multicultural Quality of Life Index (MQLI) in a Peruvian sample Rev Bras Psiquiatr. 2006;28(1):24-8
7. Mezzich J.E., Cohen N.L., Ruiperez M.A. A quality of Life Index: brief description and validation. In: Paper presented at the International Congress of the International Federation for Psychiatric Epidemiology. Santiago de Compostela: Spain; 1996.
8. Savka S.D. Patopsychological features of patients with rheumatoid arthritis and nonpsychotic mental disorders. World science. 2018; 5(32):36-38.
9. Matcham F., Norton S., Scott D.L., Steer S., Hotopf M. Symptoms of depression and anxiety predict treatment response and long-term physical health outcomes in rheumatoid arthritis: a secondary analysis of a randomised controlled trial. Rheumatology (Oxford). 2016;55:268-78.
10. Rathbun A.M., Reed G.W., Harrold L.R. The temporal relationship between depression and rheumatoid arthritis disease activity, treatment persistence and response: A systematic review. Rheumatology. 2013;52:1785-94.
11. Matcham F., Davies R., Hotopf M., Kimme L., Norton H. S., Steer S., Galloway J. The relationship between depression and biologic treatment response in rheumatoid arthritis: An analysis of the British Society for Rheumatology Biologics Register Rheumatology. 2018;57(5): 835-43.
12. National Collaborating Centre for Mental Health. Depression in Adults with a Chronic Physical Health Problem: Treatment and Management. 2010. https://www.nice.org.uk/guidance/cg91/evidence/full-guideline-243876061.
13. Matcham F., Rayner L., Hutton J., Monk A., Steel C., Hotopf M. Self-help interventions for symptoms of depression, anxiety and psychological distress in patients with physical illness: a systematic review and meta-analysis. Clin Psychol Rev. 2014;34:141-57.
14. Fiest K.M., Hitchon C.A., Bernstein C.N., Peschken C.A., Walker J. R., Grafet L.A.et al. Systematic review and meta-analysis of interventions for depression and anxiety in persons with rheumatoid arthritis. J Clin Rheumatol 2017;23:425-34.

Conflict of interest:
The Author declare no conflict of interest.

CORRESPONDING AUTHOR

Svitlana Savka
65a, Heroyiv Maydanu str., flat 50, 58029, Chernivtsi, Ukraine
tel: +380679411728
e-mail: savka.svitlana@bsmu.edu.ua

Received: 18.07.2018
Accepted: 21.11.2018

PRACA ORYGINALNA
ORIGINAL ARTICLE

BASIC CLINICAL AND PATHOGENETIC ASPECTS OF DEVELOPING THE COMPLICATIONS DURING MULTIPLE PREGNANCIES

PODSTAWOWE KLINICZNE I PATOGENETYCZNE ASPEKTY ROZWOJU POWIKŁAŃ PODCZAS CIĄŻY MNOGIEJ

Volodymyr I. Boiko[1], Alla V. Boychuk[2], Irina M. Nikitina[1], Tetyana V. Babar[1], Alesya V. Boiko[1], Maryna A. Bolotna[1]
[1]SUMY STATE UNIVERSITY, SUMY, UKRAINE
[2]I. GORBACHEVSKI TERNOPIL STATE MEDICAL UNIVERSITY, TERNOPIL, UKRAINE

ABSTRACT

Introduction: In order to evaluate the value of the Placenta Growth Factor (PlGF) in the developing the gestational complications during multiple pregnancies, a study of this indicator in serum of 320 pregnant women with multiple pregnancies in the first trimester, as well as 40 pregnant women with single pregnancy, constituted a control group.
The aim: of the study is to investigate the effect of the placental growth factors on gestational process during multiple pregnancies.
Materials and methods: A prospective study of maternity pregnancy in 320 females with multiple pregnancies was conducted, which comprised the main group of the subjects and 40 healthy women with unipolar pregnancy. The level of PlGF in serum was determined by solid phase enzyme analysis using monoclonal antibody sets in the first trimester of pregnancy. Indicators of the hemostasis system (vascular thrombocyte and coagulation link) were evaluated according to generally accepted methods. Dopplerometry of placental and fetal blood flow was performed in uterine arteries, arteries and umbilical cord veins, middle cerebral artery of the fetus.
Results: Women with multiple pregnancies are at the risk of gestational complications - premature births in 67.8% ($p < 0.01$), feto placental dysfunction, pre eclampsia - in 17.5% ($p < 0.05$) cases. The revealed violations of the vascular thrombocyte and coagulation homeostasis in the first trimester of pregnancy are the main risk factors for early premature abortion. It has been shown that the low level of placental growth factor in serum of pregnant women with multiple pregnancies in the case of premature labor, feto placental dysfunction and pre-eclampsia (111.23 ± 8.4, 203.24 ± 6.4 and 305.86 ± 7.4 pg / ml) compared with the corresponding indicators for single-pregnancy (418.2 ± 10.4 pg / ml) is a prognostic marker for the development of gestational complications.
Conclusions: Timely medical correction of gestational complications during multiple pregnancies with the use of micronized progesterone, low molecular weight heparins, angio protectants allowed prolonging the pregnancy with mono choric type of placentation by 3.2 weeks (up to 34.2 ± 2.4 weeks), and in the case of dichoric twins - to full-term pregnancy.

KEY WORDS: multiple pregnancy, miscarriage, preterm labor, feto placental dysfunction, placental growth factor, pre-eclampsia

Wiad Lek 2019, 72, 1, 52-55

INTRODUCTION

The majority of clinical studies have proved the fact that multiple pregnancy is accompanied by a significant number of perinatal complications, namely premature abortion, feto placental dysfunction with delayed fetal growth, as well as pre-eclampsia, which in turn contributes to an increase in perinatal morbidity and mortality [1, 2, 6, 7] Perinatal mortality in multiple pregnancies around the world remains higher than with single-pregnancy, and the probability of antenatal death of a fetus with twins or triplets is ten times higher [2, 6, 7]. The course of pregnancy with multiple pregnancies is predicted and in the future depends on the process of implantation of the fetal egg, the type of placenta, the adaptation of the mother's body to the pregnancy, and the influence of external factors on the pregnant woman during the critical periods of the developing the fetus.

According to statistics, the incidence of pre-eclampsia in multiple pregnancy is 3 to 4 times higher than that of single-femoral pregnancy. The risk of pre-eclampsia in multiple pregnancies increases in connection with hyper placenta, as a result of violation of the placenta perfusion capacity, placental dysfunction develops with the blood flow violation [4, 8, 13]. One of the most common hypotheses concerning the pathogenetic mechanisms of pre-eclampsia is the primary utero-placental blood flow violation and concomitant violation of cyto trophoblastic invasion in spiral arteries myometrium, superficial trophoblastic invasion with subsequent incomplete remodeling of vascular structures in which there is a slowing of blood flow due to increased vascular resistance. Incomplete invasion, in turn, leads to a violation of placental angiogenesis and thus plays a key role in the development of pre-eclampsia. Dysplasia of chorionic villi is known to be observed when the concentration of placental growth factor in the blood of the mother decreases, which is related to a number of endothelial growth factors [3, 4, 9, 10, 11]. Gene coding for the synthesis of this factor is proved to be localized in

the fourteenth chromosome, on its long shoulder. PlGF is produced by trophoblast, namely endothelial cells of trophoblastic and placental macrophages [5, 6]. Placental growth factor promotes angiogenesis, with a pronounced angiogenic potential. (PlGF) is essentially a glycosylated homo dimer whose biological effect is realized by activating the vascular receptors with subsequent stimulation of vascular genesis and angiogenesis. Reducing the concentration of PlGF in tissues of trophoblast undoubtedly leads to disturbance of the developing the villi of chorion, reducing the transport of oxygen and nutrients of the fetus, creating a model of feto placental dysfunction with subsequent delay in fetal growth [3, 12]. In the mother's bloodstream, the placental growth factor enters through active transport along with numerous hormones and peptides that are secreted by the cyto- and syncytiotropho blast [4]. In this regard, the placental growth factor should be considered as a marker for a number of gestational diseases, in particular, pre-eclampsia, feto placental dysfunction and growth retardation of the fruits. Slow blood flow provokes damage to the endothelium, promotes micro thrombosis in the vessels, and development of heart attacks in the placenta. As a result of increased vascular wall sensitivity, a cascade of hemodynamic disturbances is triggered, which leads to the disruption of regulatory mechanisms and contributes to the development of chronic DIC and syndrome of decompensating placental dysfunction. In turn, the generalizing the process of endothelial dysfunction is associated with the release of cytokines, the formation of free radicals, acidosis [4, 10, 14].

The study of immunological processes that ensure the normal course of pregnancy, as well as the detection of pathogenetic mechanisms that lead to violations of its physiological course, is one of the primary tasks of reproductive immunology [5]. For the physiological course of the gestation process, it is necessary to ensure the normal functioning of the feto-placental complex. At the stage of forming the placenta, the growth factors of the placenta play a major role in the regulation processes, ensuring the normal functioning of the mother-placenta-fetus system. Placental growth factors contribute to cyto-trophoblast invasion, angiogenesis and invasion processes of the spiral arteries; they are directly related to their insufficiency and provoke the development of gestational complications: the formation of feto-placental dysfunction, miscarriage of pregnancy and the progression of pre-eclampsia [1, 6].

THE AIM

The purpose of the research: is to study the effect of the placental growth factors on the gestational process in multiple pregnancies.

MATERIAL AND METHODS

The study was conducted on the basis of the Sumy Regional Clinical Perinatal Center and the Department of Obstetrics and Gynecology Sumy State University during 2012-2017. A prospective study of pregnancy and childbirth in 320 females with multiple pregnancies constituted the main group of examined 144 (Group I): pregnant with mono chorus di-amniotic twins, 176 (group II) , patients with dihorionic di-amniotic twins. The control group consisted of 40 healthy women with unipolar pregnancy. The groups under study were homogeneous in composition and presentable. The average age of pregnant women in the main group was 29.8 ± 4.5 years, in the control group 27.6 ± 3.2 years. Differences in age, somatic pathology, frequency of complications in obstetric history between control and main groups were not revealed. Laboratory research was carried out on the basis of the clinical laboratory of the Sumy Clinical Regional Perinatal Center, the Synevo Laboratory, and the Medical-Genetic Laboratory of the Sumy State University.

The level of PlGF in serum was determined by solid-phase immunoassay analysis using monoclonal antibodies and standard R & D systems reagents in the first trimester of pregnancy. The evaluation of the state of the feto-placental complex was carried out with the help of modern sonoDIAGNOST-360 ultrasound devices from Philips (Netherlands) and Aloka SSD-2010 (Japan), in real time using the early transvaginal sensor of 6.5 MHz, in more late terms of convection sensors 3, 5 and 5 MHz in two-dimensional echo modes; it included definition of chorality, placenta metry, feto metry, determination of the state and number of amniotic fluid, dopplero metry. Dopplero metry of placental and fetal blood flow was performed in uterine arteries (MA), arteries (PA) and umbilical cord veins (PV), middle cerebral artery (SMA) fetuses. The following parameters were measured: the maximum blood flow velocity during systole, early ventricular diastole, average blood flow velocity throughout the cardiac cycle, pulsation and resistance index and systole diastolic ratio. Indicators of the hemostasis system (vascular platelets and coagulation link) were evaluated according to generally accepted methods.

Statistical processing and analysis of the data were carried out using Microsoft Excel programs using the methods of mathematical statistics and software package Statistics 8.0. Charts and diagrams were built using Microsoft Excel.

RESULTS AND DISCUSSION

According to the results of the research conducted on the progress of multiple pregnancy and the development of gestational complications, not only the presence of chronic inflammatory diseases in the history, but also the exacerbation of infections in the first trimester of pregnancy had a significant impact, as it is during this period of pregnancy undergoing implantation processes, trophoblast invasion, further development and normal functioning of the feto-placental complex. According to our data, only 43 (13.4%) women with multiple pregnancies had a physiological course of gestational process. Interruption of pregnancy up to 12 weeks was observed in 17 (5.3%) patients with multiple pregnancies, and reduction of one of

the fruits was observed in 8 (2.5%) pregnant women. The course of multiple pregnancies was accompanied by the symptoms of a recurring threat of abortion in 180 (56.2%) cases, which resulted in inpatient treatment in the period of 8-12, 14-16, 18-22 and 24-28 weeks of gestation. Among the main etiologic factors that provoked the threat of early termination of pregnancy, 107 (33.4%) of the pregnant women in the first place had a history of chronic endometritis, in the control group this was observed in 24 (7.5%) pregnant women. In the microscopic examination of excretions from the cervical canal and vagina in 168 (52.6%) patients of the main group, the conditionally pathogenic micro flora was detected, while the control group was 5 (12.5%). A combined bacterial and viral infection (Epstein-Barr virus in combination with Urea plasma urea liticum) was detected in cervical canal sows in 107 (33.4%) patients in the main group, and in 3 (7, 5%) control women, pathogenic staphylococcus and streptococcus in 60 (18.7%) of the pregnant women in the main group and 2 (5.0%) in the control group.

The study of the hemostasis of the examined pregnant women has shown that during multiple pregnancies changes were noted in the first trimester of pregnancy. These abnormalities were manifested by the characteristic changes of the vascular platelet unit: the platelet count was 181.2 ± 8.7 × 109 / l, with a control group of 236.4 ± 8.7 × 109 / l, and there was also an inhibition of the ADF-induced platelet aggregation and its decrease by 1.2 times (32.4 ± 1.7%) in almost half of the pregnant women in the main group compared to the average control group, which was 56.2 ± 2.6% ($p < 0.01$). Investigation of the coagulation link of hemostasis showed an increase in the level of fibrinogen in the main group to the level of 5,5 ± 0,6 g / l for the control group 2,89 ± 0,8 g / l ($p < 0,05$), the increase of the soluble complexes of fibrin- monomer in the blood plasma up to 12, 0 ± 1.2 mg / 100 ml in the main group, with a control index of 4.8 ± 0.6 mg / 100 ml ($p < 0.05$), a shortening of the activated partial thromboplastin time to 26.4 ± 1.2 s compared with the control group - 31.8 ± 2.2 s, ($p < 0.05$). The results of the studying vascular-platelet and coagulation of hemostasis indicate an increase in the processes of coagulation in the pregnant women of the main group, which in turn serves as one of the pathogenetic mechanisms of the development of feto-placental dysfunction and pre-eclampsia. In this connection, there is a slowing of the blood flow in the intervertebral space with the subsequent increase in local pressure, which serves as an obstacle to further blood flow in the spiral arteries and leads to the development of placental ischemia. When conducting a dopplero-meter in 23 (7.2%) patients of the main group the reverse blood flow was detected in the umbilical artery, which we did not observe in the control group. An antenatal death of one of the fruits occurred in 8 cases in the pregnant women of the main group. As a result of our study, we found that hemodynamic disorders in multiple pregnancies were always accompanied by growth retardation of one of the fruits - in 105 (32.8%) pregnancies, or both fruits - in 56 (17.5%).

Violation of feto-placental blood flow along with changes in rheological and coagulation properties of blood during multiple pregnancies causes the development of a higher frequency of gestational complications, such as miscarriage, placental dysfunction with subsequent growth retardation, and pre-eclampsia, as compared to single-pregnancy rates. Due to the violation of the utero-placental blood flow, which is based on morphofunctional changes in the basin of the spiral arteries and intervertebral space; in the main group premature births were noted in 217 (67.8%) cases ($p < 0.01$), the development of severe forms of pre-eclampsia - in 56 (17.5%) cases, ($p < 0.01$), in the control group, this indicator was 3 (7.5%) and 1 (2.5%) respectively.

Studying the factors of gestational complications prognosis in multiple pregnancies, leading to its premature abortion, confirmed the role of the growth factor of the placenta in the regulation of trophoblast invasion processes. Analyzing the Indicators of the PlGF level in the blood serum of pregnant women in the main group, we have found a significant decrease in cases of developing premature births to 111.23 ± 8.4 pg / ml, in the case of feto-placental dysfunction to 203.24 ± 6.4 pg / ml, in pregnant women with pre-eclampsia, this figure was 305.86 ± 7.4 pg / ml compared with the control group, which was 418.2 ± 10.4 pg / ml ($p < 0.01$).

The study of the dynamics of the PlGF level in serum of pregnant women allowed to develop an algorithm for the early prevention of gestational complications in multiple pregnancies during pregnancy 12-14, 16-18, 22-24 and 30-32 weeks of gestation. In the scheme of preventive treatment was necessarily included micronized progesterone (lutein), nitric oxide donators (tirovortin), disaggregates (acetylsalicylic acid), and anticoagulants - low molecular weight heparins (cybernea) according to risk factors and obligatory dynamic monitoring of blood parameters. From the 14th week of pregnancy, taking into account clinical and laboratory parameters, angio-protective diosmin (phlebodia) was used which has high tropism to the vessels and allows to improve the condition of the vascular wall, helps to eliminate angiopathy in the spiral arteries and normalize hemodynamic processes in the feto-placental complex. Due to the timely correction of existing clinical and laboratory disorders, it became possible to prolong the pregnancy with a mono chorative type of placentation for 3.2 weeks (up to 34.2 ± 2.4 weeks), and in the case of dichoric twins, it was possible to give birth to the twins.

So, summarizing the research, it should be noted that determining the level of placenta growth factor in pregnant women with multiple pregnancies can be used as an early criterion for predicting gestational complications. Early treatment and prophylactic measures in pregnant women with multiple pregnancies in critical terms have allowed prolonging pregnancy and improving perinatal effects as much as possible.

CONCLUSIONS

1. Women with multiple pregnancies are at risk of developing gestational complications - premature births in 67.8%

($p < 0.01$), feto-placental dysfunction, pre-eclampsia - in 17.5% ($p < 0.05$) cases.
2. Low levels of PlGF in serum of pregnant women with multiple pregnancies in the case of premature delivery, feto placental dysfunction and pre-eclampsia (111.23 ± 8.4, 203.24 ± 6.4 and 305.86 ± 7.4 pg / ml) in compared with the corresponding indicators for single-pregnancy (418.2 ± 10.4 pg / ml) is a prognostic marker for the development of gestating complications, which is reliably confirmed by the study ($p < 0.01$).
3. The revealed violations of vascular thrombocyte and coagulation homeostasis in the first trimester of pregnancy are the main risk factors for premature abortion.
4. Timely medical correction of gestational complications during multiple pregnancies with using the micronized progesterone, low molecular weight heparins, angio protectants allowed prolonging the pregnancy with mono choric type of placentation by 3.2 weeks (up to 34.2 ± 2.4 weeks), and in the case of dichoric twins - to full-term pregnancy.

REFERENCES

1. Baranov YY, Tokova ZZ, Tadevosian AA. Perynatalnye yskhody pry mnohoplodnykh rodakh [Perinatal outcomes in multiple births] Akusherstvo y hynekolohyya. 2012;1:98 – 102. 2. Vdovychenko YuP. Bahatoplidna vahitnist : navchalnyy posibnyk (dlya vykladacha) [Multiple pregnancy: A manual. Part II (for the enclave)]. Kyiv: 2011:360.
3. Krasnopolskyi VY, Novykova SV, Kapustyna MV, Tytchenko LY, Aksenov AN, Zharova AA. Sovremenny probl'emi mnohoplodnoi beremennosty [Modern problems of multiple pregnancies] Rossyiskyi vestnyk akushera-hynekoloha. 2009; 2:79 – 81.
4. Botting BJ, MacDonald-Davies I, MacFarland AJ. Recent trends in the incidence of multiple birth and associated mortality. Arch. Dis. Child. 2011; 62: 941-948.
5. Nikitina I, Boychuk A, Babar T, Dunaeva M. Prediction of threats to multiple pregnancy interruption depending on the cause of its occurrence. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2016; 7: 764 – 771.
6. Nikitina I, Boychuk A, Kalashnik N, Pabot E, Kolesnikova M, Prasol D. Immunomorphological features of the placenta in multiple pregnancies. Georgian medical news. 2016; 6: 12-17.
7. Almonte L, Davis M, Ward C, Brown D, Craparo F. Spontaneous and non - spontaneous twins: a comparasion study of preterm labor, preterm premature rupture of membranes, gestational age at delivery, maternal age, and len th of hospital stay. Twin Research and Human Genetics. 2012; 15:2: 170.
8. Hassan SS, Romero R. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, doubleblind, placebocontrolled trial. Vidyadhari et al. Ultrasound in Obstetrics & Gynecology. 2011; 1:18 –31.
9. Management of preterm labor. Practice Bulletin No. 127. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;119:1308–13.
10. Romero R, Nicolaides K, Conde Agudelo A. et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. Am. J. Obstet. Gynecol. 2012; 2.124:1–19.
11. Salazar EL, Calzada L. The role of progesterone in endometrial estradiol and progesterone-receptor synthesis in women with menstrual disorders and nabitual abortion. Gynecol. Endocrinol. 2007; 23 (4): 222–225.
12. Maruo T. Insulin like growth factor 1 as a local regulator of proliferation and differentiated function of the human trophoblast in early pregnancy. Early Pregnancy 1995; 1: 1: 54–161.
13. Shore V.N., Wang T.N., Wang T.L. Vascular endothelial growth factor, placenta growth factor and their receptors in isolated human trophoblast. Placenta.1997; 18: 657–669.
14. Boiko VI, Nikitina IM, Babar TV, Boiko AV. The problem of miscarriage in multiple pregnancy. Wiadomości Lekarskie. 2018; 7 (71) : 1195-1199.

The work is carried out within the framework of the research work "Optimization of diagnosis and prevention of diseases of the reproductive system and development of pathogenically grounded methods for their correction" (state registration number 011U001801).

Authors' contributions:
According to the order of the Authorship.
Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Irina M. Nikitina
Sumy State University
12 Rymskoho-Korsakova St., Sumy, Ukraine
tel: +380662947360
e-mail: nikitina1med@gmail.com

Received: 10.09.2018
Accepted: 27.12.2018

PRACA ORYGINALNA
ORIGINAL ARTICLE

SAMOBADANIE PIERSI – WSZYSTKO CO CHCIELIBYŚMY, ABYŚCIE O TYM WIEDZIELI – BADANIE ANKIETOWE

BREASTS SELF EXAMINATION – EVERYTHING WE WANT YOU TO KNOW ABOUT IT – SURVEY STUDY

Agnieszka Staciwa[1], Marta Sprawka[1], Hubert Stachowicz[1], Weronika Topyła[1], Anna Taracha[1], Robert Ściślak[1], Agnieszka Wójtowicz[1], Norbert Stachowicz[2], Agata Smoleń[2]

[1]STUDENCKIE KOŁO NAUKOWE PRZY KATEDRZE I ZAKŁADZIE EPIDEMIOLOGII I METODOLOGII BADAŃ KLINICZNYCH; UNIWERSYTET MEDYCZNY W LUBLINIE, LUBLIN, POLSKA

[2]KATEDRA I ZAKŁAD EPIDEMIOLOGII I METODOLOGII BADAŃ KLINICZNYCH; UNIWERSYTET MEDYCZNY W LUBLINIE, LUBLIN, POLSKA

STRESZCZENIE

Wstęp: Samobadanie piersi stanowi pierwszą linię diagnostyki zmian nowotworowych. Badanie to jest łatwe, nic nie kosztuje i każda kobieta może je wykonać samodzielnie. Powinno również stanowić jeden z elementów badania fizykalnego wykonywanego przez lekarza.

Cel pracy: Oszacowanie wiedzy dotyczącej nowotworów piersi oraz umiejętności wykonywania samobadania. Badanie było skierowane głównie do osób związanych ze środowiskiem medycznym, najbardziej zaangażowanych w proces wykrywania i leczenia nowotworów.

Materiały i metody: Badanie zostało przeprowadzone poprzez internetowy kwestionariusz zawierający 19 pytań. Wzięły w nim udział 204 osoby, w tym 53% kobiet i 47% mężczyzn. Wśród badanych 93% stanowiły osoby związane ze środowiskiem medycznym. Średnia wieku wynosiła 23,5 roku. Udział w badaniu był dobrowolny i anonimowy.

Wyniki: 57% respondentek regularnie bada swoje piersi, natomiast 43% nie robi tego w ogóle lub robi rzadko. Niestety tylko 23% respondentek wykonuje samobadanie piersi regularnie co miesiąc. Badani są w stanie prawidłowo wskazać objawy oraz czynniki ryzyka nowotworu piersi. Na pytanie czy badani czuliby się pewnie, wykonując badanie piersi u pacjentki, około 61% odpowiedziało pozytywnie, natomiast na pytanie czy mieli okazje wykonać badania piersi podczas studiów pod okiem specjalisty, 78% odpowiedziało negatywnie.

Wnioski: Wiedza badanych dotycząca samobadania oraz nowotworu gruczołu piersiowego jest na dobrym poziomie, jednakże efektywność oraz umiejętności wykonywania badania są na poziomie niezadowalającym. Brakuje możliwość zdobywania umiejętności praktycznych. Zmiana tego jest trudna, ale i konieczna. Należy włożyć więcej wysiłku w edukację studentów medycyny, aby zwiększyć skuteczność w walce z nowotworem piersi przez nauczanie i przekonywanie pacjentek do stosowania samokontroli gruczołu piersiowego, co jest pomocne w późniejszej praktyce lekarskiej.

SŁOWA KLUCZOWE: nowotwory gruczołu piersiowego, samobadanie piersi, badanie piersi, gruczoł piersiowy

ABSTRACT

Introduction: Breasts self examination is first line prevention in case of breast cancer. It is cheap, it is easy and it can save your life. That is why it is so important that every woman and even man know how to do it.

The aim: To estimate the level of knowledge about breasts self examination among women and also among people connected with medicine.

Materials and methods: The data were gathered through the internet questionnaire, which contained of 14 questions. There were 204 respondents : 53% women and 47% men. Among them there were 93% people related with medicine. Average age was 23,5 years. The participation was voluntary and annonymous.

Results: Among female respondents 57% admit doing breasts self examination, however only 23% of them do that regularly every month. Also only 36% of the respondents know how to do proper examination. When asked if they ever had their breasts examined by the doctor, only 20% replied positively. We also prepared questions for people connected with medical field: we asked them if doing breasts examination for the patient they would feel confident (61% replied negatively.) and also if they had a chance to do breasts examination during studies most of them replied negatively.

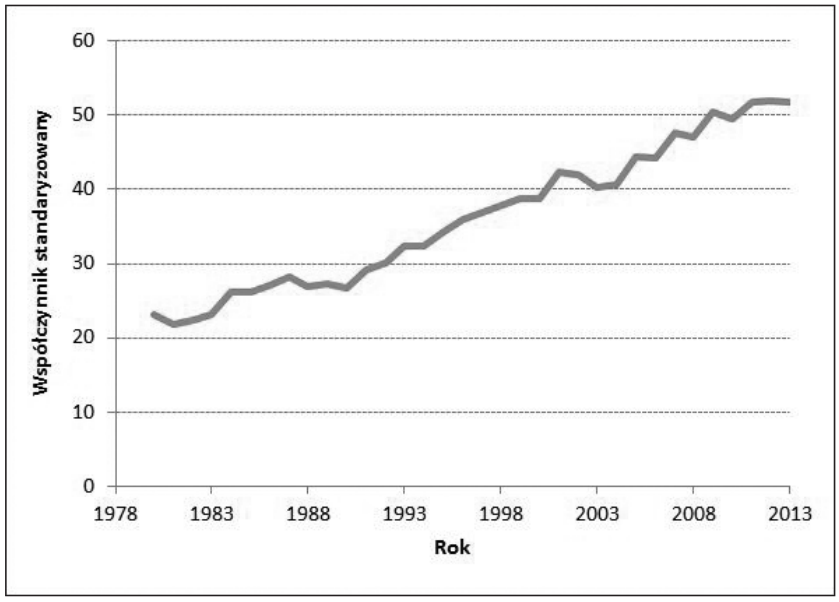
Conclusions: To conclude, even among women connected with medical field the knowledge is not enough, which is the most concerning since they should educate others and diagnose concerning symptoms. We should put more afford to break the tabu and pay more attention to breast examination.

KEY WORDS: breasts self examination, breast cancer, breast, breast examination

Wiad Lek 2019, 72, 1, 56-63

WSTĘP

Badanie piersi to badania przesiewowe mające na celu zmniejszenie śmiertelności w przypadku danej choroby poprzez wczesne wykrycie zmian chorobowych. Samobadanie piersi każdy może wykonać samodzielnie w domu, w intymnej atmosferze, co eliminuje stres i skrępowanie związane z badaniem wykonywanym przez osobę obcą. Systematyczne wykonywanie samobadania umożliwia



Ryc. 1. Trendy zachorowalności w okresie od 1980 do 2013 roku; Krajowy Rejestr Nowotworów.

	Najczęstsze typy nowotworów złośliwych	Szacowane nowe przypadki 2018	Szacowana śmiertelność 2018
1.	Rak piersi (kobiety)	266,120	40,920
2.	Rak płuc i oskrzeli	234,030	154,050
3.	Rak prostaty	164,690	29,430
4.	Rak jelita grubego	140,250	50,630
5.	Czerniak skóry	91,270	9,320
6.	Rak pęcherza moczowego	81,190	17,240
7.	Chłoniaki nieziarnicze (non-Hodgkin lymphoma)	74,680	19,910
8.	Rak nerki i miedniczki nerkowej	65,340	14,970
9.	Rak macicy	63,230	11,350
10.	Białaczka	60,300	24,370

Ryc. 2. Przypadki nowotworu piersi w roku 2018; National Cancer Institute

poznanie własnego ciała, dzięki czemu jesteśmy bardziej wyczulone na wszelkie zachodzące w nim zmiany i znamy również punkt odniesienia. To umożliwia wczesne wykrycie wszelkich podejrzanych objawów, dzięki czemu wzrastają szanse na wyleczenie nowotworu [1–3]. Samodzielne badanie powinno wchodzić w skład okresowej kontroli stanu zdrowia, włączając w to badanie wykonywane przez lekarza oraz badania obrazowe. Zmiany, jakie możemy wyczuć to: guzki, zgrubienia, zmiany wielkości czy kształtu piersi, zmiany zapalne skóry, zmarszczenie skóry, zaczerwienienia, wciągnięcie sutka oraz wyciek z sutka [4–6].

W ostatnich latach zwiększa się natężenie chorób nowotworowych, a w szczególności nowotworu piersi (Ryc. 1). W roku 2018 odnotowano już prawie 300 tysięcy nowych przypadków nowotworu piersi (Ryc. 2) [7]. Ponadto obserwujemy tendencję ogólnoświatową do rozwoju nowotworów w coraz młodszych grupach wiekowych [8].

Nowotwór gruczołu piersiowego jest najczęściej występującym nowotworem u kobiet, chociaż może również występować u mężczyzn (rzadko i jest zwykle późno rozpoznawany). Ten typ nowotworu może występować miejscowo oraz dawać przerzuty do płuc, wątroby, kości i mózgu [1, 6, 10]. Według szacunków rocznie rozpoznaje się nowotwór piersi u 1,5 miliona kobiet na całym świecie, a umieralność wynosi 400 tysięcy rocznie. Szacunkowo 13% kobiet będzie miało postawioną diagnozę nowotworu piersi w swoim życiu [7–10]. Nowotwór piersi jest najczęściej diagnozowany w przedziale wiekowym pomiędzy 55.

Tabela I. Rozkład procentowy osób samobadajacych piersi i badanych przez lekarza (%)

	TAK	NIE
Wykonujących i nie samobadanie piersi	57	43
Które miały i nie miałybadania piersi przez lekarza	20	80

a 64. rokiem życia (średnia w momencie zdiagnozowanie to 62 lata). Najwyższy wskaźnik umieralności zawiera się w przedziale wiekowym 65–74 lata (średnia 68 lat) [7]. W związku z tymi danymi jasne jest, że należy włożyć więcej wysiłku w edukację młodych kobiet dotyczącą samobadania piersi, jako wczesnej profilaktyki nowotworowej.

Nadal brakuje dostatecznej wiedzy na temat przyczyn rozwoju nowotworu gruczołu piersiowego, jednak poznano już wiele czynników zwiększających częstość jego występowania. Czynniki ryzyka nowotworu gruczołu piersiowego obejmują: płeć żeńska; wiek powyżej 50. roku życia; występowanie mutacji w genach BRCA 1 i BRCA2; [4, 6, 11–13] czynniki hormonalne, stosowanie antykoncepcji doustnej oraz hormonalnej terapii zastępczej; styl życia [14, 15]. Wyniki badań naukowych wykazały też korelację między nadmiernym spożywaniem tłuszczów oraz otyłości oraz spożywania alkoholu, a rozwojem nowotworu gruczołu piersiowego [16, 17–19]; występowanie nowotworu gruczołu piersiowego w przeszłości, jak również nowotworów jajnika i trzonu macicy; również występowanie zmian łagodnych w obrębie gruczołu piersiowego, takich jak atypowy rozrost przewodowy i zrazikowy może stanowić istotny czynnik ryzyka rozwoju nowotworu gruczołu piersiowego [4, 6, 11, 12].

Objawy nowotworu gruczołu piersiowego zależą od stanu zaawansowania zmiany. Stadium początkowe może przebiegać bezobjawowo, a jedynym objawem może być przypadkowo wykryty guzek [4]. Dzięki rozwojowi medycyny, coraz częściej możliwe jest wykrywanie nowotworów piersi w stadium przedobjawowym. Zwykle pierwszym objawem jest palpacyjne wykrywalny, niebolesny, twardy guzek. Inne niepokojące objawy to zmiany w obrębie skóry gruczołu piersiowego oraz samej brodawki [4–6, 20].

Badania profilaktyczne, w tym samobadanie piersi, to pierwsza linia walki z nowotworem, więc powinno być stale i regularnie wykonywane. Większość zmian nowotworowych piersi jest wykrywana przez kobiety podczas samodzielnego badania. Kobieta regularnie wykonująca samobadanie i znająca dobrze swoje ciało jest niejednokrotnie w stanie wykryć nawet drobne zmiany, które mogą być przeoczone podczas standardowego badania lekarskiego [10, 21]. Samobadanie powinno się rozpocząć od oglądania gruczołów piersiowych w lustrze, w pozycji stojącej, z rękami podpartymi na biodrach. Na tym etapie można zaobserwować zmianę wielkości lub kształtu piersi, obecność zgrubień, zmianę stanu skóry czy brodawki sutkowej. Następnie przystępuje się do badania palpacyjnego, wykonywanego ruchem okrężnym, w tym momencie kobieta poszukuje guzków i zgrubień. Badanie palpacyjne należy wykonać zarówno w pozycji stojącej, jak i leżącej. Ocena gruczołów piersiowych powinna być wykonywana regularnie, raz w miesiącu, w pierwszym tygodniu po miesiączce, najlepiej tego samego dnia [8, 21, 22]. Tylko w ten sposób wykonywane badanie można uznać za wiarygodne.

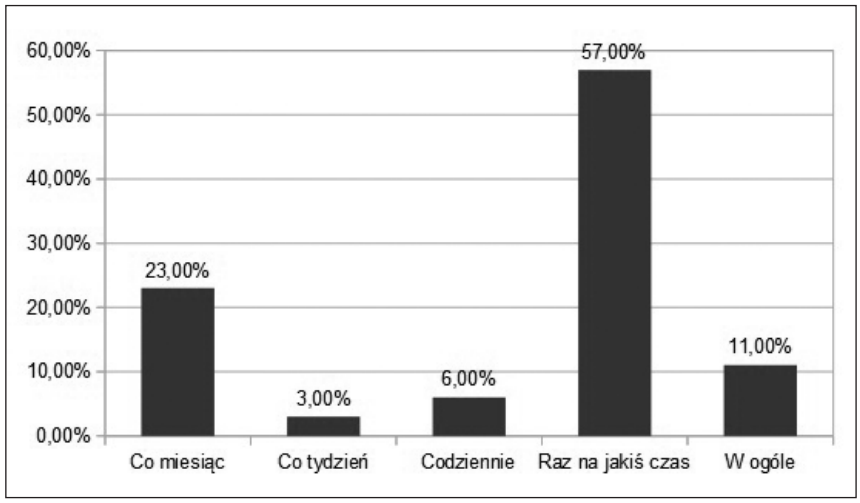
Poza badaniem piersi dysponujemy również szeroką gamą badań obrazowych na przykład ultrasonograficzne badania gruczołu piersiowego, mammografia, rezonans magnetyczny [23–25]. W przypadku mammografii istnieje Narodowy Program Profilaktyczny zakładający badania mammograficzne piersi u kobiet w wieku między 50. a 69. rokiem życia co dwa lata oraz w tej samej grupie wiekowej co roku w przypadku występowania obciążeń rodzinnych [26].

Kobiety w większości mają świadomość zagrożenia, jakim jest nowotwór piersi, ale nie każda zdaje sobie sprawę, jak ważne jest wczesne wykrycie zmian niepokojących. Dlatego tak istotna jest edukacja kobiet w tej dziedzinie. Ważne jest również, aby badanie piersi stanowiło podstawowy element standardowego badania fizykalnego podczas wizyty u lekarza. Badanie piersi to nadal dla wielu kobiet sprawa bardzo intymna i wstydliwa, a dla młodych lekarz przełamanie niechęci pacjentki stanowi duże wyzwanie. Ponadto brakuje programów ćwiczeń umożliwiających studentom medycyny nabycie odpowiednich umiejętności praktycznych. Teoria to jedno, ale umiejętność skutecznego wykonania i oceny badania to sprawa wymagająca praktyki.

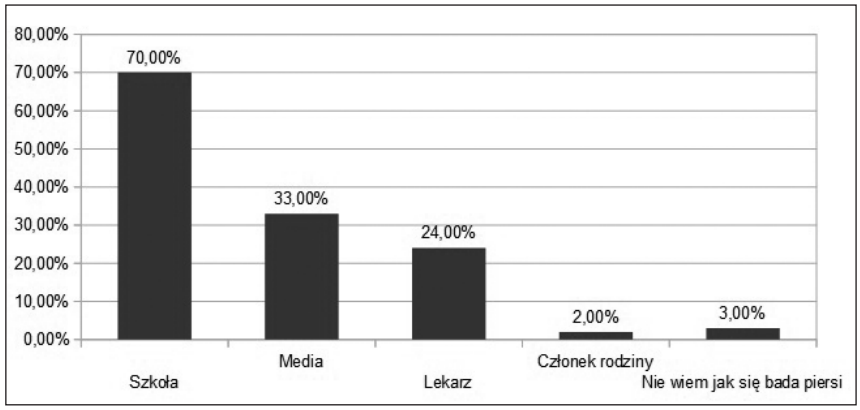
Celem badania było oszacowanie wiedzy społeczeństwa na temat nowotworów piersi oraz ryzyka ich rozwoju. Dodatkowy aspekt pracy stanowiła ocena wiedzy, umiejętności i skuteczności badanych w wykonywaniu samobadania piersi jako profilaktyki rozwoju nowotworów gruczołu piersiowego. Badanie zostało skierowane głównie do osób związanych ze środowiskiem medycznym, ponieważ badanie gruczołu piersiowego to również jedna z podstawowych umiejętności, bardzo ważna w codziennej praktyce medycznej.

MATERIAŁY I METODY

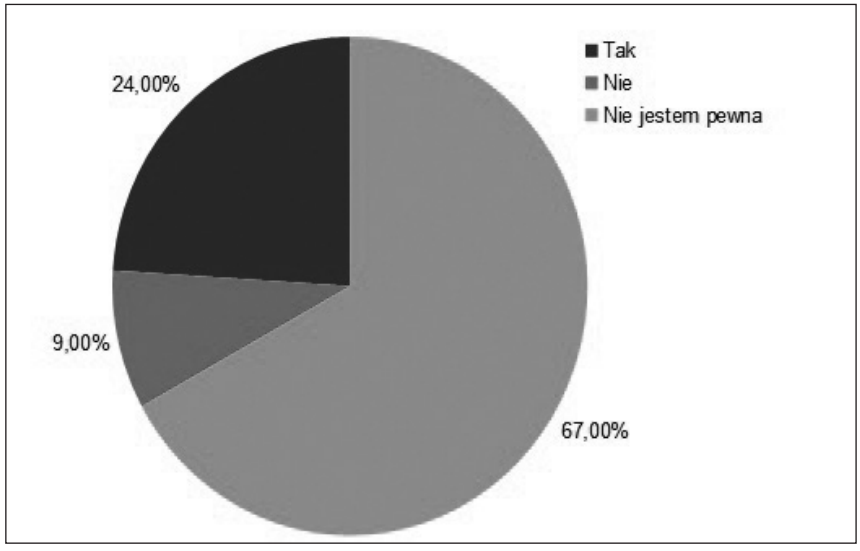
Badanie przeprowadzono poprzez autorski, internetowy kwestionariusz pytań w roku 2018. Udział w badaniu był dobrowolny oraz anonimowy. Naszą ankietę skierowaliśmy głównie do osób związanych ze środowiskiem medycznym, ponieważ takie osoby powinny wykazywać się największą wiedzą w dziedzinie zdrowia oraz być przykładem zachowań prozdrowotnych. Ankieta składała się 19 pytań, 14 pytań dotyczyło kwestii nowotworu piersi oraz umiejętności badania piersi. Wzięły w niej udział 204 osoby, w tym 53% kobiet i 47% mężczyzn. Średnia wieku wynosiła 23,5 roku. Wśród badanych 93,0% stanowiły osoby związane ze środowiskiem medycznym (w tym 63,5% lekarzy i studentów medycyny, 33,3% pielęgniarek i studentów pielęgniarstwa, 3,2% osób innych specjalności medycznych – ratownictwo, fizjoterapia etc.).



Ryc. 3. Częstość wykonywania samobadania piersi.



Ryc. 4. Wybrane przez respondentów źródła wiedzy na temat badania piersi.



Ryc. 5. Określenie występowania zmian niepokojących w obrębie piersi w subiektywnej ocenie badanych.

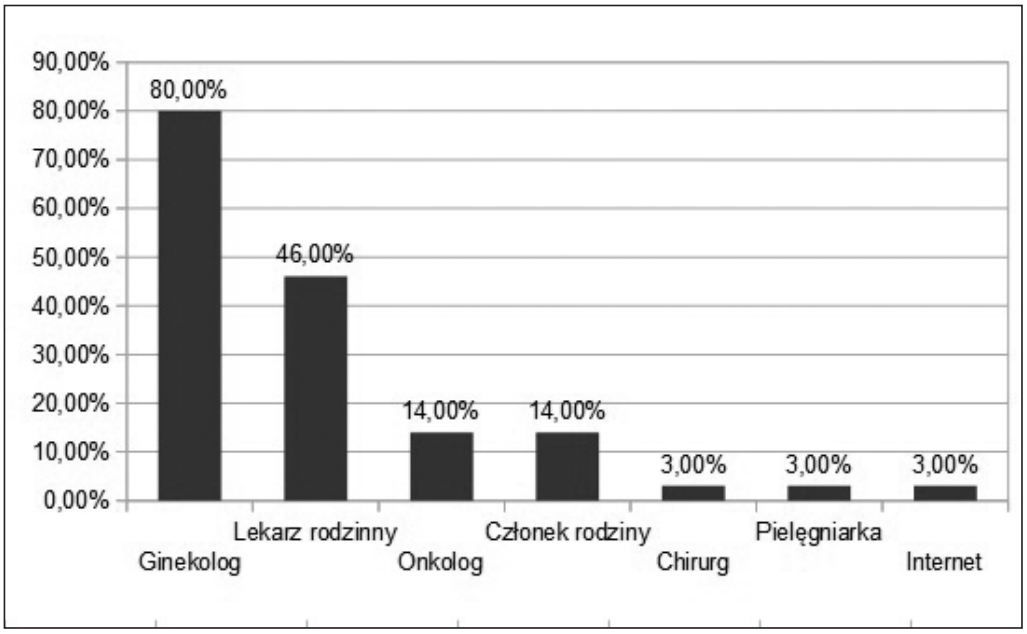
WYNIKI

Badanie zostało podzielone na trzy części. Pierwsza dotyczyła wiedzy oraz umiejętności badanych związanych z przeprowadzaniem badania gruczołów piersiowych. Pytania w tej części zostały dodatkowo podzielone na skierowane tylko do kobiet oraz na skierowane do obu grup płciowych. Druga część dotyczyła oceny podstawowej wiedzy na temat nowotworów gruczołu piersiowego, natomiast trzecia część została skierowana *stricte* do osób związanych ze środowiskiem medycznym.

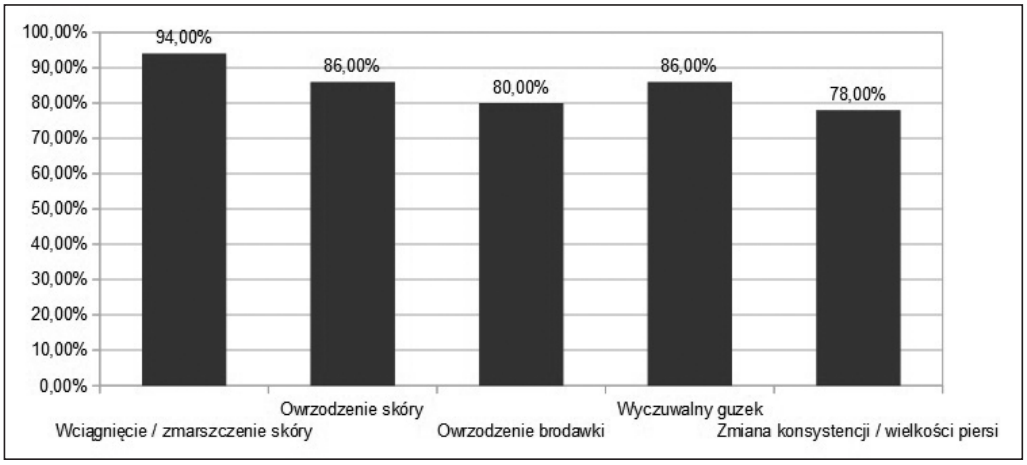
W pierwszym pytaniu zapytano respondentki, czy regularnie dokonują samobadania piersi (Tab. I).

Jak widać na w Tabeli I tylko 57% badanych kobiet regularnie wykonuje ocenę swoich piersi. 43% robi to rzadko lub wcale. W przypadku pań, które wykonują samobadanie piersi, wiek zainicjowania samobadania wynosił średnio 19 lat.

Następnie zapytano respondentki, jak często dokonują samobadania piersi (Ryc. 3).



Ryc. 6. Rozkład procentowy podmiotów, do których badane zgłosiłyby się w przypadku wystąpienia tak zwanych objawów niepokojących.



Ryc. 7. Wiedza badanych na temat objawów nowotworu piersi.

Tylko 23% odpowiedziało, że wykonuje takie badanie regularnie raz w miesiącu. 57% kobiet wykonuje samobadanie rzadko, a 11% nie robi tego w ogóle. 6% wykonuje samobadania codziennie, a 3% raz w tygodniu. Na pytania dotyczące wiedzy, w jaki sposób powinno się wykonywać badanie piersi respondenci prawie w 100% odpowiedzieli prawidłowo. Jedyne co zaniepokoiło autorów, to fakt że tylko 36% badanych było świadomych, że badanie gruczołu piersiowego powinno być przeprowadzane zarówno w pozycji stojącej, jak i leżącej.

Zapytano również, skąd badani uzyskali wiedzę, jak prawidłowo wykonywać badanie piersi (Ryc. 4.).

Było to pytanie wielokrotnego wyboru. 70% respondentów wskazało „szkołę" jako źródła informacji, 33% „media", takie jak: internet, telewizja, kampanie edukacyjne, 24% wskazało „lekarzy", a 2% „członka rodziny". Tylko 3% respondentów wybrało odpowiedź: „Nie wiem, jak się bada piersi".

W kolejnym pytaniu zapytano czy badane kobiety kiedykolwiek zaobserwowały lub wyczuły jakieś niepokojące zmiany w obrębie swoich piersi (Ryc. 5).

Pytanie to miało na celu subiektywne oszacowanie efektywności wykonywania samobadania piersi. 67% kobiet stwierdziło, że „nie jest pewne", czy zaobserwowały lub wyczuły jakąś anomalię, 24% odpowiedziało pozytywnie i tylko 9% zaprzeczyło. Kolejną kwestią było zbadanie, do kogo badane zgłosiłyby się w razie zauważenia niepokojących zmian (Ryc. 6).

Było to pytanie wielokrotnego wyboru. Autorzy chcieli oszacować, czy badane darzą bardziej zaufaniem lekarzy, czy, zgodnie z powszechną tendencją, źródła internetowe. W tym przypadku tylko 3% badanych zaznaczyło odpowiedź „internet". 80% badanych zgłosiłoby się do ginekologa, 46% do lekarza rodzinnego oraz 14% do onkologa.

Autorzy postanowili oszacować również, czy w praktyce lekarskiej badanie piersi rzeczywiście stanowi podstawowy element badania fizykalnego. W tym celu zapytano badane kobiety, czy kiedykolwiek miały wykonane badanie piersi przez lekarza jakiejkolwiek specjalności (Tab. I). Tylko 20% badanych odpowiedziało twierdząco. Nie można oczywiście na tej podstawie określić efektywności wykonywania badania piersi przez lekarzy w Polsce ze względu na zbyt małą grupę badanych, jednak budzi to niepokój.

Tabela II. Rozkład procentowy osób związanych ze środowiskiem medycznym (%)

	TAK	NIE
Które czułyby się pewnie podczas wykonywania badania piersi u pacjentki	39	61
Które miały i nie miały okazji wykonać badania piersi u pacjentki w trakcie studiów	32	68

Kolejną częścią badania było oszacowanie podstawowej wiedzy na temat nowotworu gruczołu piersiowego. W tym celu zadano pytania dotyczące możliwych objawów nowotworu gruczołu piersiowego, czynników ryzyka jego rozwoju oraz możliwych metod diagnostyki. Wiedza badanych w tej dziedzinie był na zadowalającym poziomie.

W kolejnym pytaniu oceniono wiedzę badanych w kwestii możliwych objawów nowotworu gruczołu piersiowego (Ryc. 7).

Co ciekawe, najczęściej wskazywanym objawem nie był „wyczuwalny guzek", a „wciągnięcie lub zmarszczenie skóry". Prawdopodobną przyczyną takich wyników stanowiła duża liczba możliwych odpowiedzi w kwestionariuszu pytań, które mogły spowodować przeoczenie niektórych stwierdzeń. Pozostałe objawy były prawidłowo wskazywane przez około 80% respondentów.

Podobna sytuacja w wynikach kwestionariusza pojawiła się w przypadku możliwych czynników ryzyka rozwoju nowotworu gruczołu piersiowego. Było to pytanie wielokrotnego wyboru. 95% badanych wskazało odpowiedź „wystąpienie nowotworów gruczołu sutkowego w rodzinie", 94% „wystąpienie nowotworów gruczołu sutkowego w przeszłości", 90% „czynniki genetyczne", 80% „wiek powyżej 50. roku życia", 75% „płeć żeńska", 69% „długotrwała hormonalna terapia zastępcza", a 63% „stosowanie doustnej antykoncepcji" i „łagodne zmiany w obrębie piersi".

Badani prawidłowo wskazywali również znane im badania obrazowe wchodzące w skład diagnostyki nowotworów piersi: Mammografia (100% odpowiedzi), USG (73%), biopsja (55%), rezonans magnetyczny (36%), tomografia komputerowa (30%), RTG (27%). To potwierdza, że badani są świadomi możliwych czynników ryzyka oraz możliwości diagnostycznych współczesnej medycyny.

W ostatniej części badanie zostało skierowane do osób związanych ze środowiskiem medycznym. Zapytano badanych, czy przeprowadzając badanie piersi u pacjentek czuliby się pewnie i komfortowo. Tylko 39% badanych odpowiedziało twierdząco (Tab. II).

Kolejnym pytaniem było, czy badani mieli okazję wykonania takiego badania podczas studiów pod okiem doświadczonego specjalisty (Tab. II]). W tym przypadku tylko 32% miało okazję wykonać takie badanie. Warto tutaj zaznaczyć, że 20% badanych stanowiły osoby z wyższym wykształceniem (lekarze i pielęgniarki), a 60% osób wciąż studiujących stanowili studenci V i VI roku.

DYSKUSJA

Najbardziej dyskusyjnym jest twierdzenie, że wykonywanie samobadania przez kobiety nie jest zalecane, spowodowane jest to w głównej mierze zwiększeniem częstości wykonywania kosztownych badań inwazyjnych u kobiet z łagodnymi zmianami sutka, a także tym, że badanie to nie powoduje spadku śmiertelności z powodu tego nowotworu [27–32]. Jednakże, według zaleceń Polskiego Towarzystwa Ginekologicznego, każda kobieta od 20. roku życia powinna wykonywać comiesięczne samobadanie piersi [21]. Wiele kobiet jest przekonanych o konieczności wykonywania takiego badania, jednak odczuwa braki w umiejętności jego przeprowadzenia [33]. Jest to niepokojące, biorąc pod uwagę fakt, że 90% badanych stanowią osoby związane ze środowiskiem medycznym (głównie studenci kierunku lekarskiego i pielęgniarstwa), czyli osoby, które już są lub wkrótce będą odpowiedzialne za wykrywanie nowotworów [33]. Problem leży zarówno po stronie studentów, jak i nauczycieli akademickich. Badanie piersi to nadal temat tabu. Studenci nie wykonują badania piersi, ze względu na poszanowanie intymności i komfort pacjentek. Niejednokrotnie nawet lekarze pomijają to badanie, chociaż stanowi ono jeden z elementów badania fizykalnego podczas wizyty lekarskiej. Mogłoby się wydawać, iż skoro respondentki w przeważającej większości są młode, fakt, iż nie wykonują jeszcze samobadania piersi nie jest tak niebezpieczny. Samobadanie piersi pozwala rozpoznać nowotwory piersi na wcześniejszym etapie, jednak doniesienia nie potwierdzają, aby regularne wykonywanie samobadania piersi przez kobiety spowodowało spadek śmiertelności z powodu nowotworów gruczołu sutkowego [31, 32]. Warto jednak tutaj wspomnieć, że w nowej Podstawie Programowej dla Szkół nie zawarto lekcji na temat nowotworów oraz metod ich zapobiegania, co niewątpliwie ograniczy świadomość społeczeństwa oraz wczesne wykrywanie zmian patologicznych, chociaż duży odsetek respondentów jako źródło wiedzy na temat samobadania dalej wskazuje szkołę. Według badań nie jest zalecane wykonywanie samobadania piersi częściej niż raz w miesiącu, ze względu na fakt, że gruczoł piersiowy podlega w ciągu miesiąca zmianom hormonalnym. Z tego względu ciężko znaleźć fizjologiczny punkt odniesienia, tak ważny dla określenia odstępstw od normy [8, 21]. Uważa się, że wykrycie objawów nowotworu piersi, takich jak: zmiana wielkości, symetrii czy konsystencji piersi, zmarszczenie skóry, wyciek z brodawki czy wyczucie guzka możliwe jest podczas zwykłych aktywności, jak np. kąpiel czy ubieranie się [29, 30]. Sama teoria jest niestety niewystarczająca, aby kobiet mogły efektywnie dokonywać samobadania piersi. Konieczne jest wprowadzenie programów ćwiczeniowych na fantomach piersi na szeroką skalę, aby zwiększyć efektywność wykonywania badania, a dużo pań jest zainteresowanych organizowaniem warsztatów o tej tematyce [33]. Dzięki temu nabiorą one umiejętności i poznają swój fizjologiczny punkt odniesienia. Będą bardziej wyczulone, a co więcej rozwiną samoświadomość możliwych objawów nowotworu

gruczołu piersiowego. Niektóre doniesienia sugerują, że wykonywanie samobadania piersi może powodować wzrost stresu u kobiet i negatywnie wpływać na ich zdrowie psychiczne, zwłaszcza w sytuacjach, gdy pacjentka nie jest pewna, czy dobrze przeprowadza to badanie, co wynika z jej niedostatecznej wiedzy w tej dziedzinie, co sygnalizują same pacjentki [33–35]. Trzeba jednak pamiętać, że kobiety nie tylko mogą wstydzić się samego badania, ale również przyznania się do istnienia zmian niepokojących w obrębie gruczołów sutkowych. Powoduje nimi strach przed diagnozą nowotworu złośliwego. Dlatego jako lekarze musimy wykazywać się inicjatywą: uświadamiać pacjentki co do zagrożenia, jakim jest nowotwór oraz korzyści, jakie przynosi jego wczesne wykrycie, edukować, jak mogą wykonywać takie badanie samodzielnie oraz rzetelnie i regularnie przeprowadzać badanie piersi u pacjentek. Co więcej, kobiety mogą zastępować samobadaniem piersi inne, ważne badania obrazowe i nie doceniać wagi badań profilaktycznych [32, 36]. Jednakże z praktyki lekarskiej wynika, że w większości przypadków nowotworów piersi występuje u kobiet zgłaszających się do lekarza po wykryciu niepokojących zmian podczas samobadania. Kobiety powinny być świadome fizjologicznej budowy swoich piersi i wykazywać czujność podczas samobadania na każdą zmianę tego stanu i być zachęcane do zasięgnięcia porady lekarskiej w przypadku wykrycia nawet drobnej zmiany w sutku [32, 34, 37].

WNIOSKI

1. Wiedza badanych dotycząca samobadania piersi oraz nowotworu gruczołu piersiowego jest na dobrym poziomie, jednakże efektywność oraz umiejętność wykonywania badania jest na poziomie niezadowalającym.
2. Brakuje możliwość zdobywania umiejętności praktycznych, jest to trudne do zmiany, ale i konieczne.
3. Należy włożyć więcej wysiłku w edukację studentów medycyny, aby zwiększyć skuteczność w walce z nowotworem piersi przez przekonywanie i nauczanie pacjentek do stosowania samokontroli gruczołu piersiowego w późniejszej praktyce lekarskiej.

PIŚMIENNICTWO

1. Mazurkiewicz M. Profilaktyka i metody wczesnego rozpoznawania raka gruczołu piersiowego. Med Rodz. 2000;2:29-32.
2. Harris R, Kinsinger LS. Routinely Teaching Breast Self-Examination is Dead. What Does This Mean? Nat Cancer Inst. . 2002;94(19):1420-1421.
3. Baxter N. Preventive health care, 2001 update: Should women be routinely taught breast self-examination to screen for breast cancer? CMAJ. 2001;164(13):1837-1846.
4. Kordek R. Onkologia – Podręcznik dla studentów i lekarzy. Gdańsk: Via Medica, 2007, 202-232.
5. Zwrotnik Raka: Objawy Raka piersi; https://www.zwrotnikraka.pl/objawy-raka-piersi-sutka/
6. Krajowy Rejestr Nowotworów : Piersi u Kobiet; http://onkologia.org.pl/rak-piersi-kobiet/
7. National Cancer Institute: Cancer Stat Facts: Female Breast Cancer; https://seer.cancer.gov/statfacts/html/breast.html
8. Zwrotnik Raka: Jak wykonać badanie piersi i wykryć guza; https://www.zwrotnikraka.pl/jak-wykonac-badanie-piersi/
9. McGuire A, Brown JA, Malone C et al. Effects of age on the detection and management of breast cancer. Cancers, 2015:7(2):908-929.
10. Bojakowska U, Kalinowski P, Kowalska ME. Epidemiologia i profilaktyka raka piersi; J Edu Health Sport. 2016;6(8):701-710.
11. Hayes J, Ricahrdson A, Frampton C. Population attributable risks for modifiable lifestyle factors and breast cancer in New Zealand women. IMJ 2013,43(11):1198-1204.
12. Reeder JG, Vogel VG. Breast cancer prevention. Cancer Treat Res. 2008;141:149-164.
13. Malone KE, Daling JR, Thompson JD et al. BRCA1 mutations and breast cancer in the general population: analyses in women before age 35 years and in women before age 45 years with first-degree family history. JAMA. 1998:279(12):922-929.
14. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. N Engl J Med. 2006;354(3):270-282.
15. Mazzucco A, Santoro E, DeSoto M et al. Hormone Therapy and Menopause. National Research Center for Women & Families. 2009
16. Institute of Medicine. Breast Cancer and the Environment: A Life Course Approach (Institute of Medicine). Washington, D.C: National Academies Press. 2012. 52-53.
17. Allen NE, Beral V, Casabonne D et al. Moderate alcohol intake and cancer incidence in women. JNCI. 2009;101(5):296-305.
18. Fuchs CS, Stampfer MJ, Graham AC, Giovannucci EL et al. Alcohol Consumption and Mortality among Women. N Engl J Med. 1995;332:1245-1250.
19. Sonestedt E. Do both heterocyclic amines and omega-6 polyunsaturated fatty acids contribute to the incidence of breast cancer in postmenopausal women of the Malmö diet and cancer cohort?. Int J Cancer 2008:1;123(7):1637-1643
20. Merck Manual of Diagnosis and Therapy (2003) Breast Disorders: Breast Cancer. Retrieved 5 February 2008.
21. Spaczyński M. Rekomendacje Zarządu Głównego PTG w sprawie profilaktyki i wczesnej diagnostyki zmian w gruczole sutkowym. Gin Prakt. 2005;84 (3):14-15.
22. Polska Z. Samodzielne badanie piersi - profilaktyka raka sutka, http://www.forumonkologiczne.pl/artykul/samodzielne-badanie-piersi-profilaktyka-raka-sutka/535
23. Breast Cancer and Mammograms. WebMD, 2018.
24. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. An Intern Med. 2009;151(10):716-726.
25. Berg WA, Blume JD, Cormack JB et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA. 2008;299(18):2151-2163.
26. Ministerstwo Zdrowia. Narodowy Program Zwalczania Chorób Nowotworowych; Populacyjny program wczesnego wykrywania raka piersi. 2011
27. Nelson HD, Tyne K, Naik A et al. Screening for Breast Cancer: Systematic Evidence Review Update for the US Preventive Services Task Force. Rockville (MD). Agency for Healthcare Research and Quality (US); 2009 Nov. (Evidence Syntheses, No. 74.)
28. Guidelines for preventive activities in general practice, 8th edition, 9.3 Breast cancer". Royal Australian College of General Practitioners. Retrieved 2016-05-21.
29. American Cancer Association; Breast Cancer early detection and diagnosis https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/american-cancer-society-recommendations-for-the-early-detection-of-breast-cancer.html
30. McCreadyy T, Littlewood D, Jenkinson J. Breast self-examination and breast awareness: a literature review. J Clin Nurs. 2005;14(5):570-578.

31. Thomas DB, Gao DL, Ray RM et al. Randomized Trial of Breast Self-Examination in Shanghai: Final Results. J Nat Cancer Inst. 2002;94(19):1445-1457
32. Kosters JP, Gotzsche PC. Regular seld-examination or clinical examination for early detection of breast cancer. Cochrane Breast Cancer Group, Cochrane Database Syst Rev. 2003;(2):CD003373. 2010
33. Kamieniecka-Janicka Z, Kiełbratowska B, Olszewska J. Nurses' attitude to brest self examination. Annal UMCS 2005;60(Suppl. 16/181):321-325.
34. Baxter N. Canadian Task Force on Preventive Health Care. Preventive health care, 2001 update: should women be routinely taught breast self-examination to screen for breast cancer?.CMAJ. 2001;164(13):1837-1846
35. Absetz P, Aro AR, Sutton SR. Experience with breast cancer, pre-screening perceived susceptibility and the psychological impact of screening. Psychooncology 2003:12(4):305-318.
36. Sulik GA. Pink Ribbon Blues: How Breast Cancer Culture Undermines Women's Health. USA: Oxford University Press. 2010
37. Ziayifard Z, Abdolahi Kh, Zahedi R et al. A survey of the knowledge of the 20 year and older women on breast self-examination and mammography, southern Iran. 2009. J Jahrom Univers Med Scien. 2012;10(2):42-47

Konflikt interesów:
Autorzy deklarują brak konfliktu interesów.

AUTOR KORESPONDUJĄCY
Norbert Stachowicz
Katedra i Zakład Epidemiologii i Metodologii Badań Klinicznych;
Uniwersytet Medyczny w Lublinie
ul. Radziwiłowska 11, 20-080 Lublin, Polska
e-mail: norberts@umlub.pl

Nadesłano: 29.07.2018
Zaakceptowano: 09.01.2018

PRACA ORYGINALNA
ORIGINAL ARTICLE

POSSIBILITY FOR NON-INVASIVE DIAGNOSIS OF CHRONIC ENDOMETRITIS IN WOMEN AT RISK DURING PREGRAVID PREPARATION

MOŻLIWOŚCI NIEINWAZYJNEJ DIAGNOSTYKI PRZEWLEKŁEJ ENDOMETRIOZY U KOBIET Z GRUPY RYZYKA W TRAKCIE PRZYGOTOWYWAŃ DO CIĄŻY

Olena O. Taranovska, Volodymyr K. Likhachov, Ludmyla M. Dobrovolska, Oleg G. Makarov, Yanina V. Shymanska
UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY, POLTAVA, UKRAINE

ABSTRACT

Introduction: Detection and treatment of chronic endometritis (CE) is clinically significant, though involves intrauterine intervention to collect endometrium.

The aim: To estimate the possibility to use fertility α2-microglobulin (FAMG) as the marker of the high risk for CE.

Materials and methods: 70 women with CE who were planning pregnancy were tested for FAMG in menstrual blood. 40 of them received treatment of CE. The other 30 women refused from the proposed treatment. The control group involved 30 women who had neither CE nor luteal phase deficiency (LPD). Additional group (20 women) had LPD without CE.

Results: The decrease of FAMG by 2.4 times was noted in women with CE (16.3 ± 3.9 μg/ml against 39.8 ± 8.3 μg/ml in the controls). In LPD the index was 5.6 times lower. After treatment the level of FAMG was increasing.

Conclusions: The decrease of the amount of FAMG in menstrual blood is specific for women both with CE and LPD. Detection of abnormally low rates of FAMG in all women with CE enables, with the exception of absolute hypoprogesteronemia and LPD, using it as a simple method of estimation of the functional state of endometrium. Its application can be very useful both for non-invasive diagnosis of CE and subsequent evaluation of treatment of this pathology.

KEY WORDS: chronic endometritis, luteal phase deficiency, fertility α2-microglobulin, preconception

Wiad Lek 2019, 72, 1, 64-67

INTRODUCTION

The successful onset of pregnancy and its development requires simultaneous favorable combination of three factors: genetically good embryo, the state of immunologically tolerant acceptance by the body of a pregnant woman and sufficient implantation potential of the endometrium [1]. It is the last component of this triad that can often be the cause of reproductive losses and unfavorable pregnancy outcomes [2]. Carrying of a pregnancy and occurrence of such pathology as placental insufficiency, intrauterine growth retardation and preeclampsia is associated with the disorders of the processes of gestational rearrangement of the uterine spiral arteries and formation of the trophoblast [3]. Therefore, implantation capabilities of the endometrium are crucial for the successful onset and progress of pregnancy [2].

Consequently, detection and successful treatment of chronic endometritis (CE) at the stage of pregravid preparation is of particular importance [2], especially for the patients with reproductive losses in the past history [4, 5]. Apparently, termination of pregnancy, especially missed abortion, is accompanied by the formation of CE in the endometrium with high concentration of pro-inflammatory cytokines, and occurrence of the succeeding pregnancy along with such endometrial changes is doomed to repeated termination [4, 6].

Since the clinical picture of CE is oligosymptomatic, thorough analysis of the anamnestic data, namely, recurrent pregnancy loss, experienced intrauterine interventions (hysterosalpinography; curettage, made with therapeutic or diagnostic purposes; intrauterine contraception; in vitro fertilisation, etc.) is of critical importance to reveal the risk factors for this pathology. The onset of CE is also possible in high level of contamination of the lower and upper genital tracts with pathogen bacteria even in women without invasive intrauterine interventions in the past history [7]. Although the frequency of detection of infection in the lower genital tract is significantly higher the frequency of intrauterine infection, the spectrum of microorganisms in the cervical canal and vagina generally coincides with the similar one in the uterus [7].

The accurate CE diagnosis requires endometrial biopsy (pipille biopsy or target biopsy during hysteroscopy) for histological confirmation of the diagnosis, associated with the intrauterine intervention [8]. Diagnostic curettage is an old-fashioned, though still used method of obtaining the material, which is the most traumatic and problematic among other invasive diagnostic methods. It is the fact

of intrauterine intervention that is problematic in the perception of this group of diagnostic activities for both a physician and a patient.

Practically, the gap between a high significance of CE in the concept of the development of the reproductive losses and low level of its diagnosis (and, consequently, treatment) could be reduced by the presence of non-invasive diagnostic marker. Substances that are synthesized by the endometrium itself and easily identified in the biological materials, available for sampling, can play the role of the marker.

Such marker is the fertility α2-microglobulin (FAMG, glycodelin), i.e., a dimeric glycoprotein, which is synthesized by the endometrial glands [9,10]. The methods of immunodiffusion and immunohistochemical analysis show that the FAMG is presented in the epithelium of the fallopian tubes and decidua. The protein was not expressed in the normal tissues of the vagina, ovaries, myometrium, mammary glands, as well as in any tissues, which are not related to the reproductive system [11].

FAMG is synthesized and secreted by glandular epithelium only, but not endometrial stromal cells [10]. It appears in the endometrial tissue within a few days before a possible implantation, its amount increases during the "implantation window" and preserves in high amount to the onset of menstruation and during the first days of the next cycle, after which the production of protein in the endometrium temporarily ceases [10,12]. Once the pregnancy occurred, the synthesis of FAMG continues and in the first gestation trimester its amount in the decidual tissue constantly grows [9,13].

FAMG is crucial in the embryo implantation (as a local immunosuppressor), protecting it from the maternal immune response [13]. FAMG also plays one of the leading roles in the processes of trophoblast invasion, since it is involved in the cascade activation of the cell adhesion molecules [9,13]. Moreover, the transport of hydrophobic molecules from the tissue environment that are essential for fetal development can be the important function of FAMG in early pregnancy at the stage of the placenta formation and no placental circulation exists [13].

The efficacy of the FAMG synthesis is dependent from the functional state of endometrial glands and the level of progesterone [12]. It enables to use FAMG as a specific protein, decreasing production of which is accompanied by the damage to the mucous membrane of the uterus and may serve as a non-invasive marker for CE detection.

THE AIM

The paper was aimed at evaluation of the possibility to use FAMG as a marker of the high risk for CE, differentiation of CE with luteal phase deficiency (LPD), as well as identification of effective treatment of CE during pregravid preparation.

MATERIALS AND METHODS

We examined 120 women of reproductive age who were planning pregnancy in the offices of family planning in Poltava during the period from 2010 to 2017. In addition to general clinical examination, pipille biopsy of the endometrium was made on the 18^{th} -25^{th} day of the cycle with subsequent histological study of the biopsy material. Menstrual blood was collected in all women to determine the level of FAMG by the enzyme-linked immunosorbent assay (ELISA) using the "FAMG – Fertitest-M" test system. The ultrasound structure of the endometrium was also studied. Special attention was given to the CE signs: discrepancy between the thickness of endometrium and the day of menstrual cycle, uneven thickening of the functional and basal layers of the endometrium, occurrence of fibrosis, sclerosis, calcifications, deformation of the linear structure or polyposis, thinning of the transitional zone of endometrium before menstruation (< 5 mm).

Histological study of pipille biopsy collected from 70 women confirmed the events of CE (the main group). 40 women out of 70 (subgroup A) received the appropriate treatment, which included antibiotic therapy, anti-inflammatory, antiviral and metabolic drugs, as well as hormone therapy for 3 months with the use of progesterone (in hypertrophic forms of CE) or 2/10 femoston (in case of atrophic form of CE). After the treatment, the repeated control of FAMG was made. The other 30 women in this group (subgroup B) refused from the proposed treatment for various reasons and that was documented by the relevant statements. The control group involved 30 women without CE and LPD.

Patients with absolute hypoprogesteronemia and luteal phase deficiency (LPD) have not been assigned to the main group of examined women, since the occurrence of this pathology itself has a regulating effect on the synthesis of endometrial proteins, including FAMG. However, considering that FAMG may be reduced both in CE and LPD, it was appropriate to investigate, which differential values of FAMG are specific for women with CE and LPD. Therefore, we have examined an additional group of individuals (20 women) with LPD but without signs of CE.

In order to confirm or exclude the LPD, folliculometry was made to all women with subsequent determination of the duration of the luteal phase of the cycle from the moment of ovulation to the onset of menstrual bloody discharge. The increase in progesterone in the luteal phase was also determined by calculating the ratio between the level of the hormone at the beginning of menstrual cycle (MC) (3-5 day from the beginning of menstruation) and in its second phase (6-8 day after ovulation). The discrepancy between the ultrasound structure of the endometrium and a day of menstrual cycle was also considered.

RESULTS

We have found that among 70 women with histologically confirmed CE, ultrasound signs, which can indicate the presence of this pathology, were detected in 52 women (74.3%). The ultrasound examination of other 18 women (25.7%) showed no signs that indicated the change in the structure of endometrium.

Discrepancy between the edometrium and the phase of menstrual cycle occurred the most often among the ultrasound signs of CE: the endometrium was too thin for the corresponding day of the menstrual cycle (20 women; 28.57% of the total number of women of the main group). In the main group other signs of CE were also found: thickening of the functional and basal layers of the endometrium (16 women; 22.86%), polyposis (12 women; 17.14%), presence of hypoechoic inclusions in the endometrium (4 women; 5.71%).

In the additional group (women with LPD) the findings of the ultrasound examination revealed discrepancy between the endometrium and the phase of menstrual cycle only. This feature occurred in 80% of women (16 patients).

The comparison of the increase in progesterone in the luteal phase (on the 6-8 day after ovulation, confirmed by folliculometry) relative to its original level, defined at the beginning of the menstrual cycle (3-5 day from the beginning of menstruation) has found that this index was 16.6 ± 2.8 in women of the control group. In women with LPD the index of the increase in progesterone was on the average of 6.5 ± 2.1 that is 2.5 times lower than in the control group. In women with CE the increase in the level of progesterone in the second phase of the cycle was almost similar to the one in the control group (16.3 ± 2.1).

The duration of the luteal phase was also almost similar to the one in the control and main groups (13.2 ± 0.8 days and 13.6 ± 1.2 days, respectively). In women of additional group (LPD) the second phase of the cycle was shortened to 7.6 ± 0.7 days that reliably differed from the reference values ($p<0,05$).

The significant decrease in the level of FAMG in relation to the indices in the control group was revealed in all 70 women with histologically confirmed events of CE. In this way, in the healthy women of control group this index was 39.8 ± 8.3 μg/ml. In women with CE the level of FAMG was 16.3 ± 3.9 μg/ml ($p < 0.05$), that was 59% lower than the reference values.

In women of additional group the recorded level of FAMG was reduced to 7.0 ± 2.2 μg/ml. It is reliably lower than the reference values (by 75.9%; $p < 0.01$) and indices in women with CE (by 42.9%; $p < 0.05$). In the case of anovulatory cycles (they were detected in 6 women of additional group) the level of FAMG was so low, that could not be identified within the sensitivity of the method.

DISCUSSION

The resulting data revealed insufficient diagnostic value of histological approach in diagnosis of CE, showing that in women with histologically confirmed CE the ultrasound signs of this pathology were found only in 74.3% of women, whilst no ultrasound signs of pathological state of the endometrium were found in the every fourth woman. Determination of the FAMG level in the menstrual blood of a woman is more informative method, since reduction of this index in women with CE was recorded in all 100% of examined women.

Ultrasonography has shown that discrepancy between the thickness of endometrium and the day of menstrual cycle (28.57%) was detected more often than other ultrasonic signs in women with CE. Noteworthy, histological study of endometrial biopsy showed that such discrepancy was recorded in 100% of examined women. It can be explained by the fact that ultrasound examination reveals the thickness of the endometruim only, not considering the fact that the glands of the endometrium with normal thickness have insufficient secretory transformation that can be assessed histologically.

Apparently, the discrepancy between the endometrium and one or another phase of menstrual cycle, detected by ultrasonography or confirmed histologically, is the specific feature for both women with CE and patients with LPD. However, in CE (the main group) it is due to the altered structure of the cells of glands and stroma, whereas in CE (additional group) it is the consequence of a limited influence of low concentration of progesterone on the endometrium, synthesized insufficiently by the yellow body of the ovary. It is evidenced by the folliculometry, showing the shortened luteal phase of the cycle (7.6 ± 0.7 days) and low increase in progesterone in the second phase of menstrual cycle (6.5 ± 2.1) in women of additional group.

Reduced amount of FAMG in menstrual blood in the luteal phase of menstrual cycle was also recorded in women of additional group; however, it is more prominent than in women with CE. In this way, in CE and LPD the level of FAMG was 2.4 and 5.6 times, respectively, lower as compared with the reference values. We hypothesize that this fact can be explained by the ability of FAMG to be synthesized by the secretory transformed endometrium only that is confirmed by other authors [11,12]. The successful transformation of the endometrium in the second phase of menstrual cycle can be performed due to histologically normal structure of the endometrium in the first phase, well expressed and sensitive progesterone receptors [10] and sufficient level of progesterone. In CE the first factor is violated, limiting production of FAMG. In case of LPD both mechanisms are disturbed (primarily, progesterone effect on the structure of the endometrium decreases and secondly, its secretory transformation is disrupted), which causes even more marked suppression of synthesis of FAMG.

We also evaluated the changes in FAMG in women with CE after individualized comprehensive treatment with antibacterial, metabolic, anti-inflammatory drugs, antiviral drugs and hormonal therapy, provided to some of them. It has been found that after treatment the level of FAMG reached the control values that are specific for healthy women. We hypothesize that it is associated with the elimination of the causative agent, enhancement of the trophism and receptivity of the endometrium under the effect of treatment, which led to the activation of the synthesis of FAMG by the endometrial glands.

CONCLUSIONS

Determination of FAMG in menstrual blood of women in the late second phase of the cycle is a simple and informative

method of estimation of the functional state of the uterine glandular epithelium. Its application under the conditions of the exclusion of absolute hypoprogesteronemia and LPD can be very useful both for non-invasive diagnosis of CE and subsequent assessment of treatment of this pathology.

REFERENCES

1. Kovaleva YV. The application of low-frequency ultrasound for the comprehensive treatment and rehabilitation of the patients presenting with chronic endometritis. Vopr Kurortol Fizioter Lech Fiz Kult. 2017;94(3):32-38
2. Kotaro K., Hidehiko M., Kohei Y. et all. Chronic endometritis: potential cause of infertility and obstetric and neonatal complications. Am J Reprod Immunol.Volume 75, Issue 1.January 2016 Pages 13–22.
3. Winship A, Dimitriadis E. Interleukin 11 is upregulated in preeclampsia and leads to inflammation and preeclampsia features in mice. J Reprod Immunol. 2017 Nov 26;125:32-38.
4. Suzuki S, Nakashima N, Kageyama M et all. A phytoestrogen supplement prevents the altered gene expression associated with pregnancy implantation induced by IL-1β in endometrial epithelial cells. Reprod Biol. 2017 Sep;17(3):259-267.
5. Radzinsky VE, Kostin IN, Petrov YA et all. Diagnostic significance of chronic endometritis macrotypes differentiation among women with reproductive losses.// Gynecol Endocrinol. 2017;33(sup1):36-40.
6. Kushnir VA, Solouki S, Sarig-Meth T et all. Systemic Inflammation and Autoimmunity in Women with Chronic Endometritis. Am J Reprod Immunol. 2016 Jun;75(6):672-677.
7. Likhachov VK, Taranovska OO, Safonova OH ta in. Rol mikrobnoho faktoru u formuvanni khronichnoyi vnutrishnomatkovoyi infektsiyi. Materialy Plenumu Asotsiatsiyi akusheriv-hinekolohiv Ukrayiny. 2012: 270-272.
8. Kosei N, Zakharenko N, Herman D. Endometrial polyps in women of reproductive age: clinical and pathogenetic variations. Georgian Med News. 2017 Dec;(273):16-22.
9. Lee CL, Lam KK, Koistinen H et all. Glycodelin-A as a paracrine regulator in early pregnancy. J Reprod Immunol. 2011 Jun;90(1):29-34.
10. Mikhaleva LM, Boltovskaya MN, Mikhalev SA, et all. Endometrial dysfunction caused by chronic endometritis: clinical and morphological aspects. Arkh Patol. 2017;79(6):22-29.
11. Hansen YB, Myrhoj V, Jorgensen FS, et all. Investigation on the ability of first trimester glycodelin and angiopoietin-2 to predict small-for-gestational age pregnancies at delivery. Clin Chem Lab Med. 2016 Sep 1;54(9):1481-1486.
12. Dorostghoal M, Ghaffari HO, Marmazi F et all. Overexpression of endometrial estrogen receptor-alpha in the window of implantation in women with unexplained infertility. J Fertil Steril. 2018 Apr;12(1):37-42.
13. Dundar B, Dincgez Cakmak B, et all. Maternal serum glycodelin levels in preeclampsia and its relationship with the severity of the disease. J Matern Fetal Neonatal Med. 2017 Aug 9:1-9.

The paper has been written within the research scientific work made at the Department of Obstetrics and Gynecology II of HSEEU "UMSA" within 2017-2022, entitled "The role of chronic uterine infection and lower genital tracts in the origination of obstetric and gynecological pathology" (State registration No. 0117U005276).

Authors' contributions:
According to the order of the Authorship.
Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Volodymyr K. Likhachov
42 Stritenska Str., app. 19, Poltava 36011, Ukraine
tel: +380952212112.
e-mail: vladimir.lihachov@gmail.com

Received: 11.07.2018
Accepted: 05.12.2018

PRACA ORYGINALNA
ORIGINAL ARTICLE

SUPERFICIAL CANDIDOSIS COURSE IN PATIENTS WITH CARBOHYDRATE METABOLISM DISORDER AND DIABETES MELLITUS

PRZEBIEG POWIERZCHOWNEJ KANDYDOZY U PACJENTÓW Z ZABURZENIAMI METABOLIZMU WĘGLOWODANÓW I CUKRZYCĄ

Orysya O. Syzon, Solomiya A. Turkevych, Tetyana I. Rudnyk, Svitlana V. Volbyn, Marianna O. Dashko
DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

ABSTRACT

Introduction: One of the pressing issues of modern dermatology is the prevalence of diseases of skin and mucous membranes caused by yeast-like fungi.

The aim: To study specific features of the course of skin and mucous membranes superficial candidosis against the background of initial carbohydrate metabolism disorders or diabetes mellitus.

Materials and methods: We have examined 93 patients aged 18-75 suffering from superficial candidosis. Candidosis was diagnosed based on anamnesis data, results of clinical tests and laboratory studies. The study of carbohydrate metabolism included determining of the glucose level under fasting conditions to establish possible diabetes mellitus and glucose tolerance test (75 g glucose load), glycosylated hemoglobin (Hb_{A1c}) and fructosamine (FR).

Results: In patients with mild and moderate candidosis we have detected an increased rates of Hb_{A1c} and fructosamine, as compared with the like indicators received in the control group, by 1.54 and 1.21 times respectively. In patients with severe candidosis and relapses the concentrations of Hb_{A1c} increased by 2.59 times, FR – by 2.26 times against the indicators received in the control group. Thus, increased levels of blood glycosylated protein indicate the pathogenetic importance of these processes in the development of candidosis.

Conclusions: Consequently, increased levels of blood glycosylated protein indicates the pathogenetic importance of these processes in the development of candidal lesions. Tests for Hb_{A1c} and FR proved to be sensitive and allow reliable detection of individuals with diabetes mellitus and glucose intolerance among candidosis patients.

KEY WORDS: mycoses, superficial candidosis, carbohydrate metabolism disorder, diabetes mellitus

Wiad Lek 2019, 72, 1, 68-71

INTRODUCTION

According to the WHO, more than a quarter of the Earth's population suffers from mycosis, and mycotic lesions cause a variety of skin and mucosal diseases, often of severe and prolonged course, with frequent relapses [1,2,3]. Recently, Ukraine has also witnessed a significant increase in the incidence of mycoses, a tendency towards the development of complicated forms, which lead to the long-term labour capacity loss [4]. Sensitizing effect produced by mycosis agents on a body can cause mycosis eczema, allergic vasculitis, etc. [5].

Damages of skin, its appendages and visible mucous membranes by potentially pathogenic agents, i.e. Candida fungi, are commonly referred to as the "superficial candidosis". These fungi are the part of the body normal microflora and are saprophytes found on skin, its appendages and mouth mucous membranes. In candidosis pathogenesis, factors of endogenous and exogenous nature contributing to the transformation of Candida from its vegetative form to the pathogenic one are distinguished [6,7,8]. At that, the crucial importance belongs to such endogenous factors as the age of patients, metabolic disorders, hypovitaminosis, the presence of common infections, chronic somatic and oncological diseases, various gastrointestinal pathologies, as well as side effects occurred due to the long-term use of antibiotics, corticosteroids [2,3].

The effect of such a factor as carbohydrate metabolism disorder on candidosis development should be noted separately since in hyper-glycaemia conditions yeast-like fungi intensively propagate actively using sugar for their own metabolic processes [5,9]. The carbohydrate metabolism disorder is testified by the of blood glucose concentration [10 11, 12], i.e. labile indicator reflecting the carbohydrate metabolism status at the time of the study. At that, for a diagnostic purpose, the level of fasting glycaemia and urine glucose is measured, and glucose tolerance tests are performed. However, the informativity of such tests is rather low, in particular, the level of blood glucose indicates glycaemia for the last 10-15 minutes, and the level of urine glucose – for over the past 5-6 hours [13,14,15]. In turn, changes in the rhythms of endocrine regulation at carbohydrate metabolism disorders often show an erroneous picture of improvement with repeated determinations of blood glucose concentration, which requires the use of additional tests of glucose tolerance [16].

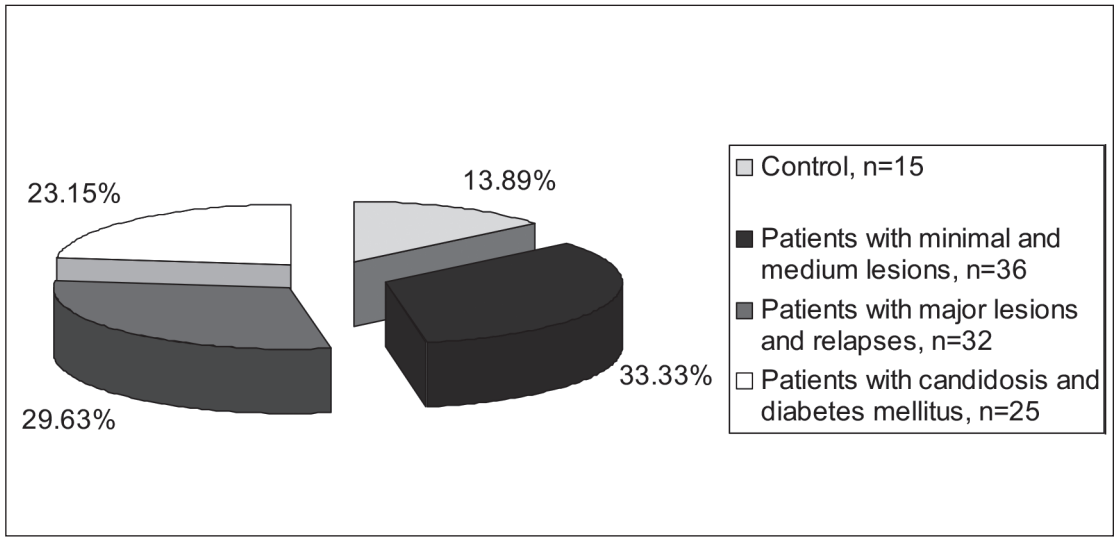


Fig. 1. Distribution of patients per the candidosis lesions severity grade

Table I. Distribution of patients per the clinical forms of candidosis lesion

Clinical form	Males		Females		Total
	Indiv.	%	Indiv.	%	Indiv.
Candidiasis of large folds	17	32.69	35	67.31	56
Candidiasis of hand and foot interdigital folds	5	41.67	7	58.33	12
Oral candidosis	3	20.00	12	80.00	15
Balanoposthitis candidosis	5	100	0	0.00	5
Candidal paronychia and onychomycoses	2	22.22	7	77.78	9

THE AIM

To study the specific features of superficial candidosis course in respect of the skin and mucous membranes against the initial carbohydrate metabolism disorders or the presence of diabetes mellitus.

MATERIALS AND METHODS

To determine the parameters of carbohydrate metabolism and their effects on the superficial candidosis course we examined 93 patients with superficial candidosis aged 18-75 years including 32 (34.41%) males and 61 (65.59%) females. The control group consisted of 15 practically healthy persons, out of them 4 (26.67%) men and 11 (73.33%) women (Figure 1). The distribution of patients per the lesion clinical forms is presented in Table. I.

The candidosis diagnosis was based on the anamnesis, results of clinical examinations and laboratory tests that included microscopic examination of scrapings from skin folds, oral mucosa and nail plates, as well as mycological (cultural and microscopic) studies.

The study of carbohydrate metabolism included determining the level of fasting glucose to detect the manifested diabetes mellitus, glucose tolerance test (with 75 g glucose load). In 32 patients, glucose intolerance was detected, therefore they were additionally determined by the level of glycosylated haemoglobin (Hb_{A1c}) and fructosamine (FR). The content of Hb_{A1c} was determined through ion-exchange chromatographic method in whole blood. The content of FR was determined through colorimetric-kinetic method in serum and in blood plasma. Blood was sampled under fasting condition from the basilic vein, the study was carried out immediately after sampling. Sentinel CH test system by Intero (Italy) and spectrophotometer with a 405-425 nm filter were used to perform studies.

The study results were processed via generally accepted statistical methods.

RESULTS AND DISCUSSION

Diabetes mellitus is a major risk factor for fungal infections, and mortality increases when diagnosis and treatment of fungal infections are delayed in diabetic patients. The most common fungal infections in diabetic patients are candidiasis [7,8].

Manifestations of candidosis were detected in patients at different areas of their skin and visible mucous membranes, predominantly in the areas of large skin folds (60.22%), oral candidosis (16.13%), and candidosis of interdigital folds (12.90%). Less commonly, candidal paronychia of hand fingers and onychomycosis (9.68%) and candidal onychomycosis (5.38% among all the examined or in 16.80% men) were detected.

The performed studies have shown that in examined patients among the concomitant diseases various pathologies

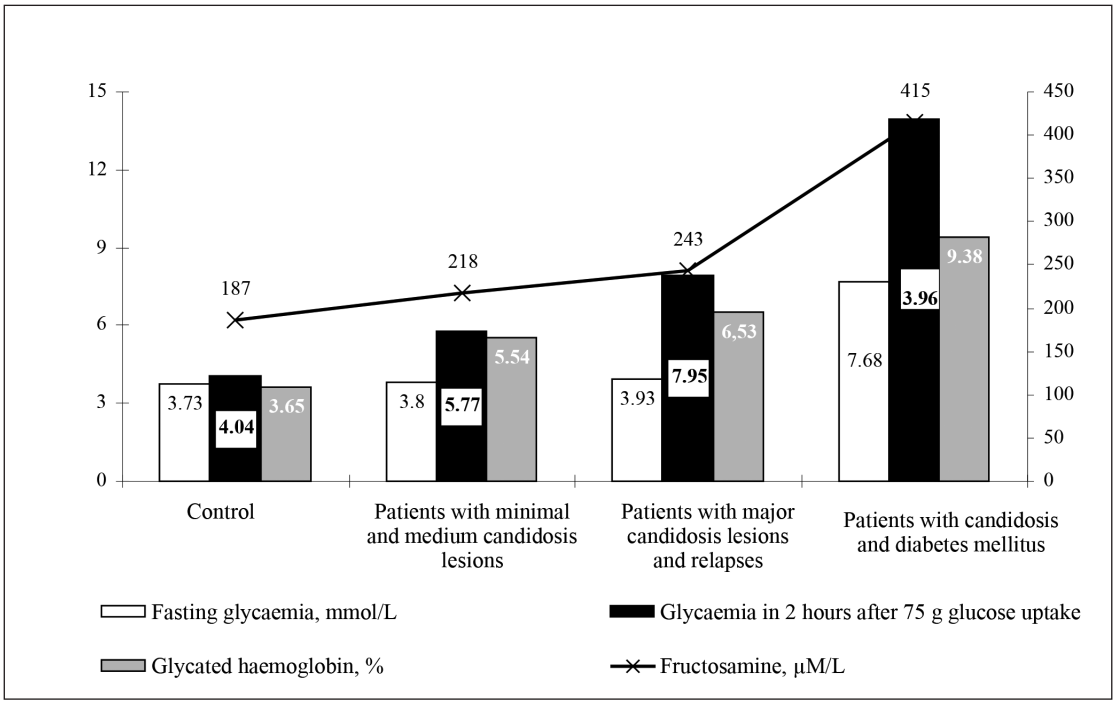


Fig. 2. Carbohydrate metabolism rates in patients of control and study groups

of endocrine (diabetes mellitus – in 15% of the examined, and among patients with excess body weight and obesity - in 36%) and cardiovascular systems (ischemic heart disease – in 14%, varicose lesions – 11%, arterial hypertension – in 15% of examined patients) predominated.

In patients under the age of 50, fasting glucose rates were within the normal range, and in patients aged 50-65 years and in patients older than 66 years, these rates were 4.15±0.24 mmol/L and 6.38±0.20 mmol/L, respectively. Also, among patients aged 50-65 years, 5 individuals were diagnosed with type 2 diabetes, in patients older than 66 years - 9 individuals.

According to the study results, it was established that in the control group all carbohydrate metabolism parameters were within the normal range (Figure 2).

The fasting glycaemia rates in patients with minimal and medium candidosis lesions were within the norm (3.80±0.015 mmol/L). In patients with major candidosis lesions and relapses the rates reached 3.93±0.024 mmol/L. In 15 patients with concomitant pathology in the form of diabetes mellitus the fasting glycaemia rates were 7.68±0.082 mmol/L. Thus, a comparative analysis of fasting glycaemia rates in patients with candidosis lesions affirmed that fasting glycaemia rates depend on the patients' age and degree of lesion severity.

At the same time, due to the insufficient informativity of glycaemic testing additional study was required. In this case, patients with the confirmed diabetes mellitus underwent a glucose tolerance test upon having a trial breakfast. In patients with minimal and medium candidosis lesions the glycaemic rates of in 2 hours after intake of 75 g of glucose were 5.77±0.149 mmol/L, in patients with major candidosis lesions and relapses – 7.95±0.174 mmol/L (which allowed detecting latent diabetes mellitus in 13 patients for the first time), respectively. In the group of patients with candidosis and affirmed diabetes mellitus, glycaemic rates were the highest and amounted to 13.96±0.57 mmol/L.

The evaluation of the stability of carbohydrate metabolism disorders was determined via the degree of blood proteins glycosylation. It is known, that half-life of blood haemoglobin lasts about 120 days, during which it gradually becomes glycosylated. The high informativity of this test is determined by the independence of the Hb_{A1c} level from exercises, dietary preferences, and the use of medicines, and it permits to record even minor carbohydrate tolerance disorders. Therefore, Hb_{A1c} content is considered an integral characteristic of the glycaemic level for the past 3-4 months. The half-life period of the glycosylated albumin is 20 days, and the determination of fructosamine content in blood reflects the average level of glucose in blood over the last 2-3 weeks.

The study has shown that in the group of patients with candidosis lesions there is a direct dependence of Hb_{A1c} and fructosamine on the disease severity. Thus, in patients with minimal and medium candidosis lesions an increase in Hb_{A1c} and fructosamine values was observed as compared to the same rates in the control group by 1.54 and 1.21 times, respectively, in patients with major candidosis lesions and relapses the concentration of Hb_{A1c} increased by 2.59 times, and FR – by 2.26 times in relation to the rates of the control group. Thus, we have justified a direct correlation between the degree of candidosis severity and the levels of glycosylated haemoglobin and fructosamine.

Hence, the detection of increased levels of glycosylated blood proteins indicates the pathogenetic importance of these processes in the development of candidosis lesions. The determination of Hb_{A1c} and FR is a sensitive test that

can reliably detect individuals with diabetes mellitus and glucose intolerance among candidosis patients.

The detection of these correlation patterns is an important element in the development of a comprehensive pathogenetically valid treatment of patients with skin and mucous membrane candidosis lesions.

CONCLUSIONS

The results of the study have shown that in patients with anamnestic diabetes mellitus the clinical manifestations of candidosis were more pronounced than in those patients who did not suffer from this pathology. Superficial candidosis against the background of diabetes mellitus was of a disseminated course, characterized by intense itching and expressed inflammatory reaction, and eczematization and frequent relapses were observed.

In patients with minimal and medium candidosis lesions, glucose intolerance was not detected, and there was no correlation between Hb_{A1c} and FR rates and the intensity of candidosis lesions. At the same time, there was a direct correlation between Hb_{A1c} and FR rates and the intensity of candidosis lesions in patients with impaired glucose tolerance, which allows using it as an additional diagnostic criterion for early forms of diabetes mellitus. Therefore, as a result of the studies, there was an undoubted direct correlation between the degree of lesions in patients with superficial candidosis and Hb_{A1c} and FR established.

REFERENCES

1. Lichtenstern C, Herold C, Mieth M et all. Relevance of Candida and other mycoses for morbidity and mortality in severe sepsis and septic shock due to peritonitis. Mycoses. 2015;58(7):399-407
2. Chen S.C., Sorrell T.C. Newdrugs, olddrugs. Antifungalagents. Med. J. Austral.2007;187(7):404-409.
3. Gupta A.K. Dermatophytes: diagnosis and treatment. J. Am. Acad. Dermatol. 2006;54(6):1050-1055.
4. Kutsenko I.V. Principles of rational treatment of superficial skin candidosis. Ukrainian Journal of Dermatology, Venereology, Cosmetology. 2005:3 (18):52-54.
5. Turkevych S.A. Disorders of carbohydrate metabolism in patients with superficial candidosis of skin and mucous membranes. Ukrainian Journal of Dermatology, Venereology, Cosmetology. 2006;4:51-54.
6. Sokolova G.A., Yarobkova N.D., Mirzabalaeva A.K. et all.: Epidemiology, pathogenesis, clinic and therapy of candidosis in patients with diabetes mellitus. Annals of Dermatology and Venereology. 1999;2:64-66.
7. Man A, Ciurea C.N., Pasaroiu D. et al. New perspectives on the nutritional factors influencing growth rate of Candida albicans in diabetics. An in vitro study. Mem Inst Oswaldo Cruz 2017;112(9):587-592.
8. Na Ra Yun Fungal Infection in Patients with Diabetes Mellitus. J Korean Diabetes. 2017;18(1):20-25.
9. Garcia Nava R.E., Rodriguez Moctezuma R., Mungula Mirand C. et al.: Comparacion de la glucemia en ayuno y doshoras postpradial en control de pacientes con diabetes. Rev. Invest. Clin. 2003:55(1):26-30.
10. Lee CMY, Colagiuri R, Magliano DJ, et al. The cost of diabetes in adults in Australia. Diabetes Research and Clinical Practice. 2013;99(3): 385-90
11. Varkonyi T, Putz Z, Keresztes K, et al. Current options and perspectives in the treatment of diabetic neuropathy. Current Pharmaceutical Design. 2013;19(27):4981-5007.
12. Pace R., Brazeau A.-S. Meltzer S. et al. Conjoint Associations of Gestational Diabetes and Hypertension With Diabetes, Hypertension, and Cardiovascular Disease in Parents: A Retrospective Cohort Study. American Journal of Epidemiology. 2017;10(186):1115–1124.
13. Harris Maureen I., Flegal Katherine M., Cowie Catherine C. et al.: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. Diabetes Care. 1998;21(4):518-524.
14. Shaw J.E., Zimmet P.Z., Hodge A.M. et al.: Impaired fasting glucose. How low should it go? Diabetes Care. 2000;23(1):34-39.
15. Madsbad S, Holst J. Glycaemic control and weight loss with semaglutide in type 2 diabetes. The Lancet Diabetes and Endocrinology. 2017;5:315-317
16. Kosukhin A.B., Kim E.A., Keshileva Z.B. et all. The significance of detection of non-enzymatic glycosylated haemoglobin in dermatologic clinic. Annals of Dermatology and Venereology. 1998:1:30-33.

Authors' contributions:
According to the order of the Authorship.
Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Marianna Dashko
Department of Dermatology, Venereology,
Danylo Halytsky Lviv National Medical University
Konovalets str., 1, 79014, Lviv, Ukraine
tel: +380677691977
e-mail: mariannadashko@gmail.com

PRACA ORYGINALNA
ORIGINAL ARTICLE

PECULIARITIES OF PRENATAL VAGINA MORPHOGENESIS

CHARAKTERYSTYKA MORFOGENEZY POCHWY W OKRESIE PRENATALNYM

Tetiana V. Khmara[1], Ihor I. Zamorskii[2], Mariana O. Ryznychuk[3], Mariana I. Kryvchanska[4], Oleh M. Boichuk[1], Roman R. Dmytrenko[5]

[1] DEPARTMENT OF HUMAN ANATOMY NAMED AFTER MG TURKEVICH, HIGHER STATE EDUCATIONAL ESTABLISHMENT OF UKRAINE "BUKOVINIAN STATE MEDICAL UNIVERSITY", CHERNIVTSI, UKRAINE
[2] DEPARTMENT OF PHARMACOLOGY, HIGHER STATE EDUCATIONAL ESTABLISHMENT OF UKRAINE "BUKOVINIAN STATE MEDICAL UNIVERSITY", CHERNIVTSI, UKRAINE
[3] PEDIATRICS AND MEDICAL GENETICS DEPARTMENT, HIGHER STATE EDUCATIONAL ESTABLISHMENT OF UKRAINE "BUKOVINIAN STATE MEDICAL UNIVERSITY", CHERNIVTSI, UKRAINE
[4] MEDICAL BIOLOGY AND GENETICS DEPARTMENT, HIGHER STATE EDUCATIONAL ESTABLISHMENT OF UKRAINE "BUKOVINIAN STATE MEDICAL UNIVERSITY", CHERNIVTSI, UKRAINE
[5] DEPARTMENT SURGICAL DENTISTRY AND MAXILLAR-FACIAL SURGERY, HIGHER STATE EDUCATIONAL ESTABLISHMENT OF UKRAINE "BUKOVINIAN STATE MEDICAL UNIVERSITY", CHERNIVTSI, UKRAINE

ABSTRACT

Introduction: The rapid development of perinatal gynecology requires from the anatomists comprehensive studies of the patterns of prenatal morphogenesis and the development of topographic and anatomical relationships of female reproductive organs in the human fetuses of different age groups.

The aim: To study the development and formation of the vaginal topography in the prenatal period of human ontogenesis.

Materials and methods: The study has been conducted based on 23 series of histological and topographic-anatomical sections of human prefetuses aged 9-12 weeks with 31.0-80.0 mm of crown-rump length (CRL) and 83 specimens of female human fetuses aged 4-9 months with 81.0-345.0 mm of CRL by means of a complex of adequate morphological methods of investigation.

Results and conclusions: Vaginal formation occurs during the 9th week of embryogenesis (prefetuses of 31.0-41.0 mm of CRL) due to the fusion of two different embryonic structures: mesodermal paramesonephral ducts and endodermal urogenital sinus. In this case, the caudal regions of the paramesonephral ducts are transformed into the uterus and the superior two thirds of the vagina, and the inferior third of the vagina develops from the urogenital sinus.

Common uterovaginal canal, divided into right and left cavities by mesenchymal septum, is formed in the female prefetuses of 38.0-43.0 mm of CRL due to the fusion of the caudal regions of the paramesonephral ducts in the area of the posterior wall of the urogenital sinus. Complete dissolving of the septum of the uterovaginal canal occurs in prefetuses of 55.0-58.0 mm of CRL. The anterior and posterior vaginal vaults of the same depth are formed in 5-month-old fetuses. Canalization of vagina in the caudo-cranial direction is observed in the fetuses of 170.0-185.0 mm of CRL, with no clear boundary between the uterovaginal canal and the urogenital sinus. The vaginal epithelium in the upper third part originates from the uterovaginal canal, and in the lower two thirds of the vagina – from the urogenital sinus.

In the 6-month-old fetuses there was detected the variability of the shape of the superior, middle and inferior third of the vagina, namely: oval (5 cases), elongated-oval (2 cases), stellate (1 case); in the lower third, the H-shaped form was predominantly found (6 fetuses).

The proliferation of the hymen membrane occurs in fetuses of 220.0-245.0 mm of CRL. The absence of timely proliferation of the hymen membrane can lead to its atresia, and its premature proliferation causes the appearance of transverse vaginal septa.

KEY WORDS: vagina, development, topography, fetus, human

Wiad Lek 2019, 72, 1, 72-78

INTRODUCTION

Currently, the attention of many researchers is directed at determining the patterns of the chronological sequence of development and formation of topographic and anatomical relationships between organs and structures of different systems during the prenatal period of human ontogenesis, which is important for the elucidation of the morphological preconditions for the emergence of anatomical variants and congenital malformations [1]. The obtained and systematized embryotopographic data should play one of the decisive roles in the prevention of perinatal pathology [2, 3].

The rapid development of perinatal gynecology requires from the anatomists comprehensive studies of the patterns of prenatal morphogenesis and the development of topographic and anatomical relationships of female reproductive organs in the human fetuses of different age groups [4].

Adequate conducting of sonographic research, performing surgical operations on the fetal organs in the womb, interpreting the results of computer and magnetic resonance imaging and fetal dissections are based on objective anatomical data [3, 5]. However, there is now a paradoxical situation in which many diagnostic and therapeutic manipulations are carried out on the fetuses, but still there is a lack of systematic and generalized fetal anatomy manuals [6].

R.H. John [7] indicates that the proliferation of cells in the dorsal wall of the urogenital sinus (UGS) leads to the formation of epithelial expulsion of the entire vagina, replacing the epithelium of the uterovaginal canal up to the cervix. This conclusion is based on histological studies performed on prefetuses and female fetuses [8].

Clinical observations of full uterine and vaginal duplication, starting from vaginal vestibule, contradict the current opinion about the development of the vagina from various embryonic sources: the proximal part of the vagina – from the paramesonephral ducts (PMD), and the distal one – from the odd UGS. L.V. Adamyan, Z.N. Makyian [9] in none of their observations (in norm and with different anomalies) noted the anatomical and histological differences between the proximal and distal parts of the vagina, which would confirm their development from various embryonic sources. At the same time, the authors concluded that the uterine tubes, uterus and vagina develop from mesonephral ducts (MD). However, according to this concept, the development of vaginal vestibule occurs independently of MD and PMD. This assumption is based on the observation of the normal development of vaginal vestibule in all patients with Rokitansky-K?ster syndrome (with uterine and vaginal aplasia), with atresia of the hymen membrane and aplasia of the distal part of the vagina [10, 11]. Researchers believe that the vaginal vestibule develops from UGS, which also contradicts the development of endometrioid cysts of large vestibular glands [12, 13]. According to M. Sanchez-Ferrer, P. Acien, Sanchez Del Campo et al. hypothesis [14] the vagina develops from MD and M?ller's tubercle. PMD are brought closer until fused into a common duct and are finally connected in the region of UGS (M?ller's tubercle). The latter is the distal part of the MD. This is evidenced by the localization of markers (GZ1 and GZ2), specific for MD cell membranes, in immunohistochemical staining. Muller's tubercle was observed between these elements. A number of authors [11, 15] argue that the derivatives of MD are the source of vaginal development. Hence, the problem of normal morphogenesis of the vagina during the prenatal period of human ontogenesis remains unclear until now.

THE AIM

To study the development and formation of the vaginal topography in the prenatal period of human ontogenesis.

MATERIALS AND METHODS

The study has been conducted based on 23 series of histological and topographic-anatomical sections of human prefetuses aged 9-12 weeks with 31.0-80.0 mm of crown-rump length (CRL) and 83 specimens of female human fetuses aged 4-9 months with 81.0-345.0 mm of CRL by means of a complex of adequate morphological methods of investigation, which includes: macroscopy, manufacturing and microscopy of series of sequential histological and topographic-anatomical sections of human prefetuses, ordinary and fine preparation under the control of binocular magnifying glass, injection of vessels, three-dimensional computer reconstruction and morphometry.

The age of the objects of study was determined by B.M. Patten (1959), B.P. Khvatov, Yu.N. Shapovalov (1969) tables on the basis of CRL measurements. The study also involved the series of histological and topographic-anatomical sections of human prefetuses with 31.0-80.0 mm of CRL, as well as specimens of female urogenital organs of fetuses of various ages from the Museum of the Department of Human Anatomy named after M.H. Turkevych of Bukovinian State Medical University. Specimens of fetuses weighing over 500.0 g were studied directly in Chernivtsi Regional Children's Pathology and Anatomy Bureau. The Commission on Biomedical Ethics of Bukovinian State Medical University revealed no moral and legal violations during medical scientific research.

RESULTS

In the result of conducted study it was determined that vaginal formation occurs during the 9th week of embryogenesis (prefetuses of 31.0-41.0 mm of CRL) due to the fusion of two different embryonic structures: mesodermal PMD and endodermal UGS. In this case, the caudal regions of the PMD are transformed into the uterus and the superior two thirds of the vagina. The inferior third of the vagina develops from the UGS, in particular, from the area where M?ller's tubercle develops.

Common uterovaginal canal, around which there is a pronounced concentration of mesenchymal cells, is formed in the female prefetuses of 38.0-43.0 mm of CRL due to the fusion of the caudal regions of the PMD in the area of the posterior wall of the UGS. Mesenchymal septum divides uterovaginal canal into right and left cavities, which have the appearance of fissures. The thickness of the septum of the uterovaginal canal in the superior and inferior regions ranges from 38 to 44 μm, and in the middle region it equals to 26-29 μm. After the formation of the Y-shaped uterovaginal canal, its caudal end enters the dorsal wall of the UGS, resulting in the development of the protuberance – M?ller's tubercle. From the latter in its distal region there is the beginning of the formation of the vestibular bulb. Vestibular bulbs are paired endodermal protrusions, which, in the form of taenia, arise from the UGS to the caudal regions of the uterovaginal canal, and participate in the vaginal structures formation. The structures of the vaginal wall, along with the vestibular bulbs, separate the UGS to the

level of the perineum. Such a transformation leads to the corresponding anatomical position of the female urethra.

Dissolving of the mesenchymal septum of the uterovaginal canal begins in the female prefetuses of 44.0-53.0 mm of CRL, at the same time the thinning of its middle part occurs, and at subsequent stages (prefetuses of 55.0-58.0 mm of CRL) complete dissolving of the septum is observed (Fig. 1).

The superior vertical sections of the urogenital taenia in female prefetuses of 62.0-66.0 mm of CRL due to the reduction of MD, involve predominantly PMD, which are divided by a loose mesenchymal layer. Fallopian tubes develop from these PMD sections. Oblique (middle) PMD sections are transformed into the intrauterine portions of the fallopian tubes. The inferior PMD sections are transformed into the uterus and the upper two thirds of the vagina. Uterovaginal canal is lined with a pseudo-multirow cylindrical epithelium, outside of which there is a considerable layer of densely located mesenchymal cells (Fig. 2). There also appears a significant accumulation of mesenchymal cells between the bladder and the rectum.

In 4-month-old female fetuses the posterior surface of the bladder adjoins the body and cervix of the uterus. The latter in relation to the vagina is tilted to the front at an obtuse angle. The vagina is tube-shaped, filled with a white mushy mass. The supravaginal portion of the cervix is covered by a peritoneum and is separated from the inferior portion of the posterior wall of the bladder by a minor layer of loose cellular tissue. The peritoneum from the superior-posterior surface of the bladder passes to the anterior surface of the uterus, forming a cystic-uterine excavation. The latter has a fissure-like appearance 5.0-7.5 mm deep at the sagittal section. Longitudinal plicae of the mucous membrane of the uterus are absent. The uterine fundus in 4-month-old fetuses is not developed and is located below the level, where fallopian tubes arise. In most fetuses, the superior minor portion of the vagina adjoins the inferior part of the posterior wall of the bladder and is separated from it by a thin layer of loose cellular tissue. The latter in the pelvic section forms a flexure with convexity towards the posterior surface, and at the transition to the peritoneal section – with a backward convexity. In the frontal plane, the rectum forms two lateral flexures, which, in their convexity, are directed to the right and to the left. The rectum is more or less filled with meconium. The muscle-constrictor of the vagina, 2.8-4.5 mm in length, is represented by single fibers, which in the form of a band envelop the vaginal vestibule and cover the vestibular bulbs. The muscle-levator of the anus is usually quadrangular in shape. The internal (medial) bundles of the pubococcygeal muscle, as a part of the muscle-levator of the anus, are closely adjacent to the lateral walls of the urethra and the vagina and are attached to the anterior and lateral walls of the rectum. In 4 out of 6 examined 4-month-old female fetuses, the medial bundles of the pubococcygeal muscle inosculate with the posterior part of the lateral walls of the vagina (Fig. 3, 4).

In 5-month-old fetuses vagina is located in the lower part of the minor pelvis, in front of it there is the fundus of the bladder, and the urethra is below it. Female urethra is a short, slightly curved tube, which begins with the internal ostium of the urethra and opens on the front of the vaginal opening (Fig. 5). The length of the urethra in the 5-month-old fetuses is 10.09±0.1 mm. The peritoneum, covering the superior part of the posterior wall of the vagina, passes to the rectum. Large pudendal lips represent the skin folds, located in the sagittal plane. Small pudendal lips near the upper ends of which there is a clitoris are located medially to the large pudendal lips. In the clitoris, at this stage of development, the head, body and crura are determined. The latter are attached to the lower branches of the pubic bones. The clitoris is divided into two halves – cavernous bodies and is surrounded by a thin fascia that passes over to the pubic symphysis. Blood supply of the vagina is provided by the branches of the uterine, lower bladder, medial rectal and internal pudendal arteries. External female genital organs are supplied with blood by the branches of internal and external pudendal arteries.

At this stage of development, longitudinal folds of the mucous membrane of the uterine cavity are observed. The cervix of the uterus related to vagina is bent towards the front at an obtuse angle of 110-160°. The supravaginal part of the cervix is covered by a peritoneum and separated from the lower part of the posterior wall of the bladder with a small layer of loose cellular tissue. The distance from the fundus of the cystic-uterine excavation to the anterior vault ranges from 3.2 to 4.8 mm. The cystic-uterine excavation in the sagittal section has a fissure-like appearance. The rectum is adjacent to the posterior surface of the uterus, and is separated from it by the peritoneum, passing to the vagina. It should be noted that the peritoneum covers only the upper 1/3 of the posterior wall of the vagina. The depth of the rectal-uterine excavation is 6.0-8.8 mm. The upper part of the uterus is placed at 2.0-4.5 mm above the entrance cavity into a true pelvis, and the cervix is 4.5-7.0 mm below the entrance cavity into a true pelvis. The vaginal cavity is fissure-shaped. The anterior wall of the vagina is tightly fused to the urethra's posterior wall. The female urethra has the form of a short tube, from 7.5 to 8.3 mm in length.

The rectum is adjacent to the posterior wall of the vagina. One, at least two, longitudinal and transverse folds of the mucous membrane are detected on the anterior and posterior walls of the vagina for the first time. The inferior part of the posterior wall of the vagina and the inferior part of the rectum are tightly fused to the perineum tendon center. The latter in the form of a wedge passes between them. Minor layer of loose cellular tissue adjoins the vagina on both sides. The anterior and posterior vaginal vaults of the same depth are formed at this stage of development.

By the end of the 5th month of intrauterine development (fetuses of 170.0-185.0 mm of CRL), vaginal canalization in the caudo-cranial direction is observed, at the same time there is no clear boundary between the uterovaginal canal and the UGS. The epithelium of the vagina in the upper third is derived from the uterovaginal canal, and in the lower two thirds of the vagina – from the UGS. The

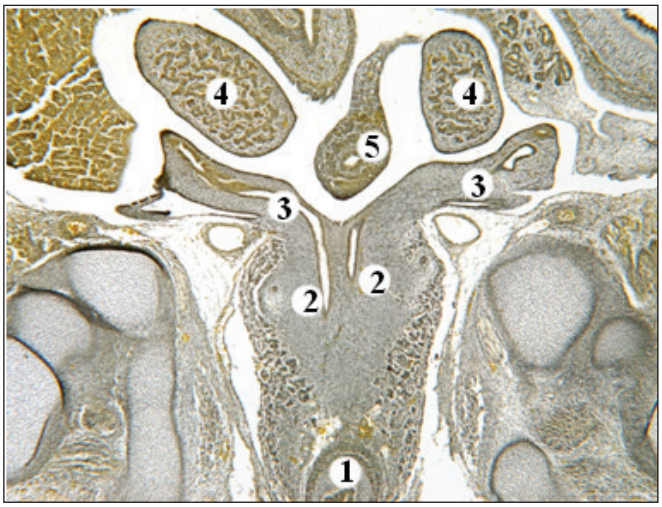


Fig. 1. Frontal section of the prefetus of 58.0 mm of CRL. Van Gieson's stain. Micro specimen. Lens 8, eyepiece 7:
1 – urethral lumen;
2 – paramesonephral ducts;
3 – mesonephral ducts;
4 – ovaries;
5 – rectum.

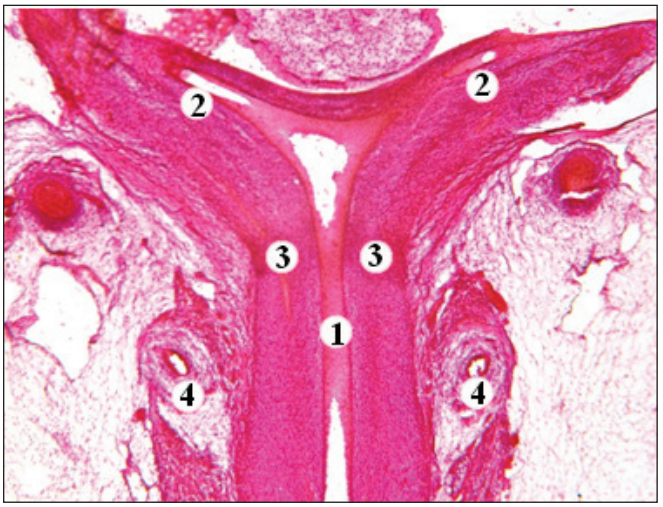


Fig. 2. Frontal section of pelvic organs of female prefetuses of 76.0 mm of CRL. Hematoxylin and eosin staining. Micro specimen. Lens 8, eyepiece 7:
1 – uterovaginal canal;
2 – paramesonephral ducts;
3 – reduced mesonephral ducts;
4 – ureters.

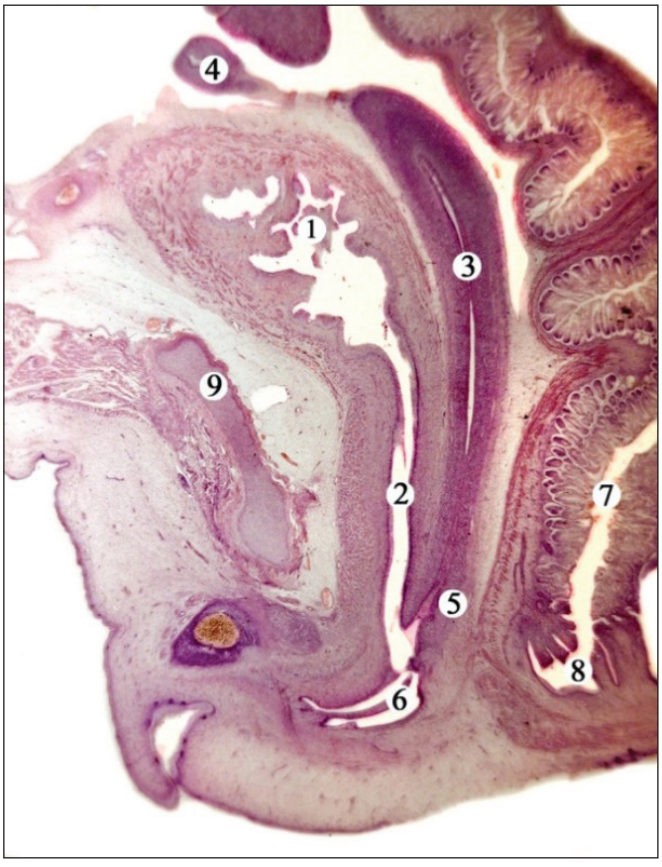


Fig. 3. Sagittal section of pelvic organs of female fetus of 110.0 mm of CRL. Micro specimen. Lens 8, eyepiece 10:
1 – bladder; 2 – urethra; 3 – uterus;
4 – uterine tube; 5 – vagina;
6 – vaginal vestible; 7 – rectum;
8 – anus; 9 – pubic bone.

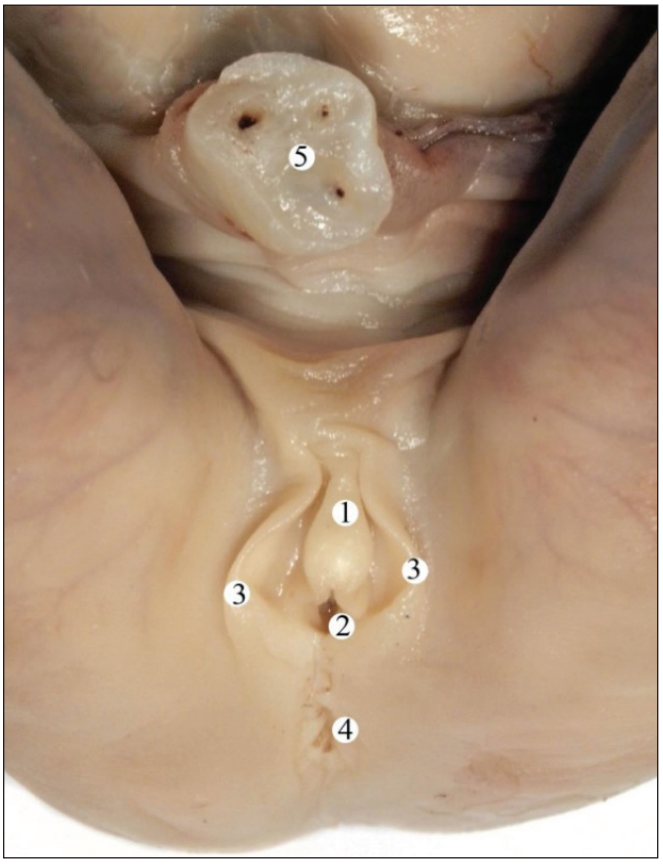


Fig. 4. External female genital organs of the fetus of 85.0 mm of CRL. Macro specimen. Magnification 3,6x:
1 – clitoris; 2 – vagina;
3 – large pudendal lips;
4 – anus; 5 – umbilical cord.

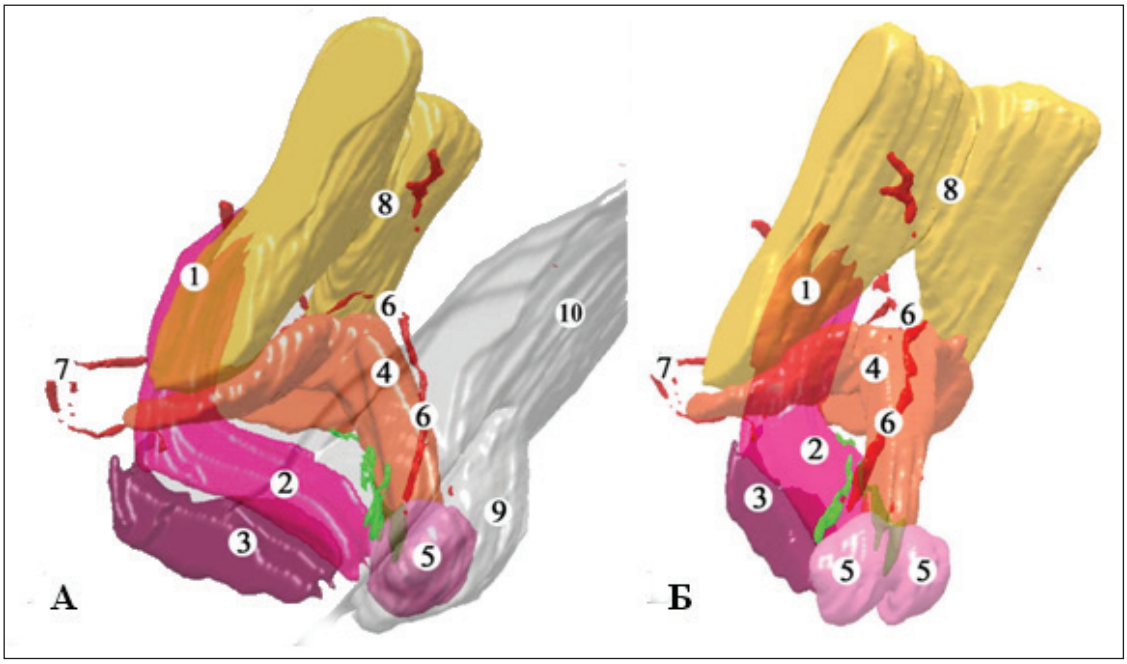


Fig. 5. Computer three-dimensional reconstruction of the pelvic organs and perineum of the female fetus of 155.0 mm of CRL. Right (A) and right anterior-lateral (B) projections. Magnification 8x:
1 – urinary bladder; 2 – urethra; 3 – vagina;
4 – clitoris; 5 – minor pudendal lip;
6 – dorsal clitoral artery; 7 – internal pudendal artery;
8 – pubic symphysis; 9 – major pudendal lip;
10 – external contours of the anterior abdominal wall.

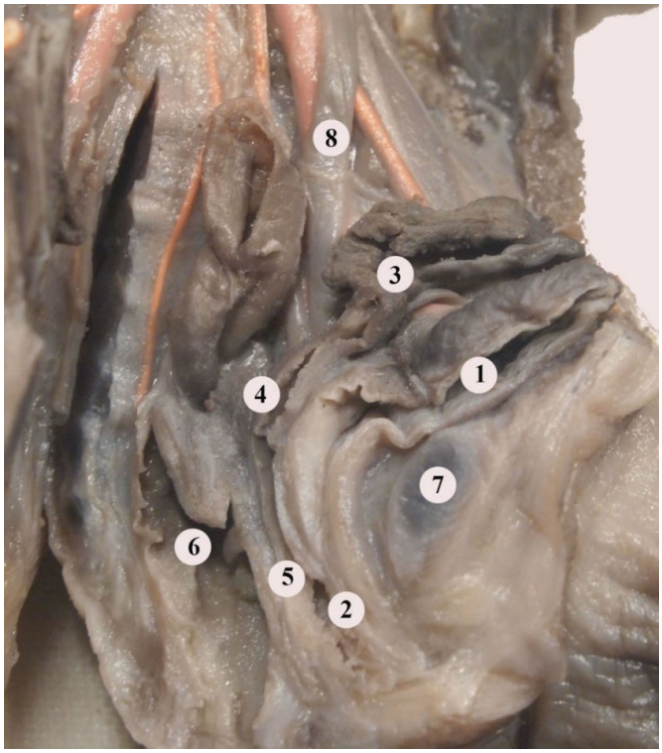


Fig. 6. Sagittal section of female fetus of 260.0 mm of CRL. Macro specimen. View from the left. Magnification 2,3x:
1 – urinary bladder; 2 – urethra;
3 – body of uterus; 4 – cervix;
5 – vagina; 6 – rectum;
7 – pubic symphysis; 8 – ureter.

fibrous-muscular wall of the vagina is developed from the surrounding mesenchyma.

In 6-month-old female fetuses in the front part of the bladder, the pubic symphysis is determined, and in the back part there is the body and cervix of the uterus, ovaries and rectum. The peritoneum extends between the urinary bladder and the uterus, forming a cystic-uterine excavation. Between the urinary bladder and the cervix the sagittal section demonstrates the bladder-cervical fissure, bounded from above by the peritoneum of the cystic-uterine excavation, in the front – by the fascia of the urinary bladder, behind – by the fascia of the cervix and from the bottom by the fusion of the cystic fascia with the cervix. The cystic-vaginal cavity, in accordance with the position of the vagina, is directed downwards and to the front. Upwards cystic-vaginal fissure reaches the fusion of the bladder fascia with the cervix. It should be noted that at the level of the urethra, the cystic-vaginal fissure is not determined, since the urethra is tightly connected with the vaginal fascia. The cystic-cervical and cystic-vaginal fissures are limited by connective tissue taenia, forming cystic-uterine ligaments.

Rectal-vaginal fissure is narrow, placed frontal and filled with loose cellular tissue. The rectal-vaginal fissure is limited by the peritoneum of the uterine-rectal excavation from above, by the fascia of the vagina in the front, and by the fascia of the rectum from the back side. On the sides, the rectal-vaginal fissure is transformed into the rectal taeniae containing vessels of the rectum, and lymph vessels of the uterus. The distance from the fundus of the cystic-uterine

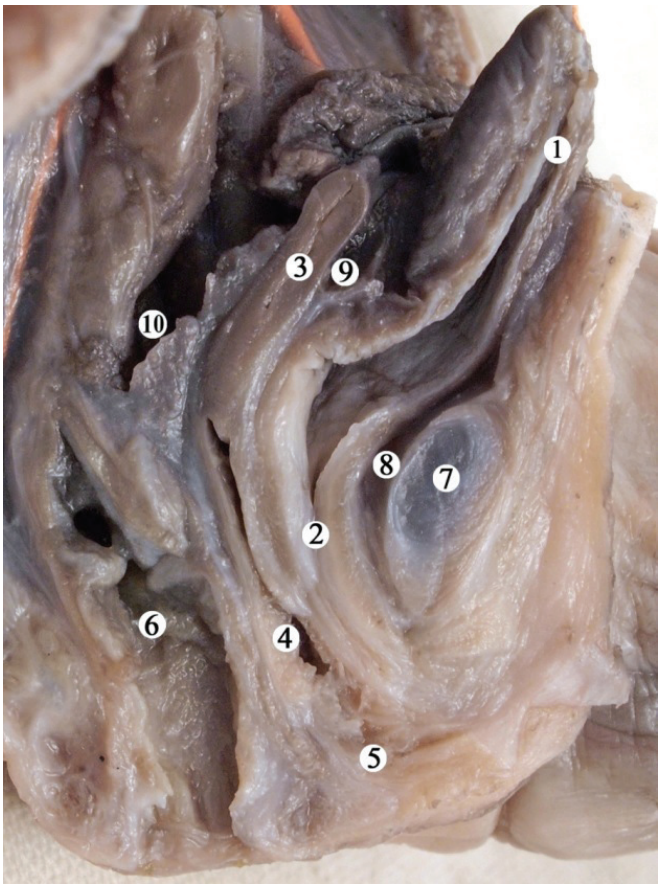


Fig. 7. Sagittal section of pelvic organs of female fetus of 290.0 mm of CRL. Macro specimen. View from the left. Magnification 3,4x:
1 – urinary bladder; 2 – urethra;
3 – uterus; 4 – vagina;
5 – vaginal vestibule; 6 – rectum;
7 – pubic symphysis;
8 – bladder-umbilical cellular space;
9 – cystic-uterine excavation;
10 – rectal-uterine excavation.

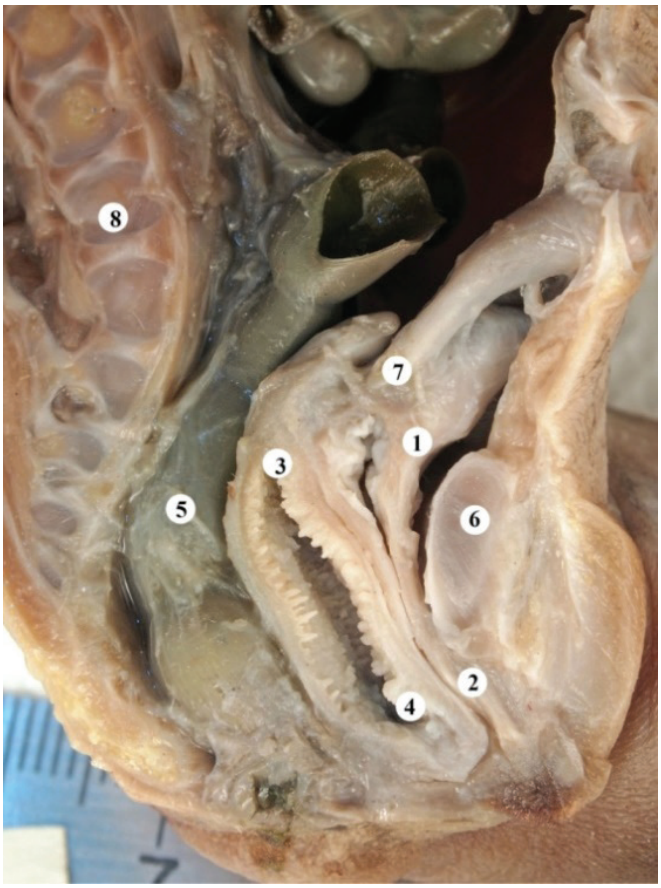


Fig. 8. Sagittal section of female fetus of 315.0 mm of CRL. Macro specimen. View from the left. Magnification 2,6x:
1 – urinary bladder; 2 – urethra; 3 – uterus; 4 – vagina;
5 – rectum; 6 – pubic symphysis; 7 – umbilical artery;
8 – vertebral column.

excavation to the anterior vault of the vagina is 4.0-6.5 mm. Transverse folds of the mucous membrane of the uterine cavity are observed for the first time at this stage of development. The cervix of the uterus is placed 5.0-7.3 mm lower than the entrance cavity into a true pelvis. It should be noted that the cervix in relation to the vagina is inclined at an obtuse angle of 110-165°. Only the superior minor part of the vagina adjoins the inferior part of the posterior wall of the urinary bladder. The variability of the shape of the vaginal cavity in the 6-month-old fetuses has been revealed. Thus, in the superior and middle third of the vagina, the following types of shape occur: oval (5 cases), elongated-oval (2 observations), stellate (1 case); in the lower third, the H-shaped form was predominantly found (6 fetuses). Transverse folds are found throughout the mucous membrane of the vagina. They are better pronounced in the region of the upper third of the vagina. In two cases (fetuses of 195.0 and 220.0 mm of CRL) of 8 examined fetuses aged 6 months the vaginal vaults were not determined at the sagittal section. The anterior wall of the vagina is tightly connected to the urethra's posterior wall. Venous outflow in female fetuses occurs into the vaginal venous plexus.

The hymen membrane is formed as a result of the expansion of the caudal vaginal regions, followed by the invagination of the posterior wall of the UGS and till the end of the fetal period of ontogenesis it serves to separate the lumen of the vagina and the UGS cavity. Hymenorrhexis occurs in the perinatal period, and its remains represent a thin duplication of the mucous membrane. In the sources of literature, there are the data that the hymen membrane is a part of the urogenital membrane. The proliferation of the hymen membrane occurs at the end of the 6^{th} – at the beginning of the 7^{th} month of prenatal development (fetuses of 220.0-245.0 mm of CRL). It should be noted that the absence of timely proliferation in the hymen membrane can lead to its atresia, and premature proliferation of the hymen membrane leads to the appearance of transverse vaginal septa.

The longitudinal and transverse folds of the mucous membrane of the uterine cavity are clearly determined in

the 7-month-old fetuses. The cervix of the uterus relatively to vagina is inclined to the front at an angle of 115-160°. The anterior uterine wall is adjacent to the lower half of the posterior wall of the bladder (Fig. 6). An insignificant layer of loose cellular tissue separates the supravaginal part of the cervix from the lower part of the posterior wall of the bladder. The peritoneum covers the upper 1/3 or 1/4 part of the posterior wall of the vagina which the rectum adjoins. The anterior wall of the vagina is adjacent to the posterior wall of the urethra. It should be noted that if in the early fetuses the vagina looked like a narrow tube, then in the 8-month-old fetuses the vagina becomes considerably wider compared to the urethra (Fig. 7).

In the fetuses of 315.0-330.0 mm of CRL the anterior wall of the vagina tightly adjoins the bladder and urethra (Fig. 8). The anterior wall of the vagina is shorter than the posterior one. 6.0-7.5 mm of the superior part of the posterior wall of the vagina is covered by the peritoneum, and its inferior part is tightly adjacent to the rectum, separating from it by the plate of the pelvic fascia. Small and large vestibular glands open between the vaginal and the external urethral ostium.

CONCLUSIONS

1. The formation of the vagina occurs during the 9th week of embryogenesis (fetuses of 31.0-41.0 mm of CRL) due to the fusion of two different embryonic structures: mesodermal paramesonephral ducts and endodermal urogenital sinus. In this case, the caudal regions of the paramesonephral ducts are transformed into the uterus and the upper two thirds of the vagina, and the lower third of the vagina develops from the urogenital sinus.
2. In the female prefetuses of 38.0-43.0 mm of CRL due to the fusion of the caudal regions of the paramesonephral ducts in the area of the posterior wall of the urogenital sinus common uterovaginal canal develops, mesenchymal septum divides it into the right and left cavities. Complete dissolving of the septum of the uterovaginal canal occurs in prefetuses of 55.0-58.0 mm of CRL.
3. The anterior and posterior vaginal vaults of the same depth are formed in 5-month-old fetuses. Canalization of vagina in the caudo-cranial direction is observed in the fetuses of 170.0-185.0 mm of CRL, with no clear boundary between the uterovaginal canal and the urogenital sinus. The vaginal epithelium in the upper third part originates from the uterovaginal canal, and in the lower two thirds of the vagina – from the urogenital sinus.
4. In the 6-month-old fetuses there was detected the variability of the shape of the superior and middle third of the vagina, namely: oval (5 cases), elongated-oval (2 cases), stellate (1 case); in the lower third, the H-shaped form was predominantly found (6 fetuses).
5. The proliferation of the hymen membrane occurs in fetuses of 220.0-245.0 mm of CRL. The absence of timely proliferation of the hymen membrane can lead to its atresia, and its premature proliferation causes the appearance of transverse vaginal septa.

REFERENCES

1. Pronyayev DV, Hmara TV. Peredumovi viniknennya porushen morfogenezu zhinochih statevih organiv Ukr. zhurnal klinichnoyi ta laboratornoyi medicini. 2013; 8(3): 162-7.
2. Akhtemiichuk YuT. Narysy embriotopohrafii. Chernivtsi: Vydavnychyi dim «Bukrek», 2008. S. 6-9.
3. Akhtemiichuk YuT. Perynatalna anatomiia yak napriam naukovykh doslidzhen. Materialy 2-ho nauk. sympoziumu Anatomo-khirurhichni aspekty dytiachoi hastroenterolohii (21 travnia. 2010, Chernivtsi) Chernivtsi, 2010. S. 5-7.
4. Pronyaev DV, Hmara TV. Fetalnaya anatomiya vnutrennih zhenskih polovyh organov. LAP LAMBERT Academic Publishing. 2014; 61 s. (Nimechchina)
5. Ahtemiychuk YuT, Slobodyan AN, Pronyaev DV. i dr. Issledovanie zakonomernostey morfometricheskih parametrov organov i struktur v perinatalnom periode ontogeneza. Mater. X kongressa assots. morfologov Funkts. morfologiya cheloveka i zhivotnyih (29-30 veresnya2010, Yaroslavl). Morfologiya. 2010; 137(4) S. 22.
6. Ahtemlychuk YuT, Slobodyan OM, Hmara TV. ta In. Narisi perinatalnoYi anatomIYi; za red. Yu.T. Ahtemlychuka. ChernIvtsI: BDMU, 2011. 300 s.
7. John RH. Vaginal agenesis and embryology of vaginal epithelium. J. Obstet. Gynaecol. 1994; 34: 562.
8. Akhtemiichuk YuT, Piatnytska TV. Embriohenez zhinochykh vnutrishnikh statevykh orhaniv ta peredumovy rozvytku pryrodzhenykh vad. Visnyk problem biolohii i medytsyny. 2010; 3: 13-9.
9. Adamyan LV, Makiyan ZN. Klinicheskiy vzglyad na embriogenez mochepolovoy sistemyi. Otsenka s pomoschyu laparoskopii, gisteroskopii, MRT. Sb.: Laparoskopiya i gisteroskopiya v ginekologii i akusherstve. M.: Pantori, 2002. S. 186-188.
10. Adamyan LV, Glyibina TM, Okulov AB i dr. Sravnitelnyiy analiz kliniko-morfologicheskih variantov anomaliy zhenskoy reproduktivnoy sistemyi s dannyimi embriologii. Problemyi reproduktsii (spetsvipusk). 2008; 151-153.
11. Adamyan LV, Kurilo LF, Glyibina TM i dr. Anomalii razvitiya organov zhenskoy reproduktivnoy sistemyi: novyiy vzglyad na morfogenez. Problemyi reproduktsii. 2009; 4: 10-9.
12. Vyisotskiy MM, Sazonova EO, Digaeva MA. K voprosu ob embriogeneze mochepolovoy sistemyi u zhenschin: klinicheskie nablyudeniya formirovaniya endometrioidnyih kist bolshoy zhelezyi preddveriya vlagalischa. Endoskopicheskaya hirurgiya. 2009; 3: 57-9.
13. Mùller IP. Anatomie des Menschen. Berlin. 1931; 272-5.
14. Sanchez-Ferrer M, Sanchez Del Campo et al. Experimental contributions to the study of the embryology of the vagina. Human Reprod. Embryol. 2006; 21: 6.
15. Acien P, Acien M, Sanchez-Ferrer M. Complex malformation of the female genital tract. New types and revision of classification. Hum. Reprod. 2004; 19: 10.

Authors' contributions:
According to the order of the Authorship.
Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Mariana Ryznychuk
Department of Pediatrics and Medical Genetics
Teatralna sq., 2, 58001, Chernivtsi, Ukraine
e-mail: rysnichuk.mariana@gmail.com

Received: 10.09.2018
Accepted: 28.12.2018

PRACA ORYGINALNA
ORIGINAL ARTICLE

PECULIARITIES OF ANTIBIOTIC-ASSOCIATED DIARRHEA DEVELOPMENT IN CHILDREN WITH ACUTE RESPIRATORY INFECTIONS

ODMIENNOŚCI ROZWOJU BIEGUNKI POANTYBIOTYKOWEJ U DZIECI Z OSTRYMI INFEKCJAMI GÓRNYCH DRÓG ODDECHOWYCH

Sergii V. Popov, Oleksandr I. Smyian, Andrii N. Loboda, Olena K. Redko, Svitlana I. Bokova, Oleksandr P. Moshchych, Viktoriia O. Petrashenko, Svitlana N. Kasian, Olena V. Savchuk
SUMY STATE UNIVERSITY, DEPARTMENT OF PEDIATRICS, SUMY, UKRAINE

ABSTRACT

Introduction: Acute respiratory infections (ARI) are the main cause of morbidity in most countries. The probability of complications and age determine antibiotics administration. Antibiotic associated diarrhea (AAD) is one of the side effects of antibiotics.

The aim: The study of the prevalence rate of AAD and the characteristics of its development in children with ARI.

Materials and methods: The study included 75 children aged from 1 to 12 y diagnosed with ARI, who were treated with age-specific doses of antibiotics. The influence of children's anamnesis, parents' health on the development of AAD was studied with odds ratio calculation (OR).

Results: In general, AAD incidence was 52%. The highest frequency 59.3% was observed in children under 3 y. AAD most often developed in children treated with amoxicillin – 92%. The greatest dependence of AAD development was connected with breastfeeding less than 6 months – OR was 7.65, preterm birth – 2.9, functional GIT disorders in anamnesis – up to 3.14, allergy – 2.33. The risk of AAD development increased with the age of parents more than 35 y – 5.03, at the age of parents less than 18 and older than 35 y – 4.09, parents' allergies - 3.74 and parents smoking - 2.43.

Conclusions: The most important factors of AAD development on antibiotics therapy in children with ARI are breastfeeding less than 6 months, functional GIT disorders and allergic conditions in anamnesis. Suboptimal age and parents' health (GIT disorders, allergic conditions and unhealthy habits) also increase the risk of AAD development.

KEY WORDS: Antibiotic associated diarrhea, children

Wiad Lek 2019, 72, 1, 79-83

INTRODUCTION

Acute respiratory infections (ARI) are the main cause of morbidity and mortality in both developed and developing countries [1; 2]. A child may have up to 6-8 cases of acute respiratory infection during a year. The incidence of acute respiratory infections is recorded throughout the year but more abundantly in the autumn and winter. Around 90% of children have respiratory pathology during flu epidemic. Viruses dominate the etiology of ARI, they are considered to constitute 55-90% of cases [3]. Respiratory syncytial virus is most often revealed. It is pointed out that it is responsible for the development of acute respiratory disease in 60% of children and in 80% of infants at the peak of viral season [4]. A number of authors emphasize the role of rhinovirus in infants (human rhinovirus, HRV), which can be detected in 38% of infants with ARI. Respiratory syncytial virus is detected less often in children of above mentioned group – 5-7% of cases. [3]. The frequency of bacterial infection at ARI in infants can reach 10%, however, the frequency of its detection depends on viruses present in the body [3]. In general, the availability of bacteria as etiological factor may be 27% for all age groups of children [1].

The probability of bacteria presence, ARI severity, duration, age and other factors condition antibiotics administration. Unfortunately, despite the high probability of complications of antibiotic therapy, the frequency of their use at acute respiratory infection is rather high. It is pointed out that it constitutes 52-66% depending on the type of ARI [1]. The number of side effects of antibiotic therapy is large and includes the development of allergic conditions, the formation of pathogenic microflora resistance, the formation of intestinal microbiome disorders and the development of antibiotic associated diarrhea (AAD).

THE AIM

The research aim is to study the prevalence rate of AAD and the characteristics of its development in children with ARI.

MATERIALS AND METHODS

We have examined 75 children aged from 1 to 12 years old diagnosed with of ARI bacterial etiology treated in in-patient department. All of them were treated with age-spe-

Table I. Prevalence antibiotic-associated diarrhea

	Group 1	Group 2	Group 3	Total
Antibiotic-associated diarrhea, n/N/%	16/27/59,3	14/29/48,3	9/19/47,4	39/75/52

Note: n - number of cases; N - total number in groups; % - percent.

Table II. Characteristics of study groups.

	Group 1d	Group 1	Group 2d	Group 2	Group 3d	Group 3
	16	11	14	15	9	10
Boys, abs/%	10/62,5	6/54,5	8/57,1	6/40,0	4/44,4	5/50,0
Age, y, M±м	1,01±0,16	1,29±0,23	4,64±0,34	4,33±0,33	10,11±1,03	10,9±0,85
Weight, kg, M±м	9,29±0,58	10,57±0,76	16,44±1,25	17,63±0,65	29,23±4,59	32,9±3,55
Height, cm, M±м	69,50±3,37	77,09±2,95	106,57±2,54	105,47±2,50	138,11±5,76	147,5±5,28

Note: M±м – Mean and Mean Error, abs/% - absolute value of the characteristic/percent of the characteristic.

cific doses of antibiotics. The children were divided into 3 groups depending on age, group 1 – children aged from 2 months to 3 years old, group 2 – children aged from 4 to 6 years old, group 3 – children aged from 7 to 12 years. Each group was divided into 2 subgroups depending on the presence or absence of AAD signs. Antibiotic-associated diarrhea was defined as 3 or more cases of loose stool after antibiotic administration [5].

The influence of some factors of children's anamnesis, the peculiarities of parents' health, their age and some habits on AAD development in a child on the background of ARI and antibiotic therapy were studied.

The obtained results were processed by descriptive statistics methods calculating average error share, mean, its error, obtaining of odds ratio (OR), calculation of significance test $\chi 2$, F-test (F), Student's t-test (r).

RESULTS

The incidence rate of antibiotic-associated diarrhea was 52% for all examined patients (Table I). There was a tendency to large values in infants, although there was no significant difference in the study groups. The highest frequency - 59.3% was noted in the children of group 1 under the age of 3 years old. The lowest value was recorded in the patients of group 3 - 47.4%. The further analysis of OR value showed that the age-dependent value less than 1 year and AAD development in group 1 was 1.75 at $p = 0.69$. The calculation of analogous dependence for three groups revealed the value of OR as 2.17 at $p = 0.34$.

AAD most often developed in children who were treated with antibiotics of penicillin line. We have treated 92% of patients with amoxicillin, who later developed symptoms of antibiotic-associated diarrhea. We have detected 86% of ADD cases in children who were treated with third generation cephalosporins. The incidence rate of AAD at macrolides therapy was the lowest – 25% of patients who took these antimicrobial drugs.

The assessment of gender composition showed a tendency for boys to prevail in groups 1 and 2 among children with antibiotic-associated diarrhea (Table II). At the same time, these differences were not significant. The maximum number of boys was in the group 1d, where they constituted 62.5%. The group 2d included less number of boys – 57.1%. At the same time, the girls predominated in the group 3d. The indices of physical development did not have significant differences in the study groups either depending on age or presence or absence of diarrhea. Nevertheless, there was a tendency to large values of mass and height in the groups of AAD children.

The value of odds ratio was studied to determine the dependence of some anamnesis features and development of antibiotic-associated diarrhea (Fig. 1). The values of OR were determined for preterm birth, previous signs of functional diarrhea and/or vomiting, intestinal colic, allergy and also breastfeeding less than 6 months. The highest value of OR was obtained for a pair of breastfeeding less than 6 months and AAD development – 7.65. The influence value of preterm birth on AAD development was 2.9. The presence of functional disorders in anamnesis also increased the risk of AAD development from 2.7 to 3.14 units. The value of dependence of AAD development on allergy was somewhat less – 2.33. All these values were significant.

The next group of indices included the hereditary history peculiarities, age and lifestyle of the parents of the studied children (Fig. 2). The greatest value of OR was determined for pairs of parents' age and AAD development. At the parents' age over 35 years old the frequency of AAD increased by 5.03 units. Odds ratio at the age of less than 18 years old was 2.91, but its value was not significant. The indices combination of parents' age less than 18 years old and older than 35 years old increased the risk of AAD development by 4.09 times. The presence of allergic conditions also increased the probability of AAD. In this case, OR was 3.74 units. In fact, the risk of AAD in children in the study groups increased by the same value at periodic bowel disorder in parents' anamnesis.

The influence of parents' smoking and alcohol on the risk AAD development in children of the study groups was

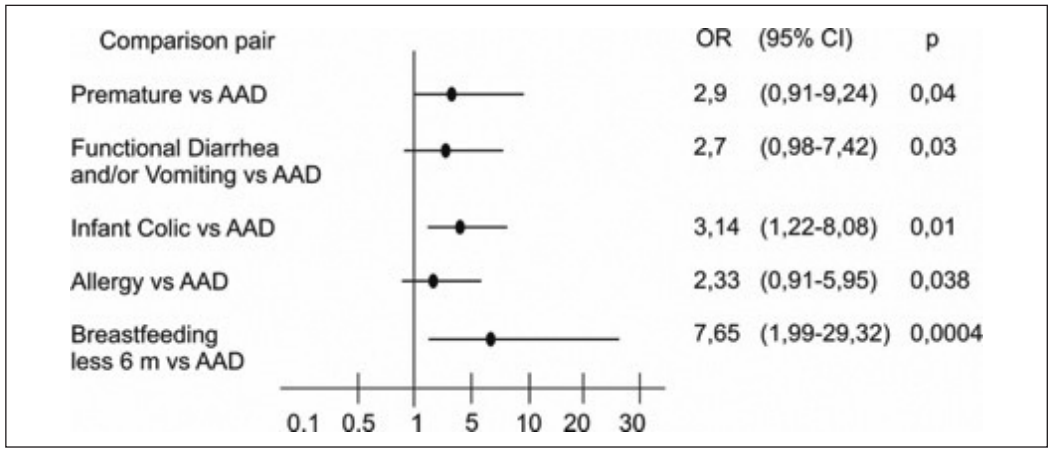


Fig. 1. Effect of selected anamnesis characteristics on development of the antibiotic associated diarrhea

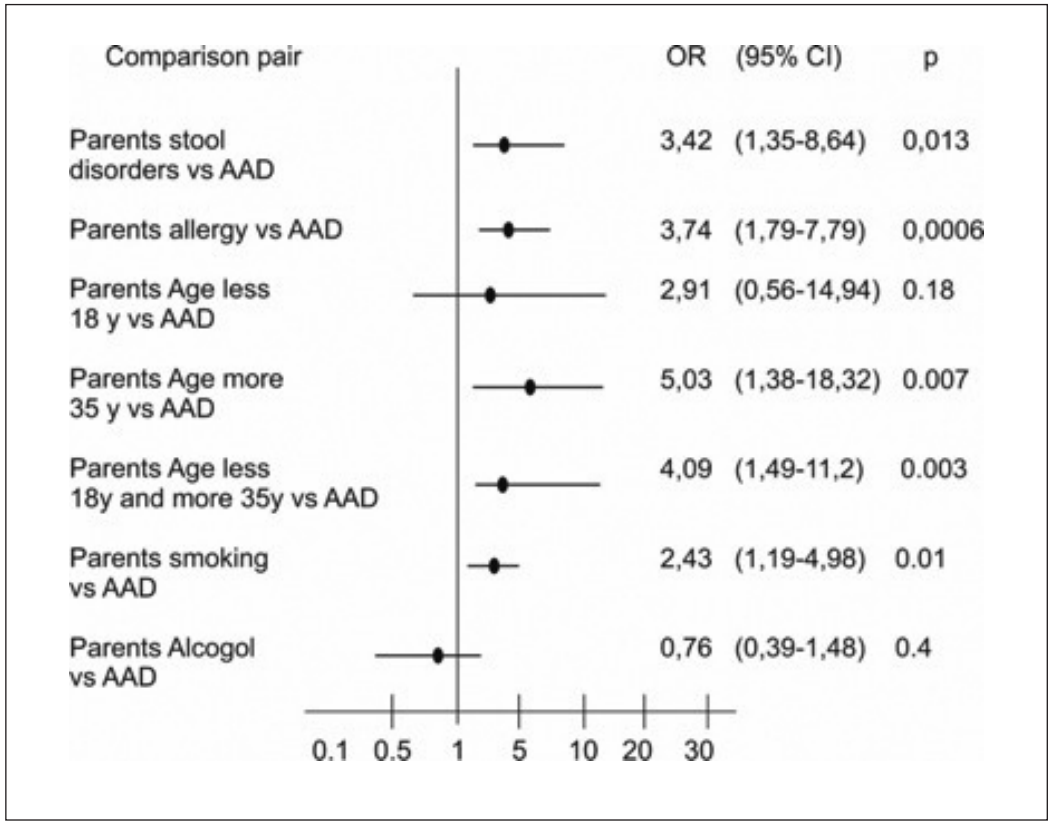


Fig. 2. Effect of selected parents' anamnesis characteristics on development of the antibiotic associated diarrhea

studied. The index in the pair of smoking – AAD appeared to be 2.43, while OR for the pair alcohol consumption – AAD was only 0.76 units.

DISCUSSION

Our data showed that the incidence rate of antibiotic-associated diarrhea was 52% in all examined children. This complies with the data of other researchers. The literature indicates that AAD frequency can be from 5 to 60% [5, 6, 7, 8]. The dependence of AAD development on age is also mentioned by some authors [9] for 2-year-old children and younger. At the same time, other researchers deny the existence of such connection [10]. Our data did not show any significant differences as to age, although such trend existed, especially for children under 1 year old according to odds ratio. The possibility of such influence can be determined by the formation of intestinal microflora, which is modulated by breastfeeding, mother's diet and introduction of complementary feeding in infants [11, 12, 13].

Among the antibiotics, amoxicillin most often caused the development of AAD, less often – cephalosporins and macrolides. The literature also indicates that amoxicillin with clavulanic acid often caused the development of AAD which is confirmed by our data [7, 9, 10].

The most significant increase in risk of AAD development was observed at breastfeeding less than 6 months. The role of breastfeeding in the development of microbiome and immune system is extremely important and crucial [14, 15]. It has been established that breast milk has its own microbiota [16]. Not only its direct transfer to a child is possible, but also the indirect influence of other factors on the microflora formation of a child such as pro- and prebiotics, oligosaccharides, immunoglobulin, immunomodulation

factors. Moreover, the effect of breastfeeding can be traced up to the age of 3 [11]. In this regard, the composition of microflora in children at breast and formula feeding is different [17, 18], which can determine the probability of antibiotic-associated diarrhea development.

An important factor in AAD development was preterm birth, OR was 2.9 units. Some scientists suggest that the peculiar features of a baby's intestinal microbiome are formed during intrauterine growth under the influence of microflora composition of uterine cavity, amniotic fluid, in some cases having an influence on preterm birth.[19, 20, 21, 22]. The peculiarities of condition, care, diseases and feeding of premature babies influence the mechanisms of microflora formation, which, possibly, leads to its greater sensitivity to antibiotics.

The duration of breastfeeding and preterm birth could affect the indices of physical development in children with antibiotic-associated diarrhea. They did not differ significantly from those in children without AAD, although there was a tendency to higher weight and height in all study groups.

A number of events of a child's life were identified, the presence of which increased the risk of antibiotic-associated diarrhea development. The presence of functional disorders such as diarrhea and vomiting increased the risk of AAD development. The cases of intestinal colic in anamnesis increased the risk of AAD development to greater degree. The pathogenesis of functional disorders development is connected not only with the dissociation "brain-intestine" relationship, but also with the changes in CNS activity, microbiota composition and immune status [23]. It is indicated that microbiota regulates and participates in the metabolism of micro- and macronutrients [24]. In addition, it is a virtual endocrine organ [25]. Thus, the features of formation and composition of microflora determine the level and characteristics of gastrointestinal tract functioning, including the development of pathological conditions. This also proves our finding that allergic conditions have significant influence on AAD development in children. It is indicated that differences in microbiota composition during neonatal period may precede the development of allergic conditions [26, 27] and, in fact, determine their development.

The parents' health, the peculiarities of life style also influenced AAD development. The significant relationship was observed between parents' allergic conditions and bowel disorders with the probable development of antibiotic associated diarrhea in a child. The role of hereditary factors in the formation of diseases is widely recognized. The results of human microbiota studies show its significant genetic predetermination, especially at initial stages, but also throughout life, which is realized through inflammatory reactions and immune response condition [27, 28]. The role of hereditary factors could be confirmed by the influence of age factor of parents on AAD development. At the age less than 18 and over 35 years old of both parents at child's birth, the probability of AAD development increased.

The presence of bowel disorders in a child and parents and their connection with AAD may indicate the role of hereditary factors in disorders formation of axis connection "brain-intestine" [23, 29]. Probably, preterm birth also plays a certain role in dissociation of this connection.

Also, the dependence of some parents' unhealthy habits on the risk of AAD development in a child was found. In particular, the influence of alcohol and smoking was studied. Smoking increased by 2 times the probability of antibiotic associated diarrhea in a child. Perhaps, this influence was mediated through the duration of feeding in socially disadvantaged families.

CONCLUSIONS

The most important factors of antibiotic-associated diarrhea development in children with ARI are breastfeeding less than 6 months as well as signs of previous functional disorders and allergic conditions.

A number of features of parents' health – bowel disorders, allergic conditions, suboptimal age of parents at child's birth, unhealthy habits – increase the risk of developing antibiotic associated diarrhea in children with ARI.

REFERENCES

1. Kronman MP, Zhou C, Mangione-Smith R. Bacterial Prevalence and Antimicrobial Prescribing Trends for Acute Respiratory Tract Infections. PEDIATRICS. 2014 Oct 1;134(4):e956–65.
2. Hall KK, Chang AB, Anderson J, Arnold D, Goyal V, Dunbar M, et al. The Incidence and Short-term Outcomes of Acute Respiratory Illness with Cough in Children from a Socioeconomically Disadvantaged Urban Community in Australia: A Community-Based Prospective Cohort Study. Frontiers in Pediatrics [Internet]. 2017 Oct 31 [cited 2018 May 9];5. Available from: http://journal.frontiersin.org/article/10.3389/fped.2017.00228/full
3. Blaschke AJ, Korgenski EK, Wilkes J, Presson AP, Thorell EA, Pavia AT, et al. Rhinovirus in Febrile Infants and Risk of Bacterial Infection. Pediatrics. 2018 Feb;141(2):e20172384.
4. Piedimonte G, Perez MK. Respiratory Syncytial Virus Infection and Bronchiolitis. Pediatrics in Review. 2014 Dec;35(12):519–30.
5. Hayes SR, Vargas AJ. Probiotics for the Prevention of Pediatric Antibiotic-Associated Diarrhea. EXPLORE: The Journal of Science and Healing. 2016 Nov;12(6):463–6.
6. Alam S, Mushtaq M. Antibiotic associated diarrhea in children. Indian Pediatr. 2009 Jun;46(6):491–6.
7. Johnston BC, Goldenberg JZ, Vandvik PO, Sun X, Guyatt GH. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2011 [cited 2018 May 9]. Available from: http://doi.wiley.com/10.1002/14651858.CD004827.pub3
8. Goldenberg JZ, Lytvyn L, Steurich J, Parkin P, Mahant S, Johnston BC. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane IBD Group, editor. Cochrane Database of Systematic Reviews [Internet]. 2015 Dec 22 [cited 2018 May 9]; Available from: http://doi.wiley.com/10.1002/14651858.CD004827.pub4
9. Turck D, Bernet J-P, Marx J, Kempf H, Giard P, Walbaum O, et al. Incidence and Risk Factors of Oral Antibiotic-Associated Diarrhea in an Outpatient Pediatric Population: Journal of Pediatric Gastroenterology and Nutrition. 2003 Jul;37(1):22–6.

10. Damrongmanee A, Ukarapol N. Incidence of antibiotic-associated diarrhea in a pediatric ambulatory care setting. J Med Assoc Thai. 2007 Mar;90(3):513–7.
11. Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, et al. Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. Cell Host & Microbe. 2015 May;17(5):690–703.
12. Cabrera-Rubio R, Collado MC, Laitinen K, Salminen S, Isolauri E, Mira A. The human milk microbiome changes over lactation and is shaped by maternal weight and mode of delivery. The American Journal of Clinical Nutrition. 2012 Sep 1;96(3):544–51.
13. Voreades N, Kozil A, Weir TL. Diet and the development of the human intestinal microbiome. Frontiers in Microbiology [Internet]. 2014 Sep 22 [cited 2018 May 27];5. Available from: http://journal.frontiersin.org/article/10.3389/fmicb.2014.00494/abstract
14. Thompson AL, Monteagudo-Mera A, Cadenas MB, Lampl ML, Azcarate-Peril MA. Milk- and solid-feeding practices and daycare attendance are associated with differences in bacterial diversity, predominant communities, and metabolic and immune function of the infant gut microbiome. Frontiers in Cellular and Infection Microbiology [Internet]. 2015 Feb 5 [cited 2018 May 27];5. Available from: http://journal.frontiersin.org/Article/10.3389/fcimb.2015.00003/abstract
15. Korpela K, Salonen A, Virta LJ, Kekkonen RA, de Vos WM. Association of Early-Life Antibiotic Use and Protective Effects of Breastfeeding: Role of the Intestinal Microbiota. JAMA Pediatrics. 2016 Aug 1;170(8):750.
16. Fernández L, Langa S, Martín V, Maldonado A, Jiménez E, Martín R, et al. The human milk microbiota: Origin and potential roles in health and disease. Pharmacological Research. 2013 Mar;69(1):1–10.
17. Torrazza RM, Neu J. The developing intestinal microbiome and its relationship to health and disease in the neonate. Journal of Perinatology. 2011 Apr;31(S1):S29–34.
18. Donovan SM, Wang M, Li M, Friedberg I, Schwartz SL, Chapkin RS. Host-Microbe Interactions in the Neonatal Intestine: Role of Human Milk Oligosaccharides. Advances in Nutrition. 2012 May 1;3(3):450S-455S.
19. DiGiulio DB. Diversity of microbes in amniotic fluid. Seminars in Fetal and Neonatal Medicine. 2012 Feb;17(1):2–11.
20. Mendz GL, Kaakoush NO, Quinlivan JA. Bacterial aetiological agents of intra-amniotic infections and preterm birth in pregnant women. Frontiers in Cellular and Infection Microbiology [Internet]. 2013 [cited 2018 May 27];3. Available from: http://journal.frontiersin.org/article/10.3389/fcimb.2013.00058/abstract
21. Gantert M, Jellema RK, Heineman H, Gantert J, Collins JJP, Seehase M, et al. Lipopolysaccharide-Induced Chorioamnionitis Is Confined to One Amniotic Compartment in Twin Pregnant Sheep. Neonatology. 2012;102(2):81–8.
22. Abdulkadir AA, Kimimasa T, Bell MJ, MacPherson TA, Keller BB, Yanowitz TD. Placental Inflammation and Fetal Hemodynamics in a Rat Model of Chorioamnionitis. Pediatric Research. 2010 Dec;68(6):513–8.
23. Mayer EA, Savidge T, Shulman RJ. Brain–Gut Microbiome Interactions and Functional Bowel Disorders. Gastroenterology. 2014 May;146(6):1500–12.
24. Bäckhed F. Programming of Host Metabolism by the Gut Microbiota. Annals of Nutrition and Metabolism. 2011;58(s2):44–52.
25. Clarke G, Stilling RM, Kennedy PJ, Stanton C, Cryan JF, Dinan TG. Minireview: Gut Microbiota: The Neglected Endocrine Organ. Molecular Endocrinology. 2014 Aug;28(8):1221–38.
26. Kalliomäki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. Journal of Allergy and Clinical Immunology. 2001 Jan;107(1):129–34.
27. Fujimura KE, Sitarik AR, Havstad S, Lin DL, Levan S, Fadrosh D, et al. Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. Nature Medicine. 2016 Oct;22(10):1187–91.
28. Koren O, Goodrich JK, Cullender TC, Spor A, Laitinen K, Kling Bäckhed H, et al. Host Remodeling of the Gut Microbiome and Metabolic Changes during Pregnancy. Cell. 2012 Aug;150(3):470–80.
29. Mayer EA, Tillisch K, Gupta A. Gut/brain axis and the microbiota. Journal of Clinical Investigation. 2015 Mar 2;125(3):926–38.

The article was carried out in the framework of research work "Regional features of the state of health and levels of morbidity among children" [0117U004937], the term of implementation till 2020, the head professor Olexander Smiyan, is carried out at Sumy State University

Authors' contributions:
According to the order of the Authorship.
Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Sergii Popov
Medical Institute,
Sumy State University
31, Sanatornaya st, 40018, Sumy, Ukraine
tel: +380668129367
e-mail: sergevit66lex@gmail.com

Received: 21.08.2018
Accepted: 19.12.2018

PRACA ORYGINALNA
ORIGINAL ARTICLE

NON-PHARMACOLOGICAL TREATMENT OF CHRONIC NECK–SHOULDER MYOFASCIAL PAIN IN PATIENTS WITH FORWARD HEAD POSTURE

NIEFARMAKOLOGICZNE METODY LECZENIA PRZEWLEKŁEGO ZESPOŁU BÓLOWEGO MIĘŚNIOWO-POWIĘZIOWEGO SZYI I BARKU U PACJENTÓW Z POSTAWĄ GŁOWY PRZODUJĄCEJ

Oleksandr A. Iaroshevskyi, Olga G. Morozova, Anna V. Logvinenko, Yana V. Lypynska
KHARKIV MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KHARKIV, UKRAINE

ABSTRACT

Introduction: Today, chronic pain remains a pressing medical and socio-economic problem, despite the rapid development of medical technologies, the presence of a vast arsenal of drug and non-drug treatments. Estimates for chronic pain prevalence ranged from 8% to 60%. At the same time, about 40% of patients report insufficient effectiveness in the treatment of chronic pain syndrome.

The aim of the study was to compare the effectiveness of MTrPS management by biomechanical correction of the musculoskeletal system combined with therapeutic exercises, DN and TrPs–pressure release with the effectiveness of MTrPS management by therapeutic exercises combined with DN and TrPs–pressure release in patients with chronic neck–shoulder myofascial pain and FHP.

Materials and methods: 87 patients (mean age – 39±4,9 years) with chronic neck–shoulder myofascial pain and FHP were randomly assigned to 2 treatment groups. Group 1 received a biomechanical correction, DN, TrPs–pressure release. Group 2 – therapeutic exercises, DN, TrPs–pressure release. Study protocol included CVA-measurement, assessment of pain intensity with VAS, assessment of QoL using MOS SF-36.

Results: increase of CVA (59,07°±1,41 in the 1st group, and 51,2°±2,01 in the 2nd group (p=0,036)), decrease of pain and decrease of influence of neck pain in performance of everyday activities, the improvement of QoL immediately after treatment occurred in both groups. However, after 3 months of therapy, 1-st group revealed more improvement than the 2-nd.

Conclusion: Comparison of the effectiveness of MTrPS management by biomechanical correction of the musculoskeletal system combined with therapeutic exercises, DN and TrPs–pressure release with the effectiveness of MTrPS management by therapeutic exercises combined with DN and TrPs–pressure release in patients with chronic neck–shoulder myofascial pain and FHP demonstrated no significant differences between the therapeutic approaches in the short term. In the medium term, the inclusion of biomechanical correction in the treatment protocol demonstrated higher efficiency compared with the combination of therapeutic exercises, DN and TrPs–pressure release.

KEY WORDS: Myofascial pain; Trigger point; Forward head posture; Biomechanical correction, Dry needling

Wiad Lek 2019, 72, 1, 84-88

INTRODUCTION

Today, chronic pain remains a pressing medical and socio-economic problem, despite the rapid development of medical technologies, the presence of a vast arsenal of drug and non-drug treatments. Estimates for chronic pain prevalence ranged from 8% to 60%. At the same time, about 40% of patients report insufficient effectiveness in the treatment of chronic pain syndrome [1, 2].

Chronic pain significantly impairs the quality of life of patients, negatively affecting their physical, mental and cognitive functioning, causing the development of anxiety and depressive disorders. Emotional stress arising from chronic pain has a detrimental effect on the fulfillment of professional, domestic responsibilities, relationships with family and friends, often leading to social isolation of patients [2, 3]. Economic losses associated with loss of productivity, job absenteeism, early retirement due to chronic pain, according to various estimates, in Europe range from three to 10% of gross domestic product [2, 4].

A special place in the structure of chronic pain belongs to musculoskeletal pain, the prevalence of which in the population is up to 68% [4, 5]. One of the most common causes of chronic non-specific neck pain is myofascial pain syndrome (MPS) [6–9], often developing due to biomechanical disorders of the musculoskeletal system, causing uneven distribution of the load on the muscles and, as a result, overloading of some and functional weakness of other muscles [11, 12].

One of the most common biomechanical disorders is the displacement of the regional center of gravity at the cervical level forward with the formation of the forward head posture, which is due to the peculiarities of the modern

lifestyle: driving a car, using smartphones, tablets, working at a computer. The development of the forward head posture results in the chronic functional overload of the muscle-extensors with the formation of myofascial trigger points (MTrPs) in them and development of myofascial pain syndrome (MPS) and myofascial pain dysfunction (MPD) of cervical – brachial localization [13].

Standard treatments which are employed in the management of MPS, include stretching the affected muscle using aerosol fluoromethane, therapeutic exercises, massage, therapeutic ultrasound, injection of local anesthetics, steroids or botulinum toxin into TrPs, TrPs–pressure release, dry needling (DN) and taking nonsteroidal anti-inflammatory drugs for the relief of pain [10, 14]. At the same time, in some researches the positive immediate effect of biomechanical correction of the musculoskeletal system, based on the use of manual therapy techniques in MPS–treatment have been reported [11, 12, 15].

THE AIM

The aim of our study was to compare the effectiveness of MTrPS management by biomechanical correction of the musculoskeletal system combined with therapeutic exercises, DN and TrPs–pressure release with the effectiveness of MTrPS management by therapeutic exercises combined with DN and TrPs–pressure release in patients with chronic neck–shoulder myofascial pain and forward head posture.

MATERIALS AND METHODS

87 patients (43 male & 44 female) aged 18–44 years with chronic neck–shoulder myofascial pain and forward head posture participated in the study. Their mean age was 39±4,9 years. The diagnosis of MPS was based on the diagnostic criteria of myofascial pain [16]. The mean duration of pain syndrome was 14 ± 2,43 months.

Inclusion criteria were: age ranges from 18 to 44 years old, presence of chronic neck–shoulder myofascial pain and FHP.

Exclusion criteria were: less than 4 months duration of MPS, damaged skin or infection in the MTrPs area, specific neck pain, cervical radiculopathy, history of previous neck surgery or whiplash injury, fibromyalgia, bleeding disorders, autoimmune connective tissue diseases, rheumatism, cardiopulmonary disease with decreased activity tolerance, renal disorders, pregnancy, receiving other treatment (drug or non-drug treatment of pain syndrome). All patients were informed about the nature of the study, procedures, risks benefits, treatment schedules and were asked to sign an Informed consent document, which corresponds to International Ethical Guidelines for Biomedical Research.

Patients participating in the study were randomly assigned to two treatment groups. Group 1 included 43 patients (22 women, 21 men), group 2 included 44 patients (22 women, 22 men). The groups were similar for age, sex and duration of pain syndrome. Study protocol included clinical–neurological, vertebro–neurological examination (visual assessment of violations of statics of the musculoskeletal system, manual diagnostics) and measurement of craniovertebral angle (CVA) using the photogrammetric method. The CVA measurement is considered to be a valid and reliable assessment tool to assess the FHP. The CVA ≥55° were considered normal. Subjects with FHP had the CVA <55° [13, 17].

The mobility of the vertebral motor segments (VMS) of the cervical spine, the presence of their functional blocking, pain and swelling of the surrounding tissues were determined using manual diagnosis. The presence of MTrPs was detected using flat palpation techniques. The Visual analogue scale (VAS) was used to measure the intensity of pain (Huskisson E. C. (1974)). Neck Disability Index (NDI) (H. Vernon, S. Mior, 1991) was used to evaluate the influence of neck pain in performance of everyday activities. The quality of life of patients was assessed using the Russian version of MOS SF-36 (Medical Outcomes Study-Short Form) (1998). Patients were assessed prior to the study, immediately after the end of therapy and 3 months after the end of therapy.

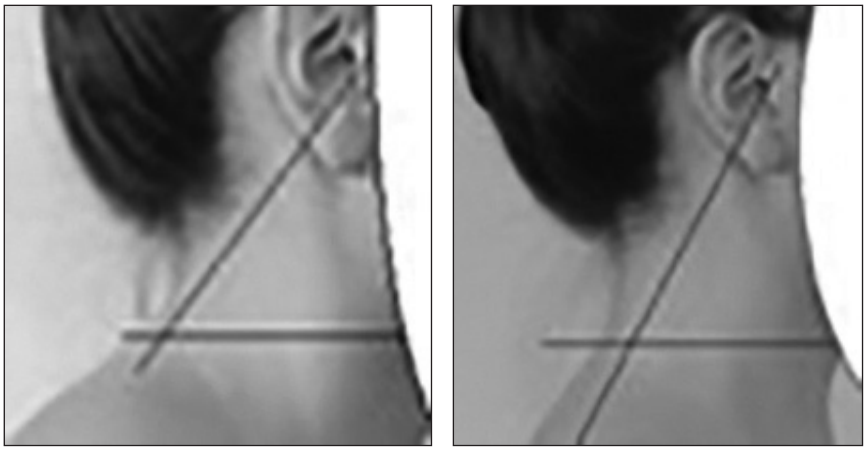
The treatment of patients of the first study group included biomechanical correction of the musculoskeletal system combined with therapeutic exercises, DN and TrPs–pressure release. Biomechanical correction of the musculoskeletal system based on the use of manual therapy techniques (joint mobilization and joint manipulation) which mechanically eliminate functional blockade of VMS and restore the physiologic range of motion in them, improve venous outflow, microcirculation, reduce soft tissue swelling and eliminate pathological afferentation from the affected VMS; musculoskeletal techniques (post-isometric, post-reciprocal, anti-gravity relaxation of the muscles, myofascial release and post-isometric spinal automobilization techniques) with the help of which the pathological consequences of functional blocking of VMS in muscles and fascia are eliminated [11, 15]. Patients received a biomechanical correction session combined with DN and TrPs–pressure release one time in 2 days. Duration of treatment: 5 sessions. Sessions of manual therapy were supplemented with individually selected therapeutic exercises aimed at consolidating the static and dynamic stereotype achieved during manual therapy, stretching the affected muscles, which contributed to the inactivation of MTrPs and the relief of pain. The number of exercises was gradually increased after deactivating the MTrPs and reducing the pain syndrome.

The treatment of patients of the 2–nd study group included therapeutic exercises combined with DN and TrPs–pressure release. The course of DN and TrPs–pressure release was five treatments over the course of 10 days. Therapeutic exercises were performed by patients daily for 10 days.

Statistical analyses were carried out in STATISTICA 10 soft–ware (Statsoft Inc., USA). The results were considered statistically significant when $p<0,05$.

RESULTS AND DISCUSSION

The main complaints of patients of both studied groups before the start of therapy were pain and stiffness in the neck



A. B.

Fig.1. Patient G., 27 years old, with chronic neck–shoulder myofascial pain and FHP.
A. – before treatment (CVA=50°), B. – after treatment (CVA=60°).

and shoulder girdle, the increase of which they attributed to the presence of long-term static loads (e.g. computer work or driving a car). Visual diagnosis of biomechanical disorders in patients of both groups revealed: displacement of the regional center of gravity at the cervical level forward with the formation of the forward head posture, compensatory enhancement of thoracic kyphosis with internal rotation of the shoulder joints, elevation of the clavicle and the entire shoulder girdle.

The mean value of the CVA in the 1-st group was 49,4°±2,02, in the 2-nd group – 49,6°±1,98. There were no statistically significant differences between groups (p=0,093).

Muscular hypertonicity and active MTrPs causing the appearance of a typical pain pattern in patients of both groups were detected in the superior and inferior oblique muscles of the head, large and small posterior rectus muscles, sternocleidomastoid muscles, anterior scalene muscles, in the upper portions of trapezius muscles, levator scapulae, in the supraspinatus, subscapularis, infraspinatus, and deltoid muscles.

An average value of pain syndrome according to VAS in the 1-st group was 43,1±6,8, in the 2-nd group – 42,9±5,7. There were no statistically significant differences between groups (p=0,071). Mean NDI score was 34,7±9,3 in the 1-st group and 34,1±8,7 in the 2-nd group (p=0,067).

The results of the study of quality of life (QoL) using the MOS SF-36 scale before therapy starting showed a decrease in the quality of life in both groups (Table I). Both the mental and physical scores of the SF-36 quality of life scale were reduced. There were no statistically significant differences between groups.

The main factors leading to a decrease in QoL in patients of both groups were: chronic neck–shoulder myofascial pain, chronic daily headaches, sleep disturbances caused to chronic pain, presence of affective disorders (anxiety and depression), fatigue. Both groups of observation demonstrated positive dynamics after the end of therapy. Patients noted a decrease in the severity of pain, sleep disturbances, a decrease in the severity of emotional disturbances and fatigue.

A visual diagnosis, carried out 10 days after the start of therapy, revealed in both groups a decrease in the severity of biomechanical changes in the cervical-thoracic region (reducing of the severity of FHP and thoracic spine kyphosis). Objectification of the degree of FHP using the measurement of CVI by photogrammetric method revealed a more significant positive dynamics in the regression of biomechanical disorders in patients of the 1-st study group. (Fig.1).

The CVI, measured by the photogrammetric method on the 11th day was 59,07°±1,41 in the 1st group, and 51,2°±2,01 in the 2nd group (p=0,036). Manual diagnosis carried out after the end of treatment revealed a significant decrease in the severity of hypertonicity and active MTrPs in the muscles of the neck and shoulder region in patients of both groups. An average value of pain syndrome according to VAS on the 11th day was 6,1±1,03 in the 1-st group and 6,4±1,08 in the 2-nd group. There were no statistically significant differences between groups (p=0,09). Mean NDI score on the 11th day was 6,2±0,97 in the 1-st group and 6,4±0,86 in the 2-nd group (p=0,087).

The analysis of the MOS SF-36 questionnaire, carried out on day 11, demonstrated an improvement in the physical and mental health component in both of the studied groups with no statistically significant differences between groups (Table II). All patients reported increased work ability, improved sleep quality and mood.

The analysis of complaints of patients 3 months after the treatment showed that 11/25,58 % of patients of the 1-st and 36/81,82 % of patients of 2-nd group suffered from pain and stiffness in the neck and shoulder girdle. An average value of pain syndrome according to VAS 3 months after treatment was 7,3±1,05 in the 1-st group and 37,7±5,4in the 2-nd group (p=0,021). Mean NDI score 3 months after treatment was 6,8±1,1 in the 1-st group and 23,9±2,08 in the 2-nd group (p=0,0007). Evaluation of QoL after 3 months showed significantly higher rates of both physical and mental health in patients of group 1 (Table II).

Table I. Study of QoL (MOS SF-36) before therapy starting in both groups

Subscale	1 group (n=43)	2 group (n=44)	P
Physical Functioning (PF)	39,03±3,57	38,97±3,96	0,092
Role-Physical Functioning (RP)	39,4±4,77	39,21±4,67	0,071
Bodily Pain (BP)	34,17±4,98	33,98±4,81	0,67
General Health (GH)	36,3±4,23	35,9±4,75	0,072
Vitality (VT)	37,45±3,46	37,73±3,27	0,069
Social Functioning (SF)	39,4±3,91	39,12±3,82	0,63
Role-Emotional (RE)	39,3±3,24	39,6±3,51	0,082
Mental Health (MH)	39,8±5,12	39,11±5,09	0,54

Table II. Study of QoL (MOS SF-36) after therapy starting in both groups

Subscale	1 group (n=43)	2 group (n=44)	P
On the 11th day			
Physical Functioning (PF)	91,7±4,21	91,03±4,11	0,87
Role-Physical Functioning (RP)	90,32±4,63	90,11±4,71	0,69
Bodily Pain (BP)	92,4±2,77	91,9±2,7	0,52
General Health (GH)	94,8±3,11	94,6±3,2	0,91
Vitality (VT)	93,42±2,4	93,21±2,36	0,738
Social Functioning (SF)	92,7±2,18	92,64±2,21	0,56
Role-Emotional (RE)	94,1±2,32	93,9±2,19	0,098
Mental Health (MH)	93,6±3,08	93,09±3,1	0,54
3 months later			
Physical Functioning (PF)	91,2±3,74	76,1±5,09	0,027
Role-Physical Functioning (RP)	90,09±3,87	74,23±4,89	0,03
Bodily Pain (BP)	90,9±1,15	72,3±4,5	0,042
General Health (GH)	92,35±2,8	79,4±4,1	0,031
Vitality (VT)	92,67±3,02	78,04±3,62	0,02
Social Functioning (SF)	90,86±1,92	76,64±2,21	0,033
Role-Emotional (RE)	92,6±2,71	73,82±3,14	0,021

Thus, our clinical observations have shown that the application of drug-free treatment ensures high efficiency of therapy, which corresponds to the world trends in treating patients with myofascial pain syndrome [17]. In accordance with the recommendations of the American Physiotherapeutic College, non-pharmacological methods in treating myofascial pain must go before pharmacological ones, and a combination of as many adequate techniques of drug-free therapy as possible is very important.

Manual therapy is essential for restoring muscle functions. Our research has completely confirmed this claim, since the treatment of patients without application of biomechanical correction of the vertebrae has had a lesser effect in a long-term perspective.

CONCLUSION

Comparison of the effectiveness of MTrPS management by biomechanical correction of the musculoskeletal system combined with therapeutic exercises, DN and TrPs–pressure release with the effectiveness of MTrPS management by therapeutic exercises combined with DN and TrPs–pressure release in patients with chronic neck–shoulder myofascial pain and forward head posture demonstrated no significant differences between the two therapeutic approaches in the short term. At the same time, in the medium term, the inclusion of biomechanical correction in the treatment protocol for chronic neck–shoulder myofascial pain and forward head posture demonstrated higher efficiency compared with the combination of therapeutic exercises, DN and TrPs–pressure release.

REFERENCES

1. Phillips C. J. The Cost and Burden of Chronic Pain. In Reviews in pain. 2009; 3 (1): 2–5.
2. Breivik H., Eisenberg E., O'Brien T. The Individual And Societal Burden Of Chronic Pain In Europe: The Case For Strategic Prioritization And Action To Improve Knowledge And Availability Of Appropriate Care. BMC Public Health; 2013; 13: 1229.

3. Kroenke K., Outcalt S., Krebs E. Association between anxiety, health-related quality of life and functional impairment in primary care patients with chronic pain. General Hospital Psychiatry. 2013; 35: 359–365.
4. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. In Lancet. 2017; 390: 1211–1259.
5. Ashina S., Bendtsen L., Lyngberg A. C. et al. Prevalence of neck pain in migraine and tension-type headache: A population study S. Cephalalgia. 2015; 35 (3): 211–219.
6. Saxena A. Myofascial Pain Syndrome . Indian Journal of Physiotherapy and Occupational Therapy. 2015; 9 (3): 221–226.
7. Gerwin R. D. Diagnosis of Myofascial Pain Syndrome. Physical Medicine and Rehabilitation Clinics. 2014; 25 (2): 341–355.
8. Rivers W. E., Garrigues D., Graciosa N. et al. Signs and Symptoms of Myofascial Pain: An International Survey of Pain Management Providers and Proposed Preliminary Set of Diagnostic Criteria. Pain Medicine. 2015; 16 (9): 1794–1805.
9. Dommerholt J. Myofascial Pain Syndrome: Trigger Points. Journal of Musculoskeletal Pain. 2014; 22 (1): 111–117.
10. Murphy D. R., Schneider M. J., Bise Ch. G. et al. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain. Annals of Internal Medicine. 2017; 167 (11): 833–834.
11. Yaroshevskii A.A. Biokhimicheskije aspekty miofascyalnykh sindromov shejno-plechevoi lokalizacii. Ukrainskyi morfologichnyi almanakh. 2013; 2 (64): 73–76.
12. Morozova O.G., Yaroszevskii A.A. Skieletno-myshechnaia bol grudnoi kletki. Semeinyi doktor.
13. Jaroshevskyi O., Logvinenko A., Morozova O. et al. Features of Hemodynamics in Vertebrobasilar Arterial System in Young People, Depending On Biomechanical Disorders Of The Musculoskeletal System. Georgian medical news. 2018; 7(8): 48–53.
14. Lugo L. H. García H. I., Rogers H. L. Plata Treatment of myofascial pain syndrome with lidocaine injection and physical therapy, alone or in combination: a single blind, randomized, controlled clinical trial. BMC Musculoskeletal Disorders. 2016; 17 (1): P. 1.
15. Jaroshevskyi O. Nonspecific symptoms of pain syndromes of cervicobrachial localization and their dynamics under the influence of non - pharmacological treatment. Wiadomości Lekarskie. 2016; 69 (1): 10–3.
16. Singla, D., Veqar, Z., Hussain, M. E. Photogrammetric Assessment of Upper Body Posture Using Postural Angles: A Literature Review. Journal of Chiropractic Medicine. 2017; 16(2): 131–138. doi: 10.1016/j.jcm.2017.01.005.
17. Qaseem A., Wilt T. J., McLean R. M. et al. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2017; 166: 514–530.

Authors' contributions:
According to the order of the Authorship.
Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Olga G. Morozova
Department of Reflexology,
Kharkiv Medical Academy of Postgraduate Education
58 Amosova str., 61176, Kharkiv, Ukraine
e-mail: morozova.olga.0201@gmail.com

Received: 23.09.2018
Accepted: 17.12.2018

PRACA POGLĄDOWA
REVIEW ARTICLE

MODERN APPROACHES TO PREVENTION OF PERIODONTAL DISEASES IN PREGNANCY: A REVIEW

NOWOCZESNE STRATEGIE ZAPOBIEGANIA CHOROBOM PRZYZĘBIA W CIĄŻY: PRZEGLĄD LITERATURY

Liudmyla I. Ostrovskaya
UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY, POLTAVA, UKRAINE

ABSTRACT

Introduction: In the modern literature, a variety of treatment regimens for periodontal diseases in pregnant women have been suggested and recommended for use in practical public health. And yet the concept of "dental diseases prevention in pregnancy" does not fully reflect the essence of the necessary measures to maintain the dental health of women during this period.

The aim: The aim of the present paper is to study the scientific literature on the issue of preventing periodontal diseases in pregnancy.

Materials and methods: The subject under discussion was considered on the basis of 59 sources on this issue, using the method of content analysis, comparative and contrastive, analytical and biblio-semantic methods.

Review and conclusions: The analysis of scientific literature justifies the need for an integrated approach to treatment and prophylactic measures during the entire pregnancy period. Furthermore, the review of literature sources allows us to advocate the need to improve the existing approaches and to develop new individual programs for primary and secondary prevention of periodontal diseases in pregnant women, taking into account pathogenesis and the peculiarity of their course. Diagnosis of dental status in pregnant women with assessment of early and long-term clinical observations provides a prognostic model of the course and outcome of dental diseases. Meanwhile, the introduction of the follow-up observation for the maternity leave group enhances the dental health of pregnant women and prevents multiple pathological conditions of the unborn child.

KEY WORDS: pregnant women, periodontal diseases, prevention, treatment

Wiad Lek 2019, 72, 1, 89-94

INTRODUCTION

Currently, dental diseases in pregnancy form a separate link in cariology and periodontology [1]. Hence, in the modern literature, a variety of treatment regimens for periodontal diseases in pregnant women have been suggested and recommended for use in practical public health. And yet the concept of "dental diseases prevention in pregnancy" does not fully reflect the essence of the necessary measures to maintain the dental health of women at a high level due to the features of clinical presentation and the influence of general status of the body during this period.

When analyzing the scientific literature data, it should be noted that modern dentistry possesses a potent arsenal of various methods and means for the prevention and treatment of periodontal disease in pregnant women. The variety of therapeutic and prophylactic measures is conditioned by diverse and unequal approaches of the researchers to the analysis of causes, mechanisms of origin and development of gingivitis in pregnant women [2, 3, 4].

THE AIM

The aim of the research is to study the scientific literature on the issue of preventing periodontal diseases in pregnancy. It is known that a woman's pregnancy is an important period in the formation of the child's dental health and preservation of a woman's health. Therefore, the problem of prevention and treatment of periodontal tissue and dental caries in this category of patients remains relevant, despite the numerous findings of domestic and foreign scientists, devoted to the prevention of dental diseases in pregnant women [1, 2, 5, 6].

MATERIALS AND METHODS

The subject under discussion was considered on the basis of 59 sources on this issue, using the method of content analysis, comparative and contrastive, analytical and biblio-semantic methods.

Measures for the prevention of dental diseases during pregnancy should be conducted from the time of the first visit to the maternity welfare center and pregnancy registration; although the optimal time to start their implementation is a period of 3-6 months of pregnancy planning. At present, the scientific literature suggests a new view upon this issue: prevention should be carried out not only during pregnancy and after the child's birth, but also

during the period of pregnancy planning – progenesis, or the preparatory stage for pregnancy [7, 8]. Numerous scientific studies, justifying the preventive and therapeutic schemes, recommend taking into account the activity of the carious process [1, 2, 3 ,5, 6,10, 18, 23, 24, 27], the condition of periodontal tissues, general and local risk factors for the development of dental diseases, the state of oral hygiene [9, 10], the somatic pathology and diversity of nutrition in pregnant women [2, 5].

REVIEW AND DISCUSSION

In Ukraine, it is considered relevant and necessary to achieve the maximum effect in the prevention of dental diseases through the implementation of women's medical examination during pregnancy and coordinated work of gynecologist, psychologist, geneticist and dentist, to whom the woman should be referred after the first visit to the maternity welfare center [11]. At the dentist's office, it is necessary to organize the individual oral hygiene training for pregnant women, help them in selecting basic and accessory items and hygiene products, sanitation of the oral cavity, and professional hygiene. It is considered that the emphasis on prevention in pregnant women should be exerted by the integrated efforts of obstetricians, gynecologists, pediatricians, parents and with the support of healthcare facilities [12, 13]. Thus, domestic studies have introduced a scheme for dental prophylactic medical examination of pregnant women, which includes preventive measures during pregnancy and after the infants' birth until they reach the age of two years [13]. This scheme contains individually selected programs for the prevention of dental diseases in accordance with the trimesters of pregnancy. The prophylactic regimens use products manufactured by R.O.C.S. enterprise.

It is known that the purpose of preventive measures is the improvement of the woman's health, enhancing her dental status and carrying out antenatal prevention of caries in milk and permanent teeth, the anlage of which occurs during pregnancy [14]. Therefore, it has been proven that under modern conditions, the optimal way to organize dental care is to conduct prophylactic medical examination of pregnant women [13].

Pregnancy is a complex physiological process, during which the periodontal tissues undergo pronounced changes. A number of major causes that affect the periodontal tissues of pregnant women have been revealed: they include the change in the concentration of hormones, actively produced for optimal fetal development; the increase of oral flora pathogenicity; the change in calcium phosphorus homeostasis, which leads to decreased resistance of periodontal tissues in a pregnant woman [15, 16, 17]

It is important to note that in deterioration of the general condition of the body during pregnancy, reduced quality of individual oral hygiene or complete disregard of this set of actions is quite possible [2, 3, 5, 10].

The latter affects not only the course of pregnancy, but also the frequency and nature of dental pathology in this period. From the scientific literature it is known that dental status of pregnant women is characterized by high prevalence of caries and periodontitis (more than 90%), the severity of which depends on the severity of extragenital pathology [18], and pregnancy in its turn aggravates the course of inflammatory and dystrophic processes in the periodontium. As a result, oral cavity sanation is required in 92.06% [19].

Most researchers advocate the opinion about high preventive efficiency of rational individual oral hygiene in combination with professional hygiene during the gestation period and fostering motivation to implement the recommendations of specialists [12, 14, 20].

To date, there are numerous items and means for personal oral hygiene; general schemes of treatment and prevention for inflammatory gum diseases have been developed.

Therapeutic and prophylactic regimens, used to improve the oral condition of pregnant women are known [2, 5, 6, 21, 22] to be aimed at reducing plaque formation, inhibition of oral microflora, increase of hard dental tissues resistance [23]. However, taking into account the specificity of the group on maternity leave, the choice of effective therapeutic and prophylactic schemes remains a rather difficult task. Meanwhile, the development of effective methods for prevention and treatment of local gingivitis in women during pregnancy is relevant and at the same time remains insufficiently effective.

It is known that pregnancy is a physiological process that requires the body to reorganize many types of metabolism and subsequently leads to changes in the body's environment, in particular blood and saliva [15, 21, 24].

According to the scientific literature, the greatest manifestation of inflammatory phenomena in the periodontal tissues is observed in the second trimester of pregnancy, whereas the critical growth of cariogenic situation in the oral cavity occurs in the third trimester, which allows us to determine the optimal periods of dental examinations and develop a differential approach to preventive measures [1,2, 25, 26]. Yu.G. Chumakova [27] further suggests the use of measures aimed at normalizing the function of the salivary glands and maintaining homeostasis of the oral cavity, correction of mineral metabolism and local remineralizing therapy.

In order to prevent dental caries and periodontal diseases, it is recommended to prescribe, as topical agents, solutions of sodium fluoride, calcium gluconate or glycerophosphate, Remodent, combining them with the action of helium-neon laser, the use of antihypoxant and mexidol antioxidant in toothpastes (Mexidol dent) [23], coating varnishes, gels, sealants for teeth, hemostimulants [8]. It is also considered expedient to use non-medicinal products – auto- and hydromassage, chewing dense food.

Yu.G. Romanova [21] developed a course for prevention of diseases of hard dental tissues and periodontium during pregnancy with the use of toothpaste and dental elixir "Fitodent" topically and the use of purple echinacea extract per os.

For secondary pathogenetic prevention of dental diseases in pregnant women, the effectiveness of oral intake of calcium [26], fluoride, mono- and multivitamins, extracts

of eleutherococcus, echinacea, biologically active additives "Bioca lutevit" and sea kale has been proven [5, 24]. O.V. Kravchenko [25] recommends the introduction of a set of preventive measures, including individual oral hygiene with coating of hard dental tissues with fluorine-containing varnish, prescription of "Calcium-D3 Nycomed" preparation during pregnancy to prevent major dental diseases, improve the functional properties of the fetoplacental system, prevent fetal hypotrophy and promote the correct development of the dentoalveolar system. The use of "Calcium-D3 Nycomed" chewing tablets leads to saturation of oral fluid with basic mineral components and contributes to the decrease of dental enamel permeability in women.

N. Gadzhula [5] showed the effectiveness of individual approach to the prevention of dental caries in women in gestational and lactational periods using local and systemic ("Biocalcovite") influencing factors.

At the same time, the mechanisms of the formation and development of the carious process, as well as the pathology of periodontal tissues have individual characteristics with respect to the reactivity and resistance of each individual, and in particular pregnant women [28, 29].

The result of scientific and practical research is the development of primary and secondary prevention regimens [2, 3, 5, 11, 21, 22, 23, 26, 27, 30, 31] of dental pathologies during pregnancy, based on modern diagnostic methods.

It is highly important to be aware of the correct information approaches to clinical and additional examination of women during pregnancy, which will allow us to substantiate the high-quality, individualized, etiological, pathogenetic treatment and prevention of periodontal diseases.

Borisenko A.V. et al. advocate the identification of correlation relationships between clinical and laboratory (cytological) indicators: new gradations of semiquantitative and qualitative cytological indices from the sites of oral mucosa and periodontium have been discovered, which allows improving diagnosis, predicting the course of mucous diseases of the oral cavity and periodontium, development of adequate and modern therapeutic measures in pregnant women [32]. Virtually every pregnant woman in the third trimester develops latent iron deficiency, against the background of which IDA develops in 30-40% [33, 34]. According to the literary data [Budanov], changes in the hemogram and the parameters of iron metabolism increase respectively to the degree of iron deficiency. It was found that the serum erythropoietin values were significantly different in the same degree of anemia, which depends on the absolute parameters of hemoglobin and hematocrit. That is why the study of adequacy in serum erythropoietin production, reduction in red blood cell count, saturation ratio of iron transferrin, increase in the total iron binding capacity of blood serum – pathogenetic mechanisms of the onset of anemia – is reasonable and justified. The above data occupy a significant place in the planning of therapeutic and prophylactic measures for women during pregnancy.

L.N. Denisenko [35] recommends to identify pregnant women with iron deficiency anemia as a risk group for dental pathology with an increase in the number of examinations every two months to prevent dental changes and development of complications. The author suggests compulsory prophylactic medical examinations in the postpartum period. Meanwhile, in the group of increased risk for development of dental diseases, it is necessary to pay closer attention to primigravida women aged 18-20 with IDA and to increase the number of examinations and sanation for these patients (monthly).

Interesting are the data provided by Skryabin V.V. [36], in which the evaluation of the LII index in pregnant women as an integrative indicator of "white blood" is more informative than the standard blood test. Thus, the increase in the digital values of LII and the tendency to increase in the percentage of lymphocytes during the first trimester is prognostically unfavorable for the development of any complications of pregnancy – inflammatory reactions and increase in endogenous intoxication.

At present, the scientific literature provides the data that the development of inflammatory periodontal diseases in pregnant women is determined by the action of many factors acting at the systemic level and arising during pregnancy, in particular, determination of the immune and hormonal status, bone metabolism [37]. The authors [38] conducted studies on the clinical and immunological features of periodontal status and cytokine profile in the oral cavity of pregnant women, which showed an increase in frequency and severity of the pathology in both hard and periodontal tissues, oral mucosa in pathological pregnancy.

Thus, Dubrovskaya M.V. et al. (2013) have established the effect of exogenous and endogenous factors acting locally and systemically: deterioration of oral hygiene, smoking, extragenital pathology, immunosuppression and local cytokine imbalance, which is closely related to gestosis [37]. In order to enhance the diagnostics and prognosis for the development of inflammatory diseases in pregnant women, the authors recommend using the analysis of cellular immunity indices (CD 3 -, CD 4 -, CD 8 -, CD 16 -, CD 22 - lymphocytes) and the content of the tumor necrosis factor-α, interleukin 4, less pronounced interleukin-8, transforming growth factor-β 1 in the oral fluid. Furthermore, disorders of immune homeostasis in pregnancy complicated by gestosis (significantly more pronounced) have been established, which contributes to the development of gingivitis and periodontitis. Imbalance of cytokines in the oral fluid can be used as a diagnostic and prognostic marker of the onset of periodontal diseases and even the severity of their course [38]. The latter should be taken into account when planning individual preventive measures for the period of pregnancy.

At the same time, the researchers' attention is attracted by a new molecular biological method – polymerase chain reaction (PCR), imitating the normal replication of nucleic acids using universal primers and giving the opportunity to obtain fragments of DNA sequences sufficient for detection. The PCR technique allows to determine microorganisms in sufficiently small amounts when it is not possible to detect them by another method [39]. In addition, the quantitative

and qualitative detection of major parodontopathogens DNA allows to assess the degree of dysbiotic disorders of oral microflora, to prescribe adequate therapy and to evaluate the effectiveness of treatment [40]. In dentistry, modern molecular methods open up new perspectives in solving the problems of etiology and pathogenesis of dental diseases, and, consequently, in addressing prevention and treatment issues.

It is important to observe that Toll-like receptors constitute the most powerful cell modulators. Due to the atraumatic nature of the material sampling for PCR diagnostics, this method is acceptable for women during pregnancy.

Thus, domestic clinical and laboratory studies of buccal epithelium in pregnant women established the presence of allele G, which is reliably associated with the occurrence of inflammation in the tissues of periodontium. Therefore, today it is necessary to take into account the diagnostics of genes polymorphism, namely Asp299Gly of Toll-like receptor (TLR 4), in order to predict the occurrence and development of inflammatory diseases of periodontal tissues, which is important for justification and development of prophylactic and therapeutic measures in pregnant women [41, 42, 43].

It should be noted that pregnancy and childbirth are extremely powerful emotional factors, which significantly affect all psychosomatic components of women. The problem of cause-and-effect relations in the formation and development of periodontal tissue diseases remains important from the point of view of the role of psychosomatic relationships. Thus, according to the scientific literature, the indices of vegetative regulation and the psychoemotional status of pregnant women indicate the sufficient vegetative support of activity and a high level of adaptive and compensatory possibilities of the body [44]. The obtained data are included in the scheme for prophylaxis of periodontal diseases during pregnancy [45].

It is known that the level of health in a pregnant woman largely forms the somatic and dental health of a future child, determines the physiological course of pregnancy, childbirth and the postpartum period, as well as further optimal functioning of the woman's body [11].

It should be noted that the problem of preventing dental diseases in pregnant women have always attracted the attention of dentists. In most European countries, the prevention programs for dental diseases have been implemented, and they have yielded positive results [7, 46, 47, 48, 49].

The American Academy of Periodontology (AAP) offers recommendations as follows: all pregnant women, as well as women planning pregnancy, should undergo periodontal examinations with possible implementation of preventive or therapeutic procedures [50]. To date, the effectiveness of preventive measures has been proven. They are implemented by dentists during the period of pregnancy and in the postpartum period [1, 2, 5, 19, 21, 13, 23].

It is important to remember that during pregnancy and breastfeeding, the need for vitamins and trace elements is increased; the deficiency of them is due to intensification of metabolic processes.

It is necessary to pay attention to the significant amount of data from the scientific literature on the prescription of vitamin and mineral complexes, as well as studies of their interaction in pregnant women [51]. It is known that increased diet does not ensure the satisfaction of requirements of the woman's body during pregnancy. Deficiency of vitamins and microelements during pregnancy adversely affects the health of not only the future mother, but also the vitamin and mineral status of the fetus, which greatly increases the risk of perinatal pathology, the rate of physical, mental and psychic disorders, as well as congenital malformations [52, 53].

Improper nutrition of pregnant women can be reflected as an excessive increase in the body weight of a pregnant woman and fetus, as well as decrease in the body's defense systems. During pregnancy, the intensity of metabolism and elimination of vitamins and microelements undergoes changes [54]. A number of foreign authors indicate the need for significant changes in the diet of pregnant women. At the same time, future mothers should not "eat for two", but the level of micronutrients during this period should be increased by 20-40% [55, 56, 57, 58, 59].

At present, foreign authors discuss the concept of micronutrient programming for the development of the future baby during pregnancy [57]. The expediency of using multivitamin complexes today should be considered through the prism of the body's physiological need, and not as an action of medications [52]. The main task of dentists, obstetricians and gynecologists is to create a conscious understanding of the importance of timely dental care in pregnant women by forming a positive motivation for dental care in mothers-to-be [4].

When carrying out dental preventive and therapeutic measures in pregnant women, it is necessary to take into account that the woman should be in a semilying position. During manipulations, one should monitor the blood pressure, heart rate, whose changes are caused by psychoemotional stress in anticipation of pain and are possible during the visit at the dentist's.

Very important and interesting are the data from the scientific literature in which a comprehensive individualized treatment of pregnant women with inflammatory changes in gingival tissues is substantiated for the first time with the use of topical medications "Tonzinal", "Propol", "TsM-2" plates with calcium, and "Apilaka", Magne B6 for combined action on the body [45].

In the research, the leading indicators of changes in the woman's body during pregnancy are the psychological and hemodynamic characteristics of the pregnant woman, the mineralizing function of the oral fluid, the state of oral hygiene, and the intensity of the carious process. The concept of primary prevention of periodontal diseases in pregnant women has been developed, based on individualized activities and means taking into account the general state of health, gynecological anamnesis, features of nervous regulation, dental status, living conditions, the presence of bad habits, and the level of education of the pregnant woman [60, 61].

CONCLUSIONS

In the present article, the main schemes and modern approaches to the prevention of periodontal diseases in pregnant women have been examined. Analyzing the above, it can be concluded that an individual approach to primary and secondary prevention of changes in the periodontal tissues of pregnant women is obviously seen as the only way for the problem solving. This can be implemented through the detailed study of somatic and dental history, functional systemic changes of the entire body, establishing a set of individual preventive measures and improving therapy of the revealed disturbances in the periodontal tissues.

REFERENCES

1. Zharkova OA, Dubovets AV, Polyakova DD. Aspekty profilaktiki osnovnykh stomatologicheskikh zabolevaniy v period beremennosti. Vestnik VSMU. 2014;T.13.No.4:126-132.
2. Tolmacheva SM, Lukinich LM. Stomatologicheskiye zabolevaniya v period beremennosti i ikh profilaktika. Moscow: Meditsinskaya kniga; 2005, 150.
3. Pokrovsky MYu. Osobennosti patogeneza i prognozirovaniya techeniya stomatologicheskikh zabolevaniy v period beremennosti: Dissertation for the degree of candidate of medical sciences: 14.00.21. Nizhniy Novgorod; 2002, 179.
4. Yakubova II, Kuzmina VA. Sekrety stomatologicheskogo zdorov'ya budushchikh mam i ikh detey. Prophylaxis Today. 2015;No.19:16-21.
5. Gadzhula NG. Indyvidual'na profilaktyka kariyesu zubiv u zhinok u periody vahitnosti ta laktatsiyi: Dissertation for the degree of candidate of medical sciences: 14.01.22. Lviv; 2009, 18.
6. Parpalei EA, Parpalei EI. Ratsional'nyye podkhody k stomatologicheskoy profilaktike i lecheniyu zhenshchin v period beremennosti. Dental'nyye tekhnologii. 2004;No.3-4(17):10-13.
7. Yakubov II, Krigalko OV, Shulgina TV. Prohenez, abo pidhotovchyy etap do vahitnosti u stomatoloha. Ukrayins'kyy stomatolohichnyy al'manakh. 2007;No.1:71-74.
8. Parpalei EA, Syruk NA, Kolesnik SI, Novitsky AV. Stomatologicheskoye zdorov'ye beremennoy – put' k stomatologicheskomu zdorov'yu rebenka. Sovremennaya stomatologiya. 2006;No.3:21-24.
9. Bakhmudov MV, Alieva ZB, Bahmudov BR. Gigiyenicheskoye sostoyaniye polosti rta i porazhennost' kariyesom zubov u beremennykh s pervonachal'no zdorovoy polost'yu. Stomatologiya. 2010;No.3:16-18.
10. Kalinovska NI, Kalinovsky YuT, Orikhivska NV. et al. Stan hihiyeny porozhnyny rota u vahitnykh. Medytsyna transportu Ukrayiny. 2011;No.3:63-66.
11. Kutsevlyak F, Bozhko KV, Lyubchenko OV. et al. Poisk novykh podkhodov v antenatal'noy profilaktike. Stomatolog. 2011;No.5(155):20-21.
12. Harris R, Nicoll AD, Adair PM, Pine CM. Risk factors for dental caries in young children: a systematic review of the literature. Community Dent Health. 2004;Vol.21:71-85.
13. Yakubova II, Kryzhalko OO. Orhanizatsiya stomatolohichnoho dyspansernoho sposterezhennya vahitnykh zhinok. Visnyk stomatolohiyi. 2011;No.2 (75):111-115.
14. Seidbekov OS, Kafarova DK. Profilaktika vospalitel'nykh zabolevaniy parodonta u beremennykh zhenshchin. Rossiyskiy stomatologicheskiy zhurnal. 2011;No.3:39-41.
15. Fanchenko ND, Yekimova YeV. Endokrinologiya fiziologicheskoy beremennosti. Rossiyskiy meditsinskiy zhurnal. 2007;No.5:43-46.
16. Skryabina VV. Sravnitel'naya otsenka informativnosti traditsionno analiziruyemykh pokazateley obshchego analiza krovi i leykotsitarnogo indeksa intoksikatsii u zhenshchin s fiziologicheskim i oslozhnennym techeniyem beremennosti. Klinicheskaya laboratornaya diagnostika. 2013;No.12:23-25.
17. Grishchenko OV, Storchak AV, Shevchenko OI. et al. Osteopenicheskiy sindrom pri beremennosti i v period kormleniya grud'yu. Khar'kov; 2004, 28.
18. Bakhmudov BR, Aliyeva ZB, Bakhmudov BR. Porazhayemost' kariyesom zubov v "vozrastnykh" beremennykh v zavisimosti ot akushersko-ginekologicheskogo anamneza. Ros. stomat. zhurn. 2012; No.20:18-20.
19. Yakubova II. Analiz sytuatsiyi po nadannyu stomatolohichnoyi dopomohy vahitnym zhinkam. Visnyk stomatolohiyi. 2012;No.2:62-64.
20. Ulitovskiy SB. Rol' pravil'nogo otnosheniya vracha-stomatologa v formirovanii u patsiyenta motivirovannogo ispol'zovaniya sredstv oral'noy gigiyeny. Novoye v stomatologii. 2003.;No.1:167-170.
21. Romanova YuG. Obosnovaniye primeneniya adaptogena rastitel'nogo proiskhozhdeniya dlya povysheniya zashchitnykh i mineralizuyushchikh svoystv v rotovoy polosti beremennykh zhenshchin: Dissertation for the degree of candidate of medical sciences: 14.01.22. Odessa; 2000, 136.
22. Antonenko MY, Sidelnikova LF, Budyakivs'ka OV. Pryntsypy profilaktyky zakhvoryuvan' parodonta u vahitnykhю Sovremennaya stomatolohyya. 2007;No.4:35-37
23. Orekhova NS, Mikheeva EYe. Klinika, lecheniye i profilaktika gingivita v beremennykh. Stomatologiya detskogo vozrasta i profilaktika. 2007;No.2:3-6
24. Kulygina VN, Gadzhula NG. Effektivnost' profilaktiki kariyesa zubov u zhenshchin v period beremennosti po pokazatelyam mineral'nogo obmena rotovoy zhidkosti. Vestnik stomatologii. 2006;No.4:40-46.
25. Kravchenko OV. Effektivnost' primeneniya preparata «Kal'tsiy D3 Nikomed» dlya profilaktiki stomatologicheskikh zabolevaniy u beremennykh. Dental forum. 2006;No.2:33-35.
26. Petrushanko TO, Ostrovska LY, Ivanitskiy IO. Dyferentsiyovana profilaktyka ta likuvannya porushen' homeostazu kal'tsiyu pry khvorobakh zubiv ta tkanyn parodonta. Information letter on the innovation in the health care system. 2008; No. 109.
27. Chumakova YuG. Obgruntuvannya pryntsypiv profilaktyky kariyesu zubiv i zakhvoryuvan' parodontu u zhinok u rizni stroky vahitnosti: Synopsis of dissertation for the degree of candidate of medical sciences: 14.01.22. Kyiv; 1996, 22.
28. Xiong X, Buekens P, Fraser WD. et al. Periodontal disease and adolescent pregnancy outcomes: a systematic review. BJOG An International Journal of Obstetrics and Gynecology. 2006;Vol.113(2):135-143.
29. Lief S, Boggess KA, Murtha AP. The condition and pregnancy study: periodontal of cohort of pregnant women. Periodontol. 2004;Vol.75(1):116-126.
30. Popruzhenko TV, Terekhova TN. Profilaktika osnovnykh stomatologicheskikh zabolevaniy. M.:"MEDpress-inform"; 2009, 462.
31. Alexandrov EI. Sovremennyye vzglyady na problemu sostava i svoystv rotovoy zhidkosti vo vremya beremennosti. Aktual'ni problemy suchasnoyi medytsyny: Visnyk Ukrayins'koyi medychnoyi stomatolohichnoyi akademiyi. 2011;Vol 11(4:36):124-127.
32. Borisenko AV, Grigorovskiy VV, Timoina TA. Vzaimosvyaz' tsitologicheskikh i klinicheskikh pokazateley sostoyaniya slizistykh obolochek rta i parodonta u beremennykh s zhelezodefitsitnoy anemiyey. Rossiyskiy stomatologicheskiy zhurnal. 2012;No.4:7-12.
33. Budanov PV. Zhelezodefitsitnaya anemiya v beremennykh. Voprosy ginekologii, akusherstva i perinatologii. 2006;T.5. No.1:92-95.

34. Murashko AV. Anemiya, zhelezo i iskhod beremennosti (obzor literatury). Zdorov'ye zhenshchiny. 2002;T.4. No.4:31-33.
35. Denisenko LN. Vliyaniye zhelezodefitsitnoy anemii na sostoyaniye polosti rta beremennykh zhenshchin: Synopsis of dissertation for the degree of candidate of medical sciences: 14.00.21. Volgograd; 2007, 24.
36. Skryabin VV. Sravnitel'naya otsenka informativnosti traditsionno analiziruyemykh pokazateley obshchego analiza krovi i leykotsitarnogo indeksa intoksikatsii u zhenshchin s fiziologicheskim i oslozhnennym techeniyem beremennosti. Klinicheskaya laboratornaya diagnostika.2013;No.12:23-25.
37. Dubrovskaya NV, Lepilin AV. Immunologicheskiye narusheniya v formirovanii zabolevaniy tkaney parodonta v beremennykh. Saratovskiy nauchno-meditsinskiy zhurnal. 2010;T.6.No.2:392-396.
38. Dubrovskaya NV, Yeremin AV, Savina Ye, Ivashchenko YY. Faktory riska pri formirovanii zabolevaniy parodonta u beremennykh. Saratovskiy nauchno-meditsinskiy zhurnal. 2013T.9.No.3:383-386.
39. Simbirtseva AS, Gromova AYu. Funktsional'nyy polimorfizm genov regulyatornykh molekul vospaleniya. Tsitokiny i vospaleniye. 2005;T.4.No.1:3-10.
40. Ivanyushko TP, Tumbinskaya LV, Donnikov AYe. Issledovaniya uslovno-patogennykh mikroorganizmov metodom PTSR v real'nom vremeni v bol'nykh parodontitom. Stomatologiya. 2011;No.5:22-26.
41. Ostrovskaya LI, Petrushanko TA, Kaydashev IP. Polimorfizm Asp299Gly gena Toll-podobnogo retseptora 4 v genezise izmeneniy desen u beremennykh. Ukrainskiy stomatologicheskiy al'manakh. 2009;No.6:17-21.
42. Kirichenko TS, Koval' TI, Kaidashev IP. et al. Clinical and immunological characteristics of HIV-infection in patients with Asp299gIly polymorphism of the Toll-like receptor 4 gene. Georgian Medical News. 2013;224:30-35.
43. Shinkevich VI, Kaidashev IP. The role of the immune cells in the remodeling of gingiva at chronic generalized periodontal disease. Stomatologija. 2012;91(1):23-27.
44. Petrushanko TA, Ostrovskaya LI, Purdenko TI. Dynamics of the dental status of pregnant women in interrelation with their vegetative and psychoemotional indices. Georgian Medical News. 2014;No.11(236):21-27.
45. Petrushanko TA, Ostrovskaya LI. A method for comprehensive treatment of gingivitis in pregnant women. Patent for utility model No. 47941 Ukraine, IPC (2009) A61K 6/00. No. 200910313 as of 12.10.09; publ. 25.02.10.
46. Compendium of pharmaceuticals and specialties. The Canadian reference for health professionals. Ontario: Canadian Pharmaceutical Association; 1999, 1264.
47. Detman LA, Cottrell BH, Denis-Luque MF. Exploring dental care misconceptions and barriers in pregnancy. Birth. 2010;Vol.37(4):318-324.
48. Simark-Mattsson C, Emilson CG, Hakansson EG. et al. Lactobacillus-mediated interference of mutans streptococci in caries-free vs. caries-active subjects. Eur. Journ. Oral Sci. 2007;Vol.115(4):308-314.
49. Marchi KS, Fisher-Owen SA, Weintraub JA. et al. Most pregnant women in California do not receive dental care: findings from a population-based study. Public Health Rep. 2010;Vol.125(6):831-842.
50. Gogilashvili K, Gvantsa T, Samkharadze S. Gingivit beremennykh. DentArt. 2013;No.3:59-64.
51. Sidorova I, Unayan A. Osobennosti primeneniya vitaminno-mineral'nykh kompleksov dlya beremennykh i kormyashchikh zhenshchin. Vrach. 2007;No.11:66-67.
52. Strizhakov AN, Budanov PV. Sinergichnaya vitaminoterapiya – osnova optimizatsii predgravidarnoy podgotovki i vedeniye beremennykh. Vopr. ginekologiy, akusherstva i perinatologii. 2006;No.6:75-80.
53. Khoroshilov IYe. Pravil'noye pitaniye beremennykh i kormyashchikh zhenshchin. Ginekologiya. 2006;T.08.No.5:7-9.
54. Sumyatina LV, Skvortsova MYu, Podzolkova NN. Izucheniye effektivnosti i otsenka usvoyayemosti foliyevoy kisloty pri razlichnykh rezhimakh primeneniya vitaminno-mineral'nogo kompleksa "Alfavit Mamino zdorov'ye" vo vremya beremennosti. Akusherstvo i ginekologiya. 2008;No.4:45-47.
55. Black E. Micronutrientis in pregnancy. Br. J. Nutr. 2001;Vol.85 (2):193-197.
56. Studenikin VM. Polivitaminnyye preparaty i vitaminno-mineral'nyye kompleksy dlya beremennykh. Lechashchiy vrach. 2007;No.4:63-65.
57. Udipi SA, Ghugre P, Antony U. Nutrition in pregnancy and lactation. J.Indian Med.Assoc. 2000;Vol.98:548-557.
58. Ortega RM. Dietary guidelines for pregnant women. Public Health Nutr. 2001;Vol.4:1343-1346.
59. Ashworth CJ, Antipas C. Micronutrient programming of development throughout gestation. Reproduction. 2001;Vol.122:527-535.
60. Petrushanko TO, Ostrovska LY. Osoblyvosti pervynnoyi profilaktyky stomatolohichnykh khvorob vahitnykh. Ukrayins'kyy stomatolohichnyy al'manakh. 2010;No.3:32-35.
61. Ostrovska LY. Faktornyy analiz kliniko-laboratornykh pokaznykiv zhinok v dynamytsi vahitnosti. Aktual'ni problemy suchasnoyi medytsyny. 2009;Vol.9 (4.28):182-187.

Conflict of interest:
The Author declare no conflict of interest.

CORRESPONDING AUTHOR
Liudmyla I. Ostrovskaya
10 Stanislavsky Str., Ap. 289, 36023, Poltava, Ukraine
tel: +380506344489
e- mail: lyudmilaostrovsk@gmail.com

Received: 09.07.2018
Accepted: 21.12.2018

PRACA POGLĄDOWA
REVIEW ARTICLE

THE STUDY OF REGIONAL PECULIARITIES OF PARENTERAL VIRAL HEPATITIS INCIDENCE DYNAMICS AMONG CHILDREN AS AN INSTRUMENT OF DEVELOPING COMPLEX REGIONAL SOCIAL PROGRAMS ON THE PREVENTION OF ITS INCREASE

BADANIE REGIONALNYCH ODMIENNOŚCI DYNAMIKI WYSTĘPOWANIA PARENTERALNEGO WIRUSOWEGO ZAPALENIA WĄTROBY U DZIECI JAKO NARZĘDZIE SŁUŻĄCE ROZWOJOWI KOMPLEKSOWYCH REGIONALNYCH SPOŁECZNYCH PROGRAMÓW MAJĄCYCH NA CELU ZAPOBIEGANIE WZROSTOWI TEGO TYPU ZAKAŻEŃ

Nataliia V. Medvedovska[1], Valeriy I. Bugro[2], Ivan I. Kasianenko[3]
[1] SHUPYK NATIONAL MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KYIV, UKRAINE
[2] SHUPYK NATIONAL MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KYIV, UKRAINE
[3] PUBLIC INSTITUTION "UKRAINIAN INSTITUTE OF STRATEGIC RESEARCHES OF MINISTRY OF HEALTH IN UKRAINE", KYIV, UKRAINE

ABSTRACT

Introduction: the problem of increase of viral hepatitis incidence which are transmitted in the haemocontact (parenteral) way remains unresolved in the majority countries of the world. The special relevance is acquired lately by a problem of increase of risk of transfer of an infection among children of teenage age, youth, in the main ways of transmission of infection among which there is a risky behavior, addictions (the injection use of narcotic substances) and the unprotected sexual relations due to the lack of informing and awareness of risk of a disease and irreversible losses of health in the future.

The aim: Studying of regional features of incidence of parenteral viral hepatitis among children and teenagers with justification of the priority directions of prevention of its increase in the context of implementation of regional comprehensive programs became a research objective.

Materials and methods: Data from official forms of the statistical reporting on cases of diseases of viral hepatitis (sharp and chronic) in forms No. 1, No. 2 "The report about separate infections and parasitic diseases" (annual) MZ of Ukraine became primary material for a research. For achievement of a goal methods have been used: system approach, medico-statistical, graphic and conceptual modeling, and organizational experiment.

Review: During a research of 2007-2016 it has been established that the majority of viral hepatitis's in Ukraine (58,79 ± 0,44%) is diagnosed in a chronic stage of a disease, and especially in the Kirovohrad region (80,35 ± 2,14%). Increase of incidence of parenteral viral hepatitis's B and C in the Kirovohrad region has happened in age group of children of 15-17 years to prevalence in structure of incidence of children of chronic viral hepatitis's of hepatitis C (52,7 ± 5,8%) that demands search of the medico-organizational reasons of formation of the established incidence tendencies for a solution of the problem of their distribution due to early preventive intervention within complex program social influence.

Conclusions: Accounting of regional features of incidence of parenteral hepatitises became scientific justification for acceptance to execution of the comprehensive regional social program of prevention of their distribution among teenagers and youth of the Kirovohrad region.

KEY WORDS: integrated social approach, children's population of teenage age, parenteral viral hepatitis's

Wiad Lek 2019, 72, 1, 95-98

INTRODUCTION

According to public data provided by the World Health Organisation (WHO) 3.5% of the world population (in the uncertainty interval 95%: 2.7-5.0%), or 257 million people (199-368 m) have chronic HBV-infection (with positive serology HBsAg for at least 6 months), and 686 thousand people die of HBV-infection every year. World Hepatitis Day has been annually held on July 28 since 2011 on the initiative of World Hepatitis Alliance (WHA) to commemorate the birthday of Nobel Laureate, professor Baruch Samuel Blumber, whose scientific research was dedicated to the fight with HBV-infection, and other parenteral/hemocontact types of viral hepatitis, that indicates the recognition of the global scope of this problem [1-5].

Studied by us dynamics of the viral hepatitis incidence rate among children and teenagers in Ukraine, as well as among the total population demonstrates yearly growing tendencies (from 25.8 in 2007 to 29.67 per 100 thousand

of the total population in 2016 and from 11.87 in 2007 to 18.16 per 100 thousand in 2016).

The specific aspect of the spread of parenteral viral hepatitis is its hemocontact transfer mechanism, when the virus is present practically in all the fluids of the infected person (saliva, urine, blood, nasopharyngeal fluids, tears, sperm, cervicovaginal fluids and so on). Infection through the contact of the damaged epithelium of the healthy person with fluids contaminated with parenteral viral hepatitis is plausible, and it should be noted that this virus can be transmitted starting from the middle of the incubation period [6-8].

Parenteral viral hepatitis (especially hepatitis C, the course of which can be accompanied by jaundice at the ratio 1:4, and which can also develop chronic state (up to 80.0% of cases) sometimes can be asymptomatic at early stages. Epidemic spreading also takes place due to the fact that infected people simply are not aware that they have already become the source of infection. The spread of parenteral viral hepatitis among teenagers and youth becomes a pressing problem due to their risky behavior (for example, making tattoo, piercing with violation of aseptic rules), unprotected intercourse and bad habits (use of parenteral narcotics) [9, 10].

THE AIM

The aim of the study: to examine regional peculiarities of the incidence of parenteral viral hepatitis among children and teenagers with the following verification of its key methods of prevention in the context implementation of regional, complex programmes.

MATERIALS AND METHODS

Starting material for research became data from official forms of statistical accounting on viral hepatitis cases (acute and chronic), namely accountability forms # 1 and # 2 "The Report on Definite Infections and Parasitic Diseases" (annual), The Ministry of Health of Ukraine. To successfully reach the research aim the following methods were used: systemic approach, medico-statistical analyses, graphic and conceptual modeling, organizational experiment.

REVIEW AND DISCUSSION

The analysis of viral hepatitis incidence rate among children in Ukraine showed gradual increase of the index from 11.87 in 2011 to 18.16 in 2016, that is 1.53 times more as much ($p<0,01$). Regional peculiarities of high indicator values in 2016 (Zakarpatska Region (162.45), Zhytomyrska Region (62.15) – by comparison, the average indicator in Ukraine is 18.16 per 100 thousand of the total population) – were caused by high incidence rate of viral hepatitis A (in Zakarpatska Region (161.07), Zhytomyrska region (58.86), by comparison, the average indicator in Ukraine is15.18 per 100 thousand the corresponding population). Viral hepatitis B incidence rate was the highest among children of Vinnytska Region (5.12), Zhytomyrska Region (2.47) and Kirovogradska Region (2.35), by comparison, the average indicator in Ukraine is 1.13 per 100 thousand of the total population. Chronic viral hepatitis occurred in children more often in Vinnytska Region (4.09), Ivano-Frankivska Region (2.86), Khersonska Region (2.84), Poltavska Region (2.55), Zaporizka Region (1.71), Ternopilska Region (1.48), and Kirovogradska region (1.17), the average indicator in Ukraine is 0.97 per 100 thousand of the total population.

The increase in incidence rate is observed with the increase in age. Thus, the highest indicators of disease incidence rate are among early teens (10-14 years) and mid teens (15-17 years). As for acute viral hepatitis B and C, the highest incidence rate was in the age group from 15 to 17 years (3.69 and 0.51 per 100 thousand of the total population) (Fig.1. and 2.).

Chronic hepatitis incidence rate among children from birth up to 17 years was the highest among late teenagers from 15 to 17 years old with negligible fluctuations (1.72 per 100 thousand of the total population) (Fig. 3).

In the structure of chronic hepatitis incidence rate parenteral viral hepatitis B and C show almost the same prevalence with negligible predominance of chronic viral hepatitis C (52.7 ± 5.8 % and 44.6 ± 5.78 % respectively), with significant predominance among children in the age group from 15 to 17 (369 and 0.51 per 100 thousand persons of the total population respectively).

With the knowledge of the main ways of parenteral viral hepatitis transmission among teenagers, domestic and world's experience, results of our research, we have suggested complex intersectoral approach to prevention of the parenteral viral hepatitis spread among teenagers as exemplified by Kirovogradska Region. Today's teenagers, namely peculiarities of their growth, as well as shaping in them health-conscious behavior, are in the center of attention. Enforcement of preventive work, thanks to combined efforts of medical, educational sector and health care services. The latter requires organizational and managemental interventions on all the components of quality health care provision (according to A. Donabedian: structure, process, outcomes). The structural component concerns resource's provision (staff acquisition, material and technical facilities), organization of work of primary health care professionals, that provide accessibility of health care to the population. It also requires quality management of specialized health care (with the involvement of clinics "Friendly to the Youth") with the aim of identifying groups of increased risk of parenteral viral hepatitis spread and providing prophylactic observations. The structural component is directly connected to the process component, which implies taking necessary preventive, diagnostic and treatment and rehabilitation measures among teenagers.

The first positive results of scientifically justified innovations were in Kirovogradska Region, where the regional programme was adopted. Regional departments of health care, education and science, physical culture and sport, tourism took part in the implementation of this programme. The first stage of implementation of the suggested approach became the improvement of educational work among teenagers, with the help of mass media, non-governmental organizations, specialists on healthy lifestyle from Health centers, «Clinics Friendly to the Youth», volunteers, medical specialists, educators that are in every day contact with teenagers. Combined educational work and consulting teenagers and their families on psychosocial

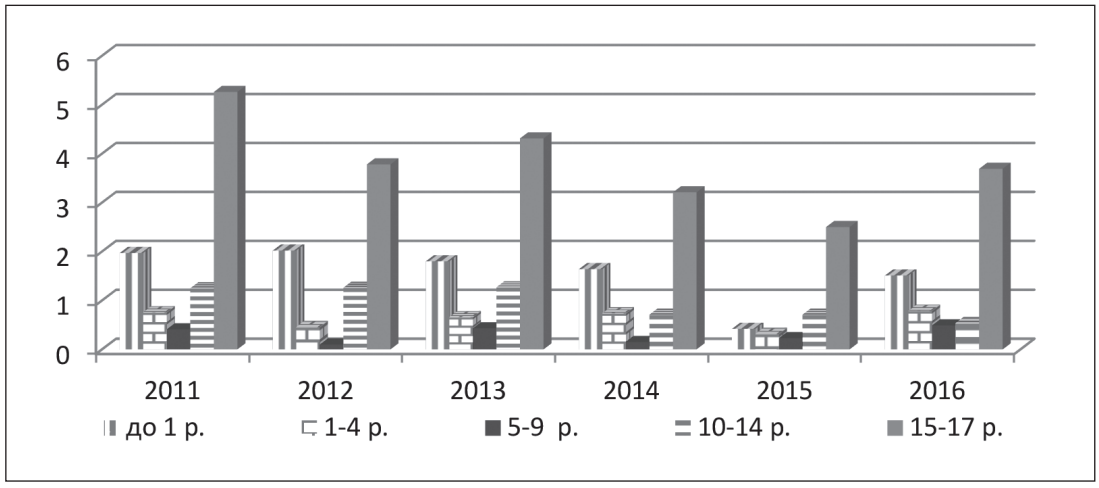


Fig. 1. Dynamics of viral hepatitis B incidence rate over a period from 2011 to 2016 (per 100 thousand of the total population)

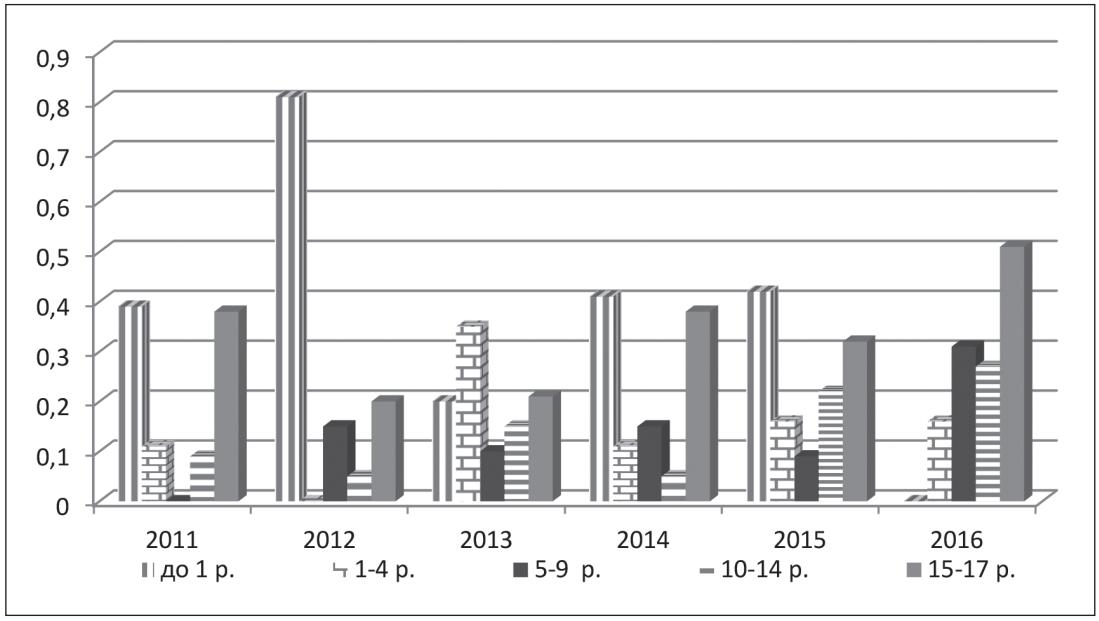


Fig. 2. Dynamics of acute viral hepatitis C incidence rate in children of different age groups over a period from 2011 to 2016 (per 100thousand of the total population)

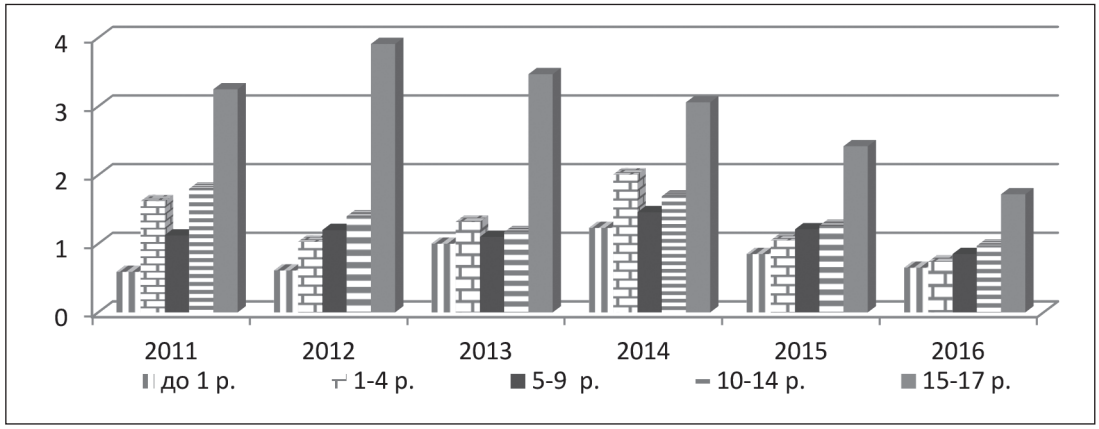


Fig. 3. Chronic viral hepatitis incidence rate among children of different age groups over the period from 2011 to 2016 (per 100 thousand of the total population)

issues is also practiced. We expect positive medico-psychological results from the safe behavior of teenagers. It can help solve problems, connected to risk factors and ways of transmission of parenteral hepatitis viruses, as well as provide freedom of choice for the people with the maximum awareness. Psychosocial consulting helps teenagers develop certain psychological skills that are necessary for solving conflicts with the peers, resisting group pressure. Detecting conditions for the proper development of teenagers, individual approach to education and prophylactic influence are very important. Programmes on healthy leisure organization were developed, with the involvement of the youth and teenagers into socially useful, creative and sociocultural activities, sports, tourism, art etc. Trainings for parents were also introduced. Not only

medical professionals but also cultural and social workers took part in these trainings. Accessible for parents training system ONLINE is planned to be launched. Medical professionals will give consultations on reproduction issues, prevention of the spread of infections including hemocontact (parenteral) way. Social workers, psychologists and lawyers will also take part in the project. In addition "Health Day", "Family Day", «Child Health Day» where held. Teenagers and their families got additional knowledge about parenteral viral hepatitis risk factors and ways of transmission. Free of charge possibility to make laboratory test on the presence of parenteral viral hepatitis infection was offered during the event. We must admit that most of the participants used this possibility.

United work of general practitioners and educators targeted at detection of teenagers in the risk group of spreading parenteral viral hepatitis is planned for the next stage. For these teenagers personalized recommendations on the frequency of prophylactic observations will be worked out, quite possibly pediatric gynecologists, urologists, dermatologists and psychologists will be involved.

Prevention of parenteral viral hepatitis spread among teenagers is still the issue of the day in today's difficult socio-economic situation. The study of the regional problem of the increase in parenteral viral hepatitis incidence among teenagers of Kirovogradska Region, justifying measures directed at improving prevention of its spread starting from teenage years, which were included into the regional social programme adopted on the level of the regional state administration, and resolutions on its implementation with the list of planned measures on the township and district levels in Kirovogradska Region proved to be medically and socially effective. Implementation of justified approaches showed the readiness of the primary health care professionals, educationalists, workers of social and cultural sectors for taking an active part in shaping healthy attitude to personal health among teenagers. We hope it will help to prevent parenteral viral hepatitis in the region. This experience became of immediate interest in light of the local authority reform, when local communities have the right to solve local health care issues. According to the law of Ukraine from 05.02.2015 # 157-VIII "On Volunatry Association of Communities", local communities are responsible for primary health care provision. In such a way, changes in the current rules and regulations promote cooperation between local communities, and local self-government, which includes prevention of spread of parenteral viral hepatitis among teenagers. Identified regional peculiarities of the state of health of the population should be at the core of future cooperation with implementation of early preventive interventions with the aim of prevention irreversible loss, especially among children and teenagers.

CONCLUSIONS

Found regional peculiarities of increase in parenteral viral hepatitis case rate among teenagers in Kirovogradska region induced us to work out approaches to improvement of its prevention specifically among teenagers of the region. Suggested steps were approved by the regional state administration; they were taken into account and became a scientific foundation for developing and implementation of the complex regional social programme targeted at prevention of parenteral hepatitis spread among teenagers of Kirovogradska region.

REFERENCES

1. Barut H. S., Günal Ö., Göral A., Etikan I. Prevalence of hepatitis B virus infection in children of HBsAg positive parents. Mikrobiyol. Bul. 2011; 45 (2): 359 – 365.
2. Gural A. L., Mariyevsky V. F., Sergeyev T. A. et al. Characteristic and trends of development of epidemic process of hepatitis C in Ukraine. Profilaktical medicine. 2011;1 (13):9 – 18.
3. World Health Organization. WHO country office in Pakistan. Blood Safety (2009). Access mode: http:// www.Embo.who.int/pakistan/programmeareas_bloodsafety.htm.
4. World Health Organization: Hepatitis B. 2008: http://www.who.int/mediacentre / factsheets/fs204/en/.
5. Sheikh S.M. Hepatitis B and C value of universal antenatal screening. J. Coll. Physicians. Surg. Pak. 2009;19:179—182.
6. Galan R. J. , Cidoncha E. C. , Martin M. F., Rodriguez C. C. , Almeida C. V. , Verdugo R. M. Antiviral regimen complexity index as an independent predictor of sustained virologic response in patients with chronic hepatitis C. MMWR Recomm Rep. 2012;61:1—32.
7. Argentini C. , Genovese D. , Dettori S. , Rapicetta M. Argentini C. HCV genetic variability: from quasispecies evolution to genotype classification. Future Microbiol. 2009;4 (3):359 – 373.
8. Antonelli A., Ferri C., Galeazzi M. [et al.]. HCV infection: pathogenesis, clinical manifestations and therapy. Clin. Exp. Rheumatol. 2008;26 (1 Suppl 48):39 – 47.
9. Carney K. , Dhalla S. , Aytaman A. [et al.]. Association of tattooing and hepatitis C virus infection: A multicenter case-control study. Hepatology. 2013;57(6):2117 – 2123.
10. Grebely J., Applegate T.L., Cunningham P., Feld J. J. Hepatitis C point-of-care diagnostics: in search of a single visit diagnosis. Expert Rev Mol. Diagn. 2017;17(12): 1109—1115.

Research work «Scientific ensuring implementation of the European policy Health for all - 21 in the conditions of optimization of a health care system of Ukraine» (number of the state registration: 0112U002809) was performed in Public institution «Ukrainian institute of strategic researches of the Ministry of Health of Ukraine».

Authors' contributions:
According to the order of the Authorship.
Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Nataliia V. Medvedovska
Zoologicheskaya St. 6B, apartment 524, Kiev, Ukraine
e-mail: valeriybugro@ukr.net

Received: 02.09.2018
Accepted: 28.12.2018

PRACA POGLĄDOWA
REVIEW ARTICLE

THE GENESE OF PREDICTIVE-PERSONIFIED MEDICINE AND THE PROBLEMS OF ITS IMPLEMENTATION IN UKRAINE

POWSTANIE PREDYKCYJNO-SPERSONALIZOWANEJ MEDYCYNY I PROBLEMY Z JEJ WDROŻENIEM NA UKRAINIE

Olena O. Terzi
ODESA NATIONAL MEDICAL UNIVERSITY, ODESA, UKRAINE

ABSTRACT

The concepts, content and significance of predictive-personified medicine that are able to improve the quality of treatment, using genetic information when choosing the medical procedures that are necessary for a particular person are considered. Characteristic of the principles of predictive-personified medicine and its fundamental foundations are carried out: genomics; proteomics; metabolism; bioinformatics The history of the formation and development of predictive-personified medicine in the world is investigated, the relevant legal documents are analyzed.

The main advantages of predictive-personified medicine are determined: detection of an illness at an earlier stage, when its treatment is more efficient and cheaper; division of patients into similar groups for the choice of optimal therapy; reduction of adverse reactions to drugs by more effective early assessment of individual negative reactions; improvement of the selection of new biochemical indicators, allowing to control the action of medicinal products; reducing the time, cost, and the number of failures in clinical trials of new treatments.

It is noted that in Ukraine none of the well-known projects approved by the American and European committees on gene therapy are implemented. However, the priority direction of research in the field of genetics is chosen annually by more and more medical institutions of Ukraine. Examples of the introduction of predictive-personified medicine into medical institutions and scientific institutes in Ukraine are presented.

It is concluded that ensuring the effectiveness of this direction of modern medicine depends on the elimination of many problems of socio-managerial and regulatory nature. In addition to their solution, the priority tasks in this area include the carrying out of significant informational and enlightening work with the population; increase of state funding for the development of preventive medicine; creation of public-private partnership of base centers.

KEY WORDS: predictive-personified medicine, genetic predisposition of a person, molecular-genetic level, social-managerial and regulatory-legal problems

Wiad Lek 2019, 72, 1, 99-102

INTRODUCTION

The concept of predictive-personified medicine is actively discussed in many countries around the world, including in Ukraine. According to most scholars, predictive-personified medicine can add to substantially improve the quality of treatment. On the basis of genetic information, the physician should identify at the molecular-genetic level the patient's individual inclination to the disease and identify the pathways for early prophylaxis and, by correction, mitigate the adverse effects of functionally defective products of polymorphic genes. Predictive medicine can forecast the disease [1]. As for personified medicine, this fact proves its significance. According to numerous pharmacological studies, 40% of medications are not effective enough because they are aimed at a standard approach to the patient. At the same time, knowing about the genetic features of a person, the doctor will be able to choose the most effective medication and optimal, effective, safe dosage for the organism of a specific person. The effectiveness of the implementation of theoretical developments of predictive-personified medicine in practical medical activities is hampered not by solving a number of issues of an organizational-a managerial, organizational, medical, legal, social, moral and ethical nature.

THE AIM

The aim of the article is a consideration the essence of predictive-personified medicine in relation to its effectiveness, as well as to identify socio-management and legal-regulatory problems of its implementation.

MATERIALS AND METHODS

Methods of research selected based on the purpose of the study. In order to establish the objectivity and validity of scientific statements and conclusions, during the conducted research a complex of general scientific and special scientific methods was used, in particular such as: the formal legal method, comparative legal method, analyt-

ical, etc. The formal legal method was used to clarify the content and essence of European legal documents in this area; with the help of the comparative legal method the approaches to the introduction of predictive-personified medicine in the world and in Ukraine were elucidated; the analytical method contributed to the study of problems and disadvantages of the introduction of predictive-personified medicine in order to eliminate them.

Also the scientific-heuristic potential of such philosophical methods of research as synthesis, deduction, induction, abstraction is used.

REVIEW AND DISCUSSION

The only and unequivocal term for the definition of predictive-personified medicine has not yet acquired its final form, in the USA and European countries, for the most part, use the term predictive-preventive and personified medicine (PPPM). Its meaning is seen in determining the individual inclination to the development of diseases at the molecular genetic level, resulting from a mutation and genetic polymorphisms. The main tasks of the PPPM include: 1) the detection of signs of the disease at the stage of preclinical pathology with the identification of targets adequate for pharmaco-prevention; 2) pharmaco-correction of the revealed violations for the purpose of pharmaco-prevention, which belongs to the category of preventive measures that contribute to suppressing the pathological process at the preclinical stage [2].

The PPPM is based on the following principles:

- predictability (prediction), which allows predicting the disease based on the individual features of the genome and create a probable health outlook based on genetic research;
- prevention (prophylaxis), which at the preclinical level helps to prevent the emergence of diseases through their prevention, as well as vaccines and drugs for «repair» of damaged genes;
- personalization, based on an individual approach to each person (creation of a unique genetic passport for patient treatment and control of the health);
- wide collaboration of various doctors-specialists and patients, and also on the transformation of the patient from the subject of treatment into the object of the medical process.

The fundamental basis of the PPPM include:

- genomics (a chapter of genetics that investigates the genomes of living organisms and the principles of coding proteins; genomics provides scientific information about individual genetic features of the patient, thus determines the charecter of the disease and reaction to certain types of treatment);
- proteomics (the branch of molecular biology, which defines a complete set of proteins that are associated with a specific physiological or pathological state; its main task is to quantitatively analyze the expression of proteins in cells, depending on their type, state or influence of external conditions);
- metabolomics (engaged in the study and analysis of metabolism - a collection of all low molecular weight metabolites of biological fluids, tissues and cells of the body; some of the low molecular weight metabolites can become indicators of pathological conditions);
- bioinformatics (creates informative information bases in the sphere of PPPM).

Predictive medicine was initiated in the 80's and 90's of the twentieth century and formulated by the Nobel Prize winner Jean Dausset, whose the innovative work outlines the main principles that have contributed to the development of key ideas by the description of systems of antigenic tissue compatibility (HLA, human antigens of leukocytes) in predictive, preventive, personalized, and participative medicine (4P medicine) and subsequently reflected in the human genome project.

Today, the concept of PPPM is thoroughly discussed at international conferences, including the Cambridge, Oxford University (2010-2012), the International Symposium on Biopredictors (Dresden, Germany, 2011), the First European Congress on the PPPM (September 2011) , which founded the European Association of PPPM (EPMA). The Association has a clear structure for achieving the best coordination of multiaspecting activities related to the principles of the PPPM throughout Europe, which includes National Representatives of all 27 EU Member States and Associate Members (eg Israel, Serbia, etc.). Note that on July 1, 2011, the Board of Directors of EPMA approved the National Representative in Ukraine.

To the basic European legal documents, we will attribute the Universal Declaration on the Human Genome and Human Rights dated 11.11.1997 (UN, UNESCO), the International Declaration on Human Genetic Data of 16.10.2003 (adopted by the resolution of the General Conference of UNESCO on the report of the Commission III on 20th plenary meeting), the Resolution of the Inter-Parliamentary Assembly of the CIS member-states 329-12 "On the ethical and legal regulation and safety of genetic medical technologies in the CIS member states", the Explanatory report to the Additional Protocol to the Convention on Human Rights and biomedicine concerning genetic testing for medical purposes.

The modern concept of the PPPM provides for a complex integrative function of scientific, medical, preventive and educational institutions, requires the use of not only modern diagnostic tests and equipment, but also appropriate modernization of the system of state guarantees, financing, with the possible involvement of private sources, and legal norms of interaction between the physician and the patient [3,]. The main advantages of PPPM include: identifying a disease at an earlier stage, when its treatment is more efficient and cheaper; division of patients into similar groups for the choice of optimal therapy; reduction of adverse reactions to drugs by more effective early assessment of individual negative reactions; improvement of the selection of new biochemical indicators, allowing to control the action of medicinal products; reduction of time, cost and number of failures in clinical trials of new treatment methods [4, 17].

Experts have proved the genetic predisposition to such diseases as: hereditary thrombophilia, cardiovascular diseases, respiratory diseases (bronchial asthma), joint pain, miscarriage, gastrointestinal tract (celiac disease), endocrine diseases (diabetes mellitus), oncological diseases (breast cancer).

In Ukraine, none of the well-known projects approved by the American and European Gene Therapy Committees are being implemented. However, the priority direction of research in the branch of genetics is chosen annually by more and more medical institutions of Ukraine [5, p. 35]. Here are some examples.

The major research center is the Institute of Genetic and Regenerative Medicine of the National Academy of Medical Sciences of Ukraine, which has departments of cell and tissue technologies with laboratories of immunology; of cell and tissue cultures, experimental modeling; genetic technologies with laboratories of genetic-engineering biotechnologies; of gene-cell modifications; of genetic diagnostics with laboratories of DNA-diagnostics, cytogenetics, metabolomics.

The concept of strategic development of the Odessa National Medical University for the period 2017 - 2019 as one of the main tasks of the introduction of the work of the departments provides a new scientific direction, taking into account predictive medicine, neurology, NBIC-technologies.

Scientific researches related to molecular genetic markers in sports are conducted jointly by the Department of Human Biology of the National University of Physical Education and Sports of Ukraine and the Laboratory of Theory of Methodology of Sport Training and Reserve Opportunities of athletes at the Research Institute of the National University of Physical Education and Sports of Ukraine.

Today, person-based research can be conducted in selected regions of Ukraine. So, at the Interregional Center for Medical Genetics and Prenatal Diagnostics in Kryvyi Rih (Dnipropetrovsk Region), a laboratory of molecular genetics "Genomics", which equipped with the latest unique equipmentwas, opened.

Specialists have developed and successfully implement such areas as diagnosing the genetic causes of male, female infertility and other reproductive disorders; detection of predisposition to oncopathology (breast and ovarian cancer); cardiovascular diseases (heart attacks, stroke, hypertonic disease); diabetes mellitus (type I, type II); individual selection of medicaments (medication against hypertension, allergies, antitumour, etc.). In addition, thanks to unique equipment for the first time in Ukraine is introduced the most complete and quick diagnosis of cystic fibrosis - a widespread hereditary disease that can manifest itself in the form of pathology of the respiratory, gastrointestinal and reproductive systems, and without timely treatment it leads to the death of the patient and can not be diagnosed with general clinical methods. Furthemore, the mild form of this disease manifests itself in the form of male infertility of unclear origin [6].

The formation and development of the PPPM requires solving many tasks. S.Suchkov, M.Legg, M.Paltsev, O.Golubnichna among tasks allocate, first of all, the creation of a regulatory and legal framework that would meet all the requirements for the protection of individual health (rules of state guarantees of the system of PPPM; channels of financing of the industry, which include both state and private sources, the rules for regulating the relationship between a doctor and a patient, a system for familiarizing the population with a new approach to health care); secondly, the novelty of the task requires radical retraining of medical personnel, qualitative changes in their level of qualification, the range of services provided by them to the population, etc. [2].

The professional literature identifies such problems in these and other areas. To socio-managerial problems D. Horin [7] includes:

1) the problem of social inequality and the spread of predictive-personified medicine. It is that low-income groups of the population can not afford high-quality medical care. The introduction of predictive-personified medicine should be carried out in compliance with the principle of social justice and contribute to reducing the social gap in access to new genetic services;

2) the proliferation of predictive-personified medicine and the problem of aging population. Increasing the life expectancy inevitably leads to an increase in illnesses of the elderly, the need to seek additional resources to provide them with comprehensive, well-qualified care and the limiting the capacity of the health care system to provide predictive-personified health services;

3) the principle of social justice in the dissemination of predictive-personified medicine is that health workers should not be motivated to profit and use patients to receive it. They should focus on the needs of patients, not on their solvency, while adhering to the equally high standard of provision of medical genetic services for all.

A team of foreign scholars highlights a wide range of organizational, legal, economic, and moral-ethical aspects during the introduction of predictive medicine [8, p.6-12]. Organizational problems are connected with the necessity of carrying out significant researches, lack of necessary organizational resource for this, adequate state financing, and the lack of interest of public healthcare authorities and medical institutions in their conduct. Economic problems are caused by the lack of proper and necessary funding of projects for predictive medicine and personified prevention. Legal problems arise when obtaining permits for the use of new methods of prevention, diagnosis and treatment of diseases (examination of documents and decision on granting such permission takes place over a long period of time, and also a long period of registration of a patent). To moral-ethical issues include the need to address the following issues: at what age should genetic testing? Who should have access to its results? Should close relatives know about the research results? Where and how should results from genetic research be stored? etc.

To organizational and medical measures, we also include: 1) an active detail of the history of the patient; 2) deter-

mining the risk factors for the patient and his relatives; 3) referral to the cabinet of oncological counseling; 4) compilation of the genetic map + genotyping of the patient patient, as well as his relatives (in the case of diagnosis of mutations); 5) blood collection from relatives who are in the risk group; 6) discussion of the results obtained by the oncologist and geneticist; 7) statement of the genetic diagnosis and determination of the principles of prevention and follow-up monitoring to protocol. After obtaining the necessary results an individual map of prevention, routing and detected chronic pathology is taken into account taking into account the established risks [3].

O. Minczer and V. Vishnevsky also called such problems of the introduction of personalized medicine - its high cost (however, if eight hundred years ago genome sequencing cost hundreds of thousands of dollars, today this amount does not exceed one thousand dollars); undevelopment of the correct methods for assessing the dynamics of risk factors in time suitable for clinical practice, due to their large number; the ambiguity of the interpretation of the concept of "risk factor dynamics", etc. [9].

Specialists express the following proposals for the development of the Ukrainian health care system of the innovative concept of predictive medicine: to create and test a pilot model of predictive help on the example of one of the regions of Ukraine; to develop and implement training programs for the training of relevant specialists; to open departments and faculties of predictive medicine on the basis of leading educational institutions of Ukraine [10].

CONCLUSIONS

The formation of predictive-personified medicine is due to the development of genomics, proteomics, metabolomics, bioinformatics. In Ukraine, predictive-personified medicine is still at the initial stage of its development. At the same time, in this area, projects are being developed that involve the transition from studying the genetic predisposition of a person to the diagnosis and prevention of its diseases, individual treatment. Ensuring the effectiveness of this direction of modern medicine depends on the elimination of many problems of socio-managerial and regulatory nature. In addition to solving them, to the priority tasks in this area include conducting significant info-sensitization with the population; increase of state funding for the development of preventive medicine; creation of public-private partnership of base centers.

REFERENCES

1. Prediktivnaya meditsina i targetnaya terapiya [Predictive medicine and targeted therapy]. Retrieved from: prezi.com/blvwy2hm_dks/presentation/ [in Russian].
2. Suchkov, S.V., Legg, M., Paltsev, M.A., Golubnichaya, O. (2014). Prediktivno-preventivnaya i personifitsirovannaya meditsina kak novaya stupen v sisteme ohranyi zdorovya terapiya [Predictive-preventive and personalized medicine as a new step in the system of health care therapy]. Retrieved from: http://ukros.ru/wp-content/uploads/2014/07/suchkov_legg.doc [in Russian].
3. Kalinkin, M.N., Chirkov, R.N., Terehov, O.V. (2017). Kontseptsiya prediktivnoy, profilakticheskoy, personifitsirovanoy meditsinyi v Tverskom regione: ot teorii k praktike [The concept of predictive, preventive, personalized medicine in the Tver region: from theory to practice]. Verhnevolzhskiy meditsinskiy zhurnal – Verhnevolzhskiy Medical Journal, 3, 4-6 [in Russian].
4. Kobrinskiy, B.A. (2017). Personalizirovannaya meditsina: genom, elektronnoe zdravoohranenie i intellektualnyie sistemyi. Chast 1. Genomika i monitoring klinicheskih dannyih [Personalized medicine: genome, e-health and intelligent systems. Part 1. Genomics and monitoring of clinical data]. Rossiyskiy vestnik perinatologii i pediatrii – Russian herald of perinatology and pediatrics, 62 (5), 16-20 [in Russian].
5. Kriuchko, T.O., Vovk, Yu.O., Tkachenko, O.Ya. (2012). Perspektyvy diahnostyky ta likuvannia henetychno determinovanoi atopichnoi bronkhialnoi astmy [Prospects for the diagnosis and treatment of genetically determined atopic bronchial asthma]. Dytiachyi likar – Children's doctor, 7, 33–36 [in Ukrainian].
6. Novatsii v medytsyni. Diahnostuvannia henetychnykh prychyn khvoroby vidteper mozhlyve u Kryvomu Rozi [Innovations in medicine. The diagnosis of genetic causes of the disease is now possible in Kryvy Rih]. Retrieved from: http://www.girnyk.com.ua/blog/novaciyi-v-medicini-diagnostuvannya-genetichnih-prichin-hvorobi-vidteper-mozhlive-u-krivomu [in Ukrainian].
7. Gorin, V.D. (2013). Sotsialno-upravlencheskie problemyi rasprostraneniya prediktivno-preventivnoy i personifitsirovannoy meditsinyi [Socio-administrative problems of the spread of predictive-preventive and personalized medicine]. Srednerusskiy vestnik obschestvennyih nauk – Central Russian Herald of Social Sciences, 4, 27-34 [in Russian].
8. Belevantseva, A.V., Lifshits, G.I., Suhoveeva, O.A. (2008). Prediktivnaya meditsina sotsialno znachimih zabolevaniy: organizatsionnyie, yuridicheskie, ekonomicheskie i moralno-eticheskie aspektyi [Predictive medicine of socially significant diseases: organizational, legal, economic and moral-ethical aspects]. Vestnik NGU. Seriya: Biologiya, klinicheskaya meditsina – Bulletin of NSU. Series: Biology, Clinical Medicine, T.6., V. 2, 6-12 [in Russian].
9. Mintser, O.P., Vyshnevskyi, V.V. (2016). Realni horyzonty personalizovanoi medytsyny. Stratehiia ta varianty rozvytku [The real horizons of personalized medicine. Strategy and options for development]. Medychna informatyka ta inzheneriia – Medical informatics and engineering, 4, 7-11 [in Ukrainian].
10. Talalaiev, K.O. (2016). Predyktyvna medytsyna – vyklyky i dosiahnennia [Predictive medicine – challenges and achievements]. Odeskyi medychnyi zhurnal – Odessa Medical Journal, 4, 69 [in Ukrainian].

Conflict of interest:
The Author declare no conflict of interest.

CORRESPONDING AUTHOR

Olena O. Terzi
Odesa National Medical University
2 Valikhovskii St., 65000, Odesa, Ukraine
tel: +380934307777
e-mail: terzi.elena@ukr.net

Received: 10.07.2018
Accepted: 20.12.2018

PRACA POGLĄDOWA
REVIEW ARTICLE

THE USE OF MEDICAL KNOWLEDGE IN THE CRIME INVESTIGATION

WYKORZYSTANIE WIEDZY MEDYCZNEJ W DOCHODZENIACH KRYMINALISTYCZNYCH

Viktoriia O. Yaremchuk
YAROSLAV MUDRYI NATIONAL LAW UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

Introduction: Investigation of many types of crimes is accompanied by the involvement of health care workers. They, with the help of their special skills in the sphere of medicine, assist the investigator in identification, fixation and caption of evidence. Health care workers take part in many investigative procedures, carry out forensic, psychiatric and other kinds of examinations.

The aim: To reveal modern forms of using medical knowledge during the crime investigation.

Materials and methods: The abstract is based on the teachings of scholars of forensic physicians, criminologists, the results of our survey of investigators and forensic experts, the results of our generalization of criminal proceedings regarding the investigation of murders, normative and legal acts of Ukraine and other sources. The system of scientific knowledge methods: historical, statistical, questionnaires, generalizations and others, was used during the research.

Review: Our research reveals the following forms of using medical knowledge during crime investigation. This is the participation of physicians as specialists in investigative procedures, like the review of the scene, interrogation, investigation experiment, examination, participation in the selection of biological samples for carrying out expert examinations, physicians' assistance in the form of the recreation of the deceased person's face with a view of its identification, also the consultations of physicians - cardiologists, traumatologists, surgeons, forensic experts, etc., carrying out of forensic and forensic and psychiatric examinations, use of medical knowledge in the form of molecular genome research with the view of person's identification. The argumentative issues on the interaction between the investigator and the physician during the review of the scene, interrogation and other investigative procedures, implementation of molecular genome research and certain issues arising in the appointment of forensic and forensic psychiatric examinations are reviewed in the abstract.

Conclusions: The use of medical knowledge is necessary for investigation of many types of crimes. The forms of using medical knowledge in the crime investigations such as the participation of physicians as specialists in the carrying out of investigative procedures, the physicians' assistance in the form of the recreation of the deceased person's face with a view to its identification and physicians' consultations are widely spread nowadays. The conduct of forensic, medical and forensic and forensic psychiatric examinations is the most widespread. The use of medical knowledge in the form of genotyposcopic and molecular genome research carried out in order to identify a person during the crime investigations is popular nowadays.

KEY WORDS: forensic knowledge, physicians, medical knowledge, medical forensics, molecular genome research, crime investigation, forensic medicine

Wiad Lek 2019, 72, 1, 103-106

INTRODUCTION

The crime investigation has never existed without the use of special knowledge, and medical knowledge occupy the main place among it. Forensic medicine has been used to establish the truth in the crime investigation for centuries. Physicians and forensic experts are widely involved for participation in investigative procedures, carrying out of the molecular genomic investigations for the identification of the deceased and so on. In Ukraine there are different legal acts that regulate medical relations between the subjects of such relations. The main legal act regulates not only the medical relations but also all the relations that may exist on the territory of Ukraine and sets up the main rules of behavior, rights, freedoms and duties of the citizens and other person that are on the territory of Ukraine on legal grounds. The Constitution of Ukraine [1, p. 57]. The rights and responsibilities of forensic physicians with their participation in investigative procedures and carrying out of the expert investigations are determined by a number of normative and legal acts in detail. These are the "Regulation on the bureau of forensic examination of oblast executive committees' health departments and on the republican bureau of the Autonomous Republic of Crimea" [2], the "Rules for carrying out forensic examination (investigations) of corpses at the bureau of forensic examination" [3] and other normative and legal acts.

Today, a big number of health care workers take part in the criminal proceedings. However, the scientific literature does not adequately cover the possibilities of healthcare workers in their participation in the investigation. Thus, the participation of physicists in pre-trial investigation and in court sessions is very briefly described in a book edited by V. F. Moskalenko and B. V. Mykhailychenko, that is used for preparation of the future physicists[4, p. 36-37].

THE AIM

To reveal modern forms of using medical knowledge during the crime investigation.

MATERIALS AND METHODS

The abstract is based on the teachings of scholars of forensic physicians, criminologists, normative and legal acts of Ukraine the results of our survey of investigators and forensic experts, the results of our generalization of criminal proceedings regarding the investigation of murders, and other sources. The system of scientific knowledge methods: historical, statistical, generalizations(73 criminal proceedings on the murder investigation), questionnaires (230 investigators of the Ministry of Internal Affairs of Ukraine and Security Service of Ukraine and also forensic experts of the Ministry of Health of Ukraine) and others, was used during the research.

REVIEW AND DISCUSSION

Our generalization of 73 criminal proceedings on murders shows that forensic physicians are involved into inspection the scene in 64.47% of these proceedings. Even Hans Gross said that the physician should be invited in cases of forensic medical properties only. These include necropsy, bodily injuries, pathological phenomena, determination of physical strength, age, ability to perform a certain action and simulation, etc. [5, p. 1-3, 191-228]. The participate of the health care workers in the investigation of certain categories of crimes is a widespread practice in Ukraine. However, investigators are not yet fully use the possibilities of physicians' assistance during their mutual interaction. According to the results of the questionnaires, when investigating, for example, road traffic accidents, the physicians are involved for assistance in inspection of the place of the accident only in 23.0% of cases [6, p.128], which, in our opinion, is insufficient.

It should be mentioned that a forensic medical officer should work under the direction of an investigator during the inspection of the scene and the corpse. The questioning of investigators conducted by us shows that in their opinion, a specialized physician should act under the direction of the investigator during the inspection of scene, as it was mentioned by 43.0% of the respondents, and take into account the instructions of the investigator, as it was mentioned by 40.0% of investigators. When examining the scene the duties of the forensic expert are: the identification of signs that allow judging the time of death and the mechanism of injury creation on the human body; consultation for the investigator on the issues related to the examination of the corpse at the place of its detection and its further examination; assistance in working with physical evidence; providing by the forensic expert the explanations for all actions performed by him. At the site of a corpse examination, the forensic medical physician should make sure that all necessary for saving the life has been made, check the presence or absence of breathing and palpitation, establish early signs of death that indicate irreversible processes in the central nervous system of the person [7, p. 47-53]. The nearest physician despite his specialization is involved for examination in case of impossibility to invite a forensic expert. The former should follow the "Rules of a specialized physician's work in the sphere of forensic medicine during the external examination of the corpse in the place of its detection (incident)." Here, the explanations of the physician are provided orally and of a consulting nature. And the physician who examined the corpse at the place of its detection, can do its further opening and draw up a written conclusion [4, p. 92]. However, the debatable question about whether a physician of any specialization can help the investigator in the corpse's examination on-site arises. Ukraine has insufficient number of forensic experts in the bureau of forensic examination, who are involved as experts in the examination of the scene and corpse. That's why, in certain cases the investigator has to wait for the physician to arrive, postponing the examination of the corpse for a while.

There is also a debate about the necessary number of concurrently invited medical experts and other specialists of other sphere of knowledge for the examination. It depends on the complexity of the investigative proceeding, the number of objects to be examined, the size of the territory of the scene and the characteristics of the objects themselves, that requires the use of special knowledge of different profiles. According to the results of our generalization of criminal proceedings, in the investigation of murders such experts are involved: one medical specialist, as indicated in 64.47% of our generalized protocols; two specialists of different profiles, as indicated in 27.63% of our generalized protocols; three or more specialists on criminal proceedings, as indicated in 7.0% of our generalized protocols. It is advisable to invite concurrently several physicians in cases when the investigation of serious or especially grave crimes is held in the presence of a large number of victims.

There is a debatable question about the reflection of the forensic physician's activity during the examination of the scene. There are opinions about the need for a forensic physician to draw up his own protocol, that will be an annex to the main protocol drawn up by the investigator during the examination. The results of our generalization of criminal proceedings on murders show that the activity of a physician is reflected only in 22.41% of protocols. In our opinion, it is necessary to cover all the actions of a forensic physician during the examination of the scene and corpse.

The importance of health care workers during interrogation is tremendous. The conducted by us questioning of the investigators shows that 37.4% of investigators invite physicians for the interrogation. The forms of using physicians can be different. Thus, 52.6% of investigators coordinate with the physician the questions that are put to the interrogated person. In addition, according to the results of our survey, 13.5% of the investigators often address to a medical specialist's explanation on the interrogated person's testimony.

During our interviewing and questioning of forensic experts from the Ministry of Health, they indicate that when they participate in the interrogation, they ask questions

to the interrogated person with having the investigator's permission. 81.7% of the respondents stated that. The investigator may also agree with them the formulating of the questions. 26.0% of the questioned forensic experts stated that. It is worth pointing out that namely the physician's asking questions during the interrogation is very appropriate. Thus, 79.1% of the investigators, who we interviewed, consider it appropriate when namely the medical expert asks questions during the interrogation. When interrogation on crimes against the life and health of a person, investigators invite forensic experts from Ukraine who ask questions to an interrogated person about life-long chronic diseases that could, under certain conditions, lead to death of a person, and also about injuries, scars on the body of the victim. They help to identify the false testimony provided by the interrogated person by using their special knowledge in the sphere of medicine.

The results of our carried out survey with investigators show that 39.6% of investigators involve a medical expert during an investigative experiment. For example, the invited physician will help the investigator to confirm or refute the suspect's given evidence in the proceedings when it comes to determining from which side and at what angle the hits were made on the victim. When conducting an investigative experiment, the physician takes part in the application of the following tactical techniques: staging questions to the participants of the investigative procedure and analyzing their responses; physician's assistance to the investigator in the reconstruction of the situation, the determination of similar conditions of the experiment and individual experiments, tests (the mechanism of injury creation on the human body); the physician's assistance to the investigator in the analysis of the received results of experiments or tests and answers of the participants. When conducting an investigative experiment, a specialized physician should follow the investigator's instructions and work under his guidance.

The participation of physicians in the examining of people when it is possible to detect a trace from the tattoo, even when it is destroyed, is the form of use of medical knowledge during an investigation. Also, a physician can detect a tattoo on the corpse, even after a long time [5, p.1-3, 191-228]. The physician participates in the study of living people in order to determine the degree of bodily injuries' severity; examine sex conditions; determine the percentage of the working capacity lost; set age; determine the traces of past wounds; determine the self-injury and simulated illnesses [8, p. 1-10].

Health care workers are actively involved as experts into the selection of samples for expert investigation. These samples are material objects that are given to the expert for comparison with the objects that are identified or diagnosed [9, p. 327].

Conducting of the forensic examinations is one of the forms of medical knowledge use in the investigation of crimes. The Ministry of Health of Ukraine pays significant attention to the development of the forensic medical service, namely, to the improvement of the equipment at the bureau of forensic examinations, to the increase of scientific relevance and value-based evidence of the forensic expert's conclusion, taking into account the essential requirements for the quality of conducting the forensic examinations and its great role in the control against the crime[10, p.10-11].

Medical knowledge is closely intertwined with forensics during the crime investigation. Thus, the integration of knowledge, its association aimed at optimal solution of the tasks of counteracting the crime is the important trend of criminalistics at the present stage of its development [11, p. 4]. Thus, the debatable question is where the boundary between forensic and medical knowledge. Mykola Serhiiovych Bokarius, the world famous forensic physician and criminalist, writes about the connection between forensic medicine and criminalistics during the crime investigation for the first time, and describes the damage of the skull bones by dull objects, the mechanism of their cracks' formation, the mechanism of the skull bones damage formation from the firearms' shot, damage on the clothes of the corpse [12, p. 430-432]. The departments of "forensic medical criminology" functionate in the bureau of forensic examination in Ukraine nowadays [4, p. 41]. It should be noted that clothing, organs and tissues of the corpse, some probable means of injury are sent for the examination to these departments[3]. Among the questions arising in the investigation, a special place belongs to the definition - whether there were no damage or other traces, whose formation is connected with the crime, at the result of the action of a specific object. The solution of such questions can't be carried out only by the methods of forensic examination of a corpse or a living person. That is why the forensic medical criminalistics deals with it [13, p. 5-7]. Physicians widely use the principles of identification, which are applied during forensic examinations, when determining the instrument of crime with the help of traces or injuries on the body and clothing of the victim, during the identification of a deceased person or during interrogation[14, p. 1]. The person's identification by his skull using computer technology and special programs which is carried out at the forensic medical criminalistics branches of the Forensic Medical Examination Bureau, is also the important form of use of medical knowledge in the crime investigation. More evidential methods of personal identification with the help of the skull are used in forensic medical practice, including photographic matching and computer technologies. To be able to conduct such an examination, a lifetime picture of the face of the person to be identified and the skull of an unidentified dead body are required [15, p. 222].

New interdisciplinary studies, such as genotyposcopic, molecular-genome [16, p. 159-162], which combine medicine and criminalistics, appear. DNA (deoxyribonucleic acid) analysis was categorized there as a method of personal identification [17 , p. 260-261]. Now there is a new technology for determining the molecular genetic structure in the samples. Today the term "genome dactyloscopy" or "genome fingerprinting" is introduced to the medical lexicon. Polymeric chain reaction is in use. The method emerged at the end of the XX century and is considered to be the foundation of technologies of the XXI century. Its essence is in the ability to multiply DNA fragments by

millions of times. This provides with the opportunity to use a small amount of biological residues for expertise. These studies are actively conducted during the expertise in the Odessa Regional Bureau of Forensic Medicine [18, p. 3-7].

The conduct of psychiatric expertise is the popular form of using medical knowledge during criminal proceedings. In 95.0% of criminal proceedings, forensic psychiatric expertise can be appointed during the pre-trial investigation or the first instance court, which demonstrates the importance of this type of investigation [19, p.163-165]. They are conducted not only to suspects or convicted persons, but also to witnesses, victims, if the investigation or court has doubts about their mental health. A psychiatric expertise is conducted to determine the ability of a person to correctly perceive, memorize and recreate an event that he/she has seen or heard [10, p. 240-241]. Suspects are sent for treatment in the case of a psychological illness being found. At the same time, their rights must be secured [20, p. 351-352].

CONCLUSIONS

The use of medical knowledge is necessary in the investigation of such types of crimes as gunshot injuries caused by the use of firearms; poisoning; body injury by various objects; road accidents; railway accidents; fires; various types of murders (unintentional and intentional), and so on. The knowledge of forensic medicine, forensic traumatology, forensic psychiatry and other medical sciences is used during the criminal proceeding. The research carried out by us proves the existence of various forms of medical knowledge use in the crime investigation. This is the participation of physicians as specialists in the conduct of investigative proceedings, the physicians' assistance in the form of the recreation of the face of a deceased person with the purpose of its identification, consultations of physicians (cardiologists, traumatologists, surgeons, forensic experts, etc.) regarding the medical issues that are necessary for the investigator when planning an investigation. Forensic medical and forensic psychiatric expertise is the most popular forms of using medical knowledge during the investigation nowadays. Today, the use of medical knowledge in the form of medical and forensic expertise performance, as well as molecular genome research, is used.

REFERENCES

1. Study Guide on Medical Law. compiled by S. D. Riabenko, B. V. Mykhailychenko. Kyiv : AUS MedicinePublishing, 2014: 126 s.
2. Nakaz MOZ Ukrainy № 6 from 17.01.1995 "Regulations on the Bureau of Forensic Medical Examination of Health Care Departments of Oblast Executive Committees and the Republican Bureau of the Autonomous Republic of Crimea"[E-document]. Regime of access : http://zakon0.rada.gov.ua/laws/show/z0258-95 . Title from the screen.
3. Nakaz MOZ Ukrainy № 6 from 17.01.1995"Rules for conducting forensic medical examination (investigations) of corpses in the bureau of forensic medical examination"[E-document]. Regime of access: http://zakon0.rada.gov.ua/laws/main. Title from the screen.
4. Forensic medicine. Book 1. edited by V.F. Moskalenko and B.V. Mykhailychenko. The 3rd edition, corrected. Kyiv, VSV «Medytsyna». 2016. 448 s.
5. Gross Hans. A manual for forensic investigators as a forensic system. Moscow, LexEst, 2002: 1088s.
6. Klymchuk M. P. Investigation of crimes on violations of traffic safety rules and vehicle exploitation (forensic and procedural aspects): monograph. Lviv: Lviv State University of Internal Affairs, 2008: 216 s.
7. Forensic Medicine and Forensic Medical Examination. edited by I. M. Hryhus. Lviv. "Novyi Svit 2000". 2014: 208 s.
8. Forensic medical examination (inspection) of living persons. compiled by V. A. Tatarenko. Kharkov, Kharkov State Medical Academy, 2000: 60 s.
9. Shepitko V. Yu. Samples for expert examination. Great Ukrainian Law Encyclopedia. T. 20: Forensic science, forensic examination, legal psychology. Kharkiv: Law, 2018: 327-328.
10. Biletska G. A. Forensic medicine and forensic psychiatry. Kharkiv, Law, 2018: 376 s.
11. Shepitko V. Yu. Designated purpose of criminalistic knowledge and ambition to the European standards in counteracting criminality. Theory and practice of forensic examination and criminalistics. Collection of scientific works. 2017, 17: 4-11.
12. Contribution of Mykola Serhiiovych Bokarius and Mykola Mykolaiovych Bokarius to the development of forensic examination and criminalistics / A.I. Lozovoj, V.M. Lesovoy, V.V. Mousodov, V.A. Olkhovskii, L.N. Derecha, V.V. Bondarenko. Theory and practice of forensic examination and criminology. 2014 14: 430-441.
13. Forensic-medical criminalistics. edited by O. V. Fylypchuk and O. M. Hurov. KhNMU, Kharkiv. 2013: 639 s.
14. Medical and criminalistic identification: forensic medical expert's handbook. Under the general editorship of V.V. Tomilin. Moscow, NORMA INFRA-M, 2000: 472s.
15. Forensic Medicine. B.V. Mykhailychenko, A.M. Biliakov, I.G. Savka ; edited by B.V. Mykhailychenko. Kyiv: AUS Medicine Publishing, 2017: 224 s.
16. Kupyansky M.G. Investigation of serial sexual sadistic murders (organizational and tactical principles). diss. ... PhD in law. Yaroslav Mudryi national law university. Kharkiv, 2016: 221 s.
17. Criminal investigation. Charles R. Swanson, Neil C. Chamelin, Leonard Territo and others. 7th ed. Boston :McGraw–Hill, 2000: 687 s.
18. Use of DNA analysis in forensic medical examinations. edited by Yu. M. Syvolapa and G. F. Kryvda. Odessa. Odessa Medical University. 2001: 92 s.
19. Almazov B.N. Legal psychopathology. Moscow: Date Square, 2009: 376 s.
20. Vitaliy M. Pashkov, Andrii A. Olefir. Problems of Rehabilitation of Mentally Ill Persons: the International Legal Aspect (Ukrainian Experience). Wiadomosci Lekarskie. TOM LIX, Nr 4(150); 2017 : 341-353.

Conflict of interest:
The Author declare no conflict of interest.

CORRESPONDING AUTHOR

Viktoriia Yaremchuk
Department of criminalistics, Law University,
Yaroslav Mudryi National
84, Pushkinska Street, 61024, Kharkiv, Ukraine
tel. +380975115036
e-mail. viktori.yaremchuk@gmail.com

Received: 16.07.2018
Accepted: 05.11.2018

PRACA POGLĄDOWA
REVIEW ARTICLE

THE FOUNDATION OF AN EFFECTIVE HEALTH CARE SYSTEM OF UKRAINE – FAMILY MEDICINE

WPROWADZENIE SYSTEMU EFEKTYWNEJ OPIEKI MEDYCZNEJ NA UKRAINIE – MEDYCYNY RODZINNEJ

Oleh G. Shekera
SHUPYK NATIONAL MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KYIV, UKRAINE

ABSTRACT

The article discusses approaches to the reforming of the Health Care System of Ukraine, the key objectives of which are: the strengthening of preventive services, the increasing of availability and quality of health care, the enhancement of primary health care, the improving of personnel maintenance, infrastructure upgrading and the equity in health care. Conclusions: Any measures aimed at the modernization of the health care system should be accompanied by joint efforts of all parties (patients, the medical community, legislative and executive authorities, as well as local authorities) to ensure the interest of health workers and the population in an effective health care system in Ukraine.

KEY WORDS: the reforming of the Health Care System, primary health care, family medicine, the Institute of Family Medicine, health

Wiad Lek 2019, 72, 1, 107-111

INTRODUCTION

Human health is the basis for the formation of a harmonious and fully developed personality, and therefore can be recognized as one of the greatest values and objective needs of the evolution of any community. The famous German philosopher Schopenhauer wrote: "Health before exceeds all other benefits of the person that truly the healthy beggar is happier than the sick king". The world health organization (who) definition of health as a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity, is generally accepted.

In the 21st century the importance of health is significantly rethought, taking into account its understanding as an inalienable right, from the point of view of existing threats and challenges, the growing requirements for the quality of health, technological and financial capabilities of its provision.

Despite the significant progress made in recent years in terms of promoting health and life expectancy, the relative improvement among countries and at the level of individual countries had varied. Globally, more than 400 million people still lack access to basic health services. Where they are available, these health services are often fragmented or of poor quality, leaving the health system's response to these problems and satisfaction with health services in many countries low. For example, in Ukraine, as in most European countries, a significant problem is the prevalence of chronic non-communicable diseases and their risk factors. The high prevalence of chronic non-communicable diseases is a priority public health problem that has a negative impact on the health and demographic situation and leads to high levels of morbidity, disability, mortality, poor quality of life and short life expectancy. Poor health of the population is characterized by low birth rate, high mortality, negative natural growth and demographic aging, increasing the overall burden of disease.

In accordance with resolution WHA62.12 health Assembly primary health care, including the strengthening of the health system and other relevant resolutions the Secretariat of the world health organization has developed a framework for integrated, socially-oriented health services. The framework includes five independent strategic goals for more comprehensive and people-centred health services. It provides for the necessity of reforms with a view to reorienting health services so that they were completely focused on the needs of individuals, families, carers and communities and receive support from responsive services that more fully meet their needs and would coordinate their work within the framework of the health sector and beyond, regardless of the context or status of development of the country. These reforms also include an appropriate human rights approach that enshrines access to health care as a fundamental human right without any distinction based on ethnicity, religion, gender, age, disability, political beliefs, and economic or social conditions [1, 2].

Today, the total mortality of the population and mortality from individual causes in Ukraine is twice higher than the corresponding indicators of the European Union. Of particular concern is the problem of premature mortality of men of working age, which is 3.5 times higher than that of

the female population. In 2016, life expectancy in Ukraine was 7.7 years shorter than the average in the European Union, and in men – almost 12.1 years. The average life expectancy of the population is 70.1 years, which causes its gap with the European average of 6, and with the indicators of the EU countries – up to 10.3 years.

According to resolution WHA62.12, (Strategy 3). Reorientation of the model of health means creating conditions in which effective and efficient health services are developed, financed and provided in accordance with innovative models of health in which priority is given to primary and community health services and collective action for health promotion. This implies a shift in the focus of inpatient care to polyclinic care and outpatient care (primary care), as well as a shift from treatment to prevention.

The peculiarity of health care is that the user of its services is the entire population. Each person during his life repeatedly becomes a patient of medical institutions. Every year in Europe in hospitals hospitalized about 18 % of the population, or one in five. In outpatient institutions (for primary care) patients annually treated, on average, about 6-10 times. Emergency services in different countries during the year are used by 10.0 to 25.0% of the population, that is, every fifth - tenth resident. Chronic pathology affects up to 60% of adults and almost 20% of children. The trend towards the deterioration of the health status of young people, the increase in the frequency of socially dangerous diseases, including tuberculosis and HIV/AIDS, mental disorders and the like, is of concern.

The situation, which has developed as a result of a number of objective and subjective reasons, is a real threat to the emergence and development of irreversible processes in the state of physical and mental health of the population of the country and, as a result, can adversely affect the socio - economic, political, spiritual development of the Ukrainian nation as a whole, which poses a threat to the national interests of the state.

This implies the need to invest in an integrated and comprehensive health system, including health promotion and the implementation of strategies to prevent health deterioration that help to maintain health and well-being at the appropriate level, and respect gender and cultural advantages in the planning and operation of health services.

REVIEW AND DISCUSSION

Today, the health care system of Ukraine does not fully meet the needs of the population in affordable, high-quality and effective medical care. Previous reforms in the field of health care have not produced the desired result due to the fact that they were inconsistent, mostly fragmented, in General, without changing the outdated system of health care since the time of the planned economy, which made it impossible to adapt it to market relations.

In this regard, it is necessary to develop a strategic approach to the development of the health care system in Ukraine and to identify priorities in the field of medical services based on the needs throughout the life cycle. This approach means assessing the full range of health services that are offered at different levels of the health system, based on the best available data and designed for the entire life cycle. This involves the appropriate combination of methods to understand how the specific needs of the population in the areas of health, including social benefits and costs of alternative interventions on the level of the health system, which should serve as a guide in the decision-making process on the allocation of resources to health care.

Policy options and interventions: assessment of local health needs based on existing characteristics of communicable and non-communicable diseases; full range of services for all population groups, defined through a transparent process of joint decision-making; strategic approach to procurement; public health care; assessment of health technologies.

Reassessment of the principle of health promotion, prevention and public health. This approach means an increased focus on prevention and the quality of health care in activities and in the allocation of health resources.

Policy options and interventions: monitoring the health status of the population; stratification of the population by level of risk; surveillance, research and control of risks and threats to human health; increasing financial and human resources allocated to health promotion and disease prevention; regulatory and legal regulation of public health relations and their enforcement.

Establishment of reliable systems based on primary health care. To reach the entire population and guarantee universal access to services, a reliable system of services based on primary health care is needed. The establishment of such a health system requires adequate funding, adequate training and links with other services and sectors. This approach involves strengthening the coordination and delivery of health care on a continuous basis over a long period of time for those people who have health problems, which contributes to the adoption of the necessary measures in the field of health at all levels. In addition, it involves the establishment of a comprehensive health system focused on the needs of the individual, the family and the community, as one of the main areas of practice with a focus on disease prevention and health promotion.

Policy options and interventions: services in the field of primary health care focused on the needs of the individual, family and community; multidisciplinary approach to primary care; General practitioners and family doctors; coordination with the aim of providing access to other types of medical care; increasing the share of budget funds (medical subsidy) on primary health care.

A shift in the focus of work towards health care at the level of primary health care centres and outpatient clinics. This is the process of replacing one type of care with another, more effective for the health system. This approach is to find the right balance between emergency, primary care, secondary (specialized), tertiary (highly specialized) care, palliative care and medical rehabilitation, while recognizing that each of these types of care plays an important role in the health system.

Policy options and interventions: medical care at the patient's place of residence; health care facilities for patients with chronic and incurable diseases; reorientation of second-level hospitals only to provide medical care in case of acute and complex conditions; outpatient surgery; day hospital; provision of medical care to patients in the acute period of the disease.

Update and implementation of new technologies. Rapid technological progress makes it possible to develop and implement innovative technologies in the health care system. In case of proper use they can provide the continuity of the recording information, to track the quality of health care, facilitate empowerment of patients and reach communities living in conditions of geographical isolation (mountain areas and remote rural settlements).

Policy options and interventions: the electronic medical record that is used on a joint basis (the patient and healthcare institution); telemedicine; timely medical assistance.

In this regard, in modern conditions, the health system is faced with new challenges to strengthen preventive services, improve the availability and quality of health care, improve primary health care, improve staffing, modernize infrastructure and ensure equity in health care. The existing health problems are not easy to solve, have a multidimensional complex nature, which necessitates the updating of health policy, the development and implementation of new strategies and programs. Modernization of health care concerns important professional and moral issues, affects the interests of many stakeholders, including medical staff and patients. Their opposition to innovations strengthens the conservatism of the industry.

Family medicine plays a decisive role in solving public health problems and improving its determinants, reducing the prevalence of risk factors, in the introduction of modern strategies for the prevention of chronic noncommunicable diseases and the formation of a healthy lifestyle. General medical practice should be considered as one that provides long-term care for the health of the patient and all members of his family, regardless of the nature of the disease, the state of organs and systems of the body, age, psycho-emotional, professional and other features.

In order to ensure the qualitative results of the reforms in the field of health care, it is necessary to conduct a detailed analysis of the improvement of health care in previous years.

So, in 2004 the program of activity of the Cabinet of Ministers of Ukraine "Sequence was recognized as satisfactory. Efficiency. Responsibility", approved by the Decree of the Verkhovna Rada of Ukraine on 16.03.2004. N 1602-IV, including, on health protection. By the decree of the President of Ukraine of 28.04.2004 N 493/2004 the Strategy of economic and social development of Ukraine "By European integration" for 2004 - 2015 was approved [3].

For development and introduction of system of an assessment and quality control of primary health care on the principles of family medicine in Komsomolsk of the Poltava region experiment (the order of Ministry of health of Ukraine of 16.01.2004 N 16) on implementation of the project of development of local government which consisted in creation of modern innovative model of rendering high-quality medical services to the population was carried out.

In these years, according to the order of the Ministry of health of Ukraine from g 17.02.2004. H 88, also the experiment was conducted in five regions of Ukraine to develop a method of differentiated distribution of funds by levels of medical care, taking into account the needs of primary health care on the principles of family medicine.

In addition, in cooperation with the European Union, the experiment was conducted, according to the order of the Ministry of health of Ukraine from 06.07.2004. N 338 "about carrying out experiment with the international participation on introduction of modern model of family medicine in the Autonomous Republic of Crimea, Zaporozhye and Khmelnytsky areas".

In the future, new, responsible tasks for the further development of family medicine were outlined in the "National program for the development of primary health care on the principles of family medicine for the period up to 2011", approved by the Law of Ukraine from 22.01.2010 N 1841-VI; Resolution of the Cabinet of Ministers of Ukraine "Some issues of improving the health care system" d from 17.02.2010. H 208; Laws of Ukraine "on amendments to the Basics of the legislation of Ukraine on health care regarding the improvement of medical care" from 07.07.2011. 3611 n-you "on the procedure for reforming the healthcare system in Vinnytsia, Dnipropetrovsk, Donetsk regions and Kyiv" from 07.07.2011 g N 3612-VI. [3, 6]

In order to create appropriate conditions for the implementation of the principles of family medicine in the activities of primary health care institutions, the Ministry of health of Ukraine has developed and approved a package of normative documents regulating the technology of family medicine. Further development of family medicine in Ukraine was focused on the achievement of the European level, according to the strategy of the world health organization "Fundamentals of health policy for all in the European region" ("Health-XXI").

Health 2020 is the Foundation of the new European health policy. It aims to support the actions of the entire state and society to "significantly improve the health and well-being of the population, reduce health inequalities, strengthen public health and ensure the availability of universal, sustainable and high-quality human-centred health systems".

The formation and implementation of an integrated intersectoral approach is an important prerequisite for the successful implementation of modern strategic objectives in the field of health, including preventive measures to eliminate the negative impact of social determinants of health, creating conditions for the preservation and strengthening of public health, healthy lifestyles, the formation of responsible attitude of each person to personal health. In Ukraine, the optimization of the system of medical care to the population is supposed to be carried out through the priority development of primary and emergency medical

care, differentiation of inpatient medical care, improvement of the system of rehabilitation, palliative care and medical rehabilitation with the transition from public funding of health institutions to the financing of measures to provide medical care to the population, based on its needs.

On 06.04.2017, the Verkhovna Rada of Ukraine adopted the Law of Ukraine" on amendments to some legislative acts of Ukraine on improvement of legislation on health issues". The need for the adoption of this Law is caused by the following.

The existing health care system in Ukraine does not meet the needs of the population in the field of health care, because it is outdated and such that it is slowly implementing international experience and trends in strengthening health systems, which in turn limits the access of all citizens to the provision of health care of appropriate quality. Households spend a significant part of the funds for the purchase of medicines and medical services. All this creates financial barriers to access to health care, especially for the poor, and often leads to financial crisis and impoverishment.

The discrepancy between the health care system and the needs of the population is largely due to the structural inefficiency and critical condition of its main institutional component – health institutions.

Today, the majority of health care institutions, which exist in the form of budgetary institutions, do not have a sufficient level of autonomy in decision-making on the current management and activities of the institution. Health facilities are limited in their ability to set goals and priorities for the use of budgetary resources. Directions of use of budgetary funds are strictly regulated according to the estimates. Even in case of emergency, health facilities cannot reallocate funds from one budget line to another.

At the same time, the available scientific evidence suggests that in health systems, and especially in the European region, there is a tendency to use strategic ("active") procurement as a mechanism for financing health care providers to ensure the best results in terms of improving public health. Mechanisms for concluding contracts (contracts) and payment on the basis of the volume and quality of services provided are Central elements of an effective system of procurement of medical services. More active procurement (where buyer and supplier roles are differentiated) can improve the quality and effectiveness of health systems by taking into account the needs of the population for health care, regional differences, interventions and services that best meet the needs and expectations of the population, the amount of resources available, procurement mechanisms, including contractual arrangements and supplier payment systems. The introduction of strategic procurement is closely connected with the issue of changing the economic status of health institutions.

Association agreement between Ukraine, on the one hand, and the European Union, the European atomic energy community and their member States, on the other hand, strengthening cooperation in the field of health between Ukraine and the EU in order to improve its security and protection of human health as a prerequisite for sustainable development and economic growth (Chapter 22 "Public health"). Such cooperation should include strengthening the health system of Ukraine and its capacity, in particular through the introduction of reforms.

Today, the Shupyk National Medical Academy of Postgraduate Education operates the Institute of family medicine, which, in addition to educational, methodological, scientific and clinical work, performs a number of national tasks of organizational and methodological direction to improve the provision of primary health care on the principles of family medicine by:

1) development and implementation of new technologies to minimize the risk of diseases and create a healthy environment based on research data;
2) development of a strategy for the formation of a conscious and responsible attitude of the population to their own health and personal safety;
3) optimization of the organization of primary health care aimed at solving the real needs of the population;
4) improving the quality of staffing and the level of training of specialists in the prevention and early detection of diseases, diagnosis and treatment;
5) carrying out modern innovative scientific developments with the mandatory creation of an effective system of implementation of their results in the practice of health care;
6) conducting research on the preservation and promotion of public health, primary prevention of diseases, the study of the negative impact of risk factors and social determinants on health and ways to minimize them, the formation of public health.

The main directions of solving the problem of continuous improvement of the quality and effectiveness of primary health care on the principles of family medicine are:

- the maximum approach of family medicine specialists to the population and improving the availability of primary health care for all residents of territorial communities;
- ensuring coordination, preventive orientation, standardization and evidence-based diagnostic, therapeutic and rehabilitation assistance from General practitioners-family doctors with specialists of other types of medical care;
- significant improvement in the impact of primary health care on public health through the formation and implementation of the principles of a healthy lifestyle for different age groups (valeological approaches);
- improving the effectiveness of primary health care in the use of financial resources from different sources;
- involvement of individual citizens, their families, public associations, local Executive bodies and local self-government bodies in solving specific problems of individual and public health;
- creation of investment projects involving private capital in the development of primary health care on the principles of family medicine;
- public participation in the management of primary health care on the principles of family medicine and increasing the level of satisfaction of local communities with the quality of health care;
- the use of non-material and material means of motivation to improve the quality of primary health care by paying for the work of family medicine specialists according to the quality indicators of the medical care provided;

- training of highly qualified specialists in primary health care at the pre-and post-graduate stages, as well as in the process of their continuous professional development during the entire period of work in the field of family medicine;
- legal support for the activities of family medicine specialists and active involvement in the formation, preservation and strengthening of the health of individuals and territorial communities through public associations and local authorities, that is, the creation of the foundations of public health;
- protection of the interests of patients in the process of interaction with the health care system, the General practitioner-family doctor functions "guide" in a complex system of different types of medical care;
- active use of the complex mechanism of the state management of development of primary medical care on the principles of family medicine at the micro level in the centers of primary medical care, out-patient clinics of family medicine, medical centers of family medicine);
- scientific and innovative support, information support and automation of workplaces of family medicine specialists;
- improvement of non-departmental (external) control tools and implementation of internal professional audit [4].

In Ukraine, the first steps are being taken to modernize the health system, taking into account the who resolution and recommendations.

CONCLUSIONS

Any measures aimed at the modernization of the health care system should be accompanied by joint efforts of all parties (patients, the medical community, legislative and executive authorities, as well as local authorities) to ensure the interest of health workers and the population in an effective health care system in Ukraine.

REFERENCES

1. WHO, the World Bank. Tracking universal health coverage: first global monitoring report. Geneva: World Health Organization; 2015,: http://apps.who.int/iris/bitstream/ 10665/ 174536/1, as at 4 April 2016
2. World health organisation. A mechanism for comprehensive people-centred health care. secretariat report. Sixty-ninth world health Assembly A69/39 Item 16.1 of the provisional agenda 15 April 2016
3. Voronenko Yu. Normative and legal support of family medicine in the light of the reform of health care in Ukraine. Public health. 2013;1:15-22.
4. Voronenko Yu. et al. Cross-sectoral interaction of education, science and practice as the key to effective training for primary care. Public health. 2014;1-2:14-24.
5. Voronenko Yu., Shekera O. G. Family medicine, led the reform of health of Ukraine. Public health. 2016;1-2:20-23.

Conflict of interest:
The Author declare no conflict of interest.

CORRESPONDING AUTHOR

Oleh G. Shekera
Shupyk National Medical Academy of Postgraduate Education
Str. Dorohozhytska 9, 04112, Kyiv, Ukraine
tel: +380667049775
e-mail: director_IFM_NMAPO@ukr.net

Received: 08.10.2018
Accepted: 28.12.2018

PRACA POGLĄDOWA
REVIEW ARTICLE

NIEWYDOLNOŚĆ SERCA W WOJEWÓDZTWIE OPOLSKIM – EPIDEMIOLOGIA I PERSPEKTYWY NA PRZYSZŁOŚĆ

HEART FAILURE IN OPOLE VOIVODESHIP – EPIDEMIOLOGY AND FUTURE PERSPECTIVES

Piotr Feusette[1], Marek Gierlotka[1], Andrzej Tukiendorf[2], Joanna Płonka[1], Jarosław Bugajski[1], Beata Łabuz-Roszak[3,4], Robert Bryk[5]

[1]KLINIKA KARDIOLOGII, UNIWERSYTECKI SZPITAL KLINICZNY, INSTYTUT MEDYCYNY, UNIWERSYTET OPOLSKI, OPOLE, POLSKA
[2]WYDZIAŁ NAUK O ZDROWIU, ZAKŁAD ORGANIZACJI I ZARZĄDZANIA , UNIWERSYTET MEDYCZNY WE WROCŁAWIU, WROCŁAW, POLSKA
[3]ODDZIAŁ NEUROLOGII, WOJEWÓDZKI SZPITAL SPECJALISTYCZNY IM. ŚW. JADWIGI, OPOLE, POLSKA
[4]KATEDRA I ZAKŁAD PODSTAWOWYCH NAUK MEDYCZNYCH, WYDZIAŁ ZDROWIA PUBLICZNEGO W BYTOMIU, ŚLĄSKI UNIWERSYTET MEDYCZNY W KATOWICACH, BYTOM, POLSKA
[5] OPOLSKI ODDZIAŁ WOJEWÓDZKI, NARODOWY FUNDUSZ ZDROWIA, OPOLE, POLSKA

STRESZCZENIE

Niewydolność serca występuje u około 2% dorosłej populacji w Europie. U jednej na pięć osób w wieku 40 lat podczas dalszego życia dojdzie do rozwoju niewydolności serca. Dolegliwość ta dotyka 20 000 osób w województwie opolskim. Zaostrzenie niewydolności serca, w różnych postaciach, jest drugą, po ostrych zespołach wieńcowych, przyczyną pilnych przyjęć do Kliniki Kardiologii Uniwersyteckiego Szpitala Klinicznego w Opolu. W opracowaniu przedstawiono prognozę hospitalizacji pacjentów z niewydolnością serca na lata 2015—-2050 uwzględniającą procesy depopulacji zachodzące w województwie opolskim. Analiza pozwala przewidzieć, że grupą wiekową szczególnie narażoną na tego typu zachorowanie w najbliższych dziesięcioleciach będą osoby, które dzisiaj zalicza się do nastolatków i młodych dorosłych. Artykuł charakteryzuje aktualne metody farmakoterapii i leczenia interwencyjnego niewydolności serca, analizując ich dostępność z perspektywy mieszkańca województwa opolskiego. Poprawa rokowania pacjentów z niewydolnością serca może nastąpić jedynie poprzez możliwie szeroką implementację wytycznych leczenia niewydolności serca zalecanych przez Europejskie Towarzystwo Kardiologiczne. Temu celowi służyć ma wprowadzenie w naszym kraju programu „Kompleksowej opieki nad chorym z niewydolnością serca (KONS)". Przesunięcie ciężaru opieki nad pacjentem z niewydolnością serca do poradni specjalistycznych spowoduje istotne ograniczenie liczby hospitalizacji, co w konsekwencji spowoduje także znaczną redukcję ogólnych kosztów leczenia chorych.

SŁOWA KLUCZOWE: niewydolność serca, epidemiologia, kompleksowa opieka nad chorym z niewydolnością serca

ABSTRACT

Heart failure appears in 2% of the adult population in Europe. One in five people aged 40 years will develop heart failure during their lifetime. Heart failure touch 20,000 people in the Opole province. Heart failure is the second, after acute coronary syndromes, urgent cause of admissions to the Clinic of Cardiology at the University Hospital in Opole. The paper presents the prognosis of hospitalization of patients with heart failure for the years 2015-2050 taking into account the processes of depopulation taking place in our region. The analysis makes it possible to predict that the age group particularly exposed to heart failure in the coming decades will be people who today belong to teenagers and young adults. The article presents current methods of treatment of heart failure. Improvement in the prognosis of patients with heart failure can occur through the implementation of the guidelines for treatment of heart failure recommended by the ESC. This goal is to be achieved by introducing the "Comprehensive care for patients with heart failure (KONS)" program in our country. The shift of the burden of care for patient with heart failure to outpatient unit will result in a significant reduction in the number of hospitalizations.

KEY WORDS: heart failure, epidemiology, coordinated heart failure care

Wiad Lek 2019, 72, 1, 112-119

WSTĘP

Niewydolność serca występuje u około 2% dorosłej populacji w Europie. U jednej na pięć osób w wieku 40 lat podczas dalszego życia dojdzie do rozwoju tego schorzenia. Według danych Oddziału Opolskiego Głównego Urzędu Statystycznego (GUS) w 2013 r. województwo opolskie zamieszkiwało 1 004 400 mieszkańców. Ekstrapolując dane europejskie i polskie na grunt województwa opolskiego, możemy określić aktualnie liczbę chorych z niewydolnością serca w naszym regionie na około 20 000 osób. Obecnie osoby w wieku powyżej 65 lat stanowią 15,3% populacji województwa opolskiego. W liczbach bezwzględnych to

154 000 osób. Prognozuje się, że w ciągu najbliższych 5 lat liczba osób, które przekroczą 65. rok życia wynosić będzie około 17% populacji opolszczyzny. Według opublikowanej niedawno przez GUS prognozy demograficznej na lata 2014–2050 dla województwa opolskiego, odsetek osób powyżej 65. roku życia wyniesie w 2035 r. 27,3%, a w 2050 r. 36,1% całości populacji. W tym samym czasie należy spodziewać się spadku populacji ogólnej do 865 100 osób w 2035 r. i 744 600 osób w 2050 r. Przyjmując, że liczba chorych na niewydolność serca stanowi od 6 do 10% wszystkich osób powyżej 65. roku życia, należy założyć, że w 2020 r. liczba chorych na niewydolność serca w województwie opolskim tylko w tej grupie wiekowej wyniesie od 13 000 do 16 000 osób. W roku 2035 r. liczba chorych na niewydolność serca wśród osób powyżej 65. roku życia wzrośnie do około 20 000, a w 2050 r. do 26 000 osób [1].

W Klinice Kardiologii Uniwersyteckiego Szpitala Klinicznego w Opolu, do roku 2017, na Oddziale Kardiologii Wojewódzkiego Centrum Medycznego w Opolu, hospitalizowanych jest co roku około 3 700 chorych. Z tego blisko 60% hospitalizacji to hospitalizacje w trybie pilnym. Zaostrzenie niewydolności serca, w różnych postaciach, jest drugą, po ostrych zespołach wieńcowych, przyczyną pilnych przyjęć. Niewydolność serca jest drugą pod względem częstości przyczyną zgonów chorych leczonych w Klinice. Przeprowadzona analiza chorych zmarłych, obejmująca lata 2012–2017 wskazuje, że najwięcej zgonów spowodowanych było ostrymi zespołami wieńcowymi (głównie zawałem serca) – 53% oraz niewydolnością serca – 35%. Średni wiek chorych zmarłych z powodu niewydolności serca wynosił 75 lat. Przyczyną niewydolności serca w ponad 80% przypadków było niedokrwienne uszkodzenie serca. Czas pobytu chorego z niewydolnością serca był uzależniony od prowadzonego leczenia i wynosił średnio 10 dni. Przeważającą część chorych (ponad 80%) hospitalizowano w trybie ostrodyżurowym. Pozostali pacjenci byli przyjmowani w trybie planowym. Zaostrzenie niewydolności serca wymaga około 7-dniowego pobytu w szpitalu, tym niemniej ulegał on wydłużeniu, jeśli chory wymagał dodatkowej diagnostyki bądź specjalistycznego leczenia inwazyjnego. Zdarzało się, że chorzy nieodpowiadający na standardowe leczenie niewydolności krążenia, z towarzyszącymi zaburzeniami metabolicznymi i niewydolnością nerek, hospitalizowani byli nawet do kilku tygodni.

Oddziały kardiologiczne oferują znacznie więcej możliwości diagnostycznych i leczniczych dla chorych cierpiących na niewydolność serca niż oddziały internistyczne. Poprawę rokowania chorych z niedokrwienną niewydolnością serca można uzyskać poprzez odpowiednie połączenie postępowania inwazyjnego, które poprzez rewaskularyzację poprawi ukrwienie serca, z optymalizacją prowadzonej w warunkach szpitalnych farmakoterapii. Istotną poprawę rokowania i często także znaczną poprawę komfortu życia przynosi pacjentom z niewydolnością serca współczesna elektrofizjologia. Implantacja kardiowertera-defibrylatora pozwala na znaczące ograniczenie ryzyka nagłego zgonu sercowego a terapia resynchronizującą poprawia zarówno rokowanie jak i komfort życia chorych z niewydolnością serca.

LECZENIE SZPITALNE CHORYCH Z NIEWYDOLNOŚCIĄ SERCA W WOJEWÓDZTWIE OPOLSKIM

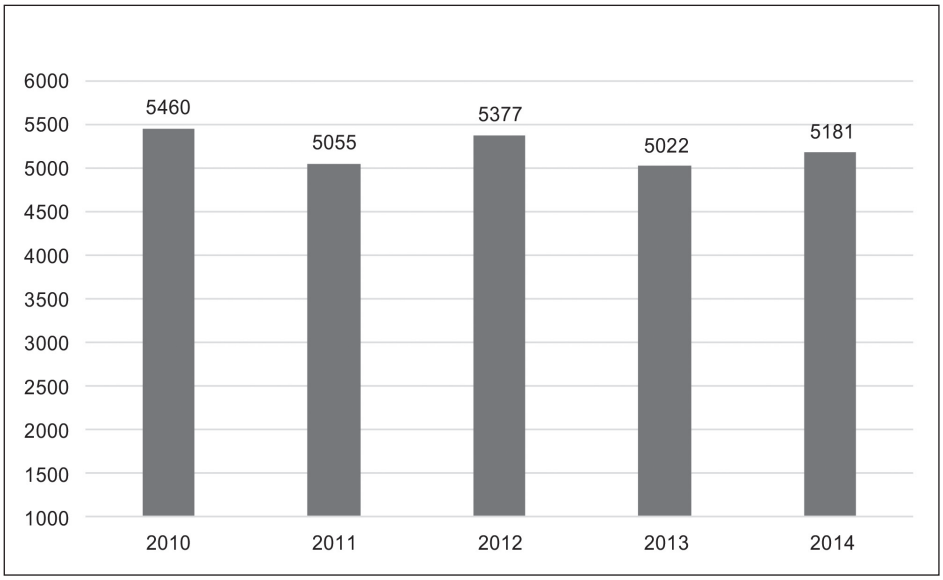
Liczba hospitalizacji pacjentów z niewydolnością serca na 100 000 mieszkańców w Polsce waha się w zależności od województwa. W 2012 r najwięcej hospitalizacji zanotowano w województwie lubelskim – 604, natomiast najmniej w województwie pomorskim – 232. W 2012 roku zanotowano w województwie opolskim 433 hospitalizacje pacjentów z niewydolnością serca na 100 000 mieszkańców. Według danych Opolskiego Oddziału Wojewódzkiego Narodowego Funduszu Zdrowia roczna liczba hospitalizacji pacjentów z rozpoznaniem niewydolności serca w latach 2010–2014 pozostawała na stabilnym poziomie (Ryc. 1).

Wśród chorych leczonych w szpitalach z rozpoznaniem niewydolności serca dominują nieznacznie kobiety. Przewagę kobiet w liczbie hospitalizacji, nieco znaczniej wyrażoną, zanotowano w danych ogólnopolskich. W 2012 r. w Polsce kobiety stanowiły 55,7% chorych hospitalizowanych z rozpoznaniem niewydolności serca, natomiast mężczyźni 44,3%. Na rycinie 2 przedstawiono rozkład hospitalizacji z niewydolnością serca w województwie opolskim wśród kobiety i mężczyzn w latach 2010–2014.

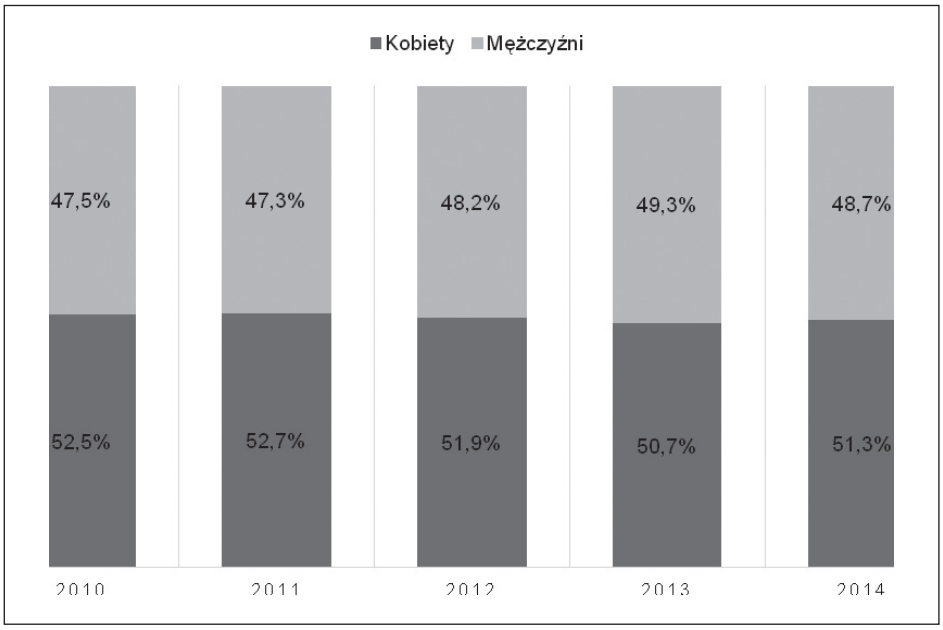
Niewydolność serca jest chorobą wieku podeszłego. Spośród pacjentów hospitalizowanych w województwie opolskim przeważającą większość stanowią osoby powyżej 65 roku życia. Stanowią one blisko 85% wszystkich hospitalizacji z powodu niewydolności serca. Dane te nie odbiegają znacząco od danych ogólnopolskich i europejskich, potwierdzając, że granicą wiekową powyżej, której lawinowo rośnie liczba hospitalizacji z powodu niewydolności serca jest 65. rok życia. Dane dotyczące hospitalizacji z powodu niewydolności serca z podziałem na dwie grupy wiekowe w województwie opolskim w latach 2010–2014 przedstawia rycina 3.

Łączna analiza danych, dotyczących hospitalizacji chorych z rozpoznaniem niewydolności serca w latach 2010–2014 i prognozy demograficznej na lata 2014–2050, przedstawionej przez Opolski Urząd Statystyczny, pozwoliła na określenie przybliżonej liczby chorych, którzy będą leczeni w szpitalach w województwie opolskim do roku 2050. Odsetek populacji województwa opolskiego, która będzie wymagała hospitalizacji z powodu niewydolności serca w latach 2015–2050 przedstawia rycina 4.

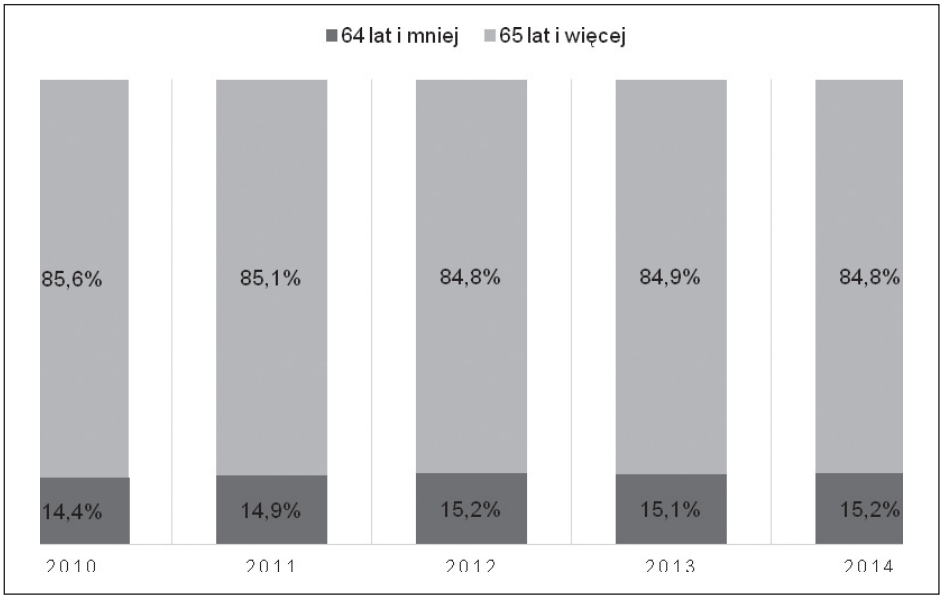
Przedstawiona prognoza wskazuje, że należy spodziewać się nieco innych trendów w hospitalizacji chorych z niewydolnością serca niż dotychczas. W grupie chorych 64 lat i mniej dojdzie do stopniowego wzrostu liczby hospitalizacji, bardziej wyrażonej w grupie kobiet niż mężczyzn. W 2050 roku należy oczekiwać, że 0,3% populacji województwa opolskiego, w tej grupie wiekowej, będzie wymagało hospitalizacji z powodu niewydolności serca. W grupie chorych 65 lat i więcej liczba hospitalizacji chorych z niewydolnością serca ulegnie zmniejszeniu. W 2050 r. 3% mężczyzn i blisko 2% kobiet, w tej grupie wiekowej, wymagać będzie hospitalizacji. Pomimo nieco zmienionych prognozowanych trendów leczenia szpitalnego, w grupie wiekowej 65 lat i więcej, nadal około 10-krotnie



Ryc. 1. Liczba hospitalizacji pacjentów z niewydolnością serca w województwie opolskim w latach 2010–2014.



Ryc. 2. Procentowy udział kobiet i mężczyzn w ogólnej liczbie hospitalizacji z powodu niewydolnością serca w województwie opolskim w latach 2010–2014.



Ryc. 3. Procentowy udział chorych w wieku 65 lat i więcej oraz młodszych w ogólnej liczbie hospitalizacji z powodu niewydolnością serca w województwie opolskim w latach 2010-2014.

więcej osób będzie wymagało hospitalizacji z powodu niewydolności serca niż w grupie wiekowej 64 i mniej. Spodziewany w przyszłości wzrost hospitalizacji w grupie osób 64 lat i mniej dotyczyć będzie populacji, którą dzisiaj stanowią nastolatki i młodzi dorośli. Aby odwrócić ten niekorzystny trend, należy już dzisiaj pomyśleć o szeroko zakrojonych działaniach profilaktycznych adresowanych to tych grup wiekowych mających na celu propagowanie zdrowego stylu życia.

PERSPEKTYWY LECZENIA NIEWYDOLNOŚCI SERCA W WOJEWÓDZTWIE OPOLSKIM

DIAGNOSTYKA

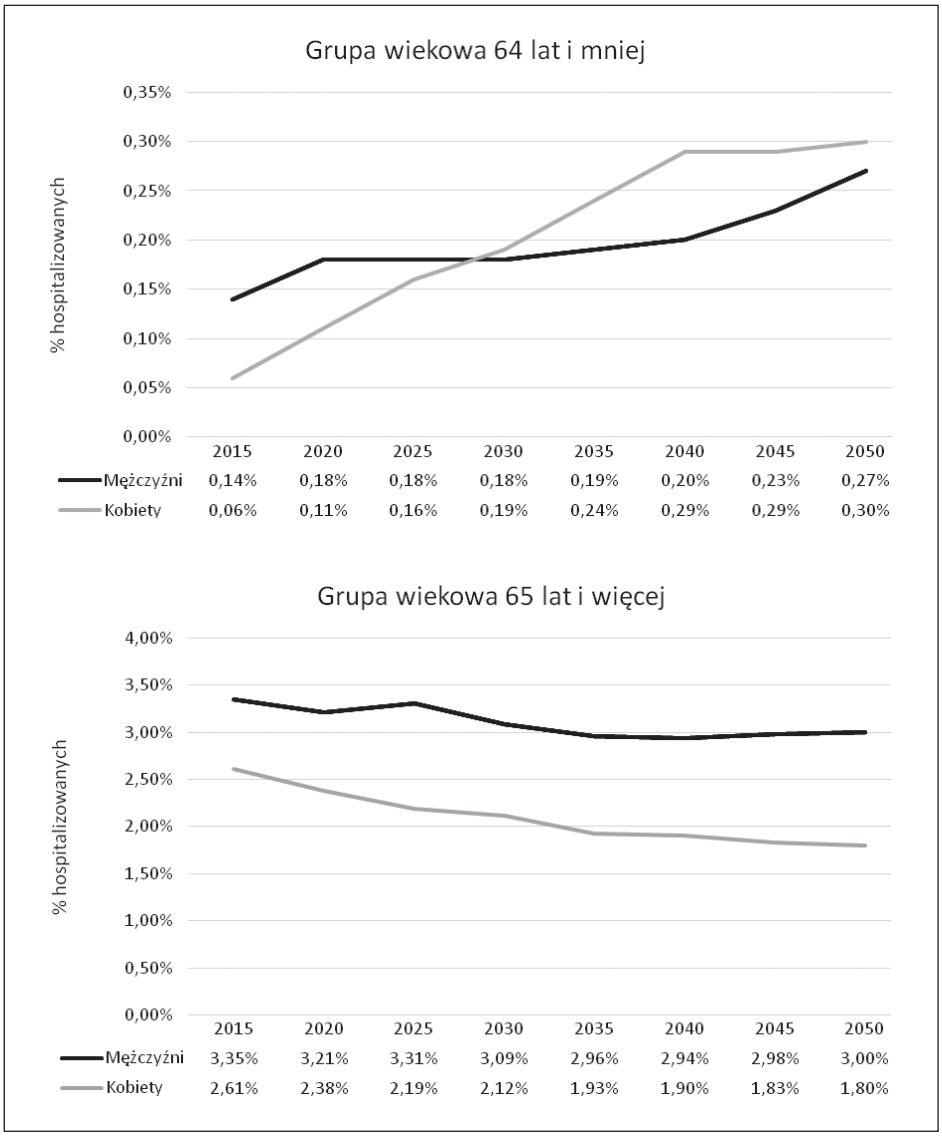
Podstawą diagnostyki niewydolności serca jest wywiad oraz badanie echokardiograficzne. Badanie echo serca, ze względu na swoją dostępność, dokładność, powtarzalność i stosunkowo niski koszt, pozostaje metodą z wyboru w diagnostyce niewydolności serca. Badanie echokardiograficzne mogłoby służyć jako metoda przesiewowa do rozpoznawania uszkodzenia serca u pacjentów z licznymi czynnikami ryzyka. Metodą obrazowania serca, która dostarcza podobnych informacji dotyczących budowy serca i jego czynności, jak echokardiografia, jest rezonans magnetyczny serca (CMR). Badanie to jest alternatywą w ocenie serca u chorych, u których istnieją trudności w uzyskaniu wiarygodnych obrazów echokardiograficznych. CMR szczególnie dobrze obrazuje cechy naciekania lub zapalenie mięśnia sercowego, guzy serca i osierdzia oraz wszystkie postacie kardiomiopatii. Metoda CMR zyskuje w ostatnich latach coraz większe znaczenie w diagnostyce kardiologicznej. W Zakładzie Diagnostyki Obrazowej USK w Opolu co roku wykonuje się ponad 400 CMR. Ponad połowa z tych badań dotyczy oceny struktur serca i jego funkcji u pacjentów z różnymi postaciami kardiomiopatii, którzy kliniczne prezentują objawy niewydolności serca.

FARMAKOTERAPIA

Aktualnie prowadzonych jest wiele badań klinicznych, które mogą przynieść nowe sposoby farmakologicznego leczenia niewydolności serca. Badania te dotyczą nowych substancji, ale też precyzują zastosowanie dotychczas już znanych preparatów. Lekiem, który stosunkowo niedawno został wprowadzony do leczenia chorych z niewydolnością serca jest iwabradyna. Iwabradyna zmniejsza akcję serca poprzez hamowanie kanałów If w węźle zatokowym i z tego powodu powinna być stosowana jedynie u pacjentów z rytmem zatokowym. Zmniejsza częstość złożonego punktu końcowego – łącznie ocenianej śmiertelności i hospitalizacji z powodu niewydolności serca – u pacjentów ze objawową niewydolnością serca oraz LVEF ≤35%, z rytmem zatokowym i akcją serca ≥70 uderzeń na minutę, którzy byli hospitalizowani z powodu niewydolności serca w ciągu ostatnich 12 miesięcy oraz otrzymywali betabloker w maksymalnie tolerowanych dawkach, ACEI (inhibitor enzymu konwertującego angiotensynę) lub ARB (antagonista receptora angiotensynowego) oraz MRA (antagonista receptora mineralokortykoidowego) w dawkach, których skuteczność udokumentowano w badaniach klinicznych [2, 3]. Wielkie zainteresowanie, podczas kongresu Europejskiego Towarzystwa Kardiologicznego w 2014 wzbudziły wyniki badania PARADIGM-HF [4]. Badany w tym programie klinicznym lek Sacubitril wykazał swoją skuteczność w terapii niewydolności serca zmniejszając ryzyko zgonu i częstość rehospitalizacji. Lek ten szybko znalazł swoje miejsce w aktualnie zalecanej farmakoterapii niewydolności serca. Zanim kolejne nowe preparaty znajdą zastosowanie w leczeniu chorych z niewydolnością serca, należy dążyć do optymalnego stosowania dotychczas zalecanych leków o udowodnionej skuteczności klinicznej. Stosowanie w praktyce aktualnie obowiązujących, pochodzących z roku 2016, zaleceń Europejskiego Towarzystwa Kardiologicznego dotyczących farmakoterapii przewlekłej niewydolności serca pozostawia wiele do życzenia, szczególnie na poziomie podstawowej opieki zdrowotnej.

LECZENIE ZA POMOCĄ URZĄDZEŃ WSZCZEPIALNYCH

Według aktualnych standardów Europejskiego Towarzystwa Kardiologicznego celem zmniejszenia ryzyka zgonu zaleca się, w ramach prewencji wtórnej, wszczepienie kardiowertera-defibrylatora u pacjentów z komorowymi zaburzeniami rytmu serca powodującymi niestabilność hemodynamiczną, u których oczekiwany czas przeżycia w dobrym stanie funkcjonalnym przekracza rok. W ramach prewencji pierwotnej nagłego zgonu sercowego wszczepienie kardiowertera-defibrylatora zaleca się u chorych z objawową niewydolnością serca i frakcją wyrzutową lewej komory ≤35% leczonych optymalną farmakoterapią przez okres ≥3 miesięcy, którzy rokują przeżycie 1 roku w dobrym stanie funkcjonalnym. Pomimo zastosowania wszczepialnych urządzeń, może dochodzić do wystąpienia zagrażających życiu arytmii komorowych. W przypadku braku efektu zastosowanego leczenia należy rozważyć wykonanie ablacji ogniska będącego źródłem uporczywej arytmii. Aktualnie nie ma wątpliwości, że pacjenci z oczekiwanym czasem przeżycia powyżej 1 roku, u których występują objawy niewydolności serca, rytm zatokowy, zapis elektrokardiogramu z zespołem QRS ≥150 ms i frakcja wyrzutowa lewej komory nie przekracza 35%, zyskują na wszczepieniu układu resynchronizującego. Terapia resynchronizująca, w połączeniu z zastosowaniem kardiowertera-defibrylatora, poprawia istotnie rokowanie, zmniejsza częstość rehospitalizacji i poprawia komfort życia pacjentów z niewydolnością serca. W roku 2017 w Pracowni Elektrofizjologii Kliniki Kardiologii USK w Opolu implantowano 123 kardiowertery-defibrylatory i łącznie wykonano 86 implantacji urządzeń resynchronizujących. Wszystkie te zabiegi wykonano u chorych z niewydolnością serca. Przyszłość terapii urządzeniami wszczepialnymi to wprowadzenie do użycia nowych, bardziej zawansowanych urządzeń, które będą dopasowywać swoją pracę do zmieniających się potrzeb chorego [3].



Ryc. 4. Odsetek populacji województwa opolskiego, jaka będzie wymagała hospitalizacji z powodu niewydolności serca w latach 2015–2050 (prognoza).

LECZENIE INWAZYJNE I OPERACYJNE NIEWYDOLNOŚCI SERCA

Poprawa ukrwienia mięśnia sercowego w obszarach serca o udowodnionej żywotności ogranicza postęp niewydolności serca, poprawia rokowanie i komfort życia chorych z niewydolnością serca. Wybór metody rewaskularyzacji – angioplastyka wieńcowa, czy też wszczepienie pomostów aortalno-wieńcowych, zależy od stopnia zaawansowania choroby wieńcowej, chorób współistniejących i preferencji pacjenta. Zaleca się, aby decyzja o sposobie leczenia, zapadała w zespole lekarskim składającym się z kardiologa inwazyjnego, kardiologa zachowawczego, kardiochirurga i anestezjologa (tzw. *Heart Team*).

Zwężenie zastawki aortalnej jest główną wadą serca osób w wieku podeszłym. Jest też jedną z ważniejszych przyczyn niewydolności serca w tej grupie wiekowej. Implantacja zastawki drogą przezskórną czy też przezkoniuszkową jest alternatywą dla klasycznego zabiegu kardiochirurgicznego. Przezskórną implantację zastawki aortalnej (TAVI) zaleca się u pacjentów z ciężką stenozą aortalną, którzy nie są kandydatami do operacji chirurgicznej w ocenie *Heart Team* z przewidywanym czasem trwania życia po TAVI powyżej roku. Należy również rozważyć TAVI u pacjentów wysokiego ryzyka z ciężką stenozą aortalną, którzy mogliby być leczeni chirurgicznie, ale w ocenie *Heart Team* TAVI jest metodą preferowaną ze względu na indywidualne ryzyko i możliwości anatomiczne [3]. Metody te zalecane są aktualnie dla chorych, którzy z uwagi na duże ryzyko, zostali zdyskwalifikowani od zabiegu operacyjnego. Czy metody inwazyjne będą zalecane także dla chorych z małym i umiarkowanym ryzykiem zabiegu kardiochirurgicznego? Na to pytanie odpowiedzą toczące się badania kliniczne. Zabiegi przezskórnej i przezkoniuszkowej implantacji zastawki aortalnej są wykonywane w Pracowni Hemodynamiki Kliniki Kardiologii USK w Opolu od wielu lat. W latach 2012–2019 wykonano 98 takich zabiegów.

Kolejnym etapem rozwoju technik przezskórnych są zabiegi naprawcze niedomykalności zastawki mitralnej metodą MitraClip, które poprawiają rokowanie chorych z niewydolnością serca w sytuacji, gdy kardiochirurgiczna

wymiana lub naprawa jest zbyt ryzykowna. Pierwsze takie zabiegi z powodzeniem przeprowadzono w Klinice Kardiologii USK w Opolu w grudniu 2018 roku, dzięki wsparciu między innymi Oddziału Opolskiego Narodowego Funduszu Zdrowia. Dotychczas wykonano 5 takich zabiegów.

Metodą, którą można zaliczyć do inwazyjnych sposobów leczenia niewydolności serca jest terapia za pomocą komórek macierzystych. Komórki macierzyste mogłyby zapewnić naprawę uszkodzonego mięśnia sercowego. Na obecnym etapie wiedzy nie ma jednak wystarczających dowodów klinicznych do rutynowego stosowania tej metod. Rozwój terapii komórkowej w leczeniu i zapobieganiu niewydolności serca wymagać będzie lepszego poznania mechanizmów zaangażowanych w regenerację i funkcjonalną naprawę mięśnia sercowego.

Współczesna kardiochirurgia oferuje wiele metod leczenia niewydolności serca. Są to przede wszystkim, wspomniane już operacyjne metody rewaskularyzacji mięśnia sercowego, zabiegi naprawcze na zastawkach serca i wszczepianie sztucznych zastawek. Wszystkie te metody są nadal rozwijane i na pewno także w przyszłości będą bardzo użyteczne w zapobieganiu i leczeniu niewydolności serca. Jedną z metod chirurgicznych stosowanych w leczeniu niewydolności serca, która kilka lat temu budziła nadzieję, jest geometryczna rekonstrukcja lewej komory z użyciem wewnątrzkomorowej łaty Dora. Metoda ta opracowana przez Dora i udoskonalona przez Menicantiego, polega na wycięciu blizny i zastąpieniu wyciętego fragmentu lewej komory przez łatę z tworzywa sztucznego. Prawidłowo wykonany zabieg, w założeniu, ma odtwarzać kształt i wymiar lewej komory serca i przywrócić odpowiednie położenie koniuszka lewej komory serca. Badanie kliniczne, które miało zweryfikować skuteczność tej metody leczenia niewydolności serca nosiło akronim STICH. Niestety opublikowane w 2011 r. wyniki tego badania nie wykazały, że optymalizacja kształtu i rozmiaru lewej komory po chirurgicznej rekonstrukcji w połączeniu z rewaskularyzacją chirurgiczną poprawia rokowanie chorych z niewydolnością serca [5–7] . Kardiochirurgia to także transplantacja serca, która jest uznaną i skuteczną metodą leczenia krańcowych stadiów niewydolności serca. W gestii kardiochirurga leży także wszczepianie układów wspomagających pracę serca. Wspomaganie takie może mieć charakter krótkoterminowy, zastępując pracę serca do czasu powrotu jego własnej funkcji bądź długoterminowy, będąc pomostem do transplantacji lub leczeniem docelowym. Trwają ciągle prace nad unowocześnieniem tego typu urządzeń i prace służące konstrukcji coraz bardziej zaawansowanych technicznie form sztucznego serca.

LECZENIE SZPITALNE NIEWYDOLNOŚCI SERCA

O leczeniu szpitalnym niewydolności serca wspomniano już wcześniej w niniejszym opracowaniu. Specjalistyczna diagnostyka i leczenie w ostrej fazie niewydolności serca winny odbywać się w warunkach dobrze wyposażonych oddziałów kardiologicznych, będących w stanie zapewnić chorym wielospecjalistyczną opiekę.

Ważną rolę odegrać również mogą dzienne oddziały niewydolności serca. Formuła ta z powodzeniem realizowana jest w Zabrzu w III Katedrze i Klinice Kardiologii w Śląskim Centrum Chorób Serca. Dzienny oddział niewydolności serca jest z jednej strony pomostem pomiędzy hospitalizacją a leczeniem ambulatoryjnym. Z drugiej strony, stanowi alternatywne dla oddziału szpitalnego miejsce leczenia dla pacjentów, którzy wymagają zastosowania przez pewien czas leków dożylnych dla opanowania zaostrzenia niewydolności serca. Klinika Kardiologii USK w Opolu czyni starania, aby taki oddział uruchomić w najbliższym czasie.

Po opanowaniu ostrej fazy niewydolności serca i po ustaleniu optymalnego sposobu leczenia, dalsza opieka nad chorym powinna odbywać się w ośrodku zajmującym się rehabilitacją kardiologiczną. Taka rehabilitacja składająca się z usprawniania ruchowego i edukacji prozdrowotnej jest niezbędna do uzyskania optymalnego wyniku leczenia niewydolności serca. Część chorych, którzy nie mogą być poddani rehabilitacji z uwagi na zaawansowane uszkodzenie serca, wymagać będzie długotrwałego leczenia w warunkach szpitalnych. Taki ośrodek leczący tę grupę chorych znajduje się w województwie opolskim, jest nim Oddział Kardiologii szpitala św. Elżbiety w Białej. Leczenie niewydolności serca stanie się także w przyszłości wyzwaniem dla oddziałów geriatrycznych. Końcowe stadium niewydolności serca wymaga postępowania paliatywnego podobnego w założeniu do opieki paliatywnej prowadzonej w chorobach nowotworowych. Taki ośrodek opieki paliatywnej dla chorych z niewydolnością serca powinien powstać w naszym regionie.

LECZENIE AMBULATORYJNE NIEWYDOLNOŚCI SERCA

Należy dążyć do poprawy leczenia ambulatoryjnego pacjentów z niewydolnością serca. Wskazane byłoby stworzenie specjalistycznych poradni leczenia niewydolności serca na bazie wybranych dotychczas funkcjonujących poradni kardiologicznych. Zespół takiej poradni powinien mieć charakter interdyscyplinarny. W jego skład oprócz kardiologa i specjalnie wyszkolonej pielęgniarki powinni wchodzić: fizjoterapeuta, dietetyk, niekiedy także farmakolog kliniczny i psycholog. W poradni takiej powinna istnieć także możliwość kontroli wszczepionych urządzeń – kardiowerterów-defibrylatorów i układów resynchronizujących przez doświadczonego elektrofizjologa. Działalność poradni niewydolności serca musi mieć także charakter edukacyjny dla pacjenta i jego rodziny i pozostawać w ścisłej współpracy z lekarzami podstawowej opieki zdrowotnej. Uzupełnieniem poradni niewydolności serca może być program pomocy domowej. Program pomocy domowej może funkcjonować w formie wizyty pielęgniarki w domu chorego lub w formie tzw. „szpitala domowego". Pierwsza forma postępowania polega na kontrolnej wizycie w domu chorego w celu edukacji i poradnictwa, a także w celu sprawdzenia stopnia realizacji zaleceń poszpitalnych. Druga forma opieki to forma pośrednia pomiędzy leczeniem ambulatoryjnym a leczeniem szpitalnym.

Intensyfikacja leczenia po kontrolnej domowej wizycie kardiologa i pielęgniarki może zapobiec rehospitalizacji chorego. Stworzenie poradni niewydolności serca i zapewnienie im źródeł finansowania będzie wymagało środków finansowych. Jeśli jednak uda się przez poprawić rokowanie chorych co do przeżycia i ograniczyć liczbę rehospitalizacji, w efekcie doprowadzi to do zmniejszenia kosztów leczenia chorych z niewydolnością serca. Leczenie szpitalne stanowi bowiem ponad 2/3 wszystkich kosztów ponoszonych przez systemy zdrowotne na leczenie niewydolności serca. [8].

KOMPLEKSOWA OPIEKA NAD CHORYMI Z NIEWYDOLNOŚCIĄ SERCA – KONS

Mając na uwadze konieczność podjęcia działań zmierzających do poprawy sytuacji chorych na niewydolność serca w Polsce, grupa ekspertów Polskiego Towarzystwa Kardiologicznego zaproponowała wprowadzenie aktywnego systemu „zarządzania chorobą", który został nazwany „Kompleksową opieką nad chorym z niewydolnością serca (KONS)". Wstępne założenia projektu KONS zaprezentowano na łamach „Kardiologii Polskiej" w lutym 2018 roku. Celem wprowadzenia modelu KONS jest uzyskanie najlepszych możliwych efektów klinicznych opieki nad chorym z niewydolnością serca, przy efektywnym wykorzystaniu istniejących zasobów opieki zdrowotnej. Proponowany model opieki nad chorym z niewydolnością serca ma trzystopniową strukturę. Podstawę tej struktury, pierwsze piętro, ma stanowić opieka podstawowa realizowana przez lekarza podstawowej opieki zdrowotnej i współpracującą z nim pielęgniarkę środowiskową. Ich zadaniem byłoby aktywne rozpoznawanie nowych przypadków niewydolności serca oraz prowadzenie stałej opieki i opieki długoterminowej nad chorymi ze „stabilną" postacią niewydolności serca. Drugim piętrem trzystopniowej struktury KONS będą szpitale ogólne i kardiologiczne oraz ambulatoryjna opieka specjalistyczna. Szpitale takie miałyby dysponować oddziałami dziennymi lub stacjonarnymi, które umożliwią leczenie zaostrzeń niewydolności serca, a także, poprzez poradnie specjalistyczne, stanowić będą wsparcie merytoryczne dla opieki podstawowej. Trzecie piętro opieki nad chorym z niewydolnością serca stanowić będą ośrodki niewydolności serca pozwalające na wysokospecjalistyczne leczenie. Niezbędnym elementem tego leczenia są interwencje z zakresu elektroterapii, kardiologii interwencyjnej, kardiochirurgii, w tym transplantacji i mechanicznego wspomagania krążenia. Ostatecznym celem wprowadzenia KONS jest uzyskanie maksymalnej długości i jakości życia chorych z niewydolnością serca poprzez optymalne wykorzystanie systemu opieki zdrowotnej. Jest to niezwykle ważne w kontekście starzenia się populacji Polski, które jest szczególnie widoczne w województwie opolskim, w regionie zagrożonym depopulacją [9].

PODSUMOWANIE

1. Problemy dotyczące chorych na niewydolność serca są w województwie opolskim podobne jak w pozostałych regionach naszego kraju. Niekorzystne prognozy demograficzne odnoszące się do naszego regionu mogą w najbliższych dziesięcioleciach prowadzić do istotnego wzrostu zachorowalności na niewydolność serca w województwie opolskim. Stanowić to będzie duże wyzwanie dla systemu ochrony zdrowia w naszym regionie.
2. Ograniczenie zapadalności na niewydolność serca można osiągnąć poprzez szerokie wprowadzenie do codziennego życia zasad profilaktyki chorób układu krążenia opartych o powszechnie dostępne standardy Europejskiego Towarzystwa Kardiologicznego.
3. Analiza prognozy demograficznej województwa opolskiego na lata 2014–2050 pozwala przewidzieć, że grupą wiekową szczególnie narażoną na zachorowanie na niewydolność serca w najbliższych dziesięcioleciach będą osoby, które dzisiaj zalicza się do nastolatków i młodych dorosłych. Oznacza to, że należy już dzisiaj pomyśleć o szeroko zakrojonych działaniach profilaktycznych adresowanych do tych grup wiekowych, mających na celu propagowanie zdrowego stylu życia.
4. Poprawa rokowania, prowadząca do wydłużenia życia pacjentów z niewydolnością serca, powinna opierać się o możliwie szeroką implementację zasad leczenia i profilaktyki wtórnej, zawartych w obowiązujących zaleceniach Europejskiego Towarzystwa Kardiologicznego. Stosowanie zalecanych sposobów leczenia powinno dotyczyć wszystkich poziomów opieki nad pacjentem z niewydolnością serca, począwszy od lekarza podstawowej opieki medycznej, poprzez ambulatoryjną opiekę specjalistyczną, skończywszy na leczeniu szpitalnym i poszpitalnej rehabilitacji.
5. Stworzenie jednolitego systemu opieki nad pacjentem z niewydolnością serca, składającego się z opieki podstawowej, ambulatoryjnej opieki specjalistycznej i ośrodków niewydolności serca, zgodnie z zaprojektowanymi zasadami KONS, jest niezbędne w województwie opolskim. Taki system opieki powinien być szczególnie efektywny w regionach zagrożonych depopulacją.
6. Przesunięcie ciężaru opieki nad pacjentem z niewydolnością serca do poradni specjalistycznych spowoduje istotne ograniczenie liczby hospitalizacji, co w konsekwencji spowoduje także znaczną redukcję ogólnych kosztów leczenia chorych. Zaoszczędzone środki będzie można przeznaczyć na rozwój wysokospecjalistycznych procedur terapeutycznych.
7. Istnieje potrzeba stworzenie ośrodka terapii paliatywnej dla chorych w terminalnym stadium niewydolności serca.

PIŚMIENNICTWO

1. Prognoza demograficzna na lata 2014-2050 dla województwa opolskiego. Główny Urząd Statystyczny. Opole, 2014.
2. Swedberg K, Komajda M, Böhm M et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet, 2010; 376: 875–885.
3. Ponikowski P, Voors AA, Anker SD et al. Wytyczne ESC dotyczące diagnostyki i leczenia ostrej i przewlekłej niewydolności serca w 2016 roku. Kardiol Pol. 2016;74:1037-1147.

4. McMurray JJ, Packer M, Desai AS et al., on behalf of the PARADIGM-HF Investigators and Committees. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med. 2014;371:993-1004.
5. Dor V, Sabatier M, Montiglio F et al. Outcome of left ventricular aneurysmectomy with patch repair in patients with severely depressed pump function. Am J Cardiol. 1995;76:557-561.
6. Dor V, Sabatier M, Montiglio F et al. Left ventricular by endoventricular patch palstr repair: a 17-years experience. Semin. Thorac Cardiovasc Surg. 2001;13(4):435-437.
7. Velazquez EJ, Lee KL, Deja MA, Jain A. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med. 2011;364(17):1607-1616.
8. Gierzyński J, Gryglewicz J, Karczewicz E et al. Niewydolność serca – analiza kosztów ekonomicznych i społecznych. Warszawa Uczelnia Łazarskiego, 2013, 12, 48.
9. Nessler J, Kozierkiewicz A, Gackowski A et al. Kompleksowa opieka nad chorymi z niewydolnością serca w Polsce: propozycje rozwiązań organizacyjnych. Kardiol Pol. 2018;76(2):479-487.

AUTOR KORESPONDUJĄCY

Piotr Feusette
Klinka Kardiologii
Uniwersytecki Szpital Kliniczny w Opolu
Al. W. Witosa 26, 45-401 Opole
tel: +48606380462
e-mail: feusette@wp.pl

Nadesłano: 25.10.2018
Zaakceptowano: 18.01.2019

PRACA POGLĄDOWA
REVIEW ARTICLE

DYSFUNKCJA AUTONOMICZNEGO UKŁADU NERWOWEGO W PADACZCE

DYSFUNCTION OF THE AUTONOMIC NERVOUS SYSTEM IN EPILEPSY

Beata Łabuz-Roszak[1, 2], Iwona Mańka-Gaca[3]
[1]KATEDRA I ZAKŁAD PODSTAWOWYCH NAUK MEDYCZNYCH, WYDZIAŁ ZDROWIA PUBLICZNEGO W BYTOMIU, ŚLĄSKI UNIWERSYTET MEDYCZNY W KATOWICACH, BYTOM, POLSKA
[2]ODZIAŁ NEUROLOGII I ODDZIAŁ UDAROWY, WOJEWÓDZKI SZPITAL SPECJALISTYCZNY W OPOLU, OPOLE, POLSKA
[3]ODDZIAŁ NEUROLOGICZNY, SZPITAL MIEJSKI W ZABRZU, ZABRZE, POLSKA

STRESZCZENIE
Zaburzenia funkcji autonomicznych mogą towarzyszyć uogólnionym lub częściowym napadom padaczkowym; mogą również przybierać formę samodzielnych napadów lub występować w okresie międzynapadowym. Natomiast arytmia, powodując zaburzenia hemodynamiczne w układzie krążenia i przedłużające się niedotlenienie ośrodkowego układu nerwowego, może prowokować wtórnie epizody o morfologii napadu padaczkowego. Diagnozując chorych z napadami o symptomatologii padaczkowej, należy zawsze mieć na uwadze możliwość ewentualnego występowania zaburzeń natury kardiogennej. U wszystkich chorych z padaczką, u których dodatkowo stwierdzono zaburzenia rytmu serca, należy rozważyć wpływ wyładowań padaczkowych na struktury autonomicznego układu nerwowego, efekt stosowanych leków, a także możliwość występowania mutacji w obrębie kanałów jonowych.

SŁOWA KLUCZOWE: padaczka, autonomiczny układ nerwowy, dyzautonomia, zaburzenia rytmu serca

ABSTRACT
Generalized or partial epileptic seizures may be accompanied by autonomic dysfunction. They may also take the form of self-inflicted seizures or be present during interictal period. Arrhythmias, resulting in haemodynamic disturbances in the circulatory system and prolonged hypoxia of the central nervous system, may itself provoke secondary episodes of seizure morphology. The doctor when diagnosing patients with epileptic seizures should always be aware of the potential for cardiogenic disorders. Consideration should be given to the effect of epilepsy on the structure of the autonomic nervous system, the effect of antiepileptic drugs, and the potential for mutations within the ion channels.

KEY WORDS: epilepsy, autonomic nervous system, dysautonomia, arrhythmias

Wiad Lek 2019, 72, 1, 120-123

WSTĘP

Padaczka jest stanem chorobowym charakteryzującym się napadowo nawracającymi zaburzeniami czynności mózgu, zazwyczaj z towarzyszącymi zaburzeniami świadomości lub zaburzeniami ruchowymi, czuciowymi czy też wegetatywnymi. Napadowe zaburzenia czynności mózgu w padaczce są uwarunkowane zmianami strukturalnymi lub funkcjonalnymi mózgu. Zaburzenia funkcji autonomicznych mogą towarzyszyć uogólnionym lub częściowym napadom padaczkowym; mogą również przybierać formę samodzielnych napadów lub występować w okresie międzynapadowym [1–4]. Uważa się, że zaburzenia autonomiczne, prowadzące do zaburzeń sercowo-naczyniowych, mogą mieć związek z występowaniem nagłych nieoczekiwanych zgonów (SUDEP – *sudden unexpected death in people with epilepsy*,) u niektórych chorych na padaczkę [5–7].

Istnieje wiele doniesień, w których autorzy próbują ustalić związek przyczynowo-skutkowy między padaczką a zaburzeniami rytmu serca, jednakże jak do tej pory brak jednoznacznych wniosków.

Napady padaczkowe mogą mieć różny obraz kliniczny, w zależności od okolicy anatomiczno-czynnościowej mózgu zaangażowanej w wyładowania. Jeśli towarzyszy im pobudzenie ośrodkowych struktur autonomicznych, mogą być błędnie rozpoznawane jako pierwotne zaburzenia kardiologiczne, gastryczne lub hormonalne.

Z drugiej strony arytmia, powodując zaburzenia hemodynamiczne w układzie krążenia i przedłużające się niedotlenienie ośrodkowego układu nerwowego, może prowokować wtórnie epizody o morfologii napadu padaczkowego [8–10].

BUDOWA I FUNKCJA UKŁADU AUTONOMICZNEGO

Układ autonomiczny wraz z układem dokrewnym odpowiada za utrzymanie stałości środowiska wewnętrznego organizmu, niezależnie od zmieniających się warunków i działania czynników zewnętrznych. Jest dodatkowo czułym wskaźnikiem stanu emocjonalnego, jak również może podlegać w pewnym stopniu działaniu zależnym od naszej woli.

Wyróżniamy dwie części układu autonomicznego o przeciwstawnym do siebie działaniu: współczulną (sympatyczną) i przywspółczulną (parasympatyczną). Autonomiczny układ nerwowy składa się z części ośrodkowej i obwodowej. Do najważniejszych mózgowych ośrodków autonomicznych należą: kora wyspy, jądro migdałowate i boczna część podwzgórza. Poza tym można jeszcze wymienić przednią część zakrętu obręczy, brzuszno-przyśrodkową korę czołową, jądro łożyskowe prążka krańcowego, istotę szarą okołowodociągową, jądro okołokonarowe, jądro pasma samotnego i brzuszno-boczną część rdzenia przedłużonego [11, 12].

Włókna układu autonomicznego biegnące odśrodkowo przedzielone są zwojami nerwowymi na część przed- i zazwojową. Włókna przedzwojowe mają osłonki mielinowe, zazwojowe są zaś pozbawione mieliny. Mediatorem we wszystkich włóknach przedzwojowych, zarówno przywspółczulnych, jak i współczulnych, jest acetylocholina. Z kolei we włóknach zazwojowych, w części przywspółczulnej transmiterem jest acetylocholina, a w części współczulnej – noradrenalina. Tylko niektóre zazwojowe włókna współczulne, a mianowicie biegnące do gruczołów potowych i tętniczek mięśni szkieletowych, są cholinergiczne [13, 14].

Nieprawidłowa funkcja układu autonomicznego (dyzautonomia) wyraża się głównie zaburzeniami w zakresie układu sercowo-naczyniowego, pokarmowego, moczowo-płciowego, regulacji oddychania, szerokości źrenic oraz termoregulacji [13, 15].

Pobudzenie części współczulnej powoduje przyspieszenie akcji serca, natomiast części przywspółczulnej jej zwolnienie. Unerwienie przywspółczulne układu bodźcoprzewodzącego serca przez nerw błędny (X) jest asymetryczne. Prawy nerw zaopatruje węzeł zatokowy, natomiast lewy węzeł przedsionkowo-komorowy. Ze względu na nadrzędną funkcję węzła zatokowego, leczenie padaczki za pomocą stymulacji nerwu błędnego przeprowadza się prawie zawsze po stronie lewej, żeby zmniejszyć możliwość powikłań sercowych. Jednocześnie można przypuszczać, że lewostronne uszkodzenie ośrodkowe obejmujące ten nerw ma mniejszy wpływ na generowanie groźnych zaburzeń rytmu [13].

DYZAUTONOMIA W PADACZCE

Uważa się, że objawy wegetatywne w padaczce są związane z obecnością ogniska padaczkowego w obrębie ośrodkowych struktur autonomicznych, wtórnym szerzeniem się wyładowań padaczkowych na te okolice oraz dodatkowo z efektem ubocznym stosowanych leków przeciwpadaczkowych [16].

Większość prac oceniających zaburzenia autonomiczne u chorych z padaczką dotyczy zaburzeń w trakcie napadu, jednak ostatnio zwraca się uwagę również na występowanie zmian międzynapadowych [4].

Wyniki wielu badań, choć niejednoznaczne, sugerują półkulową asymetrię czynności układu autonomicznego. Po stronie prawej istnieje przewaga części współczulnej, a po lewej przywspółczulnej. Co za tym idzie pobudzenie w wyniku wyładowań padaczkowych prawej półkuli – lub uszkodzenie lewej półkuli – związane jest z nadmierną impulsacją współczulną i objawia się tachykardią oraz wzrostem ciśnienia tętniczego. Odwrotna sytuacja manifestuje się bradykardią i spadkiem ciśnienia tętniczego w wyniku przewagi przywspółczulnej części układu autonomicznego [17]. Podobny efekt uzyskał Oppenheimer przy stymulacji kory wyspy [18].

Niektórzy autorzy uważają, że zaburzenia autonomiczne w padaczce występują najczęściej w napadach z ogniskiem w prawym płacie skroniowym [19, 20], co może mieć związek z dominującą rolą prawej półkuli w regulacji sercowo-naczyniowej [21].

WPŁYW LEKÓW PRZECIWPADACZKOWYCH NA CZYNNOŚĆ SERCA

Odrębnym zagadnieniem jest wpływ leków przeciwpadaczkowych na układ autonomiczny. Wpływ leków przeciwpadaczkowych na czynność serca stanowi przedmiot wielu badań, lecz ich wyniki ciągle bywają sprzeczne. Mechanizm generowania zaburzeń choć nie został do końca poznany, może wynikać z wpływu na układ autonomiczny (zarówno leku, jak i wyładowań padaczkowych) oraz bezpośredniego blokowania kanałów jonowych, co wpływa na zaburzenia depolaryzacji (kanały sodowe) i repolaryzacji (potasowe) komórki mięśnia sercowego oraz układu bodźcoprzewodzącego, manifestując się arytmią.

Najczęściej wymieniana jest karbamazepina (CBZ), która według niektórych autorów powoduje wzrost aktywności współczulnej i wywołuje większą zmienność akcji serca (HRV – *heart rate variability*) podczas badań oceniających układ autonomiczny [22]. Tomson i wsp. oraz Persson i wsp. ujawnili, że obniżenie napięcia części współczulnej oraz zmniejszenie modulacji przywspółczulnej u chorych z padaczką, jak również zmniejszenie HRV, jest częstsze u osób leczonych tym lekiem [16, 23]. CBZ wpływa na węzeł zatokowy oraz przewodnictwo przedsionkowo-komorowe, powodując wydłużenie odstępu PQ. U predysponowanych pacjentów może ujawnić chorobę węzła zatokowego. Efektem ubocznym po leczeniu karbamazepiną może być blok przedsionkowo-komorowy oraz asystolia, które wtórnie mogą wywołać napad padaczkowy, spowodować uogólnienie napadu częściowego, lub indukować objawy podobne do padaczkowych. Mogą wystąpić również zaburzenia przewodzenia śródkomorowego. SUDEP częściej występuje u pacjentów leczonych tym lekiem, być może częściowo również w wyniku wydłużenia odstępu QT. To zaburzenie obserwowano również po zażyciu dużych dawek CBZ [24–28].

Fenytoina (PTH), obecnie rzadko stosowana w przewlekłym leczeniu padaczki, ma również antyarytmiczne, a drugiej strony proarytmogenne działanie. Jej inotropowo ujemny wpływ na mięsień sercowy może wywoływać bradyarytmię prowadzącą do asystolii a nawet zgonu, jednak zdecydowanie częściej przy podawaniu pozajelitowym [29, 30].

Fenobarbital (PB), obecnie również rzadko stosowany, podany w dużych dawkach powoduje tachykardię.

W badaniach na zarodkach myszy wszystkie te leki (PTH, PB, CBZ), szczególnie w politerapii, wywoływały bradykardię oraz nieregularną akcję serca, zwiększające się z czasem trwania terapii [31].

W innym badaniu oceniającym nowe LPP – lamotryginę, topiramat i gabapentynę – sugerowano proarytmogenne ich działanie – głównie pierwszego z nich przy towarzyszących innych niekorzystnych czynnikach [32]. Lamotrygina w dużej dawce, z toksycznym poziomem we krwi może w EKG wywoływać zmiany o morfologii zespołu Brugada, predysponujące do groźnych arytmii komorowych [33].

Lacosamid (LCM), nowy lek przeciwpadaczkowy, predysponuje do wystąpienia migotania przedsionków również u osób bez czynników ryzyka chorób sercowo-naczyniowych [34]. Przeciwwskazaniem do LCM jest blok przedsionkowo-komorowy II lub III stopnia. Wśród działań niepożądanych zarejestrowano ponadto bradykardię i omdlenia.

Kwon i wsp., mimo że zauważyli wpływ leków przeciwpadaczkowych na odstęp QT, nie znaleźli różnic istotnych statystycznie w grupach monoterapii kwasem walproinowym, (VPA), CBZ/OXC, topiramatem (TPM) oraz między poli- i monoterapią [35].

Na międzynarodowej liście leków o możliwym działaniu wydłużającym odstęp QT i zwiększającym ryzyko częstoskurczu komorowego typu *torsade de pointes* z leków przeciwpadaczkowych wymieniono felbamat i fosfenytoinę [36]. Poza tym u pacjentów z zespołem Brugadów, oprócz propofolu (środka anestetycznego stosowanego również w leczeniu stanu padaczkowego), niekorzystne działanie ma także fenytoina i karbamazepina [37].

Trzeba jednak pamiętać, że jednoznaczne ustalenie, czy zmiany zarejestrowane w badaniu elektrokardiograficznym są efektem padaczki, stosowanych leków, czy może występują niezależnie od tej choroby, często bywa trudne.

PADACZKA A ZABURZENIA RYTMU SERCA

Niezależnie od wpływu leków, większość autorów sugeruje, że u chorych na padaczkę dochodzi do upośledzenia autonomicznej regulacji serca i zmniejszenia HRV [2, 38–42], co wiąże się z wyższym ryzykiem niekorzystnych incydentów zarówno u pacjentów z obecną, jak i nieobecną chorobą tego narządu.

Zaburzenia autonomiczne mogą być wtórne do defektu zależnych od napięcia kanałów potasowych w wyniku mutacji genu KCNA1, które głównie znajdują się w mózgu, a w bardzo niewielkiej ilości w sercu. W badaniach na myszach stwierdzono, że ich niedobór prowadzi wystąpienia napadów padaczkowych i wtórnie do upośledzenia kontroli rytmu serca (głównie wystąpienia bradyarytmii), ze względu na nieprawidłowe napięcie układu przywspółczulnego. Czyni to gen KCNA1, który jest kandydatem do uznania za czynnik ryzyka nagłej niespodziewanej śmierci u chorych na padaczkę [43]. Z drugiej strony mutacja genu KCNQ1 kodującego sercowe kanały potasowe prowadząca do powstania pierwszego typu wrodzonego zespołu QT może wywoływać zaburzenia ze strony ośrodkowego układu nerwowego w postaci napadów padaczkowych oraz dysregulacji autonomicznej, gdyż kanały potasowe kodowane przez KCNQ1 znajdują się także w mózgu [44].

PODSUMOWANIE

Diagnozując chorych z napadami o symptomatologii padaczkowej należy zawsze mieć na uwadze możliwość ewentualnego występowania zaburzeń natury kardiogennej. U wszystkich chorych z padaczką, u których dodatkowo stwierdzono zaburzenia rytmu serca, należy rozważyć wpływ wyładowań padaczkowych na struktury autonomicznego układu nerwowego, efekt stosowanych leków, a także możliwość występowania mutacji w obrębie kanałów jonowych.

PIŚMIENNICTWO

1. Abraira L, Grau-López L, Jiménez M, Becerra JL. Psychiatric manifestations and dysautonomia at the onset of focal epilepsy in adults: Clinical signs indicating autoimmune origin. Neurologia. 2016 Jun 13. pii: S0213-4853(16)30048-2.
2. Rangel I, Freitas J, Correia AS et al. The usefulness of the head-up tilt test in patients with suspected epilepsy. Seizure. 2014;23(5):367-370.
3. Desai R, Rupareliya C, Patel U et al. Burden of arrhythmias in epilepsy patients: a nationwide inpatient analysis of 1.4 million hospitalizations in the United States. Cureus. 2017;9(8):e1550.
4. Łabuz-Roszak B, Pierzchała K. Ocena autonomicznego układu nerwowego u chorych na padaczkę w okresie międzynapadowym. Badanie pilotażowe. Neurol Neurochir Pol. 2009;43:330-336.
5. Walczak TS. Do antiepileptic drugs play a role in sudden unexpected death in epilepsy? Drug Safety. 2003;26:673-683.
6. Duble SN, Thomas SV. Sudden unexpected death in epilepsy. Indian J Med Res. 2017;145(6):738-745.
7. Allen LA, Harper RM, Kumar R et al. Dysfunctional brain networking among autonomic regulatory structures in temporal lobe epilepsy patients at high risk of Sudden Unexpected Death in Epilepsy. Front Neurol. 2017;8:544.
8. Kouakam C, Daems C, Guédon-Moreau L et al. Recurrent unexplained syncope may have a cerebral origin: report of 10 cases of arrhythmogenic epilepsy. Arch Cardiovasc Dis. 2009;102:397-407.
9. Wan Y, Zou J, Shi Y et al. How to avoid sudden cardiac death. Eur J Prev Cardiol. 2017;24:1790.
10. Maguire MJ, Jackson CF, Marson AG, Nolan SJ. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). Cochrane Database Syst Rev. 2016;7:CD011792.
11. Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc. 1993;68(10):988-1001.
12. Mariańska K. Zaburzenia czynności układu autonomicznego u chorych na padaczkę. Pol Przegl Neurol. 2008;4(2):71-77.

13. Mathias ChJ, Bannister R (eds). Autonomic Failure. A textbook of clinical disorders of the autonomic nervous system. New York: Oxford University Press, 1999.
14. Narkiewicz O, Moryś J. Neuroanatomia czynnościowa i kliniczna. Warszawa: PZWL, 2001.
15. Goldstein DS, Robertson D, Esler M, Straus SE, Eisenhofer J. Dysautonomias: Clinical disorders of the autonomic nervous system. Ann Intern Med. 2002;137:753-763.
16. Tomson T, Ericson M, Ihrman C, Lindblad LE. Heart rate variability in patients with epilepsy. Epilepsy Res. 1998;30(1):77-83.
17. Hilz MJ, Dütsch M, Perine K, Nelson PK, Rauhut U, Devinsky O. Hemispheric influence on autonomic modulation and baroreflex sensitivity. Ann Neurol. 2001;49:575-584.
18. Oppenheimer S. Forebrain lateralization and the cardiovascular correlates of epilepsy. Brain 2001;124:2345-2346.
19. Kowalik A, Bauer J, Elger CE. Asystolic seizures. Nervenarzt 1998;69(2):151-157.
20. Saleh Y, Kirchner A, Pauli E, Hilz MJ, Neundorfer B, Stefan H. Temporal lobe epilepsy: effect of focus side on the autonomic regulation of heart rate? Nervenarzt 2000;71(6):477-480.
21. Hilz MJ, Dütsch M, Perine K, Nelson PK, Rauhut U, Devinsky O. Hemispheric influence on autonomic modulation and baroreflex sensitivity. Ann Neurol. 2001;49:575-584.
22. Devinsky O, Perrine K, Theodore WH. Interictal autonomic nervous system function in patients with epilepsy. Epilepsia 1994;35:199-204.
23. Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. Epilepsy Res. 2003;57(1):69-75.
24. Takayangi K, Hisauchi I, Watanabe J et al. Carbamazepine-induced sinus node dysfunction and atrioventricular block in elderly woman. Jpn Heart. 1998;39(4):469-479.
25. Opeskin K, Burke MP, Cordner SM, Berkovic SF. Comparison of antiepileptic drug levels in sudden unexpected deaths in epilepsy with deaths from other causes. Epilepsia. 1999;40:1795-1798.
26. Gelvan A, Pallisgaard G. Carbamazepine induced right bundle branch block in a Greenlandic patient. Int J Circumpolar. Health. 2001;60(3):407-410.
27. Langan Y, Nashelf L, Sander J. Case control study of SUDEP. Neurology. 2005;64:1131-1133.
28. Timmings PL. Sudden unexpected death in epilepsy: is carbamazepine implicated? Seizure. 1998;7(4):289-291.
29. Tomson T, Kennebäck G. Arrhythmia, heart rate variability, and antiepileptic drugs. Epilepsia. 1997;38(11):S48-S51.
30. Durelli L, Mutani R, Sechi GP et al. Cardiac side effects of phenytoin and carbamazepine. Arch Neurol. 1985;42:1067-1068.
31. Danielsson C, Azarbayjani F, Sköld AC, Sjögren N, Danielsson BR. Polytherapy with hERG-blocking antiepileptic drugs: increased risk for embryonic cardiac arrhythmia and teratogenicity. Birth Defects Res A Clin Mol Teratol. 2007;79(8):595-603.
32. Danielsson BR, Lansdell K, Patmore ., Tomson T. Effects of the antiepileptic drugs lamotrigine, topiramate and gabapentin on hERG potassium currents. Epilepsy Res. 2005;63(1):17-25.
33. Strimel WJ, Woodruff A, Cheung P, Kirmani BF, Stephen Huang SK. Brugada-like electrocardiographic pattern induced by lamotrigine toxicity. Clin Neuropharmacol. 2010;33(5):265-267.
34. Degiorgio CM. Atrial flutter/atrial fibrillation associated with lacosamide for partial seizures. Epilepsy Behav. 2010;18(3):322-324.
35. Kwon S, Lee S, Hyun M. The potential for QT prolongation by antiepileptic drugs in children. Pediatr Neurol. 2004;30(2):99-101.
36. http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm
37. http://www.brugadadrugs.org
38. Berilgen MS, Sari T, Bulut S, Mungen B. Effects of epilepsy on autonomic nervous system and respiratory function tests. Epilepsy Behav. 2004;5(4):513-516.
39. Ansakorpi H, Korpelainen JT, Suominen K, Tolonen U, Myllylä VV, Isojärvi JI. Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy. Epilepsia. 2000;4(1):42-47.
40. Galli A, Lombardi F. Heart rate variability regression and risk of sudden unexpected death in epilepsy. Med Hypotheses. 2017;99:49-52.
41. Nayak CS, Sinha S, Nagappa M, Thennarasu K, Taly AB. Lack of heart rate variability during sleep-related apnea in patients with temporal lobe epilepsy (TLE)-an indirect marker of SUDEP? Sleep Breath. 2017;21(1):163-172.
42. Jaychandran R, Chaitanya G, Satishchandra P, Bharath RD, Thennarasu K, Sinha S. Monitoring peri-ictal changes in heart rate variability, oxygen saturation and blood pressure in epilepsy monitoring unit. Epilepsy Res. 2016;125:10-18.
43. Glasscock E, Yoo JW, Chen TT, Klassen TL, Noebels JL, Kv1.1 potassium channel deficiency reveals brain-driven cardiac dysfunction as a candidate mechanism for sudden unexplained death in epilepsy. J Neurosc. 2010;30(15):5167-5175.
44. Goldman AM, Glasscock E, Yoo J, Chen TT, Klassen TL, Noebels JL Arrhythmia in heart and brain: KCNQ1 mutations link epilepsy and sudden unexplained death. Sci Transl Med. 2009;1(2):2-6.

Konflikt interesów:
Autorzy deklarują brak konfliktu interesów.

AUTOR KORESPONDUJĄCY
Beata Łabuz-Roszak
Katedra i Zakład Podstawowych Nauk Medycznych,
Wydział Zdrowia Publicznego,
Śląski Uniwersytet Medyczny
ul. Piekarska 18, 41-902 Bytom, Polska
tel: +48 605097110
e-mail: broszak@sum.edu.pl

Nadesłano: 20.12.2018
Zaakceptowano: 09.01.2019

OPIS PRZYPADKU
CASE REPORT

SEVERE METABOLIC SYNDROME AND PRIMARY AMENORRHEA AS MAIN PATHOPHYSIOLOGICAL FEATURES IN A SUBTYPE OF TURNER SYNDROME (46, X, DEL (X) Q 21)

CIĘŻKA POSTAĆ ZESPOŁU METABOLICZNEGO I PIERWOTNY BRAK MIESIĄCZKI JAKO GŁÓWNE CECHY PATOFIZJOLOGICZNE W PODTYPIE ZESPOŁU TURNERA (46, X, DEL (X) Q 21)

Igor Alexander Harsch[1], Thomas Heß[2], Peter Christopher Konturek[2]
[1]DEPARTMENT OF INTERNAL MEDICINE II, DIVISION OF ENDOCRINOLOGY AND METABOLISM, SAALFELD/SAALE, GERMANY
[2]DEPARTMENT OF INTERNAL MEDICINE II, DIVISION OF GASTROENTEROLOGY, SAALFELD/SAALE, GERMANY

ABSTRACT

Turner syndrome can be manifest with a considerable genetic and phenotypic variability. This merely accounts for about 50% of patients who do not have the "classic" 45 X genotype. We report the case of a 42-year-old female patient with a 46, X, del (X) q 21 genotype (deletion on the second X chromosome on the long arm). As the patient displayed a non-typical phenotype and was infertile, a diagnosis was established at the age of 24 with no follow-up treatment. As part of our therapy of the individual due to newly manifested diabetes mellitus, our diagnostic workup revealed a severe metabolic syndrome encompassing fatty liver disease, obstructive sleep apnea syndrome and hyperuricemia. Our observations should sensitize physicians treating female patients for one or more aspects of the metabolic syndrome and its presence in Turner syndrome. These patients have an unfavorable cardiovascular profile, in part due to the metabolic syndrome, but also due to factors intrinsic to Turner syndrome.

KEY WORDS: Turner Syndrome; metabolic syndrome; 46. X. del (X) q 21 subtype; morbid obesity; diabetes mellitus type 2; obstructive sleep apnea syndrome

STRESZCZENIE

Zespół Turnera może objawiać się znaczną zmiennością genetyczną i fenotypową. Problem ten stwierdza się u około 50% pacjentek, które nie mają „klasycznego" genotypu 45X. W poniższej pracy przedstawiono przypadek 42-letniej pacjentki z genotypem 46, X, del (X) q 21 (delecja na drugim chromosomie X na długim ramieniu). Ponieważ pacjentka charakteryzowała się nietypowym fenotypem i była bezpłodna, diagnozę postawiono dopiero w wieku 24 lat, jednakże chorą pozostawiono bez dalszego leczenia. W ramach objęcia pacjentki naszą opieką z powodu świeżo rozpoznanej cukrzycy, dalsza diagnostyka umożliwiła wykrycie ciężkiej postaci zespołu metabolicznego obejmującego stłuszczeniową chorobę wątroby, zespół obturacyjnego bezdechu sennego oraz hiperurykemię. Nasze obserwacje powinny uczulić lekarzy opiekujących się kobietami na jeden lub więcej aspektów zespołu metabolicznego i jego obecność w zespole Turnera. Pacjentki te charakteryzują się niekorzystnym profilem sercowo-naczyniowym, częściowo właśnie z powodu zespołu metabolicznego, ale także z powodu czynników charakterystycznych dla samego zespołu Turnera.

SŁOWA KLUCZOWE: zespół Turnera, zespół metaboliczny, podtyp 46, X. del (X) q 21; chorobliwa otyłość; cukrzyca typu 2; zespół obturacyjnego bezdechu sennego

Wiad Lek 2019, 72, 1, 124-128

INTRODUCTION

Turner syndrome (TS) occurs in one out of every 5000 live female births. The most common feature is a short stature. An early loss of ovarian function (ovarian hypofunction or premature ovarian failure) is also very common. About 30% of females with Turner syndrome have extra folds of skin on the neck (webbed neck), a low hairline at the back of the neck, lymphedema of the hands and feet, skeletal abnormalities, or kidney malformations. One third to one half of individuals with TS are born with a heart defect [1]. Apart from the phenotypical features, the unfavorable cardiovascular risk profile and the trend to develop obesity and other facets of the metabolic syndrome (MS) are noteworthy [2–4]. Hypertension affects up to 25% of the adolescents and 50% of the adults. It is mostly systolic and is often nocturnal [5]. The disorder is not that rare and the patients are not only treated by specialists or an interdisciplinary team, as guidelines suggest [6]. Physicians and primary care physicians in general should be aware of these non-gynecological problems, since there are sometimes significant differences between entitlement to care and care reality: This accounts for the case reported here of a patient with a severe metabolic syndrome as the main feature of her disorder and without gynecological co-treatment.

Next to the "classic" 45,X type, with one sex chromosome missing, that occurs in about the half of the cases, several

different karyotypes exist. Some show deletions (del) on the second X chromosome on the short arm (p) or the long arm (q). Other striking features may be mosaicism of a 45,X cell line with another cell line, which might be 46,XX, 46,XY or have an abnormal sex chromosome rearrangement [7].

In case of the "rare" subtypes, several have been described in case reports, where the aspect of MS had not always been addressed. Such rare subtypes were reported by Sybert and McCauley [8], e.g.: 46,X,i(Xq) (the abbreviation i stands for "isochromosome". The medical definition of an isochromosome is that of a chromosome produced by transverse splitting of the centromere so that both arms are from the same side of the centromere are of equal length and possess identical genes); (45,X/46,X,i(Xq); 45,X/46,X,+ring (ring means a breakage of chromosomes at both ends, and the ends of the chromosome join together to form a ring); 45,X/46,X,+mar (mar means marker chromosome which is a small fragment of a chromosome which generally cannot be identified without specialized genomic analysis due to the size of the fragment (the significance of a marker is variable as it depends on what material is contained within the marker); 45,X/46,XY or 46,X,Yvar/Ydel (var means a sequence variant); 45,X/46,XX/47,XXX; 45,X/46,XX; 46,X,Xp (short-arm deletions); 46,X,Xq (interstitial long-arm deletions); and others. In the report of Akbas et al. [7] the authors quote literature that indicates that patients with the 46,X,i(Xq) karyotype have characteristics similar to those observed in classical TS. The aspect of MS was not addressed in detail, maybe since many patients were very young. Some patients with deletions of Xq may merely have gonadal dysfunction as was reported e.g. by Kara et al. in the case of a 22-year-old female [9] or by Seki et al. [10] in the case of a 28-year-old old woman, or by Srivastave et al. [11] in a 19-year-old female.

As mentioned above, we transfer these descriptions of patients with a q deletion by the case on a 42-year-old, therapy naïve (!) woman with primary amenorrhoea and severe metabolic syndrome.

THE AIM

To highlight the presence of MS in TS and the elevated cardiovascular risk in TS. This does not only account for the „classic" 45,X genotype, but also for rarer subtypes as reported here.

CASE PRESENTATION

A 42-year-old Caucasian female was admitted to the outpatient department of our clinic due to newly manifested diabetes mellitus type 2 and intolerance against metformin (diarrhea). In assessing her further medical history, she also reported primary amenorrhea. As for the primary amenorrhea, she had presented herself to a gynecologist because of an unfulfilled desire to have a baby when she was 24 years old. The ovaries had been described as hypoplastic by her gynecologist and, to our surprise, she presented a chromosomic photograph with a diagnosis of 46,X,del (X) q 21 syndrome from 2003 (Fig. 1). Since the unfulfilled desire to have a baby was the main focus of her interest those days, no further diagnostic or therapeutic action had been taken.

She finished her school education at the age of fifteen (certificate of secondary education) and has been working as a caregiver for senior citizens ever since. In day-to-day interaction she shows a moderate cognitive impairment. A considerable weight gain has been taking place for 10 years. It is worth mentioning that a lipedema of the legs was diagnosed in 2012. She also consumes about 15 cigarettes daily. She had no cardiovascular events in her medical history.

PHYSICAL EXAMINATION

The patient was 167 cm tall and weighed 124 kg (BMI 44 kg/m^2 – Obesity III° or morbid obesity according to the WHO's definition). The waist circumference was 136 cm, the hip circumference was 130 cm. The blood pressure was 170/95 mm Hg. The typical short stature and the webbed neck was missing, but further physical examination showed the following features attributable to TS:

- Several multipigmented naevi;
- Low posterior hairline;
- Flat nasal bridge;
- Lipedema of the legs (Fig. 2, 3).

INSTRUMENTAL DIAGNOSTICS

In the ultrasonography of the abdomen, the sole pathological finding was a fatty liver and gallstones, the ovaries were not visualized.

The ultrasonography of the thyroid showed the right lobe with 20 x 20 x 50 ml, with an unremarkable and normal, perfused thyroid structure in the right lobe and a hypoechoic, well demarcated, 8 mm diameter nodule without increased blood flow. The thyroid volume of the left lobe was17 x 17 x 50 mm. No sonographical signs of autoimmune thyroiditis were observed.

The echocardiography showed no structural abnormalities except a diastolic relaxation abnormality.

Due to obesity, an overnight screening for sleep-disordered breathing was done, indicative of a mild obstructive sleep apnea syndrome (MiniScreen Plus™ Heinen Löwenstein). The Apnea/Hypopnea Index was 13.3, Respiratory Disturbance Index 14.8, Apnea-Index 0.4, Hypopnea-Index 12.9. Since the patient reported no daytime sleepiness, no further action was taken.

The bone density was measured by dual-energy X-ray absorptiometry (DXA Lunar Prodigy Advance™): The T-scores (the T-score is the number of standard deviations above or below the mean for a healthy 30-year-old adult of the same sex and ethnicity as the patient) of the lumbar spine were: L(lumbar)1 - L4: -0.9, right femoral neck: +0.2, left femoral neck: +0.2

The corresponding Z-scores (The Z-score is number of standard deviations above or below the mean for the patient's age, sex and ethnicity) were: L1 - L4: -2.1, right femoral neck: +0.5, left femoral neck: +0.5. That said, the patient had a normal bone density.

LABORATORY FINDINGS

Uric acid: 383 µmol/l (137-363); total cholesterol: 5.89 mmol/l (< 5.2); HDL-cholesterol: 1.02 mmol/l (> 1.2);

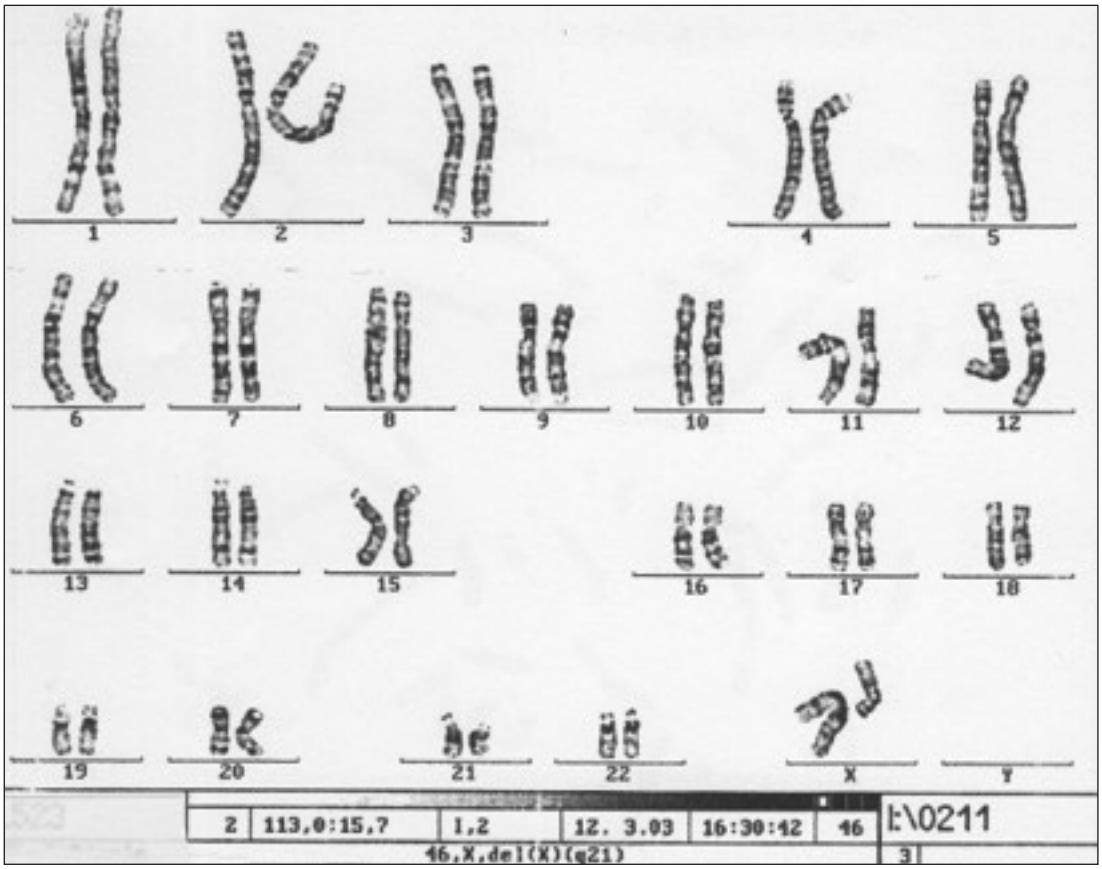


Fig. 1 Chromosomic photograph from the 42-year-old patient.

LDL-cholesterol: 4.48 mmol/l; triglycerides: 1.80 mmol/l (<1.7); Hba1c: 7.6 % (4.8-6); Thyroid Stimulating Hormone: 3.12 mU/L (0.27-4.2); Luteinizing Hormone: 18.9 IU/L; Follicle Stimulating Hormone: 29.5 IU/L; Estradiol (E2): 24.5 ng/L; Testosterone: 0.24 µg/l (0.084-0.481) (comment: as to be expected in this clinical setting, the gonadotropins are elevated and estradiol is relatively low, indicating a residual function of the ovaries). Serum transaminase levels were within the normal range.

DISCUSSION

According to the National Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (NCEP-ATP-III) [12], the diagnosis of "metabolic syndrome" is made if at least three of the following five criteria are met:

- Abdominal fat distribution, determined by an abdominal circumference of over 102 cm in men or over 88 cm in women (Caucasian).
- Serum triglycerides greater than 150 mg / dL (> 1.7 mmol / L), or therapy already initiated to reduce triglycerides.
- HDL cholesterol ≤ 40 mg / dL (<1.05 mmol / L) in men or <50 mg / dL (1.25 mmol / L) in women.
- Blood pressure of 130/85 mmHg or more, or already initiated therapy to reduce hypertension.
- Fasting blood sugar ≥ 110 mg / dL (5.6 mmol / L), or type 2 diabetes.

In the case reported here, the patient meets all 5 criteria. It is well known and has already been mentioned that TS predisposes the patients to obesity and related metabolic disorders [13]. The current epidemiological evidence suggests that patients with TS have unfavorable cardiometabolic risk factors predisposing them to adverse cardiac and cerebrovascular outcomes in ages as early as young adulthood. It remains to be clarified whether these risk factors are intrinsic to TS or whether risk factors such as obesity, hypertension and hyperglycemia are contributing to this risk [14]. Unfortunately, some study results in an investigation of 30 TS patients were indicative that adult patients with TS under hormone replacement therapy are connoted by a higher frequency of central obesity, insulin resistance, hypercholesterolemia, and hypertension [15]. Other authors reported in 26 TS patients that sex hormone administration causes a deterioration in glucose tolerance, increases fat-free mass and physical fitness, and has beneficial effects on blood pressure. The deleterious effect on glucose tolerance was discussed to be mediated by norethisterone, a gestagen known to have androgenic effects [16].

The case described here is unusual in that, up to the age of 41, there had been no specific therapy for the TS (for example sex hormone replacement therapy), nor any treatment for the several facets of the metabolic syndrome. As desirable as the recommendations in the guidelines with a therapy by interdisciplinary teams are [6], even including transition [17], this case illustrates that there may be significant differences between

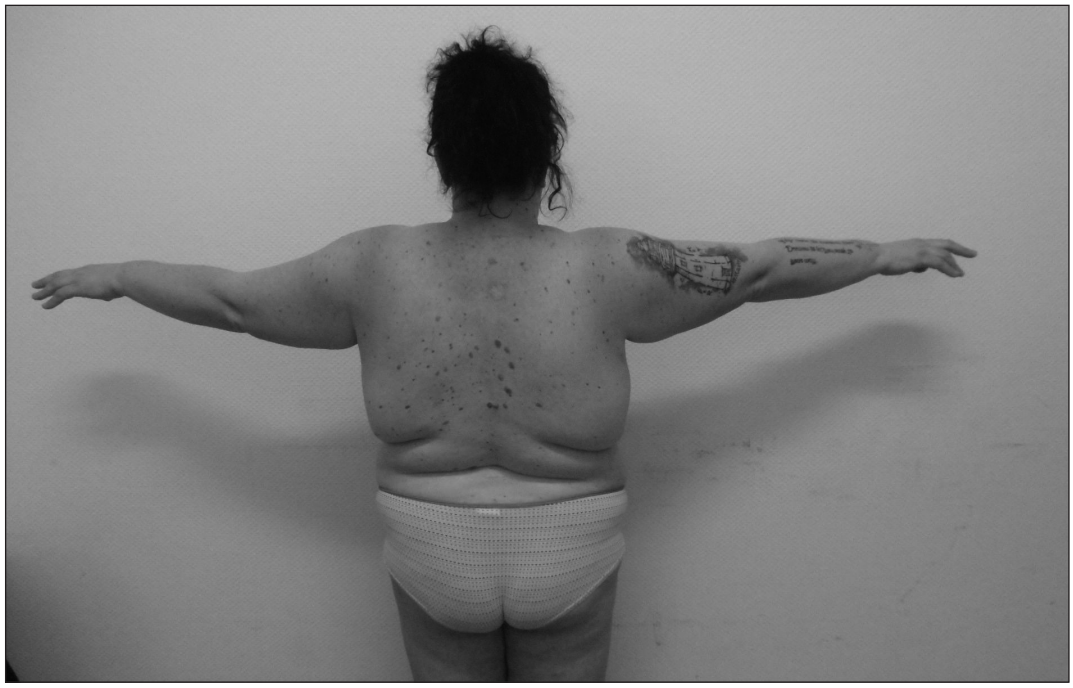


Fig. 2. The picture shows the patient from behind. Notice the rather android fat distribution.

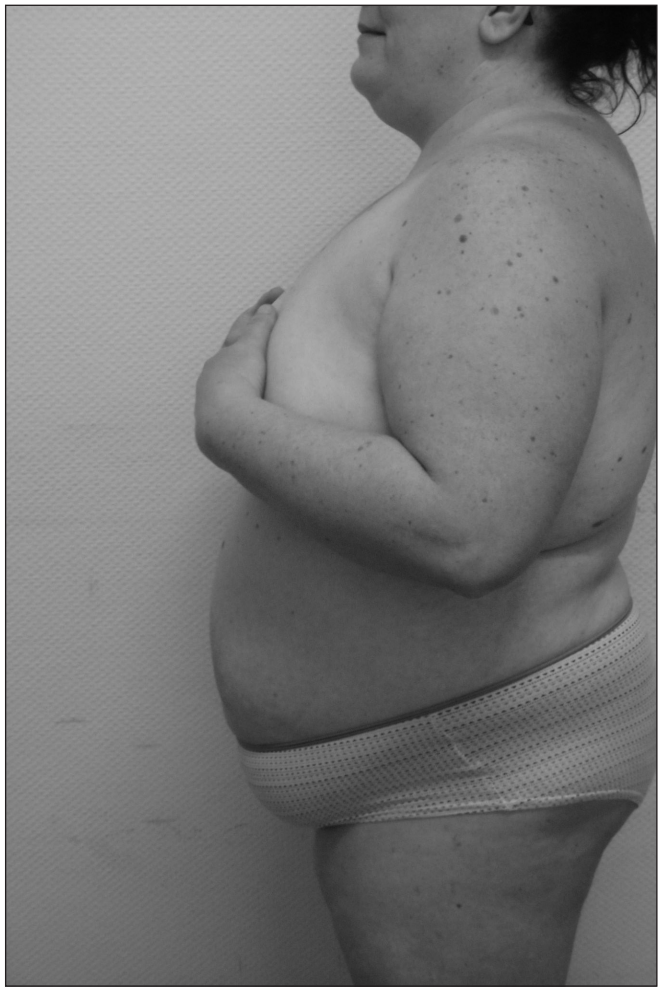


Fig. 3. The picture shows the patient from the side.
Notice the rather android fat distribution.

entitlement to care and care reality. Patient compliance with treatment is also responsible for this. Thus, the non-specialist physician, who initially only treats individual aspects of the metabolic syndrome, may suddenly be confronted with the clinical picture of TS.

It lies in the logic and the nature of the condition that patients who do not have the "classical" 45 X TS but a deletion in the second X chromosome as reported here are likely to express some features of the classic TS, although malformations did not occur in her case. As to be expected in an estrogen-deficient state, osteoporosis is considered a comorbidity of adult women with TS [18]. However, the patient reported here had normal bone density. As already mentioned in the laboratory data, estradiol was relatively low, but detectable in the serum, indicating a residual function of the ovaries that may have prevented osteoporosis yet.

Interestingly, case reports about patients especially affected with the 46, X, del (X) q 21 condition do not report such explicit metabolic syndrome characteristics as we observed in this case (e.g. Kara et al. in the case of a 22-year-old female (9) or by Seki et al. [10] in the case of a 28-year-old woman, or by Srivastave et al. [11] in a 19-year-old female). These patients may have been too young or just on the way towards developing MS. It remains speculative whether MS could have been delayed by sex hormone therapy in our very case. However, recent data suggest that sex hormone therapy may not have a preventive effect [2].

As shown in the literature, TS can be present with a great variety of chromosomal aberrations. It was not in the focus of the report to work out a precise update of the chromosomal defect in this very patient. To clarify the role of Xq in ovarian function the accurate description of such abnormalities requires a combination of cytogenetic and DNA-hybridization analysis [19]. Recently, clinical practice

guidelines for the care of girls and women with TS were published and may also be helpful for a non-specialized physician having to treat a TS patient, as in our case [6].

CONCLUSION

In treating female patients with MS, physicians should be aware of TS in general. TS goes hand in hand with a considerable variability in the phenotype. As reported here, even a diagnosis of TS does not necessarily mean that a patient had or wanted an appropriate therapy in earlier years, given the discomforts caused by the disease were not high enough to desire therapy. In treating female patients with diabetes and/or MS physical examination and a history of amenorrhea or premature ovarian failure is mandatory. Depending on the ethnicity and classification criteria, the polycystic ovary syndrome is more frequent with estimates between 5.5-16% [20]. At first glance in this case, some metabolical and phenotypical features may share similarities, especially in TS patients that do not express the "classical" phenotypes. Since the therapeutic approach and the aftercare is different, both conditions need to be considered.

STATEMENT OF ETHICS

The patient gave written permission to publish her case.

ACKNOWLEDGEMENT

The authors thank R. Harsch (BA Translation) for language editing and A. Ortloff for the help in organizing the diagnostic workup.

REFERENCES

1. Levitsky LL, Luria AH, Hayes FJ, Lin AE. Turner syndrome: update on biology and management across the life span. Curr Opin Endocrinol Diabetes Obes. 2015;22: 65-72. doi: 10.1097/MED.0000000000000128.
2. Brun S, Cleemann L, Holm K, Salskov G, Erlandsen M, Berglund A, Andersen NH, Gravholt CH. Five-Year Randomized Study Demonstrates Blood Pressure Increases in Young Women With Turner Syndrome Regardless of Estradiol Dose. Hypertension. 2019;73:242-248. doi: 10.1161/HYPERTENSIONAHA.118.11742.
3. Calcaterra V, Brambilla P, Maffè GC, Klersy C, Albertini R, Introzzi F, Bozzola E, Bozzola M, Larizza D. Metabolic syndrome in Turner syndrome and relation between body composition and clinical, genetic, and ultrasonographic characteristics. Metab Syndr Relat Disord. 2014;12:159-164. doi: 10.1089/met.2013.0075.
4. O'Gorman CS, Syme C, Lang J, Bradley TJ, Wells GD, Hamilton JK. An evaluation of early cardiometabolic risk factors in children and adolescents with Turner syndrome. Clin Endocrinol (Oxf). 2013;78:907-913. doi: 10.1111/cen.12079.
5. Dulac Y. Pienkowski C, Abadir S, Tauber M, Acar P. Cardiovascular abnormalities in Turner's syndrome: what prevention? Arch Cardiovasc Dis. 2008;101:485-490
6. Gravholt CH, Andersen NH, Conway GS, et al, International Turner Syndrome Consensus Group. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017; 177: G1-G70. doi: 10.1530/EJE-17-0430.
7. Akbas E, Altintas ZM, Celik SK, Dilek UK, Delibas A, Ozen S, Mamur, BA, Uyaniker GA. Rare Types of Turner Syndrome: Clinical Presentation and Cytogenetics in Five Cases. Lab Med. 2012; 43: 197–204.
8. Sybert VP, McCauley E. Turner's syndrome. N Engl J Med 2004;351:1227-1238.
9. Kara N, Tural S, Okten G, Kocak I, Tekcan A. Premature ovarian failure and 46,X,del (X)(q21). J Exp Clin Med. 2012;29:167-168.
10. Seki T, Fujimoto S, Abe S et al. Long arm deletion of the X chromosome, 46,X,del(xX)(q21), associated with gonadoblastoma. Jinrui Idengaku Zasshi. 1981;26:307-312.
11. Srivastava PK, Fristoe F Jr, McDavid RE, Townsend JF. A teen-ager with 46,X,del(X)(q21). South Med J. 1979;72:1461-1463.
12. National Cholesterol Education Program (NCEP): Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III Final Report), NIH Publication No. 02-5215, September 2002.
13. Błaszczyk E, Lorek M, Francuz T, Gieburowska J, Gawlik A. Selected Metabolic Markers in Girls with Turner Syndrome: A Pilot Study. Int J Endocrinol. 2018: 9715790. doi: 10.1155/2018/9715790. eCollection 2018.
14. Mavinkurve M, O'Gorman CS. Cardiometabolic and vascular risks in young and adolescent girls with Turner syndrome. BBA Clin. 2015;3: 304-309. doi: 10.1016/j.bbacli.2015.04.005. eCollection 2015 Jun.
15. Giordano R, Forno D, Lanfranco F, Manieri C, Ghizzoni L, Ghigo E. Metabolic and cardiovascular outcomes in a group of adult patients with Turner's syndrome under hormonal replacement therapy. Eur J Endocrinol. 2011; 164: 819-826. doi: 10.1530/EJE-11-0002.
16. Gravholt CH, Naeraa RW, Nyholm B, Gerdes LU, Christiansen E, Schmitz O, Christiansen JS. Glucose metabolism, lipid metabolism, and cardiovascular risk factors in adult Turner's syndrome. The impact of sex hormone replacement. Diabetes Care. 1998;21:1062-1070.
17. Conway G. Transition of Care from Childhood to Adulthood: Turner Syndrome. Endocr Rev. 2018; 33: 34-45. doi: 10.1159/000487524.
18. Wasserman H, Backeljauw PF, Khoury JC, Kalkwarf HJ, Gordon CM. Bone fragility in Turner syndrome: Fracture prevalence and risk factors determined by a national patient survey. Clin Endocrinol (Oxf). 2018;89:46-55. doi: 10.1111/cen.13614.
19. Krauss CM, Turksoy RN, Atkins L, McLaughlin C, Brown LG, Page DC. Familial premature ovarian failure due to an interstitial deletion of the long arm of the X chromosome. N Engl J Med. 1987;317:125-131.
20. Ding T, Hardiman PJ, Petersen I, Wang FF, Qu F, Baio G. The prevalence of polycystic ovary syndrome in reproductive-aged women of different ethnicity: a systematic review and meta-analysis. Oncotarget. 2017; 8: 96351-96358. doi: 10.18632/oncotarget.19180. eCollection 2017 Nov 10.

Conflict of Interest:

There is no conflict of interest.

CORRESPONDING AUTHOR

Igor Alexander Harsch
Thuringia Clinic Saalfeld "Georgius Agricola"
Rainweg 68, D-07318 Saalfeld/Saale, Germany
tel.: +49[0]3671/541569; Fax.: +49[0]3671/541403
e-mail: iharsch@thueringen-kliniken.de

Received: 30.12.2018
Accepted: 16.01.2019

OPIS PRZYPADKU
CASE REPORT

DIAGNOSTIC ERRORS DURING INTRAMEDULLAR PROCESSES

BŁĘDY DIAGNOSTYCZNE W TRAKCIE OCENY PROCESÓW WEWNĄTRZRDZENIOWYCH

Kateryna Tarianyk, Natalia Lytvynenko, Tetiana Purdenko, Viktoriia Hladka
DEPARTMENT OF NERVOUS DISEASES WITH NEUROSURGERY AND MEDICAL GENETICS, UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY, POLTAVA, UKRAINE

ABSTRACT

Introduction: The article describes a clinical case of a malignant tumor of the brain and spinal cord with metastasis, which remained undetected for many years and was treated as syringomyelia. Long-term exhausting examinations of the brain and spinal cord, dynamic follow-up of medical specialists, and repeated surgical interventions on the spine helped to differentiate this process and make the correct diagnosis.

The aim: The objectives of the present paper are to analyze the existing classifications of syringomyelia; to examine its etiology, pathogenesis, diagnostic approaches and treatment tactics; to present a clinical case of a malignant tumor of the brain and spinal cord with metastasis, which was misdiagnosed as syringomyelia.

Materials and methods: The authors analyzed the existing classifications of syringomyelia and studied its etiology, pathogenesis, diagnostic approaches and treatment tactics using the method of content analysis, analytical6 comparative and contrastive methods.

Clinical case: The described clinical case is a variant of the course of syringomyelia, associated with the spinal cord tumor, namely, in particular, anaplastic ependymoma. For a long time, the process remained undetected, despite the long-term examination and drainage of the syringomyelic cavity. Analyzing this case, it is highly important to pay attention to careful history collection, examination of the patient, analysis of the occurrence of certain disorders in order to conduct the neuroimaging examinations in time.

Conclusions: Favorable outcome of the disease is directly related to the diagnosis at early stages, especially in young people, the clinical variant of the process, progression of the course, the degree of involvement of various parts of the nervous system and extraneural formations, the severity of the lesion. The treatment tactics and the ability to restore the functions will depend on all these factors.

KEY WORDS: intramedullary tumor, syringomyelia, syringobulbia, ependymoma

Wiad Lek 2019, 72, 1, 129-132

INTRODUCTION

Syringomyelia is a chronic, polietiologic disease, characterized by the progressive development of longitudinal cavities in the spinal cord, which are filled with liquor or a liquid close to it in composition [1-3]. In all conditions, in which syringomyelia develops, there is at least a partial blockage of the normal circulation of cerebrospinal fluid. Based on this feature, the following classification of syringomyelia was proposed, according to Barnet (1973) [4,5]:

1. Communicating syringomyelia with subarachnoid space. It is associated with the anomaly of the craniovertebral junction. The sunken cerebellar tonsils impede the free flow of cerebrospinal fluid from the skull into the spinal canal. It is associated with diseases of the base of the skull (basal arachnoiditis, cysts and tumors of the posterior cranial fossa).
2. Post-traumatic syringomyelia: the syringomyelic cyst occurs at the site of injury and then spreads to other segments of the spinal cord.
3. Syringomyelia as a consequence of spinal arachnoiditis and arachnopathy.
4. Syringomyelia, associated with the spinal cord tumors.
5. Syringomyelia, caused by compression of the spinal cord by non-tumor etiology formations (herniation of cervical discs, large demyelination foci in the spinal cord in multiple sclerosis, etc.).
6. Idiopathic syringomyelia – the causes of development are unknown.

Analysis of recent research and publications. In 2000, T. Milhorat suggested a classification of syringomyelia based on MRI and morphological data [6-10]. He identified 3 types of lesions: 1. Communicating central channel syringomyelia, 2. Non-communicating central channel syringomyelia. 3. Non-communicating extracanal syringomyelia.

According to this classification, communicating syringomyelia constitutes 10–15% of all observations and, as a rule, it is combined with Chiari anomaly of type 2, hydrocephalus, and Dandy–Walker anomaly.

Non-communicating syringomyelia (75% of observations) is combined with Chiari anomaly of type 1 and basilar impression, as well as various causes of impaired patency of the subarachnoid spaces at the level of the spinal canal (injuries and degenerative stenosis of the cervical spine, tumors, etc.).

Non-communicating extracanal syringomyelia (10%) is a consequence of injuries and circulatory disorders in the

spinal cord with the primary formation of a cyst in the area of damage to the brain substance and its gradual spread along the spinal cord.

Etiology and pathogenesis. An important role in the development of the disease belongs to the defect in the embryonic development of the nervous tissue, which during the development of the organism is manifested by the dysraphic state (status dysraphicus). As a result of endogenous (heredity) and exogenous (trauma, intoxication) influences, the internal defect manifests itself, turning into a disease [1,3].

Among the cranial factors of syringomyelia development, the most common are congenital lesions of the cranio-cervical region (Chiari malformations (CM), types 1 and 2, basilar impression, Dandy-Walker anomaly, small posterior cranial fossa (PCF)), less common are arachnopathies, tumors of PCF and supratentorial tumors; spinal etiological factors of syringomyelia are caused by: malformations (diastematomyelia, "tight filum terminale syndrome", spina bifida), tumors, arachnopathies, degenerative diseases of the spine, multiple sclerosis.

The manifestations of syringomyelia, the onset of the disease regardless of age, different types of the course, the absence of pathognomy signs in the early stages of the disease, lead to the need to differentiate this disease from neurological disorders in which syringomyelic syndrome may be observed, namely:

1. Hematomyelia (after a traumatic injury, there are symptoms characteristic of syringomyelia, and then their regression occurs).
2. Chronic poliomyelitis (sensitive and autonomic disorders are not characteristic).
3. Amyotrophic lateral sclerosis (no sensitivity disorders).
4. Brachioneuritis (the progressive course is not characteristic, dissociated type of sensitivity disorders).
5. Intramedullary tumor (accompanied by the signs of spinal cord compression with minor trophic and autonomic disorders).
6. Leprosy (no signs of central lesion of lower extremities, segmental-dissociated type of sensitivity disorder, positive Hansen's bacillus).
7. Spinal amyotrophic syphilis (mixed signs of paralysis only in the lower limbs, dissociated sensory disturbances, positive reaction and Argyll Robertson symptom).
8. Myelodysplasia (disrupted sensitivity only in the lower extremities, there is no progressive course, mild paresis is characteristic).
9. Denny – Brown sensory neuropathy.
10. Disturbances of spinal blood circulation.

Diagnostic approaches: The most accurate diagnosis of syringomyelia is performed using spinal MRI or myelography. Radiography is used as an auxiliary method, because it will determine disorders of the bone structure, but will not detect cavities in the spinal cord. Electroneuromyography will clarify the nature of the sensitivity disorder and the level of damage.

Treatment. At the initial stages of the disease, radiotherapy is considered the most favorable method, which slows down the progression of the process, reducing the severity of sensitive and trophic disorders [3, 16, 17].

In advanced cases, radioactive phosphorus (P2), which has beta radiation, and radioactive iodine (Ii3i), which has beta and gamma radiation, are used to treat syringomyelia. [18].

A relatively new method in the treatment of syringomyelia is neostigmine therapy, which improves the conduction of nerve impulses. It allows to temporarily improve the neuromuscular conduction, a combination of such therapy with UHF or radon baths is possible [3,19,20].

Surgical treatment for syringomyelia is indicated for detection of voids that block the subarachnoid space in the spine, as well as in congenital disorders of cerebrospinal fluid outflow from the brain. Surgical treatment can eliminate cysts, as well as correct the defects of the spine resulting from the disease [14, 17, 18].

Another method of surgical intervention is drainage of cystic formations, that is, removal of excess fluid from the cavities.

There have been attempts of surgical treatment of syringomyelia by transplantation of embryonic nerve tissue [18–20].

In our report, we will present a clinical case of the intramedullary tumor, which remained undetected for a long time and was treated as syringomyelia.

CLINICAL CASE

Patient S., aged 39, an employee, presented with complaints of decreased sensitivity of the left half of the body, pain in the lumbar spine, radiating to the lower limbs, weakness in the right leg, grogginess, straining effort in urination.

He noted the first episodes of the disease 10 years ago, when he first noticed the decreased sensitivity in the left half of the body, and did not seek medical help. In May 2015, pain in the neck and left arm increased, the MRI scan (0.3 T) of the cervical and thoracic spine was conducted, the patient was examined by the neurosurgeon, and the following diagnosis was made: "Osteochondrosis of the cervical and thoracic spine, hernia of C5-C6, C6-C7 intervertebral discs with relative stenosis of the spinal canal at the level of C5-C6, C6-C7". The patient was prescribed therapy (vitamins, chondroprotectors, vascular medications).

In June 2015, after physical exertion, complaints of disrupted sensitivity in the shoulder and upper limb to the left increased. On this occasion, the patient consulted the neurologist, the MRI scan (1.5 T) of the cervical and thoracic spine was conducted with intravenous contrasting. The signs of intramedullary cystic formation of the spinal cord at the cervical level and cystic solid formation in the thoracic region at the level of Th1-L1 vertebrae were detected. The patient was referred for consultation and treatment to A.P. Romodanov Institute of Neurosurgery, where the following diagnosis was made: "Idiopathic syringomyelia, cervico-thoracic form". The patient was hospitalized (vascular and restorative therapy).

After discharge, the patient continued to work at the place of residence for the next 2 years. The state remained at the same level. In October 2016, the patient once again consulted A.P. Romodanov Institute of Neurosurgery of the National Academy of Medical Sciences of Ukraine. After consultation, dynamic observation was recommended.

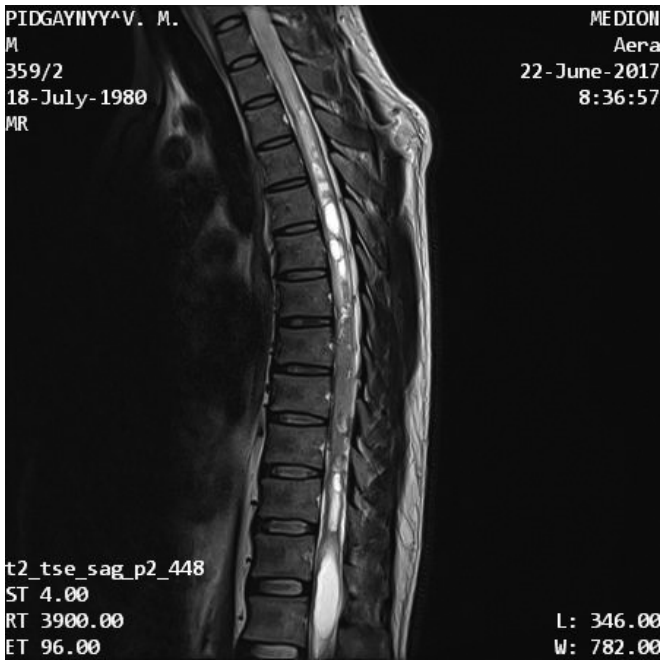


Fig. 1. MRI with contrast enhancement of the cervical and thoracic spine.

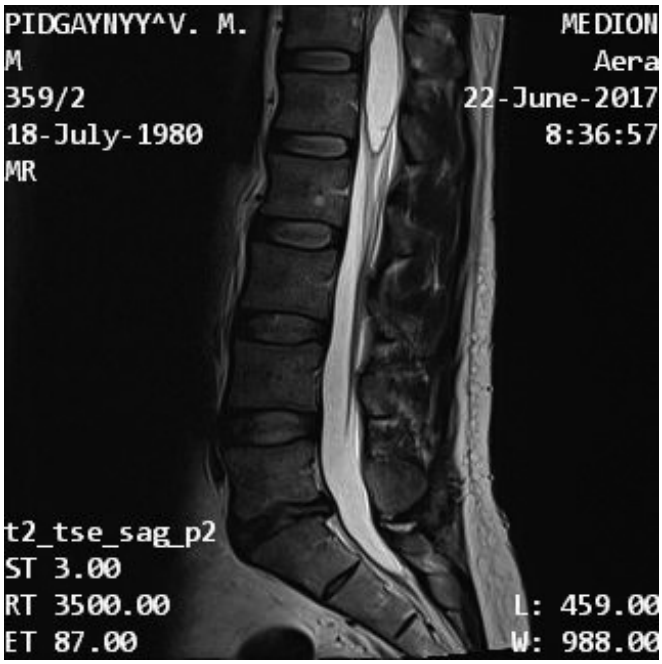


Fig. 2. MRI with contrast enhancement of the lumbar spinal cord.

In June 2017, the patient began to complain of weakness in the lower extremities, more to the right, grogginess, numbness of the left half of the body, straining effort in urination, periodic pain in the thoracic and lumbar spine. The MRI scan of the thoracic and lumbosacral spine was conducted with intravenous contrasting. According to the data obtained from MRI images, the progression of the process was revealed in the form of increased size of cavities, the lower pole of the cystic formation - at the level of L1-L2, the combination of syringomyelia with a voluminous formation is not excluded.

After consultation, the patient was, diagnosed with syringomyelia, cervico-thoracic and lumbar form, syringobulbia, with disrupted sensitivity of the "half-jacket" type to the left; myeloradiculopathy syndrome, with moderate lower paraparesis, with an emphasis to the right, moderate pain syndrome, musculo-tonic syndrome, neurotrophic syndrome, sensory ataxia against the background of osteochondrosis, deforming spondylosis, disc protrusion at C3-C4 and C5-S6, C6-C7, hernias of L5-S1 with right-sided lumbar ischialgia. The patient was prescribed conservative treatment; he was independently seeking treatment, consulting doctors from other institutions in Ukraine, Belarus and Germany.

In July 2017, the patient underwent surgical intervention at the Institute of Neurosurgery (Kyiv) – removal of the intramedullary spinal cord cyst at the L1-L2 level, drainage of the cavity. Laminectomy of L1 with subsequent dynamic observation.

In October 2017, due to increased weakness in the legs, disrupted sensitivity in the anogenital area and legs, the patient consulted A.P. Romodanov Institute of Neurosurgery of the National Academy of Medical Sciences of Ukraine.

From the life history: the patient denies TB, typhus, malaria, sexually transmitted diseases, Botkin's disease, hemotransfusion, HIV, injuries. The patient is married, has a daughter. All relatives are healthy.

Objectively: the general condition is relatively satisfactory. Normal nutrition. The skin and visible mucous membranes are pale pink, clean. Peripheral lymph nodes are not enlarged. Vesicular breathing in the lungs, no wheezing. The activity of the heart is rhythmic, the tones are clear. BP is 120/70 mm Hg; pulse - 68 per 1 min. The abdomen is soft, painless on palpation. *In the neurological status*: the patient is conscious; oriented in place, time and self. Emotionally labile. Palpebral fissures S = D, pupils are equal. No nystagmus. Asymmetry of the nasolabial folds, the left corner of the mouth is drooping. The tongue is in the middle line. Barre's test – lower positive to the right. Reduced muscle strength in the right leg to 3 points, in the left – up to 4 points. Tendon and periosteal reflexes from the hands of D> S, high, with extended reflexogenic zones. Knee and Achilles reflexes are high, D> S. No abdominal reflexes. There are no pathological stop signs on both sides. Long back muscles are strained along all parts of the spine, painfulness of the paravertebral points in the cervical, thoracic and lumbosacral spine. Lasègue symptom 45 ° to the right. The temperature sensitivity of the left half of the body is disrupted according to the "half-jacket" type in the anogenital zone. Loss of deep sensitivity in the fingers of both feet. FTN is performed indistinctly from two sides. HTS is performed with omissions and intention from both sides. Pelvic disorders by the urinary retention type. No dysraphic status.

On MRI of the cervico-thoracic and lumbar spine with contrasting, there is an intramedullary formation consisting of solid and cystic areas. A solid area – is over the bodies of the Th7-Th9 vertebrae, 6.8 cm long, 1.3 cm wide, it has an iso-intensive soft tissue MR signal. The cystic areas are located above and below it, the lower pole is at the L1 vertebra level, the width at the L1 vertebra level is up to 1.1 cm. The dimensions of the pathological area after contrasting are 0.83 × 0.93 × 6.0 cm, the cystic areas do not accumulate the contrast

medium. Degenerative changes in the thoracic spine, hernial protrusion of the intervertebral disk in the C6-C7 segment, cystic formation of the spinal cord, the upper pole is located at the level of the craniovertebral junction (Fig. 1 and Fig. 2).

Conclusion: MR signs of intramedullary cystic solid formation of the spinal cord in the thoracic spine at the level of Th1-L1 vertebrae, the lower pole at the level of the L1-L2 segments (possible combination of syringomyelia with a voluminous formation), osteochondrosis of intervertebral disks of the thoracic spine.

General clinical test: no abnormalities.

In October 2017, the patient underwent surgical treatment – laminectomy of Th8-Th10, subtotal removal of the tumor at this level. A few days later, the results of histopathological study of the tumor were as follows: anaplastic ependymoma. On the 10th day, the patient was discharged from the hospital with improvement.

After the surgical treatment, the patient underwent active rehabilitation at the place of residence. He moves indoors using walkers, notes anesthesia in the anogenital zone, lower spastic paraparesis. The patient takes anticholinesterase medications, muscle relaxants. Initially, an improvement was noted, and afterwards – increasing paraparesis.

The described clinical case is a variant of the course of syringomyelia, associated with the spinal cord tumor, namely, in particular, anaplastic ependymoma. For a long time, the process remained undetected, despite the long-term examination and drainage of the syringomyelic cavity. Analyzing this case, it is highly important to pay attention to careful history collection, examination of the patient, analysis of the occurrence of certain disorders in order to conduct the neuroimaging examinations in time.

CONCLUSIONS

Favorable outcome of the disease is directly related to the diagnosis at early stages, especially in young people, the clinical variant of the process, progression of the course, the degree of involvement of various parts of the nervous system and extraneural formations, the severity of the lesion. The treatment tactics and the ability to restore the functions will depend on all these factors.

REFERENCES

1. Ivanova M.F., Simonyan V.A., Muradyan I.E., Zinov'yeva N.N. Siringomiyeliya i yeyo maski. Mezhdunarodnyy nevrologicheskiy zhurnal. №5(51). 2012: 76-82.
2. Davletshina R.I., Mendelevich Ye.G. Techeniye siringomiyelii s nachalom v zrelom vozraste. Prakticheskaya meditsina. №1-2(69). T.1. 2013: 32-35.
3. Tondiy O.L., Zaval'naya O.P., Teslenko O.B., Sushko S.P., Merkulova V.V. Siringomiyeliya. Etiopatogenez. Klinika. Diagnostika. Lecheniye. Skhídno-yevropeyskiy zhurnal vnutrishn'oyi meditsini. T.2. 2015: 61-69.
4. Barnett H.J.M. Syringomyelia associated with spinal arachnoiditis, in Barnett H.J.M., Foster J.B., Hudgson P. (eds.). Syringomyelia. London: WB Saunders; 1973: 220-244.
5. Barnett H.J.M., Jousse A.T., Ball M.J. Pathology and pathogenesis of progressive cystic myelopathy as a late sequel to spinal cord injury, in Barnett H.J.M., Foster J.B., Hudgson P. (eds.): Syringomyelia. London: WB Saunders; 1973: 179-219.
6. Milhorat T.H., Capocelli A.L. Jr, Anzil A.P. et al. Pathological basis of spinal cord cavitation in syringomyelia: analysis of 105 autopsy cases. J Neurosurg. 82.1995: 802-812.
7. Milhorat T.H., Johnson R.W., Milhorat R.H., et al: Clinicopathological correlations in syringomyelia using axial magnetic resonance imaging. Neurosurgery. 37.1995: 206-213.
8. Milhorat T.H., Johnson W.D., Miller J.I. et al. Surgical treatment of syringomyelia based on magnetic resonance imaging criteria. Neurosurgery. 31. 1992: 231-245.
9. Milhorat T.H., Kotzen R.M., Anzil A.P. Stenosis of central canal of spinal cord in man: incidence and pathological findings in 232 autopsy cases. J Neurosurg. 80. 1994: 716-722.
10. Milhorat T.H., Nobandegani F., Miller J.I., et al: Noncommunicating syringomyelia following occlusion of central canal in rats. Experimental model and histological findings. J Neurosurg. 78. 1993: 274-279.
11. Blagodatskiy M.D., Larionov S.N., Sufianov A.A. Mal'formatsiya Arnol'da – Kiari i siringomiyeliya: metod. rek. Irkutsk; 1995: 242.
12. Yelmanova T.V. Vrozhdennyye anomalii golovnogo i spinnogo mozga: kliniko-diagnosticheskiy aspect. Spravochnik vracha obshchey praktiki. № 7. 2010: 22-38.
13. Tambiyeva M.A., Shevchenko P.P. Siringomiyeliya: Sovremennyye metody diagnostiki i lecheniya. Mezhdunarodnyy studencheskiy nauchnyy vestnik. № 2-19. 2015: 107-108.
14. Hardwidge C. Syringomyelia. Neurosurgery. V. 140. 1996: 685-690.
15. Metcalfe R.A., Johnston R.A. Craniocervical Anomalies and Non-traumatic syringomyelia. Spinal Cord Disease. London; 1997: 275-295.
16. Owler B.K., Halmagyi G.M., Brennan J., Besser M. Syringomyelia with Chiari malformation: 3 unusual cases with implications for pathogenesis. Acta Neurochir (Wien). № 146. 2004: 1137-1143.
17. Kopanitsa V.V. Gidrosiringomiyeliya (etiopatogenez, klinika, neyrokhirurgicheskiye aspekty lecheniya. Ukrains'kiy medichniy chasopis. № 6. 2000: 92-97.
18. Gorbach I.N. Differentsiatsiya v nevrologii. Bolezni: spravochnoye posobiye. Mn.: Novoye znaniye; 2002: 478 s.
19. Lemann-Khorn F., Ludol'f A. Lecheniye zabolevaniy nervnoy sistemy. Pod red. O.S. Levina. M.: MEDpress.inform; 2005: 528 s.
20. Sufianov A.A. Vozmozhnosti khirurgicheskogo lecheniya siringomiyelii putom transplantatsii embrional'noy nervnoy tkani. Dis. kand. S.-Peterburg; 1994: 192 s.

Authors' contributions:
According to the order of the Authorship.
Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Kateryna Tarianyk
Department of Nervous Diseases with
Neurosurgery and Medical Genetics,
Ukrainian Medical Stomatological Academy,
23 Shevchenko Str., 36011, Poltava, Ukraine
tel: +380669226575
e-mail: tkapolt@gmail.com

Received: 06.08.2018
Accepted: 03.12.2018

OPIS PRZYPADKU
CASE REPORT

TROMBOSIS OF MESENTERIAL VESSELS IN ACUTE LYMPHOBLASTIC LEUKEMIA (CASE REPORT)

ZAKRZEPICA NACZYŃ KREZKI W PRZEBIEGU OSTREJ BIAŁACZKI LIMFOBLASTYCZNEJ (OPIS PRZYPADKU)

Veronika M. Dudnyk, Irina I. Andrikevych, Hennadiy M. Rudenko, Tetiana G. Korol, Kateryna V. Khromykh
VINNYTSA NATIONAL PYROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSA, UKRAINE

ABSTRACT

The article presents data on classification, diagnostic problems, treatment of acute lymphoblastic leukemia in children. Remaining unresolved problems of protocol chemotherapy complications of acute lymphoblastic leukemia. The presented clinical case of successful treatment of thrombosis of mesenteric vessels in a child with acute lymphoblastic leukemia, which included the stages of thrombolytic therapy and surgical treatment for resection of necrotized part of the ileum.

KEY WORDS: Acute lymphoblastic leukemia, chemotherapy, mesenteric thrombosis, children

Wiad Lek 2019, 72, 1, 133-136

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is one of the most common malignant diseases of childhood and accounts for about 75% of all hemoblastosis. Often acute lymphoblastic leukemia affects children aged 2 to 5 years, mostly boys [1].

Diagnosis and modern classification of ALL based on studies of peripheral blood, liquor and bone marrow, namely cytological, cytochemical, cytogenetic and immunophenotyping. According to the results of a morphological study, 85% of patients have L1 variant by FAB (French-American-British classification). Majority of children, common-ALL and B-linear leukemia (85.8%) are diagnosed, whereas the proportion of prognostically unfavorable T-ALL is 14.2%, which is associated with an initial hyperleukocytosis, hepato-spleenemalemia, and the presence of mediastinal tumor by immunophenotypic signs. The presence of cytogenetic translocations t (9; 22) and t (4; 11) are prognostically unfavorable and occur in 10-15% of patients. About 20% of affected children is genetically determined location trancelocatione t (12; 21) type EVT6/RUNX1, associated with initial low white blood cells (aleukemic and leukopenic form) and has a favorable prognosis [2].

Due to modern protocols of chemotherapeutic treatment of ALL has moved from the category of non-curable to potentially curable diseases [3]. However, these adverse factors as infectious and septic conditions, disease recurrence, development of secondary tumors, toxic effects of cytotoxic drugs and disturbances in the hemostatic system can lead to fatal consequences. To date, problems of diagnostics, treatment and prevention of ALL protocol chemotherapy complications remain incompletely solved [4].

Acute abdominal conditions are relatively rare, but potentially possible as complications in the treatment of ALL. Progress in the development of chemotherapeutic drugs led to an increase in the proportion of longer duration of remission and survival with improved blood transfusion, antibiotics and supportive care resulted in increased frequency of acute abdominal abnormalities in patients with leukemia [5]. One of the most severe complications that develops in children with hemoblastosis at the treatment stage is acute cerebrovascular disruption of mesenteric vessels, the treatment of which remains difficult and does not always result in a positive outcome for the patient [6].

The development of mesenteric thrombosis is due to the combination of the Virchow triad (blood flow disorders, hypercoagulation and inflammation of the vascular wall) and observed in 5.2% of patients with ALL at the treatment stage, of which 80% dominated by venous thrombosis and in 20% of patients - arterial vessels. In addition, in 58.3% of cases, thrombi occurs in the central nervous system (28.6% of the sinus thrombosis) and in the upper limbs, often due to the presence of a central venous catheter [7].

Modern studies have shown that malignant cells are involved in the formation of endothelial dysfunction, platelet activation and blood coagulation. Cytotoxic therapy is the main factor contributing to the development of thrombosis of mesenteric vessels and disorders in the hemostasis in children with ALL. Thus, corticosteroids and L-asparaginase induced hypercoagulatione due to lower levels of natural anticoagulants, which requires the use of low fraction heparins for therapeutic or prophylactic purposes. Also, the pathogenesis of mesenteric blood vessel thrombosis may be due not only to the effect of chemotherapy,

but also to the congenital prothrombotic status of the patient, namely, the congenital antiphospholipid syndrome. For the diagnosis of thrombophilia, the most common laboratory tests indicating the causes of thrombosis are also used, namely: the mutation of the prothrombin G20210A and the gene of MTHFR, the antithrombin deficiency III, the deficiency of protein C, the hyperhomocysteinemia, the hypolipoproteinemia, the deficiency of protein S, the presence of antiphospholipid antibodies, the dysfibrinogenemia, the mutation V factor, an increase in the levels of factors VIII, IXa and XI [8].

In addition, an important factor that leads to thrombosis of mesenteric vessels is the disseminative intravessels clotting (DIC), which develops in patients with leukemia in the background of sepsis. During the last decade, molecular markers that are secret in the nucleus of cells in acute cell lysis, which include the HMGB1 protein, are studied. This factor binds to chromatin when the integrity of the membrane of atypical cells is lost and isolated in the extracellular space, which acts on Toll-like receptors and leads to cell activation through MAP kinase. In case of sepsis this marker is an inflammatory cytokine. In addition, it activates the system of coagulation, inhibits anticoagulant protein C and stimulates the expression of tissue factors on monocytes, which leads to the development of the DIC [9].

Diagnosis of mesenteric blood vessel thrombosis is very complicate and requires careful analysis of clinical changes, laboratory and instrumental research methods. The main clinical manifestation of mesenteric thrombosis is an unbearable sharp abdominal pain, multiple vomiting, and emptying with impurities of the blood. The condition of the child is severe; the skin covers pale color with an earthy gray tint. Characteristic X-ray signs of mesenteric vessels thrombosis are pronounced intestinal pneumatosis, the absence of peristalsis and the Clyber bowl with horizontal levels. However, the most informative method of diagnosis is laparoscopy, which makes it possible to carefully and qualitatively evaluate the nature and prevalence of pathological changes in the intestine.

One of the methods of treating mesenteric thrombosis is surgical intervention with resection of the necrotic area of the intestine [10]. However, the indicators of postoperative and total mortality remain rather high and make up 65 - 85%, and with the development of peritonitis reach 90-100%.

CASE PRESENTATION

The child B. (girl), 4 years old, admitted to the oncohematological department of the regional children's clinical hospital on January 5, 2018 with complaints of general weakness, slipping, refusal of food, fever to 39°C, weight loss and pronounced pallor of the skin. The above listed complaints disturbed the child for a week. The objective examination revealed: the skin and mucous membranes are pale with hemorrhagic syndrome in the form of a petechial, non-symmetrical, polychrome rash localized on the trunk and the limbs. Increase in cervical and submucosal lymph nodes in diameter up to 1 cm, with a dense consistency were found. From the side of the cardiovascular and broncho-pulmonary system of pathology were not detected. The abdomen is symmetrical, takes part in the act of breathing, the peristalsis is preserved, the liver and spleen are not enlarged, the physiological excrement is not affected. Diagnostics was performed according to the protocol ALL - BFM 2009: hematological blood test; bone marrow research, which included cytological, cytochemical, molecular genetic and immunophenotyping. Morphological study of cytocentrifugate of liquor and diagnosis: Acute lymphoblastic leukemia, FAB - variant L1, common - ALL type with coexpression of two myeloid antigens CD_{13} and CD_{33}.

The child given an induction course of chemotherapy. From the first day of chemotherapy, the child received prednisone at a rate of 60 mg/m^2, against which background, regression of peripheral tumor mass and normalization of temperature indices observed. At day 8 hematological blood test was performed, where leukopenia was detected - 1,7×10^9/l and the absence of blast cells in the leukocyte formula. In addition, the girl received infusion of Vincristine - 1.5 mg/m^2 and doxorubicin - 30 mg/m^2. On the 12th day of the induction course of treatment, the condition of the girl worsened, namely hyperthermia appeared, and leukopenia and neutropenia increased, which did not allow the continuation of the introduction of L-asparaginase. Taking into account signs of febrile neutropenia, an antibiotic and antitumor antibodies and human immunoglobulin intravenously administered. On the 15th day of protocol No. 1 a bone marrow test was performed, in which 2% of blasts were detected and a bone marrow remission was detected; an immunocytogenesis of bone marrow revealed a population of leukemic blasts, representing 4.03% of nucleated cells, which was consistent with the status of FMR (middle-risk group).

At day 18 of the induction course of chemotherapy, the child's condition deteriorated: fever and severe abdominal pain. Physical examination: pronounced pallor of the skin with earthy tint and hemorrhagic syndrome with polymorphic rashe on the limbs, legs and anterior abdominal wall. Auscultation in the lungs vesicular breathing. Tones of the heart are rhythmic, tachycardia, systolic murmur. The abdomen is enlarged, painful in all parts, peristalsis sharply weakened. The liver + 3 cm, the spleen was not enlarged. Stool 1 times scanty. Urination is free, urine is light. Hematological blood analysis: anemia (Hb 65 g/l), leukopenia 1.2×10^9/l, thrombocytopenia 10 thousand/μl. Laparoscopy performed for vital signs with revision and rehabilitation of the abdominal cavity, appendectomy, superimposition of enterostoma and cecostoma, took histological material for further morphological examination.

Intestinal wall swollen with a gray-black hue, no peristalsis and pulsation of blood vessels during examination of the abdominal cavity. From the abdominal cavity was evacuated about 2 liters of serous - hemorrhagic effusion, erythema, edema, vessels without pulsation, peritoneum in multiple hemorrhages (Figs 1 and 2).

Thrombosis of mesenteric vessels with total necrosis of the colon wall, hemorrhagic infusion and inflammatory infiltration detected at histological examination; significant edema and degenerative changes in the small intestine, with the presence of hypersecretion of mucus and desquamation of the epithelium in the mucous membrane.

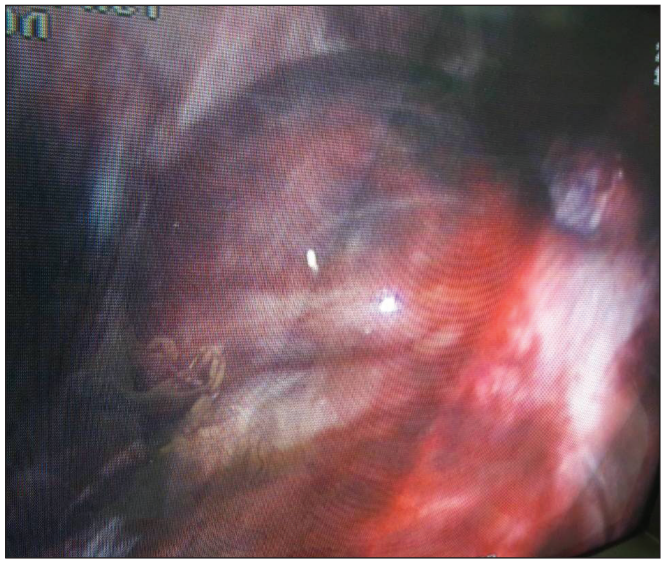


Fig. 1. Colon in mesenteric thrombosis

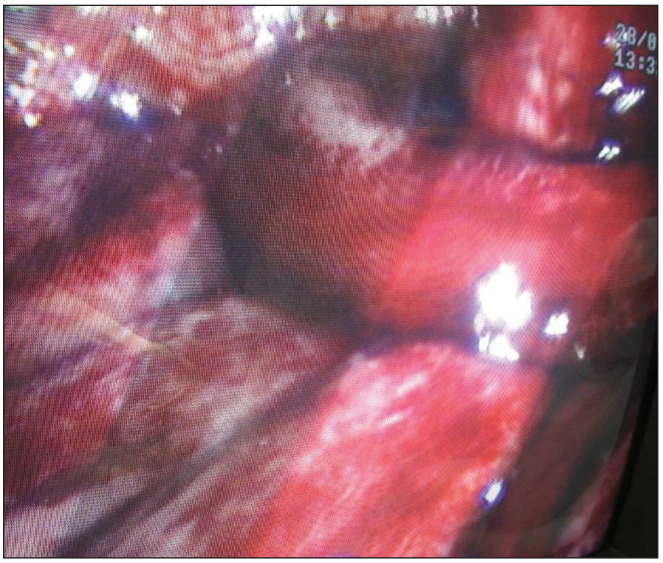


Fig. 2. Small intestine with mesenteric thrombosis

Table I. Dynamic of the hematology blood test in postoperative period

Units	27.01. 2018	28.01. 2018	29.01. 2018	30.01. 2018	31.01. 2018	01.02. 2018	02.02. 2018
Leukocytes *10⁹/l	0.5	1.0	2.6	2.6	2.0	2.2	2.3
Hb, g/l	60	58	80	60	72	76	74
Platelets, thousand/µl	0	0	10	218	70	30	48

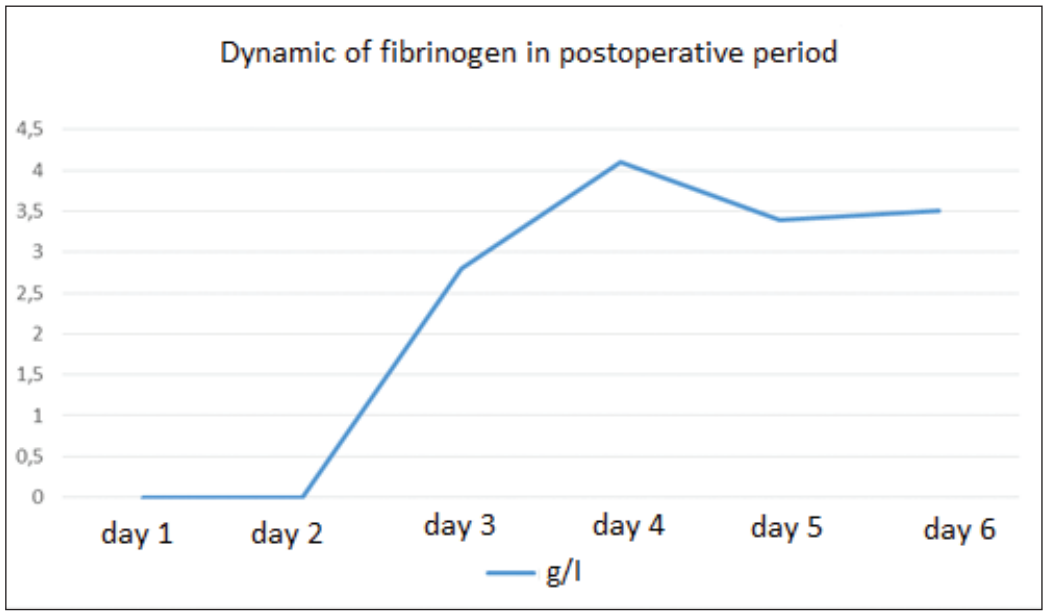


Fig. 3. Dynamics of fibrinogen indicators

In the postoperative period, the child's condition remained extremely severe, the severity was due to hemorrhagic syndrome (bleeding from postoperative wounds, hemorrhagic discharge on nasogastric probe and urinary catheter). In a dynamic study in blood hematological analysis anemia, leukopenia and thrombocytopenia preserved (Table I).

In the postoperative period, the child needed daily massive hemotransfusions of erythrocytes, platelets, and plasma. In addition, the girl received infusion therapy, antibacterial and antimycotic drugs, colony stimulating factor, Novoseven.

Test of secondary hemostasis: D-dimer 1.02 µg (N-to 0.5 µg), prothrombin time 12.8 seconds (N- 9.9-11.8 seconds), the inter-

national normalized ratio is 1.15 (N-1.0), activated partial thromboplastin time 40.7% (N- 22.7-31.8 seconds), thrombin time 18.8 seconds (N-14, 0-21.0 seconds), coagulation of the blood extended from 7 to 8 minutes hypocoagulation were observed. On the background of hemostatic therapy in the coagulogram, a positive dynamics of the fibrinogen indices observed (Fig. 1).

During the week, hemorrhagic syndrome was preserved due to thrombocytopenia and DIC, but after 10 days after surgery, it was possible to stop the bleeding, the patient's condition gradually improved, normalization of peripheral blood parameters.

To establish the presence of pathological changes in the mucous membrane of different parts of the gastrointestinal tract in the child, fibrogastroduodenoscopy and colonoscopy performed. In fibrogastroduodenoscopy, the esophagus and duodenum without pathological changes, while the mucous membrane of the stomach is hyperemic, with sharp erosions in diameter 0,2 - 0,3 cm without strain of fibrin. During colonoscopy in the direct, sigmoid and descending sections of the large intestine the mucous membrane is hyperemic with a blurred vascular pattern and multiple erosions in the diameter from 0.2 to 0.4 cm, which are covered with hemorrhagic stratification, in the lumen of the intestine, fibrinous-purulent contents. Endoscopic examination of the blind, ascending and transverse colon was also carried out through the preformed bowel movement. It was found that the mucous membranes of the cecum with cyanotic tint, contact with multiple erosions in the diameter of 0,2 - 0,3 cm covered with hemorrhagic contents. In the transverse colon, there were also isolated shallow erosions against the background of the pink mucosa.

CT scan of the abdominal cavity in the postoperative period: a small amount of free fluid and infiltration of the mesentery of the small intestine noted. True data in favor of thrombosis of mesenteric vessels not found. The transverse colon brought to the anterior abdominal wall. In the abdominal cavity on the left flank, as well as in the cavity of the small pelvis, tubular catheters.

Condition stabilized, confirmed bone and brain remission, which allowed to continue chemotherapy.

CONCLUSIONS

1. Acute lymphoblastic leukemia is the most common oncological disease of childhood, occurring in 75% of all hemoblastosis, of which the common-ALL-type is more commonly diagnosed, making up 85.8%.
2. Modern chemotherapy for acute lymphoblastic leukemia has transmitted this disease in a potentially curable one. However, chemotherapy needs further improvement aimed at reducing the toxicity of drugs and preventing severe complications.
3. In 5,2% of children, acute lymphoblastic leukemia is complicated by mesenteric thrombosis, in which the mortality is 65-85%.
4. The management of children with acute lymphoblastic leukemia requires careful examination of the hemostasis system in order to prevent the DICs syndrome.

REFERENCES

1. Lee JW, Cho B. Prognostic factors and treatment of paediatric acute lymphoblastic leukaemia. Korean J Pediatr 2017;6 0(5):129-137.
2. Jarosova M, Volejnikova J, Porizkova I, Holzerova M, Pospisilova D, Novak Z, Vrbkova J, Mihal V. Chromosomal aberrations in childhood acute lymphoblastic leukaemia: 15-year single center experience. Haematology Am Soc Hematol Educ Program 2016, 2(1):561-566.
3. van der Veer A, Zaliova M, Mottadelli F, De Lorenzo P, TeKronnie G, Harrison CJ, Cavé H, Trka J, Saha V, Schrappe M, Pieters R, Biondi A, Valsecchi MG, Stanulla M, den Boer ML, Cazzaniga G. IKZF1 status as a prognostic feature in BCR-ABL1- positive childhood ALL. Blood 2014; 123(11):1691-1698.
4. Stary J, Zimmermann M, Campbell M, Castillo L, Dibar E, Donska S, Gonzalez A, Izraeli S, Janic D, Jazbec J, Konja J, Kaiserova E, Kowalczyk J, Kovacs G, Li CK, Magyarosy E, Popa A, Stark B, Jabali Y, Trka J, Hrusak O, Riehm H, Masera G, Schrappe M. Intensive chemotherapy for childhood acute lymphoblastic leukaemia: results of the randomized intercontinental trial ALL IC-BFM 2002. J Clin Oncol. 2014 Jan 20;32(3):174-84.
5. Acute mesenteric ischemia: guidelines of the World Society of Emergency Surgery. Bala et al. World Journal of Emergency Surgery (2017) 12:38. DOI 10.1186/s13017-017-0150-5
6. C.J. Harrison, Blood spotlight on iAMP21 acute lymphoblastic leukemia (ALL), a high-risk pediatric disease, Blood 125 (9) (2015) 1383–1386.
7. S. Alexander, J.D. Pole, P. Gibson, et al., Classification of treatment-related mortality in children with cancer: a systematic assessment, Lancet Oncol. 16 (16) (2015) e604–610.
8. Mirjana Mitrovic et al. Thrombotic events in acute promyelocytic leukemia Thrombosis Research No 135 (2015) p. 588–593
9. Treatment for disseminated intravascular coagulation in patients with acute and chronic leukemia (Review) Cochrane Database of Systematic Reviews 2015, Issue 6. Art.No.: CD008562.DOI:10.1002/14651858.CD008562.pub3
10. Acute mesenteric ischemia: guidelines of the World Society of Emergency Surgery Bala et al. World Journal of Emergency Surgery (2017) 12:38 DOI 10.1186/s13017-017-0150-5

Authors' contributions:
According to the order of the Authorship.
Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Kateryna V. Khromykh
Vinnytsa National Pyrogov Memorial Medical University
56 Pirihova St., 21018, Vinnytsa, Ukraine
e-mail: kate_khromykh@yahoo.com

Received: 23.07.2018
Accepted: 25.11.2018

OPIS PRZYPADKU
CASE REPORT

ZESPÓŁ KOUNISA - ALERGICZNY ZAWAŁ SERCA. OPIS PRZYPADKU

KOUNIS SYNDROME - ALLERGIC MYOCARDIAL INFARCTION. A CASE REPORT

Olga Wajtryt[1], Tadeusz M Zielonka[1, 2], Aleksandra Kaszyńska[1], Andrzej Falkowski[1, 2], Katarzyna Życińska[1, 2]
[1]KLINIKA CHORÓB WEWNĘTRZNYCH I METABOLICZNYCH, SZPITAL CZERNIAKOWSKI W WARSZAWIE, WARSZAWA, POLSKA
[2]KATEDRA I ZAKŁAD MEDYCYNY RODZINNEJ, WARSZAWSKI UNIWERSYTET MEDYCZNY, WARSZAWA, POLSKA

STRESZCZENIE

Zespół Kounisa, czyli alergiczny zawał serca, to ostry zespół wieńcowy w przebiegu różnego rodzaju reakcji alergicznych. W odpowiedzi na swoisty czynnik pokarmowy, wziewny, środowiskowy, lek lub ukąszenie przez owady u osób uczulonych dochodzi do rozwoju reakcji alergicznej z udziałem wielu komórek i mediatorów, które mogą spowodować skurcz tętnicy wieńcowej lub zainicjować proces rozpadu i aktywacji blaszki miażdżycowej, w wyniku czego dochodzi do ostrego zespołu wieńcowego. W artykule opisano przypadek młodego mężczyzny z pyłkowicą i stwierdzonym uczuleniem na orzechy, u którego po spożyciu mieszanki orzechów rozwinął się pełnoobjawowy wstrząs anafilaktyczny i doszło do szybko przemijającego ostrego zespołu wieńcowego ze wzrostem stężenia troponiny do 4,7 µg/L. Stwierdzono także zwiększone stężenie tryptazy (15 µg/L), całkowitego IgE (>3000 IU/mL) i swoistego IgE anty-orzech (55,1 kUA/L). Na podstawie przebiegu choroby i wyników badań alergologicznych oraz kardiologicznych rozpoznano alergiczny zawał serca typu 1, czyli spowodowany skurczem naczyń wieńcowych. W trakcie hospitalizacji stan chorego szybko się poprawił i po kilku dniach opuścił on szpital bez cech trwałego uszkodzenia mięśnia serca.

SŁOWA KLUCZOWE: alergia pokarmowa, alergiczny zawał serca, ostry zespół wieńcowy, troponina, tryptaza, wstrząs anafilaktyczny, zespół Kounisa

ABSTRACT

Kounis syndrome or allergic myocardial infarction is an acute coronary syndrome in the course of an allergic reaction. In allergic patients in response to a specific condition - nourishment, inhalation, environmental substances, drug or insect bite there is an allergic reaction involving many different cells and mediators that can cause coronary artery spasm or initiate the process of rupture and activation of atherosclerotic plaque resulting in acute coronary syndrome. The paper describes a case of a young man with allergy to pollen and confirmed sensitization to nuts, who developed a full-blown anaphylactic shock after eating the nut mix and experienced a rapidly passing acute coronary syndrome with troponin up to 4.7 µg/L. An increased concentration of tryptase (15 µg/L), total IgE (> 3,000 IU/mL) and specific anti-nut IgE (55.1 kUA/L) were found. Based on the course of the disease and the results of allergic and cardiac tests, allergic type 1 myocardial infarction, i.e. caused by coronary artery spasm, was diagnosed. During the hospitalization, the patient's condition improved quickly and after a few days he left the hospital without the signs of permanent damage to the heart muscle.

KEY WORDS: acute coronary syndrome, allergic myocardial infarction, anaphylactic shock, food allergy, Kounis syndrome, troponin, tryptase

Wiad Lek 2019, 72, 1, 137-141

WSTĘP

Związki pomiędzy alergią i zawałem serca były obserwowane od dawna, ale dopiero w 1991 r. greccy lekarze Kounis i Zavras wysunęli koncepcję dusznicy alergicznej spowodowanej skurczem tętnic wieńcowych indukowanym histaminą [1]. Opisali wówczas współistnienie objawów klinicznych (stenokardialnych i alergicznych), z wynikami badań laboratoryjnych, zmianami w zapisach elektrokardiograficznych, z obrazem w badaniu echokardiograficznym i w koronarografii. Alergiczny zawał serca, tzw. zespół Kounisa, polega zatem na współistnieniu reakcji alergicznej (typu nadwrażliwości, anafilaktycznej lub anafilaktoidalnej) z ostrym zespołem wieńcowym [2]. Większość informacji dotyczących tego zespołu opiera się jedynie na opisach pojedynczych przypadków. Prawdopodobnie wiele z nich pozostaje nierozpoznanych [3].

Patomechanizm zespołu tłumaczy się rozwojem reakcji alergicznej po kontakcie ze swoistym czynnikiem pokarmowym, wziewnym, środowiskowym, po ukąszeniu przez owady lub po podaniu leku (wstrząs anafilaktyczny), a w wyniku działania komórek i mediatorów reakcji alergicznej (takich jak histamina, czynnik aktywujący płytki, proteazy, cytokiny, chemokiny) dochodzi do skurczu tętnic wieńcowych lub rozpoczyna się proces rozpadu i aktywacji blaszki miażdżycowej [2]. Początkowo wyróżniono 2 typy zespołu w zależności od współistnienia choroby wieńcowej [1, 2]. Typ 1 rozpoznaje się u osób, u których nie stwierdza się zmian miażdżycowych w tętnicach wieńcowych ani czynników ryzyka choroby niedokrwiennej serca i dochodzi do skurczu tętnic wieńcowych ze wzrostem lub bez wzrostu biochemicznych markerów martwicy mięśnia

sercowego. Typ 2 pojawia się u osób z miażdżycowymi zmianami tętnic wieńcowych, u których w przebiegu reakcji alergicznej dochodzi do rozpadu blaszki miażdżycowej. Z czasem wyróżniono także typ 3 tego zespołu, rozwijający się u osób z wszczepionymi stentami powlekanymi lekami (DES), w przebiegu alergii na lek lub materiały, z których wykonane są stenty [4]. Wczesne rozpoznanie choroby pozwala na zastosowanie właściwego leczenia.

W pracy przedstawiono przypadek młodego chorego z atopią, u którego w przebiegu wstrząsu anafilaktycznego po spożyciu orzeszków doszło do ostrego zespołu wieńcowego. Na podstawie przebiegu choroby i uzyskanych wyników rozpoznano alergiczny zawał serca.

OPIS PRZYPADKU

35-letni mężczyzna, z atopią w postaci leczonego sezonowo alergicznego nieżytu nosa i alergii pokarmowej na orzechy, został przywieziony do szpitala we wstrząsie anafilaktycznym po spożyciu mieszanki orzechów. W relacji członków rodziny chory początkowo zgłaszał drętwienie i mrowienie języka, a także ust, uczucie kołatania serca, bólu w klatce piersiowej, a następnie narastającą duszność. Wezwano Zespół Ratownictwa Medycznego, który przybył po 17 minutach i zastał chorego nieprzytomnego z nieoznaczalnym ciśnieniem tętniczym i SaO_2 60%. W trakcie transportu do szpitala założono rurkę ustno-gardłową, uzyskując drożność dróg oddechowych, podano tlen do oddychania, zastosowano adrenalinę (domięśniowo 0,5 mg w rozcieńczeniu 1:1000 i powtórzono dwa razy), a także hydrokortyzon oraz płyny dożylnie. Na Szpitalny Oddział Ratunkowy chory został przywieziony nieprzytomny i w ciężkim stanie. W badaniach laboratoryjnych stwierdzono wówczas hipokaliemię, podwyższone stężenie mleczanów, wydłużony czas aPTT, bez cech skazy krwotocznej (Tab. I). Stężenia biochemicznych markerów martwicy mięśnia sercowego nie były podwyższone z wyjątkiem niewielkiego wzrostu izoenzymu sercowego kinazy kreatynowej – CK (Tab. I).

W SOR obserwowano stopniowy powrót świadomości, ale chory był splątany i pobudzony, zgłaszał duszność oraz uczucie kołatania serca. W trakcie ciągłego monitorowania chorego odnotowano krótkotrwały, samoistnie ustępujący epizod migotania przedsionków z częstością zespołów komorowych do 160/min, ze zgłaszanym dyskomfortem w klatce piersiowej. Pojawiła się także pokrzywka na skórze całego ciała. Kontynuowano tlenoterapię, podawano płyny dożylnie, zastosowano antagonistę receptora histaminowego H_1 (klemastynę) i anatagonistę recetora H_2 (ranitydynę) oraz kolejne dawki glikokortykosteroidów (hydrokortyzon). W trakcie pierwszej godziny od przyjęcia na Oddział Intensywnej Terapii stan chorego znacznie się poprawił i ustąpiły objawy obserwowane w SOR. Chory był przytomny, negował dolegliwości, a w EKG rytm serca był zatokowy i nie obserwowano cech niedokrwienia.

W kontrolnych badaniach laboratoryjnych po 6 godzinach od przyjęcia do szpitala stwierdzono istotne zwiększenie stężenia troponiny I do 4,7 μg/L, a także wzrost aktywności CK oraz niewielki wzrost aktywności transaminaz i CK-MB (Tab. I). W EKG w obrębie niskoamplitudowego zapisu obserwowano uniesienie odcinka ST i odwrócenie złamków T w odprowadzeniach III i aVF (Ryc. 1). Wykonane wówczas badanie echokardiograficzne nie wykazało istotnych zaburzeń kurczliwości mięśnia sercowego, funkcji zastawek, ani płynu w osierdziu. Nie zdecydowano wówczas o kwalifikacji chorego do wykonania pilnej koronarografii. Z uwagi na istotnie podwyższone stężenie troponiny, zmiany w zapisie EKG, epizod utraty przytomności, brak możliwości ustalenia czy występowały wówczas objawy stenokardialne, młody wiek chorego i tylko jeden niemodyfikowalny czynnik ryzyka sercowo-naczyniowego, jakim była płeć męska, przy nieznacznie podwyższonym stężeniu cholesterolu całkowitego, wysunięto podejrzenie alergicznego zawału serca typu 1.

W toku dalszej diagnostyki wykazano zwiększone stężenie tryptazy, całkowitego IgE, a także swoistego IgE anty-orzech (Tab. I). W drugim badaniu echokardiograficznym wykonanym w piątej dobie hospitalizacji nie stwierdzono zaburzeń kurczliwości mięśnia serca. W kolejnych dniach w EKG obserwowano płaskie załamki T w odprowadzeniach III i aVF. Po 2 dniach stwierdzono normalizację stężenia troponiny, przy prawidłowym stężeniu N-końcowego propeptyd natriuretyczny typu B. Stan chorego był dobry i nie zgłaszał on żadnych dolegliwości. Kontynuowano leki przeciwhistaminowe. W dobrym stanie ogólnym został wypisany do domu po 7 dniach pobytu w szpitalu. Chory otrzymał wskazówki dotyczące diety eliminującej alergeny pokarmowe, zalecono loratydynę w dawce 10 mg/dobę, a także użycie w sytuacjach nagłych autowstrzykiwacza z adrenaliną domięśniowo w dawce 0,3 mg/dawkę oraz 40 mg prednizonu doustnie. Z uwagi na podejrzenie alergicznego zawału serca chorego skierowano do referencyjnej Poradni Kardiologicznej celem kwalifikacji do badania rezonansu magnetycznego mięśnia sercowego. Z uwagi na niewielkie ryzyko zmian miażdżycowych odstąpiono od badania angio-TK tętnic wiecowych, zalecono jednak dalszą obserwację kardiologiczną.

DYSKUSJA

Zespół Kounisa to jednostka chorobowa znana zaledwie od 28 lat [2]. Wiedza o jej objawach, diagnostyce i sposobie leczenia pochodzi głównie z opisów przypadków lub niewielkich grup chorych [5, 6]. Właściwe rozpoznanie tej choroby i leczenie zarówno komponenty alergicznej, jak i niedokrwiennej serca może być trudnym zadaniem dla klinicystów [7]. Występujące w przebiegu tego zespołu objawy kliniczne, takie jak: pokrzywka, wysypka, duszność, hipoksemia, osłabienie, ból głowy, nudności, wymioty, bladość powłok, poty, tachykardia lub bradykardia, obrzęk naczynioworuchowy, wstrząs i nagłe zatrzymanie krążenia są typowe dla reakcji alergicznych [2, 8]. Większość z nich była stwierdzona w opisanym przypadku. Objawy związane z wystąpieniem niedokrwienia serca w zespole Kounisa to: zamostkowy ból w klatce piersiowej, kołatanie serca, duszność, zaburzenia rytmu serca, omdlenie, bradykardia,

Tabela I. Wyniki badań laboratoryjnych pacjenta

Badania laboratoryjne	Normy	Badania w SOR	Doba 1 (po 6 h)	Doba 5
Troponina I (Ultra)	zdrowi <0,04 µg/L, dla oceny ryzyka > 0,1, dla zawału serca > 1,5	0,016	4,713	0,077
Izoenzym sercowy kinazy kreatynowej (CK-MB)	2-24 (IU/L)	41	37	18
Kinaza kreatynowa (CK)	26-190 (IU/L)	103	454	47
Mleczany	<1,5 (mmol/L)	9,7	3,5	0,9
N-końcowy propeptyd natriuretyczny typu B	0–125 (pg/ml)			54
Czas kaolinowo-kefalinowy (APTT)	26,0-36,0 (sekund)	> 120,0	37,4	26,8
Czas protrombinowy (PT)	8,8-13,6 (sekund)	19,7	15,4	12,4
Wskaźnik protrombinowy	78-120 (%)	60	77	96
INR	0,9-1,2	1,69	1,31	1,04
D-dimer	<500 ng/ ml	416		
Aminotransferaza asparaginianowa (AST)	10-41 U/l	39	50	32
Aminotransferaza alaninowa (ALT)	10-37 (U/L)	29	43	31
Cholesterol całkowity	115-190			202
Tryptaza	<11,4 (µg/L)			15
IgE całkowite	<100 (IU/mL)			>3000
IgE swoiste przeciw-orzechom	Zgodnie z tabelą* (kUA/L)			55,1

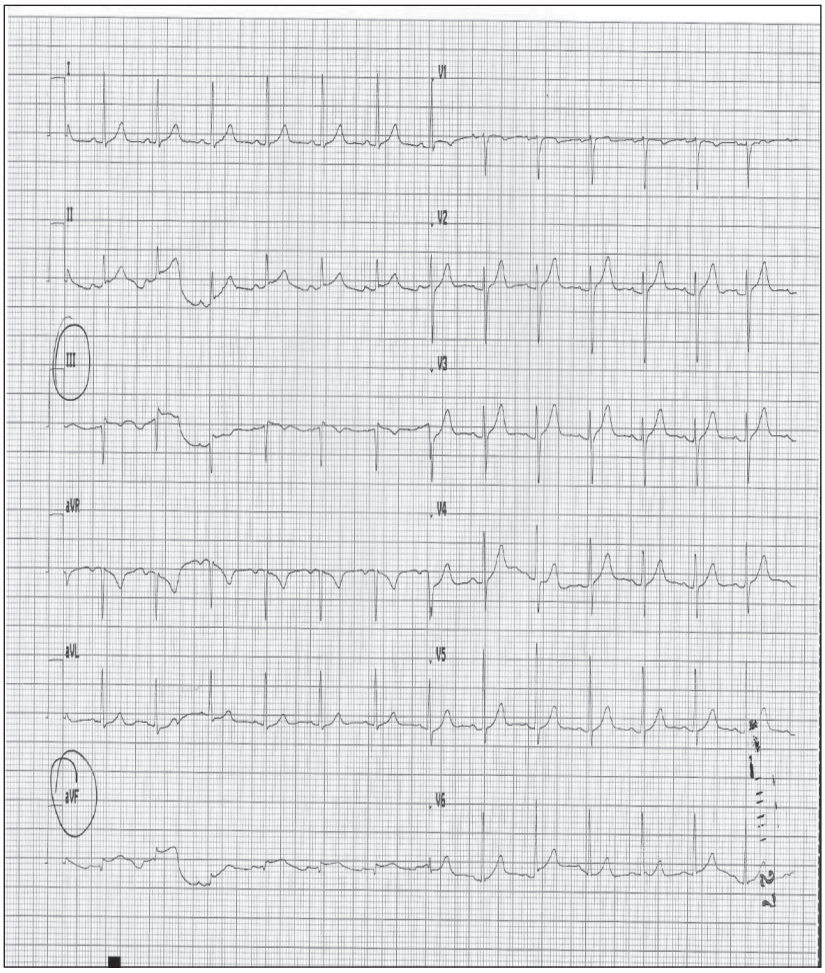
* Interpretacja wyników swoistych anty-IgE
<0,35 kUA/L – klasa 0 (niewykrywalne swoiste przeciwciała)
0,35-0,7 – klasa 1 (bardzo niskie miano przeciwciał, często bez objawów klinicznych)
0,7-3,5 – klasa 2 (niskie miano przeciwciał, istniejące uczulenie, często z objawami klinicznymi
3,5-17,5 – klasa 3 (wykryto określone przeciwciała, często objawy kliniczne)
17,5-50 – klasa 4 (wysokie miano przeciwciała, z objawami klinicznymi)
50-100 – klasa 5 (bardzo wysokie miano przeciwciała, z objawami klinicznymi)
> 100 – klasa 6 (ekstremalnie wysokie miano przeciwciała, z objawami klinicznymi)

tachykardia, pobudzenia dodatkowe i nagłe zatrzymanie krążenia [2, 8]. Część z nich, takie jak ból w klatce piersiowej, duszność, kołatanie serca i zaburzenia rytmu serca, były obserwowane u chorego. Elektrokardiograficzną manifestacją zespołu zwykle są zmiany niedokrwienne pod postacią uniesienia lub obniżenia odcinka ST w sąsiednich odprowadzeniach, ale opisywano również epizody nadkomorowych i komorowych zaburzeń rytmu serca [2, 8].

Rozpoznanie zespołu wymaga wykonania oceny kardiologicznej i alergologicznej zarówno w trybie pilnym, jak i planowym. W diagnostyce laboratoryjnej zespołu Kounisa ważny jest wzrost stężenia biochemicznych markerów martwicy mięśnia sercowego. Do oceny ryzyka sercowo-naczyniowego służy lipidogram. Zalecana jest także diagnostyka alergologiczna obejmująca całkowite i swoiste IgE, oraz prick-testy [2]. W opisanym przypadku oznaczono również stężenie tryptazy we krwi obwodowej, która jest swoistym markerem reakcji alergicznej [9]. Ze względu na krótki okres jej półtrwania (90 min) zaleca się wykonanie badania do 2 godzin od epizodu bólu. Okres półtrwania histaminy jest jeszcze krótszy (8 min), co praktycznie uniemożliwia jej wykorzystanie w praktyce klinicznej.

W opisanym przypadku obserwowano wydłużony czas kaolinowo-kefalinowy (APTT >120 s) oraz czas protrombinowy 19,7 s przy prawidłowych wartościach D-dimeru (416 ng/mL). Zaburzenia APTT oraz INR wynikają z obserwowanej w przebiegu wstrząsu anafilaktycznego aktywacji komórek zapalnych, działania mediatorów oraz aktywacji procesów krzepnięcia i fibrynolizy. Procesy te są od wielu lat przedmiotem badań zarówno klinicznych, jak i w modelach doświadczalnych [10].

W opisanym przypadku dominowała komponenta alergiczna i poprawę stanu chorego uzyskano po podaniu adrenaliny, glikokortykosteroidów i płynów, które należy stosować ostrożnie w trakcie leczenia ostrego zespołu wieńcowego. Następnie stosowano leki, takie jak antagoniści receptorów H_1 i H_2, najlepiej łącznie ze stabilizatorami komórek tucznych np. kromoglikany lub ketotifen [11]. Ważnym elementem postępowania w tym zespole jest monitorowanie i leczenie pacjenta na oddziale intensywnej terapii [9]. W przypadku skurczu tętnicy wieńcowej stosowano antagonisty kanału wapniowego oraz nitraty [2, 11], a w przebiegu ostrego zespołu wieńcowego zaleca się inhibitory ACE, ASA lub heparynę, które mogą jed-



Ryc. 1. Zapis elektrokardiogramu w drugiej dobie po przyjęciu do szpitala. Rytm zatokowy o częstości 80/min. PQ 0,16, QRS 90 ms, QT/Qtc 362/399. Uniesienie odcinka ST o 1 mm w odprowadzeniach III i aVF. Ujemne załamki T w odprowadzeniach III i aVF.

nak powodować reakcje alergiczne [11, 12]. W opisanym przypadku nie zastosowano ASA ani statyny, gdyż nie podejrzewano miażdżycowej etiologii niedokrwienia. Z tego względu nie zdecydowano się także na wykonanie koronarografii w trybie pilnym. Wobec szybkiej poprawy klinicznej, bez nawrotu dolegliwości, przy prawidłowym obrazie echokardiograficznym i braku istotnych czynników ryzyka sercowo-naczyniowego, zastosowano u chorego postępowanie farmakologiczne. Na podstawie dostępnego piśmiennictwa jest to akceptowane u młodych osób, bez czynników ryzyka choroby wieńcowej, u których obserwowano dobrą reakcję na leczenie [13]. Chory został skierowany do referencyjnej Poradni Kardiologicznej celem oceny mięśnia sercowego oraz tętnic wieńcowych w MRI, nieinwazyjnego badania obrazowego, które wraz z angio-TK tętnic wieńcowych i scyntygrafią stosowane były w diagnostyce chorych z zespołem Kounisa [13, 14].

Należy podkreślić słabą jeszcze znajomości tego zespołu, brak standardów postępowania, rolę szybkiej diagnostyki, oceny komponenty alergicznej i niedokrwiennej oraz odpowiedniego leczenia. Znajomość tego zespołu jest ważnym elementem diagnostyki różnicowej ostrych incydentów wieńcowych i reakcji alergicznych, dlatego powinna być uwzględniana w praktyce klinicznej zarówno przez internistów, kardiologów, alergologów, specjalistów medycyny ratunkowej i intensywnej terapii [15, 16].

PIŚMIENNICTWO

1. Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. Br J Clin Pract 1991;45(2):121-128.
2. Kounis NG, Hahalis G, Manola A, Kourelis T, Theoharides TC. Kounis syndrome (allergic angina and allergic myocardial infarction). In: Gallo AP, Jones ML (eds) Angina pectoris etiology, pathogenesis and treatment. Nova Science Publishers, Hauppauge 2008:77-150.
3. Yanagawa Y, Kondo A, Ishikawa K et al. Kounis syndrome should be excluded when physicians treat patients with anaphylaxis. Ann Allergy Asthma Immunol 2017;119(4):392.
4. Tsigkas G, Chouchoulis K, Kounis NG, Alexopoulos D. Allergic reaction reveals a non-lethal stent thrombosis. A new subtype of Kounis syndrome? Int J Cardiol 2011;149:281-282.
5. Gázquez V, Dalmau G, Gaig P, Gómez C, Navarro S, Mercé J. Kounis syndrome: report of 5 cases. J Investig Allergol Clin Immunol 2010;20(2):162-165.
6. Biteker M, Duran NE, Biteker F et al. Kounis syndrome: first series in Turkish patients. Anadolu Kardiyol Derg 2009;9(1):59-60.
7. Lorca R, Velasco E, Madera J et al. Kounis syndrome: Identifying the trigger. Int J Cardiol 2016;209:179-180.
8. Pietraszek N, Bil J. Zespół Kounisa. Kardiol Inwazyjna 2016;11(4):16-20.
9. Kounis NG, Tsigkas G, Almpanis G, Kounis GN, Mazarakis A, Hahalis G. Tryptase levels in coronary syndromes and in hypersensitivity episodes: a common pathway towards Kounis syndrome. Atherosclerosis 2011;219(1):28-29.

10. Guilarte M, Sala-Cunill A, Luengo O, Labrador-Horrillo M, Cardona V. The mast cell, contact, and coagulation system connection in anaphylaxis. Front Immunol 2017;8:846. doi: 10.3389/fimmu.2017.00846.
11. Doğan V, Mert GÖ, Biteker FS, Mert KU, Biteker M. Treatment of Kounis syndrome. Int J Cardiol 2015;181:133-134.
12. Kounis NG, Soufras GD, Lianas D, Patsouras N. Heparin-induced thrombocytopenia, allergy to heparins, heart failure, thrombi, and the Kounis syndrome. Int J Cardiol 2016;214:508-509.
13. Shen G, Wu Y, Bian J, Zhang YH. Kounis syndrome secondary to use in a middle-aged female. J Cardiol Clin Res 2017;5(5):1112-1114.
14. Okur A, Kantarci M, Karaca L et al. The utility of cardiac magnetic resonance imaging in Kounis syndrome. Postep Kardiol Inter 2015;11(3):218-223.
15. Garcia-Nunez I, Algaba-Marmol MJ, Barasona-Villarejo MJ, Suarez-Vergara M, Reina-Ariza EM. Kounis syndrome: a diagnosis you don't want to forge. Austin J Allergy 2014;1(1):2.
16. Juste JF, Garces TR, Enguita RG, Blasco PC, Trallero JA. Cardiac complications in a metamizole-induced type I Kounis syndrome. Braz J Anesthesiol 2016;66(2):194-196.

Konflikt intresów:
Autorzy deklarują brak konfliktu interesów.

AUTOR KORESPONDUJĄCY
Tadeusz M. Zielonka,
Katedra i Zakład Medycyny Rodzinnej,
Warszawski Uniwersytet Medyczny,
ul. Stępińska 19/25, 00-739 Warszawa, Polska
tel/fax: +48 22 3186325
e-mail: tadeusz.zielonka@wum.edu.pl

Nadesłano: 14.12.2018
Zaakceptowano: 10.01.2019

SPROSTOWANIE

W Wiadomościach Lekarskich 7/2018 w artykule **PRZEGLĄD KRYTERIÓW DIAGNOSTYCZNYCH STWARDNIENIA ROZSIANEGO** (Wiad Lek 2018, 71, 7, 1365-1371) zostało błędnie opublikowane nazwisko drugiego autora. Prawidłowa wersja to: **PRZEGLĄD KRYTERIÓW DIAGNOSTYCZNYCH STWARDNIENIA ROZSIANEGO** - Aleksandra Pietruczuk, Adriana Zasybska, Konrad Rejdak, Ewa Papuć
Autorkę i Czytelników przepraszamy.