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Original scientific paper

Case report

Brief communications

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Betimi i Hipokratit

Në çastin kur po hy në radhët e anëtarëve të profesionit mjekësor premtoj solemnisht se jetën time do ta vë në shërbim të humanitetit. Ndaj mësuesve do ta ruaj mirënjohjen dhe respektin e duhur. Profesionin tim do ta ushtroj me ndërgjegje e me dinjitet. Shëndeti i pacientit tim do të jetë brenga ime më e madhe. Do t'i respektoj e do t'i ruaj fshehtësitë e atij që do të më rrëfehet. Do ta ruaj me të gjitha forcat e mia nderin e traditës fisnike të profesionit të mjekësisë.

Kolegët e mi do t'i konsideroj si vëllezër të mi.

Në ushtrimin e profesionit ndaj të sëmurit tek unë nuk do të ndikojë përkatësia e besimit, e nacionalitetit, e racës, e politikës, apo përkatësia klasore. Që nga fillimi do ta ruaj jetën e njeriut në mënyrë apsolute. As në kushtet e kërcënimit nuk do të lejoj të keqpërdoren njohuritë e mia mjekësore që do të ishin në kundërshtim me ligjet e humanitetit. Këtë premtim po e jap në mënyrë solemne e të lirë, duke u mbështetur në nderin tim personal.

The Oath of Hippocrates

Upon having conferred on me the high calling of physician and entering medical practice, I do solemnly pledge myself to consecrate my life to the service of humanity. I will give my teachers the respect and gratitude which is their due. I will practice my profession with conscience and dignity. The health of my patient will be my first consideration. I will respect the secrets which are confided in me, even after the patient has died. I will maintain by all the means in my power, the honor and the noble traditions of the medical profession.

My colleagues will be my brothers.

I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient. I will maintain the utmost respect for human life from its beginning even under threat and I will not use my medical knowledge contrary to the laws of humanity. I make these promises solemnly, freely and upon my honor

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Mjekësia e personalizuar- paradigmë e re për shëndetësinë e shekullit XXI

Mjekësia e personalizuar është një praktikë e re e mjekësisë që përdor profilin gjenetik të një individi për të vendosur hapat e metejmë që duhet ndërmarrë për parandalimin, diagnostikimin dhe trajtimin e sëmundjes.

Përkundër arritjeve në drejtim të njohurive sa më të sakta për për të kuptuar sa më thellësisht çfaqjen e sëmundjes në erën post-genomike, akoma shumica e barnave janë efikase vetëm në një numër të limituar të pacintëve. Nga perspektiva klinike, përzgjedhja e terapisë bazuar në metodologjinë shkencore deri tani të njohur dhe në veçanti vendimi se cilin ilaç për cilin pacient duhet përdorur ose si duhet kombinuar ato, akoma mbeten sfida të mëdha. Synimi për të pasur mundësi trajtimi dhe intervenimi më efikas të destinuara për individë ose grupe të caktuara individësh me fenotipe të njëjta molekulare, mbetet i papërmbushur për shkak të reakcionit të ndryshëm të individëve. Sot në mjekësi, zakonisht vendimin për trajtimin e sëmundjes e bëjnë mbi bazën e eksperimentimit klinik dhe "strategjisë së gabimit" deri sa të gjejnë trajtimin adekuat më efektiv për pacientin e tyre.

Kjo qasje, sipas shumë të dhënave, ka rezultuar me efikasitet të dobët të shumë barnave. Përveç që është treguar si një ndër shkaktarët për rezistencën në rritje të rezistencës antimikrobiale, metodologjia aktuale e përzgjedhjes se terapisë ka shkaktuar edhe uljen e efikasitetit terapeutik edhe të shumë barnave tjerë dhe sidomos të atyre për trajtimin e sëmundjeve degjenerative, tumoreve etj. (është konstatuar se 65% e grave shkaktojnë rezistencë për Tamoxifenin si rezulat i strukturës së ndryshme gjenotipale). Rëndësia e madhe e njohurive për strukturën gjenetike të tumoreve me qëllim të përshtatjes së terapisë sa më adekuate, ka determinuar edhe zhvillimin e një fushe të veçantë në këtë drejtim – Oncogenomics.

Me mjekësi të personalizuar, këto trajtime mund të jenë të përshtatura në mënyrë më specifike për individin duke dhënë një pasqyrë të përbërjes gjenetike të tij dhe kështu duke përshatur terapinë në përputhje me gjenotipin e tij. Gjenomi personal për çdo individ do t'u mundësojë mjekëve që të kenë informacion më të detajuar mbi strukturën e tij gjenetike që do të behet bazë për vendimmarrje në aplikimin e terapisë për sejcilin person veç-e-veç. Përveç efikasitetit terapeutik, kjo formë e përcaktimit të barnave do të ketë edhe efektet e veta edhe në çmimin e trajtimit të sëmundjeve (cost-benefit). Pra, sikurse edhe është e shkruar në një artikul të publikuar në Pharmacogenomics me titull "Premtimi i Mjekësisë së personalizuar", ku thuhet: "...terapi, me barin e duhur, me dozë të duhur dhe për pacientin e duhur" duke i përshkruar kështu mundesitë e reja që hap mjekësia e personalizuar që padyshim paraqet një paradigmë të re në mjekësinë e shekullit 21.

Bazuar mbi të dhënat e shumta dhe kredibile nga Institucionet ndërkombëtare shkencore sikurse janë: International Cancer Genome Consortium, Intrnational Human Epigenome Consortium dhe të tjera, në kuadër të Programit për hulumtime shkencore të BE-së, HORIZON 2020, në vitet që vijnë do të realizohet një hulumtim në të gjitha vendet e Evropës, duke synuar stratifikimin e grupeve përkatëse të

Personalized medicine – new paradigm for the health of the XXI century

Personalized medicine is a new practice of medicine that uses the genetic profile of an individual to decide the next steps to be taken for the prevention, diagnosis and treatment of disease.

Despite the achievements in terms of more accurate knowledge to understand as deep as possible the emergence of the disease in the post-genomic era, most drugs are still effective only in a limited number of patients. From the clinical perspective, the choice of therapy based on scientific methodology known so far and in particular the decision about which medication to which patient should be used or how to combine them, they still remain as big challenges. Target to have treatment options and more effective intervention intended to certain individuals or groups of individuals with similar molecular phenotypes, remains unfulfilled because of different reactions of individuals.

Today in medicine, usually the decision to make the treatment of the disease is based on clinical experimentation and "error strategy", until they find adequate treatment and more effective one for their patients.

This approach, according to many data, has resulted of poor efficiency of many drugs. Besides being shown as one of the causes for the increasing resistance of antimicrobial resistance, current methodology for the selection of therapy has caused the reduction of the therapeutic efficacy of many other medicines, especially those for the treatment of degenerative diseases, tumors etc. (it was concluded that 65% of women cause resistance to Tamoxifen as a result of the different genotype structure)

The importance of the knowledge of the genetic structure of tumors in order to adapt the most appropriate therapy, has determined the development of a particular area in this direction - Oncogenomics.

With personalized medicine, these treatments can be adapted specifically to the individual by providing an overview of one's genetic composition and thus accommodate the therapy in accordance with one's genotype. Personal genome to each individual will enable physicians to have more detailed information on one's genetic structure that will become the basis for a decision on the application of therapy for each person separately. Besides therapeutic efficacy, this form of determining the drugs will have its effects in the treatment of drug price (cost-benefit). So, as it is written in an article published in Pharmacogenomics entitled "The Promise of Personalized Medicine", which states: "... therapy, with proper medication, the right dose and the right patient" thus describing the new opportunities that personalized medicine opens which undoubtedly represent a new paradigm in medicine of the 21st century.

Based on the numerous and credible data from international scientific institutions such as: International Cancer Genome Consortium, International Human Epigenome Consortium and the others, under the programme of the scientific research of EU, HORIZON 2020, in the coming years there will be realized a research in all European countries, aiming relevant stratification of the population groups based on

pupullacionit mbi bazë të gjenotipit të tyre, që do t'i shërbejë krijimit të metodologjisë dhe praktikave të reja klinike për vendimmarrjen në përcaktimin e terapisë për sejcilin individ (Personalized Medicine) që me siguri që do të jetë një arritje e madhe në trajtimin e sëmundjeve me efekte të pritshme pozitive për shëndetin e njeriut dhe në drejtim të uljes së kostos së tratimit si për individin po ashtu edhe për sistemet shëndetësore.

Prof. Dr. A. Pollozhani

their genotype, which will serve to create new methodology and clinical practices for decision-making in determining the therapy for each individual (Personalized Medicine) that will certainly be a great achievement in the treatment of diseases of expected positive effects on human health and in direction of reducing the cost of treatment for the individual as well as for the health systems.

Prof. Dr. A. Pollozhani

Original scientific paper

POLYMORPHISMS OF THE FSH RECEPTOR AND PREGNANCY RATES IN WOMEN OF DIFFERENT AGES IN THE OOCYTE DONATION PROGRAM

POLIMORFIZMI I FSH RECEPTORËVE DHE NORMA E SHTAZANIVE TEK GRATË NË MOSHË TË NDRYSHME NË PROGRAMIN E DHURIMIT TË QELIZAVE VEZË

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ABSTRACT

Objective: The aim of the study was to investigate the association between follicle-stimulating hormone receptor (FSH) polymorphism at position 680 and pregnancy rates in women in the oocyte donation program (IVF-ET).

Materials and Methods: This research was conducted in the period from March 2011 to February 2013 in a group of 42 women who entered the IVF procedure. The group of 42 women was composed on 21 women who were donor oocytes and the same number (21) embryo recipient who underwent IVF clinic, IVF CENTER, in Peja Republic of Kosovo. All donors underwent controlled ovarian stimulation (n=21) using rFSH in a ,,long protocol,, and receiving a GnRH agonist triggering. Basal FSH, LH, E2 concentrations, taken on day 2 or 3 of the menstrual cycle, were measured routinely in our biochemical laboratory. FSHR polymorphism was examined by polymerase chain reaction (PCR). Women from all groups were classified based on polymorphisms at Position 680, occupied either by asparagines (Asn) or serine (Ser) as Asn/Asn, Asn/Ser, and Ser/Ser genotype.

Result: In total (n=42) women the frequency distribution FSHR genotypes was; 30.9 % for the Asn/Asn variant, 40.4 % for the Asn/Ser variant, and 28.5% for the Ser/Ser variant. Differences in the AFC were observed between the genotypes 12.3 ± 4.7 Asn/Asn, 11.2 ± 2.7 Asn/Ser, 10.5 ± 2.5 Ser/Ser, with a statistical significance (P 0.001). The basal levels of FSH were significantly higher in Ser/Ser group (7.61±3.21 mIU/ml) versus to those of the Asn/Asn (5.20 ± 2.65 mIU/ml).The overall pregnancy rate for all patients who entered the program of IVF / ET were 30.9% (42/13).

Conclusion: FSH receptor polymorphism is associated with different ovarian response to controlled ovarian stimulation (COS), but is not an important factor in increasing the degree of pregnancy.

Keywords: Follicle-stimulating hormone receptor, ovarian response, ovarian stimulation, polymorphisms.

INTRODUCTION

Evaluation of ovarian reserve has been the focus of much clinical research over the past several years (1). Knowing that there is a high risk of a poor outcome of the IVF treatment may help physicians as well as patients decide to withdraw from IVF treatment and to search

for alternatives, such as adoption or oocyte donation. To prevent patients from being wrongly assigned to poor prognosis group, the markers that will be used for the prediction of a poor prognosis need to be highly specific. Assessment of ovarian reserve is valuable to determine stimulation protocols and predicting ART outcome. Many tests have been evaluated to predict cycle outcome. (2, 3, 4, 5,). None of the tests has a 100% sensitivity and specify used for poor ovarian response prediction. In order to increase the prognostic reliability of each test, combining the ovarian tests may be considered. A scoring system using the combination of age, AFC, basal FSH, basal AMH, E2 and inhibin B developed by Muttukrishna et al.(6) predicted the ovarian response more accurately than each of the parameters alone. Despite attempts to standardize COH regimens for women undergoing ART procedures, we commonly experience either low ovarian response or ovarian hyper stimulation syndrome (OHSS) even in those with smile endocrine profiles (7). This individual variability in ovarian response necessitates the identification of predictive markers of ovarian hyper-or hypo response of corresponding COH cycles, which would be of a clinical value in ART programs (8, 9, 33, 34). Differentiating clinical profiles; prediction good responders, poor responders, and hyper responder. During recent years, it has become evident that genetic factors could explain the differences between individuals in terms of drug response. These differences are due to sequence variants in the genes encoding drug targets. In the future, the treatment of a patient could be based on her individual DNA. Presently, even though the biological response to any given drug may be influenced by hundreds of genes, progress is being made in the identification of specific genetic variances, called single nucleotide polymorphisms (SNPs) that can predict the safety and effectiveness of certain drugs in individual patients (10). Polymorphisms are little genetic changes are responsible for individual variations and, new insights have been gained in the investigation of the variability in the gene that encodes hormones and receptors of human reproduction (11) In the field of reproductive health, hormonal and functional biomarkers are more established as tools to predict ovarian response, but in the future, genetic biomarkers may well be the best predictive tool to guide individualized treatment. Genetic traits that influence fertility may not have visible clinical signs or abnormalities. If a patient's genetic profile also diminishes her response to fertility treatment, the failure to consider the genotype when designing the treatment consequently leads to a suboptimal treatment strategy. For example, a subset of young, normogonadotrophic IVF patients may produce an adequate number of retrieved oocytes and normal estrogen levels, but not respond to COS as anticipated. These women require high doses of FSH over long treatment periods and, despite good prognostic indicators, have low implantation and pregnancy rates (12, 13, 14, 15). One possible reason for this hypo responder 'normal' population is that they may have a genetic predisposition to a reduced sensitivity to FSH. Follicle-stimulating hormone (FSH) is a key factor in human reproduction. FSH and its receptor (FSHR) play a major role in follicular development and regulation of steroid genesis within the ovary. One possible reason for this hypo responder 'normal' population is that they may have a genetic predisposition to a reduced sensitivity to FSH. Follicle-stimulating hormone (FSH) is a key factor in human reproduction. FSH and its receptor (FSHR) play a major role in follicular development and regulation of steroid genesis within the ovary (16). The FSHR gene is localized on chromosome 2p21 and spans a region of 54 kb. It consists of 10 exons (17, 18). Hyposensitivity to FSH may also be caused by a genetic variant of the FSH receptor. Two FSH receptor variants that have SNPs in the coding region have been identified and well characterized (19). The SNP known as the Serine^{680} (Ser^{680}) variant causes the replacement of Asn with Ser at the 680 position, which is located in the intracellular domain of the FSH receptor protein (13). The second receptor variant, known as the Alanine^{307} (Ala^{307}) variant, is generated through substitution of threonine (Thr) with Ala at the 307 position, located in the extracellular domain of the FSH receptor (14). There is a very strong linkage disequilibrium between the two SNPs. This means that women who possess Thr^{307} nearly always have Asn^{680} present on the same allele, and women who have Ala^{307} have Ser^{680} on the same allele (19). The clinical picture of the differences in sensitivity to FSH in patients who have assisted reproduction procedure is the starting point for our study in which we tested the hypothesis that different variants of the FSH receptor position 680 are responsible for the differences in FSH sensitivity and clinical pregnancy between donor oocytes women and recipient women.

PATIENTS AND CLINICAL ANALYSES

This research was conducted in the period from March 2011 to February 2013 in a group of 42 women who entered

the IVF procedure. Women were prospectively recruited in this study who underwent IVF clinic, IVF CENTER, in Republic of Kosovo. All patients were resident in Kosovo Dukagjin region. The group of 42 women was composed on 21 women who were donor oocytes and the same number (21) embryo recipient. Their mean ± SD (range) age of the donor group of women was 28.3 ± 2.8 (25-30) years, while the recipient groups of women, mean ± SD (range) 42.7 ± 3.1 (41- 44) years.

Inclusions / Exclusions criteria. All women included in the study gave their written consent for donation oocytes, peripheral blood collection and suitable for molecular analysis and other hormonal analysis. Our clinic follows these criteria inclusive donor women. In this study selected only infertility in women as donor groups which are in the ART program exclusively for male factor infertility. They must be aged between 25 and 30 years of age to have a regular menstrual cycle (16-30 days), all patients had functioning ovulation, normal body mass index (BMI) (18-25 kg/m^2), not history of endocrine disease, and not use drugs or oral contraceptives for at least 3 months before study entry, no family history of inherited diseases, undergo a complete gynecological examination, microbiological tests, karyotyping and screening for infectious diseases such as HIV, hepatitis B and C. Patients with polycystic ovary syndrome, endometriosis or a previous history of ovarian surgery were excluded from this study. Inclusion criteria recipient women obviously elevated levels FSH >25-44.0 mIU/ml. For each patient the following variables were recorded: age, body mass index (BMI), inter-menstrual interval, basal (day 3 of the menstrual cycle) FSH, LH, Prolaktin, E2, Progesteron and TSH, antral follicle count (AFC). Genetic analysis of this research was conducted at the Department of Medical Biochemistry, Faculty of Medicine, University of Prishtina. The study was approved by the Ethical Committee Faculty of Medicine, University of Prishtina and written informed consent was obtained from all participants.

Hormone assays. Basal FSH, LH, E2 concentrations, taken on day 2 or 3 of the menstrual cycle, were measured routinely in our biochemical laboratory in IVF CENTER. Serum concentrations of FSH and LH were measured by immunofluorometric assay (Amerlite: Ortho-Clinical Diagnostics. Amersham, United Kington), where serum Estradiol levels were measured by radioimmunoassay (RIA) provided by Diagnostic Products Corp, (Los Angeles, CA), as described elsewhere (Imami et al., 2000). Intra- and interassay coefficients of variation were less than 3% and 8% for FSH, less than 5% and 15 % for LH, less than 5% and 7% for E2.

DNA isolation and analysis. From each patient 10 ml venous blood was drawn with EDTA addet as anticoagulant. Genomic DNA was extracted from venous blood using phenol/chloroform method as described by Medrano et al.,(1990). The FSHR polymorphism at position 680 was determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. PCR amplification of the two DNA portions containing SNP at nucleotide positions 919 and 2039 within exon 10 of the FSHR gene were performed according to Gromoll et al (2000).PCR reaction mixture contained 0.1 ug of genomic DNA,0.4Um of each primer:(upstream5'TTT GTG GTC ATC TGT GGC TGC3'; downstream5'AAA GGC AAG GAC TGA ATT ATC ATT3'), 1.25u of Taq polymerase, 1.5 mm of MgCI2, and 200um of dNTP. Following an initial denaturation step at 94 0C for 5 min, samples were subjected to 30 rounds of PCR. Products were digested with 2IU of restriction enzyme BSrI (New England Biolabs, USA) followed by electrophoresis on 2 % agarose gel, and the digested products were identified using ethidium bromide staining. Uncleaved band indicated the asparagines homozygote (Asn/Asn), cleaved bandes the serine homozygote (Ser/Ser), and simultaneous cleaved and uncleaved bands the hetrozygote (Asn/Ser).

Ovarian stimulation Protocol. Controlled ovarian stimulation was induced in 21 donors women with the standard "long" protocol, includes a subcutaneous injection of a highly purified GnRH agonist, daily tretment with 0.4 mg Suprefact (Suprefact, Aventis Pharma,Germany) at mid luteal phase (on day 21 of the preceding cycle of stimulation cycle), and continued until down regulation of pituitary ovarian axis occurs which was detected by ultrasonography in the form of thin endometrium without ovarian activity or by occurring of menstruation, and continued until onset of menstruation, at that time the dosage was decreased to 0.20 mg daily, this continued until the day of the human chorionic gonadotrophin (hCG). Recombinant FSH (Gonal-F, Serono, Switzerland) was used for COH. Exogenous recombinant FSH was administered in daily doses (225–300 IU), varying from three to four ampoules, depending on the patient's previous or anticipated response, age, basal FSH, antral follicle count (AFC) and body mass index (BMI). Ovarian

response to rFSH was monitored by transvaginal US, serum E_2 measurement every third day from day 7 after the beginning of ovarian stimulation. Ovulation was triggered giving 10,000 IU hCG (Pregnyl®; NV Organon, Netherlands) when at least two follicles attained 18–20 mm in diameter and oocyte retrieval was performed 34–35 hours after hCG injection by transvaginal guided-ultrasound follicle aspiration under mild sedation and analgesia. Luteal support was provided with progesterone (Utrogestan®; Besins International, Montrouge, France) initiated after oocyte aspiration and extended until the 8th week of pregnancy or until the initiation of menses. The intra cytoplasmic sperm injection (ICSI) was performed according to conventional protocol(Jun et al.,2006). Up to three embryos were transferred on the third day after retrieval.

Endometrial preparation for embrio transfer in recipient women. All oocyte recipients were undergoing hormone replacement therapy. Women with ovarian activity received in the luteal phase of their previous cycle either birth control pills or, includes a subcutaneous injection of a highly purified GnRH agonist daily tretment with 0.5mg Suprefact (Suprefact, Aventis Pharma,Germany). In contrast, menopausal patients were treated with a sequential regime of estrogen and progesterone (Utrogestan 200 mg; Seid, Paris, France), a month before the real treatment. Oral estradiol valuate (Progynova; Schering, Spain, Madrid,Spain) were increased as follows:2 mg/d for the first 8 day of treatment, 4mg/d for the following 3 day, and 6mg/d until a pregnancy test was performed after embryo transfer or until vaginal spotting was identified, in which case the cycle would have been cancelled and would not have been included in the study. After 13 days of E2 valuate administration, the endometrial thickness and pattern were tested. If a trilaminar pattern was observed in an endometrium with a thickness of 7mm or more, the aforementioned dose of E2 therapy was continued at least until the pregnancy test was performed 2 weeks later. If the endometrium was not seen to be sufficiently developed, the doses of E2 valuate were increased to 8mg/day or four patches. From the day of oocyte retrieval until the pregnancy test was performed, 600 mg of micronized progesterone (Utrogestan 200 mg; Seid) were administered vaginally daily.

STATISTICAL ANALYSIS

Statistical analysis was performed by a commercially available software package (SPSS Inc, Chicago, IL). Data were analyzed for normal distribution . Data are presented as the mean (± SD) if distributed normally or as the median and range if distributed non-normally. To detect differences between grupes, Mann-Whitney or Krukskal-Wallis tests were used if data were not normally distributed. Multi linear regressions were used to evaluate the association of basal hormones levels, type of polymorphism, total rFSH dose, number of follicles, mature oocytes , fertilization and pregnancy rate. *P* values 0.05 were considered statically significant.

RESULTS

Table 1 shows the general and clinical characteristics of the donors women; no differences were observed in the donor age 26.5 ± 2.8 Asn/Asn, 28.2 ± 5. 4 Asn/Ser and 28.5 ± 3.4 years Ser/Ser ($P = 0.148$). Not statistically significant difference was observed among three groups in BMI (kg/m^2). Differences in the AFC were observed between the genotypes 12.3 ± 4.7 Asn/Asn, 11.2 ± 2.7 Asn/Ser, 10.5 ± 2.5 Ser/Ser, with a statistical significance ($P = 0.001$). As shown in Table 1; the overall frequency distribution was 33.8% Asn/Asn variant, 42.8% Asn/Ser variant, and 23.8% Ser/Ser variant. The basal levels of FSH were significantly higher in Ser/Ser group (7.61±3.21 mIU/ml) versus to those of the Asn/Asn (5.20 ± 2.65 mIU/ml) ($P = 0.001$). However, not statistically significant difference observed among three groups in these parameters: basal LH, estradiol levels, and FSH, LH, E2 levels after down regulation. Differences in the Estradiol levels on the day of the hCG administration were observed between the genotypes; Asn/Asn group 1880 ± 162 pmol/l versus to those of the Ser/Ser 1450 ± 158 pmol/l ($P= 0.001$). The gonadotropin doses correlated with the genotype in the FSHR polymorphism; women from the Ser/Ser group required significantly more gonadotropin (1825 ± 150 IU) compared with the other groups 1570 ± 65 IU for Asn/Asn and 1600 ± 150 IU for Asn/Ser ($P = 0.001$).

Table 1 General and clinical characteristics of donor women in relation to the FSHR genotype

FSHR genotype	Asn/Asn	Asn/Ser	Ser/ Ser	P value
%, (n)	33.3% (n=7)	42.8% (n=9)	23.8% (n=5)	
Female age(years)	26.5 ± 2.8	28.2 ± 5. 4	28.5 ± 3.4	ns
BMI (kg/m2)	23.3 ± 2.9	21.7 ± 2.5	22.4 ± 2.3	ns
AFC (antral folicul count)	12.3 ± 4.7	11.2 ± 2.7	10.5 ± 2.5	0.0001
Basal FSH (mIU/ml)	5.20 ± 2.65	6.10 ± 2.09	7.61 ± 3.21	0.001
FSH leveles after down regulat (mIU/ml)	3.96 ± 1.14	4.08 ± 1.32	4.43 ± 1.24	ns
Basal LH (mIU/ml)	4.96 ± 0.81	4.18 ± 2.07	4.37 ± 2.61	ns
LH leveles after down regulat (mIU/ml)	2.35 ± 1.22	2.04 ± 1.48	3.07 ± 1.06	ns
Basal E2 (pmol/l)	60.45 ± 13.20	57.23± 18.10	52.84 ± 11,18	ns
E2 leveles after down regulat (pmol/l)	29.94±15.50	26.80±12.60	20.91±9.50	ns
Total rFSH dose (IU)	1570 ± 65	1600 ± 75	1825 ± 150	0. 0001
Peak E2 at hCG day (pmol/l)	1880 ± 162	1760 ± 132	1450 ± 158	0. 0001

*Data are presented as mean ± SD; **Using student t-test , ns= not significant

The number of oocytes retrieved ten dent to be different among FSHR genotype grupes. The Ser/Ser group (8.4 ± 0.6) showed fewer oocytes compared to the Asn/Asn group (10.5 ± 1.0) and Asn/Ser (9.5 ± 0.55) (P 0.160). No difference was found between the three groups, either, in terms of fertilization rate, high quality embryos, endometrial thiknes at hCG day and number of embryos transferred (Table 2). In addition, the clinical pregnancy rates per embryo transfer in the Asn/Asn group were more than other two groups but the difference was not statistically significant (Table 2).

Table 2. The clinical characterisric of donor ovarian stimulation data in relation to the FSHR genotype

FSHR genotype	Asn/Asn	Asn/Ser	Ser/ Ser	P value
%, (n)	33.3 % (n=7)	42.8% (n=9)	23.8% (n=5)	
No.of oocytes retrieved	10.5 ± 1.0	9.5± 0.55	8.4 ± 0.6	0.160
No.of fertilized oocytes	6.5 ± 0.51	6.2± 0.39	6.0 ± 0.28	0.858
Fertilization rate (%)	61.9 ± 3.5	65.2 ± 2.8	71.4± 5.2	0.492
No.of embryos on day 2	6.2 ± 0.31	6.1± 0.39	6.0 ± 0.28	0.843
Endometriale thickness at hCG day (mm)	9.5 ± 1.7	9.4±1.6	9.1± 1.3	0.312
No of transfer embryos on day 3	2.0	2.0	2.0	0.000
Clinical pregnancy rate per transfer %, (n)	42.8% (n=3)	33.3% (n=2)	40.0% (n=2)	0.027

Data are presented as mean ± SD.Using student t-test* and Chi-square test**

Table 3. Shows the age and clinical characteristics of the recipient women were observed and distribution of FSHR genotype. No difference were observed in the recipient women age; for Asn/Asn 42.7 ±3.8 for Asn/Ser 43.2 ± 2. 4 and 43.8 ± 4.2 years for Ser/Ser (P = 0.590). No difference was found between the three groups, in endometrial thiknes at hCG day and number of embryos transferred. There were no significant differences with clinical pregnancy. The clinical pregnancy rates per embryo transfer in the Asn/Ser group were more than other two groups but the difference was not statistically significant (P= 0.408).

Table 3. Clinical characteristics of the recipient woman and cycle outcomes to donor eggs genotype

FSHR genotype	Asn/Asn	Asn/Ser	Ser/ Ser	P value
%, (n)	28.5% (n=6)	38.0% (n=8)	33.3% (n=7)	
Female age(years)	42.7 ± 3.8	43.2 ± 2.4	43.8 ± 4.2	0.590
Endometriale thickness at hCG day (mm)	10.5 ± 1.5	9.0±1.5	9.5 ± 1.5	0.492
No of transfer embryos	2.0	2.0	2.0	0.000
Clinical pregnancy rate per transfer %, (n)	33.3 % (n=2)	37.5% (n=3)	14.2% (n=1)	0.408

Data are presented as mean ± SD. Using student t-test and Chi-square test

As shown in Table (4);In total (n=42) women the overall frequency distribution FSHR genotypes was; 30.9 % for the Asn/Asn variant, 40.4 % for the Asn/Ser variant, and 28.5% for the Ser/Ser variant. The clinical pregnancy rates per embryo transfer in the Ser/Ser group were low than other two groups but the difference was not statistically significant.

Table 4. Distribution of FSHR genotypes in all patients, and outcomes pregnancy rate according to FSHR genotypes

FSHR genotype	Asn/Asn	Asn/Ser	Ser/ Ser	P value
Total (n=42) , %	30.9% (n=13)	40.4% (n=17)	28.5% (n=12)	ns
Clinical pregnancy rate per transfer between %, (n) FSHR genotype variant	38. 4% (5/13)	29.4% (5/17)	25% (3/12)	ns

The overall pregnancy rate for all patients who entered the program of IVF / ET were 30.9% (42/13). These results are not statistically significant between the donor and recipient women;. 33.3% vs. 28.5% (21/7 vs. 21/6).

DISCUSSION

Success controlled ovulation during assisted reproductive procedure depends on the application of the hormone FSH. Due to the lack of predictive parameters large number of expensive ampoules of FSH used in IVF clinics for ovulation induction, treatment carries the risk of excessive and clinical consequences (20, 21). The goal of treatment is to get FSH sufficient number of eggs capable of fertilization. Clinical studies have shown, however, that patients react differently to FSH stimulation. While some patients have a relatively low dose of FSH required to produce a sufficient number of eggs, other patients need to be stimulated with high doses of FSH in the same results in terms of a sufficient number of oocytes (22). Depending on the amount of FSH patients can be classified as a good response (low dose FSH) and poor response (high dose FSH) (23). Should adjust the dose stimulation phase in time, so that a sufficient number of eggs do not cause excessive represents a major problem in IVF treatment. Thus, it was found that the response of the patient to FSH stimulation, depending on the allelic variant of the FSH receptor (14, 24, 34). The individual amounts of FSH that can determine FSH receptor variant patient . Because of these results can be expected in the future analysis of genetic variants region FSH receptor is determined to play an important role in planning ovulation treatment. The ovarian response to FSH stimulation relies on the interaction of hormones with the membrane receptor (FSHR) in granulose cells abnormal answer depends on the proper the molecular structure of the hormone, receptor, and factors associated with their interaction (25). Defective genes FSH and its receptor may lead to resistance of the ovary, and therefore, the genotype may be fun to play a fundamental role in determining the physiological response to FSH stimulation (26). Mutations in the receptor gene can result in amino acid changes that affect the function of mutations conferring resistance to the complete FSH (27), as well as partial loss of function of FSHR were identified (14, 23), and that their frequency may vary among different ethnic groups. We found differences in distribution of the different FSH receptor genotypes between normo-ovulatory patients and hyper gonadotropic anovulatory patients. The resultes of our study in a proven infertile Albanian population show a prevalence results of the Ser/ Ser variant similar to that in anovulatory infertile women, with a significantly lower proportion of the hetrozygote form. The FSH receptor variants Ser/Ser 680 were significantly more prevalent among hyper gonadotropic anovulatory patients (recipient patients). Earlier reports failed to establish differences in prevalence of FSH receptor genotypes in fertile and infertile women (28). A higher proportion of the Ser / Ser variant in infertile women has also recently been reported by Laven et al., who in a study of 30 normo ovulatory and 148 normo gonadotropic anovulatory infertile women found a significant increased prevalence of the Ser /Ser variant in the anovulatory infertile women (40 vs.16%). Gromoll et al (11) reported in a population of 161 ovulatory women a FSHR distribution of 29% in the Asn / Asn group, 45% Asn/Ser and in Ser / Ser groups 26%. Sudo et al, reported in a population of 522 Japanese women an overall frequently of Asn/Asn, Asn/Ser, and Ser/ Ser of 41%, 46.9%, and 12.1%, respectively (29). The FSH receptor polymorphism combination Ser/Ser was associated with higher basal FSH levels compared with the Asn/Asn 680 and Asn/Ser variants. This might indicate that the Ser/Ser FSH receptor polymorphism is associated with decreased FSH sensitivity. In a recently published prediction model, the individual FSH response dose during ovulation induction therapy was determined in part by the initial basal FSH serum concentration. Lourtradis et al.,(10, 30), reported that good responders are more often the Asn/ Ser type and in addition, the Ser/ Ser variant might be related to higher serum FSH levels, while the Asn/ Ser is related to lover FSH levels. Although we have a found a subtle elevation of basal FSH levels in patients carrying the Ser 680 allele, like other authors. These data suggest that the pituitary produces steadily more FSH in the Ser/Ser group. Our data show that 3 FSH levles are much higher in the subgroup of Ser/Ser compared to the Asn / Asn and Asn / Ser (7.61 ± 3.21 vs. 5.20 ± 2.65 and 6.10 ± 2.09), Ser / Ser homozygous groups

require higher total doses of gonadotropins to achieve multiple follicular development in relation to the other two groups (Asn /Asn and Asn / Ser at position 680). Perez – Mayorga et al (14) also suggested FSHR genotype plays a fundamental role in determining the physiological response to FSH stimulation and that subtle differences in FSHR could fine tune the action of FSH in the ovary . In a study conducted in 161 young ovulation (<40 years) women undergoing IVF treatment, significant differences in the number of ampoules of FSH to achieve an adequate response has been observed. It was found that this observation may be associated with genotype FSHR patient , this type of polymorphism. Behre et al (23) also carried out , a randomized controlled trial to further study this observation and found that Ser / Ser homozygous group results in lower levels of estradiol after stimulation. This lower FSH receptor sensitivity can be overcome by high doses of FSH in the trial patients . From our results showed differential estradiol response to FSH caused by the SNP at codon 680 FSHR gene. In this study, the same dose of FSH in COH resulted in significantly lower serum estradiol levels in women with alleles Ser Ser at position 680 variants compared to women with Asn / Asn and Ser / Ser variants. This reaction can be overcome by increasing the dose of FSH lower (Table 1). Higher levels of FSH and estradiol levels reduce associated with regression of the corpus luteum occurred earlier in women with Ser680/ Ser680 genotype . Therefore , before the reduction of ovarian hormone feedback Ser680/Ser680 women appear not only encourages early increase in FSH levels at a constant level during the follicular phase . The results of this study have important evolutionary implications . In fact , the amino acid asparagines at position 680 in exon 10 in the FSH receptor is highly conserved in other species and in humans, but is now replaced by serine is detected (31). This would mean Ser680 genotype recently appeared in evolution. The emergence of Ser680 genotype in today about 40 % of all human allele shows a strong evolutionary pressure This variant , which can not be explained by mere reproductive advantage . Despite the differences in the levels of estradiol , there is no significant difference in the number of follicles or download oocytes , fertilization rate , cumulative embryo score and pregnancy rates , which means that , in accordance with existing protocols , FSH may have overdosed in some women , so putting them on the risk of OHSS , which indirectly depends on excessive FSH stimulation . This study is based on a very limited number of cases continues to be an isolated observation awaits confirmation in a larger number of samples in the women's Albanian population. Women in Kosovo society in the last 10-15 years are delaying childbearing to pursue educational and vocational goals putting you at risk for age related infertility. From our results suggest that higher levels of endogenous FSH required to achieve a physiological ovulation in Ser680/Ser680 holder genotype . Our results show that there is no evidence of differences degree clinical pregnancy in women with different polymorphisms, unlike some of the early studies that provide a greater degree of clinical pregnancy in a variant polymorphism. We found absolutely no difference in others authors like number; of antral follicles, mature pre ovulatory follicles, number of oocytes retrieved, fertilization rate and number of embryos. By today's publications give different results on whether variations in the FSHR is associated with the rate of pregnancy in women during IVF / ET procedures (3, 22, 25, 30, 31,32, 33, 34) . Our data suggest that there is no difference between genotypes in the degree of clinical pregnancies in women during stimulation in IVF / ET. Obviously , the pregnancy rate is influenced by many factors other than FSHR and other markers (35, 36, 37,). We found in this study that the outcome of the cycle is strongly associated with the quality of the embryo and the day of embryo transfer. Oocyte donation best model to estimate the determinants of stimulation and embryo implantation potential. Older people donated eggs are demographically different from yonger donors who are often young, often have cases that are divorced and remarried, and spends most successful professional career. Donor young women of the same age with normal ovarian function and , in our program of donating eggs (with primary infertility , with male factor infertility).

CONCLUSSION

In conclusion, this study shows, the Albanian population that FSHR polymorphism at position 680 may be associated with different ovarian response to COH, but is not an important factor in increasing pregnancy rates. These studies suggest that, in the future, it might be possible to tailor FSH therapy to the patient's genetic background, and therapy adjust the doses and the timing of stimulation. This would be of particular benefit in the treatment of older women, who cannot afford any delay in their race against the biological clock.

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POLIMORFIZMI I FSH RECEPTORËVE DHE NORMA E SHTAZANIVE TEK GRATË NË MOSHË TË NDRYSHME NË PROGRAMIN E DHURIMIT TË QELIZAVE VEZË

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ABSTRAKT

Objektivi: Qëllimi i studimit ishte për të studiuar lidhjen mes të polimorfizmit të receptorëve për hormonin folikulo stimuluese (FSH) në pozicionin 680 dhe normat e shtatzënisë të gratë në programin e dhurimit oocyte (IVF-ET).

Materialet dhe Metodat: Ky hulumtim është kryer në periudhën nga Marsi 2011 deri në Shkurt 2013 në një grup prej 42 grave që kanë hyrë në procedurë. Grupi i 42 grave në procedur të IVF ishte i përbërë nga 21 femra që ishin donore të qelizave vezë të të njëjtit numër (21) marrëse te embrioneve në kliniken e IVF-së, IVF CENTER, në qytetin e Pejës, Republika e Kosovës.

Të gjitha donatorët ju nënshtruan stimulimit ovarial të kontrolluar (n = 21) duke përdorur rFSH më protokoll,, të gjatë,, dhe duke marrur një agonist të GnRH . Vlerat basale të FSH, LH, E2, jane analizuar në ditën e 2 ose 3 të ciklit menstrual, janë matur në mënyrë rutinore në laboratorin tonë biokimik. FSHR polymorphism u ekzaminua me metoden e reaksionit zinxhiror të polimerazës (PCR). Gratë nga të gjitha grupet janë të klasifikuara në bazë të polymorfizmit në pozitën e 680, e pushtuar me asparagin (Asn) ose serine (Ser) si Asn/Asn, Asn/Ser, dhe Ser/Ser gjenotipe.

Rezultati: Nga numri total (n = 42) i grave frekuenca e shpërendarjës së gjenotipeve të FSHR ishte; 30.9% për variantin Asn/Asn, 40.4% për Asn/Ser variant, dhe 28.5% për variantin Ser/Ser. Dallimet në folikulet antral të numëruara (AFC) ndërmjet gjenotipeve kanë qënë; 12.3 ± 4.7 Asn/Asn, 11.2 ± 2.7 Asn/Ser, 10.5 ± 2.5 Ser/Ser, me një rëndësi statistikore (P 0.001). Nivelet basale të FSH ishin shumë më të larta në Ser/Ser grupa (7.61 ± 3.21 mIU/ml) kundrejt atyre të Asn/Asn (5.20 ± 2.65 mIU/ml). Shkalla e përgjithshme e shtatzënisë për të gjithë pacientët që kanë hyrë në programin e IVF/ET ishte 30.9% (42/13).

Përfundim: Polimorfizmi i receptorve të FSH është i lidhur me përgjigje të ndryshme ndaj stimulimit te kontrolluar ovarial (COS), por nuk është një faktor i rëndësishëm në rritjen e shkallës së shtatzënisë.

Fjalet kyqe: Receptoret e hormonit folikulo-stimulues, përgjigje ovariale, stimulimi ovarial, Polymorfizmi.

Original scientific paper

ACCESS TO TREATMET OF PEOPLE LIVING WITH HIV IN R.MACEDONIA

ДОСТАПНОСТ ДО ТЕРАПИЈА НА ЛИЦАТА КОИ ЖИВЕАТ СО ХИВ ВО Р.МАКЕДОНИЈА

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SUMMARY

Antiretroviral therapy significantly reduces transmission of HIV and has been shown to reduce mortality amongst those living with HIV. WHO recommended that people living with HIV should start treatment at an earlier stage

Objective: The aim of this paper is to present HIV/AIDS epidemiological evidence of the Republic of Macedonia with focus on ARV therapy, health needs and concerns of people living with HIV.

Methods: The paper is designed as a qualitative analitical cross sectional study, conducted during a period June – November, 2014. To collect the needed informations, the second data analysis and key informant interviews were used as methodology tools

Results: The total number of PLHIV enrolled in ARV treatment, care and support in R.Macedonia as of December 2014 is 99 (63.1%). PLHIV faced continuous stress of the lack of antiretroviral medication. Namely, the system for supplying these medications is unsustainable and leads to delays in the procurement and exhausted reserves. The created permanent risk of having the therapy terminated directly endangers the health and life of PLHIV.

Conclusion: Scale up of the care, treatment and support, addressing the challenges for sustainable provision of ARV drugs as well as the capacity building on ARV treatment monitoring are necessary. The initiatives should be made by the Health Insurance Fund of Macedonia in order to insure budget for the Clinic for infectious diseases and febrile conditions exclusively for treatment of PLHIV.

Key words: epidemiology, ARV treatment, PLHIV, testing, counselling.

BACKGROUND

At the beginning of the 21st century, very few people in low- and middle-income countries had access to HIV treatment. This was in large part because of the very high prices of antiretroviral drugs (ARVs) and the international patents that stopped them from being manufactured at cheaper prices. (1,2,3) However, in 2001 drug manufacturers in developing countries began to produce generic antiretroviral drugs under special terms in international trade law. In 2003, the World Health Organisation (WHO) launched the ambitious target of reaching 3 million people in low - and middle-income countries with ARVs by 2005. (4,5) Though the target was not attained until 2007, it was seen by some as a stepping stone to universal access. Considering the relative success of the 3 by 5 target, the international community set another target in 2006 that aimed for universal access to HIV treatment, prevention and care by 2010. However, the heads of UNAIDS, UNICEF and

WHO in 2008 conceded that most countries would not meet the 2010 targets of 80 percent of those in need receiving treatment. (5,6,7,8,9)

As the HIV epidemic matures, increasing numbers of people are reaching advanced stages of HIV infection. Antiretroviral therapy (ART) has been shown to reduce mortality amongst those infected and reduce transmission of HIV. Taking all this into consideration, in 2010 WHO recommended that people living with HIV should start treatment at an earlier stage. These changings resulted in an increase of the number of people considered to be eligible for treatment in about 4.6 millions. In 2011, the international community recommitted to the goal of universal access and this time countries committed to achieving it by 2015.(7,8,9) The goal of universal access is also part of Millennium Development Goal (MDG) 6 which includes the goal of halting and beginning to reverse the spread of HIV/AIDS by 2015.(10)

However, although significant resources have been allocated to the HIV response in recent years, evidence indicates that many countries are far from achieving universal access goals. Countries continue to face a number of challenges in expanding and sustaining the response to HIV. These include weak health systems, a critical shortage of human resources and lack of long-term sustained financing. (11,12,13)

R.Macedonia is a relatively small country from Central WHO European region with total population of 2.022.547. The total number of registered HIV/AIDS cases as of December 2014 was 232 (157 AIDS and 75 HIV cases). More than half of all HIV/AIDS cases have been reported in the last 7 years with the biggest number of 35 cases in 2014. Most of the cases 93 (40,1%) were aged 30-39, and the homosexual transmission became predominant in the last 9 years. Up to now, the death rate of the diagnosed with HIV remains at the high end, which is explained with the fact that many of the HIV cases have been registered at very late stage of AIDS as well as high level of stigma and discrimination is confrontiing people living with HIV (PLHIV). Although HIV prevalence has remained very low, including among populations considered most-at-risk, the presence of real limitations in the surveillance system need to be taken into account when interpreting the official data. R.Macedonia has ratified all legally binding international instruments on human rights. In addition, the country has committed to a number of international initiatives and declarations among which the most significant to the prevention and control of HIV/AIDS. The country has committed also to the policies and legal documents of the Council of Europe with respect to human rights protection, especially in the health area. The aim of this paper is to present HIV/AIDS epidemiological evidence of the Republic of Macedonia with focus on ARV therapy, health needs and concerns of people living with HIV. (14,15,16,17)

MATERIALS AND METHODS

The paper is designed as a qualitative analytical cross sectional study, conducted during a period June – November, 2014. To collect the needed information, the second data analysis and key informant interviews were used as methodology tools. The study was approved by the ethics committees of the Institute of Epidemiology and biostatistics with medical informatics, Medical faculty, UKIM, Skopje.

The second data

The second data or existing information reviewed was HIV/AIDS data extracted trough a review of published and publically available governmental and non governmental reports and national health agency web sides as well as puplished reports of relevant international organizations related to this issue. Several databases (WHO, UN, UNAIDS, ECDC, Eurostat, EMCDDA, Eurosurveillance) and country-specific institutions (Ministry of health of R.Macedonia, Clinic for infectious diseases and febrile conditions - CID and Institute of Public Health) were especialy accessed to obtain additional data particularly in the case of number of PLHIV enrolled in HIV treatment, care and support as well as the possibility to insign the protocol on ARV treatment and care. Reports in languages other than Macedonian and English were not the subject of analysis. All sentences and quotes in this paper used from the reviewed literature related to the issues of interest were specially acknowledged by footnotes and bibliography.

Interview procedures

Potential interviewees were provided with an explanation of the study and confidentality, and willing participants provided oral informed consent. All interviews lasted 45 minutes to 1 hour. Following semistructured in-depth interviewing procedures, a standard topic guide was applied with openended questions around the main themes as availability and affordability of ARV therapy, health needs, institutional support, and personal experiences of stigmatization/ discrimination. Interviews were conducted in private one-on-one sessions by

experienced interviewers. The total number of seventeen key informer interviews were conducted including PLHIV, health professionals, and relevant health authorities. The written notes during the interviews were taken with the agreement of the participants.

RESULTS AND DISCUSION

Health of PLWHA

The total number of PLHIV enrolled in ARV treatment, care and support in R.Macedonia as of December 2014 is 99 (63.1%). There is no official information about the total number of people who has been on treatment 12 months after the initiation of the ARV therapy. During 2014, 14 PLHIV were newly initiated on ARV therapy, out of whom 98,2% (n=13) were on continuous treatment, while one has died. In 2013, the actual number of PLHIV that received psycho-social support and peer counselling within the counselling centre at CID was (n=95) and reached with peer education (n=16).

In R.Macedonia, HAART was initiated back in 2005 with first line ARV drugs, extended with second line drugs the same year. To compare, in all neighbouring countries the effective combination ARV treatment was introduced during a period 1997/98. The most significant strategic document referring to the treatment care and support of PLHIV is the National Strategy (NS) on HIV/AIDS, which is adopted every five years. The current (third) strategy adopted in 2013 refers to the period from 2012 – 2016. Since the end of 2004, Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) is a major outstanding contributor to the funding, that significantly boosted Macedonia's ability to implement activities planed in the NS on HIV/AIDS. The Program for Protection of the Population from HIV/AIDS is of the same significance as NS on HIV/AIDS as provides the definition and budgeting of the activities in this area. World economic crisis in 2009 and the financial crisis in 2010 abrupt the steadily incline of domestic funding of the AIDS response. National funding pledges are not meeting the original forecasts, as envisaged in the GFATM proposals. As the World economic crisis affected all public expenditures, the Government decided to reduce all public costs, including all Preventive programs. Since 2011, preventive activities from the program have been drastically reduced, and the biggest part of the program budget is allocated for procurement of antiretroviral therapy. In the recent years, the program is also subjected to financial cuts that exceed 30%. This results in inadequate fulfilment of the real need of the people living with HIV.

PLHIV faced continuous stress of the lack of antiretroviral medication. Namely, the system for supplying these medications is unsustainable and leads to delays in the procurement and exhausted reserves. The created permanent risk of having the therapy terminated directly endangers the health and life of PLHIV. Since 2005, the procurement of antiretroviral therapy was made through the Global Fund to Fight AIDS, Tuberculosis and Malaria until 2011 when the obligation was undertaken by the state (as a part of the first proposal for GFATM, the Government officialy took the responsibility for covering funding need for treatment of people living with HIV/AIDS right after the international donation for ARV treatment will end). However, regardless of the undertaken obligation, the procurement of these medicines in 2011 and 2012 continued to be done through the UNICEF Supply Division. This ensured the procurement of part of the most necessary medicines under exceptionally low prices. The procurements under this mechanism are contrary to the Law on Public Procurements. (14) Moreover, the experiences show that all medication that is recommended for therapy by WHO and the European AIDS Clinical Society for certain number of patients cannot be provided through UNICEF. In particular, this refers to the so-called third line of therapy.

The medications which are procured in this way are not registered in R.Macedonia, which means that procurements continuously rely on the so-called emergency importation. This resulted in delayed supplies and several stock-out situations, the longest of which was the stock-out of the medicine with generic name Nevirapine. It was not available for use in the period of two months 2012/13.

The lack of willingness by the state to introduce functional procurement mechanisms practically results in having no consideration about the need to register more that the already registered 5 medicines for treatment of PLHIV, including the placement of these medicines on the positive list of the Health Insurance Fund of Macedonia (HIF). Among the registered medicines, only three (zidovudine, didanosine and indinavir) are currently included in the list by the HIF. According to the WHO, one of them (indinavir) should be eliminated from use. According to evidence-based medicine and WHO, these three medicines cannot be used to make a combination for antiretroviral treatment. Contrary to our country, most of the countries in the region include the antiretroviral

therapy in the List of medicines which are covered by the HIF, and each of them includes at least 15 registered ARV medicines.(18,19,20) Furthermore, there are no available pediatric formulations of therapy for children living with HIV in our country. At the end of 2012, there was an urgent need for treatment of HIV-infection in a 6 years old child.

At present, ART treatment is provided centrally at the CID in the capital city. Its capacities have been improved by establishment of a new AIDS in-patient department, provision of equipment for monitoring of HIV infection and ARV treatment. Care and support to PLHIV is provided through the special out-patient counselling centre for PLHIV at the CID as well as through home visits organized by civil society organizations. According to the CID, the administration of drugs to patients follows the European AIDS Clinical society protocol on ARV treatment and care, even though the Macednian version of the protocol used at the CID is never available to be insigned by the people receiving the treatment even they insisted on that many times. People on ARV treatment are not routinely tested for possible therapy resistance.

People living with HIV do not have access to free vaccines against Hepatitis B, influenza and Haemophilius Influenza Type B. The 2013 Program for mandatory immunization of the population foresees the mandatory immunization for the stated diseases in people with established immunodeficiency, including the people living with HIV. The CID, as the only reference institution for treatment of HIV, has not received vaccines from the Ministry of Health, although patients with HIV have submitted official requests in March 2012 and 2013. In middle 2014 200 vaccines were provided by the MoH to the CID, but unfortunately with no promises for regular procurement. (17)

CONCLUSION

Although, same achievements have been made since the HAART was first initiated in the country in 2005, there are still many important things needed to be done at country level. Streamlining ARV drugs registration and their availability on the local market is urgently needed. Further scale up of the care, treatment and support, addressing the challenges for sustainable provision of ARV drugs as well as the capacity building on ARV treatment monitoring are necessary, given the fact that provision of ARVs falls under the responsibilities of the Government as of 2010 and few stockouts have been already experienced both in 2010/11 and 2012/2013. The initiatives should be made by the HIF in order to insure budget for the CID exclusively for treatment of PLHIV.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ДОСТАПНОСТ ДО ТЕРАПИЈА НА ЛИЦАТА КОИ ЖИВЕАТ СО ХИВ ВО Р.МАКЕДОНИЈА

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РЕЗИМЕ

Антиретровирусната терапија значително ја намалува трансмисијата на ХИВ и докажано го намалува морталитетот на лицата со ХИВ инфекција. СЗО препорачува најрано можен почеток на терапија кај лицата со ХИВ.

Цел: Трудот има за цел да ги презентира епидемиолошките факти за ХИВ/СИДА во Република Македонија со фокус на АРВ третман, здравствените потреби и грижите на лицата кои живеат со ХИВ.

Методи: Трудот претставува квалитативна аналитичка студија на пресек спроведена во периодот јуни - номври, 2014. Податоците за истражувањето се добиени преку анализа на постоечката документација и интервјуа со клучни информатори.

Резултати: До декември 2014 година, вкупниот број на лица со ХИВ вклучени во АРВ третман изнесува 99 (63.1%). Луѓето со ХИВ инфекција се соочени со континуиран стрес од недостаток на антиретровирусна трапија. Системот за набавка на овие лекови е непостојан и е причина за доцнење на терапијата како и недоволни нејзини резерви. Постоењето на перманентниот ризик од немање на терапија директно делува на здравјето и животот на лицата со ХИВ инфекција.

Заклучок: Подобрувањето на грижата, третманот и поддршката во насока на постојана набавка на АРВ третман и зајакнување на капацитетите за мониторинг се неопходни. Потребни се иницијативи од Фондот за здравствено осигурување на Р.Македонија во насока на обезбедување на буџет на Клиниката за инфективни болести и фебрилни состојби со посебна намена за третман на лицата со ХИВ.

Клучни зборови: епидемиологија, АРТ третман, лица со ХИВ, тестирање, советување.

Original scientific paper

SURGICAL TREATMENT OF LOCALLY ADVANCED PROSTATE CANCER

TRAJTIMI KIRURGJIKAL I KANCERIT TE PROSTATES TE AVANCUAR LOKALISHT

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ABSTRACT

Introduction: Treatment of locally advanced prostate cancer is referred to T3 or T4 clinical condition without evidence of disease in lymph nodes or distant metastasis. In our practice we routinely recommend RP as primary treatment for locally advanced prostate cancer or high risk prostate cancer[1]. Between the years 2007 and 2013 we realized 265 radical prostatectomies from which 47 were locally advanced diseases.

Objectives:

- Evaluating the functional and oncologic result of RP in locally advanced prostate cancer.
- Comparing this data with those obtained from organ confined disease cases.
- Evaluating the discordance between clinical stage and pathological stage.

Patients and methods: From 2007 to 2013 we treated 47 patients who were evaluated to be clinically T3 diseased. Local staging was routinely performed by digital rectal examination and transrectal ultrasound. Pelvic bilateral lymphadenectomy was routinely performed in patients with Gleason score more than 7 in transrectal biopsy and PSA more than 10ng/dl. Perioperative complications and one year functional results were evaluated, as well as the % of positive margins and oncologic results.

Results: No serious in-hospital complications were noted and no reintervention was needed. Lymphatic leakage was noted in 6% of the patients. Anastomotic stricture occurred in 5% of the cases requiring internal urethrectomies. 4% of the patients experienced prolonged drainage of urine. In 12 months, complete continence was 79 % and erectile function had fully been recovered in 5% and in 12% of patients who underwent a non-nerve sparing or unilateral nerve-sparing procedure, respectively. The downstaging from clinical T3 to pathological T2 was observed in 22% of the cases.

Conclusions: Our experience with 47 patients confirms the surgical feasibility of RP for cT3 PCa, showing complication rates comparable with RP in organ-confined PCa. Continence rates were also comparable with those achieved after RP for localized PCa. The rate of impotence was more than 80%. Down staging occurred in 22% of the cases becoming an important factor for choosing RP as primary treatment of locally advanced prostate cancer.

Key words: Prostate cancer, surgery, complications, down staging.

INTRODUCTION

Despite dramatic stage migration due to widespread prostate-specific antigen (PSA) screening, many patients continue to present locally advanced prostate disease. It is estimated that in 15% - 20% of cases prostate cancer is diagnosed in T3 or T4 disease.

Nowadays, clinical stage T3 tumours (cT3) are diagnosed with lower tumour volume than in the past, enhancing the opportunity for radical prostatectomy (RP) indications in many selected cases.

Possible benefits of surgery for patients may include the possibility of an organ-confined tumour in the pathologic specimen due to over-staging of both T stage and grade. It is estimated that in more than 20% of cases there is a down staging from T3c to pathological T2 .

MATERIAL AND METHODS

From January 2007 to December 2013 we performed RP with bilateral pelvic lymphadenectomy in 47 patients with cT3 PCa.(Tab.1)

Patient and prostate cancer characteristics for Open Retropupic Prostatectomies for 47 locally advanced prostate cancer.

Table 1

Nr of patient	Age (years) median (range)	PSA level (ng/ml) median (range)	Positive cores, median (range)	% positive cores, median (range)	Biopsy Gleason score, n (%)	
47	62(48–74)	8.75(3.5-26)	4(2-10)	70 (15–95)	5-6	4(8.5)
					7	7(15)
					8	28(59.5)
					9-10	8(17)

Ultrasound guided prostate biopsies showed a median Gleason score of 7. Prostate biopsy was performed in accordance with EAU guidelines performing 12 biopsies, focusing on peripheral zone biopsies and to the sites of abnormal digital rectal examination and abnormal transrectal ultrasound findings. Local staging was routinely performed by digital rectal examination and transrectal ultrasound. In patients with PSA <10 ng/mL and a biopsy Gleason score <7, N and M staging was not performed, as the risk for nodal involvement in this group is estimated to be very low (≤4%).

Surgical Procedure

Actually, the aim was to have negative surgical margins. The majority of palpable tumours generally originate in the peripheral zone. Consequently, they are more likely to extend into the posterolateral and rectal periprostatic soft tissue. In this way, the neurovascular bundles were usually resected widely on the side of the cancer. Moreover, the posterior plane of resection was kept deep enough and we routinely realised a complete excision of the two layers of Denonvilliers' fascia to reduce the risk of positive surgical margins [3,4].

Unilateral or bilateral nerve-sparing surgery was feasible in selected young patients with small cT3a tumours who desire to keep the erectile function despite the increased risk of positive surgical margins and incomplete tumour excision. We performed extended lymphadenectomy in all cases with PSA > 10ng/dl and Gleason score more than 7.

Extended iliac lymphadenectomy does not have an impact on survival, but it optimises pathologic staging with an increased number of lymph nodes removed and number of positive nodes. Moreover, a good staging based on an extended lymphadenectomy helps us introduce adjuvant hormone therapy when needed. Such treatment has shown significant benefit on overall survival in patients with positive lymph nodes after RP.

In the perioperative period, low molecular weight heparin and compression stockings were administered as thromboembolic prophylaxis. Oral ingestion and early mobilisation was encouraged from the first postoperative day. The urethral catheter was left in situ at discharge and was removed after 12 days postoperatively. Patients who remained incontinent in 1 year were offered the possibility of an artificial urethral sphincter implant.

In 3 months postoperatively, patients were reassessed for the first time and serum PSA was measured. For the first postoperative year, patients were seen in 3-month intervals. For the second and third years, patients were re-evaluated every 6 months thereafter.

Patients who underwent a unilateral nerve-sparing procedure were offered treatment with 5-phosphodiesterase-inhibitors. Further treatment strategy was based upon final histopathology and PSA evolution. A slowly rising PSA (PSA doubling time >12 months) in the absence of positive surgical margins or positive lymph nodes was interpreted as local relapse for which the patient was treated with pelvic irradiation. A PSA persistence in the presence of negative surgical margins and any steep rising PSA (PSA doubling time ≤12 months) after a period of undetectable nadir were both considered a sign of occult metastasis. Therefore, these patients were treated with endocrine treatment.

RESULTS

The average age of the patients was 60.5 years old. The average PSA was 11.3 ng/ml. No patient had undergone pelvic radiotherapy before or neoadjuvant hormone treatment. For our 47 patients, average operative time was 125 minutes (range 60–230) with an average blood

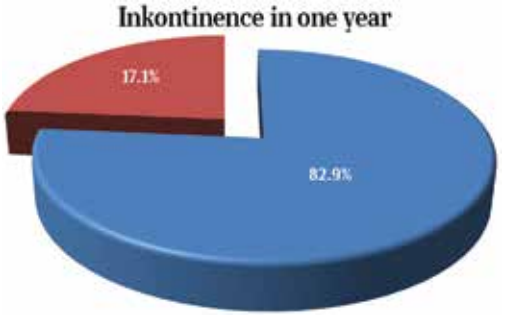
loss of 466 mL (range 150–1700). The urethral catheter was removed in day 12.

No perioperative mortality was noted.

In the perioperative period no ureteral obstruction or urinary retention occurred. In 5% of the patients, the healing of the abdominal wound was delayed. Lymphatic leakage was present in 2 cases (4.2%). When lower urinary tract symptoms were present, a uroflowmetry was performed within 12 months. 2 patients (4.2%) were diagnosed with an anastomotic stricture.

In 12 months 39 patients were completely continent (82.9 %). Incontinence, for which protective pads were needed, was only seen in 7 patients. Postoperative potency was evaluated in 12 months. 42 patients were treated by a non-nerve-sparing RP. 85.6% mentioned absence of erections; 10.4% experienced some tumescence, but not sufficient for vaginal intercourse, and 4% patients had erections, sufficient for successful vaginal intercourse. The average age of these last patients was 57.5 years (range 46.4to 65.2 years old). (table2)

Table 2. Table of incontinence



Oncologic results

In table 3 we can see the oncologic result from which we can stress the point of LN positivity around 32% with the most of nodes found positive in the area of internal iliac artery, stressing the fact that when we do the LN we have to do an extended one.

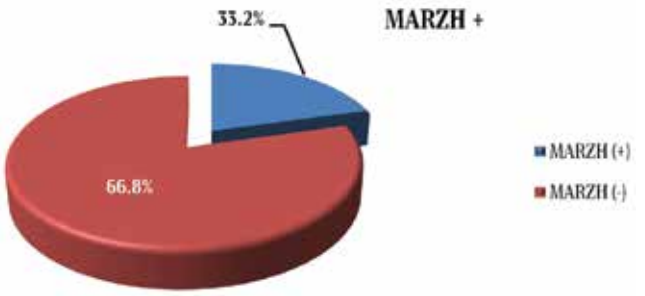
Table 3. Table of oncologic results:

No. of patients	PSM %	% of patients with NVB preserved	Unilateral/Bilateral NVB preserved	LN Positivity %	Extension of LN dissection %	% of positive nodes in IIA	BCR rates Positive %	Metastasis %	Median Follow up
47	33.2	12	12/0	32	extended	34	23	1.5	12 months

PSM = positive surgical margin; NVB=neurovascular bundle; LN=lymph node; IIA=internal iliac artery; BCR=biochemical failure

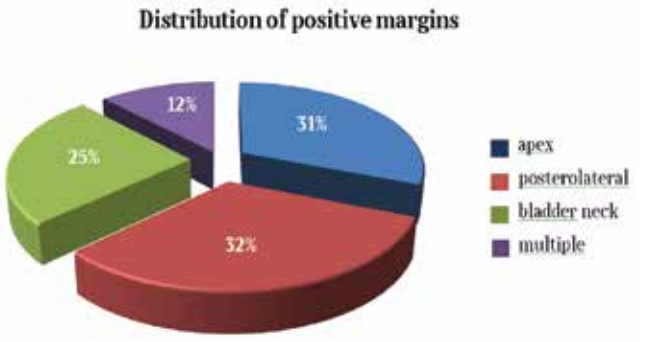
Regarding histopathology, positive surgical margins were found in 10 patients (21.2%). Of these specimens with positive surgical margins, 1 tumour was organ confined (pT2), and 9 showed extra prostatic extension (pT3a). (table 4).

Table 4. The % of marzh involvement:



The distribution of positive margins is represented in table 4, with the highest % of positive margins observed in the posterolateral border of the prostate.

Table 5. Distribution of margins:



DISCUSSION

Treatment options for locally advanced PCa represent: Watchful waiting, RT, HT, surgery, and combinations have been proposed.

In cT3 PCa, Thompson reported a 60 to 70% 5-year overall survival with watchful waiting [8]. So PCa is therefore regarded as a significant tumour with a considerable associated mortality, especially in patients with a long life expectancy. Thus, watchful waiting is only allowed in a strict minority of selected patients with a generally poor health status.

In 25-year follow-up, radiotherapy as monotherapy only added a neglectable gain in survival. When patients did not die of intercurrent disease, they were highly likely to develop recurrence and to die of PCa.

In an attempt to improve disease-free survival and overall survival, the combination of RT and HT was

evaluated. Disease-specific survival and overall survival rates in 5 years improved from 79% to 94% and from 62% to 78%, respectively, in favour of combined RT and HT. By many, the combination of external-beam RT and adjuvant HT is since considered a standard therapeutic option in patients with cT3 PCa.

Literature on the value of RP as an option for cure in cT3 PCa is limited. However, clinical evidence showing 5-year disease-specific survival rates ranging between 85% and 100% is available. Additionally, RP can prevent local tumour-associated complications and provide a clear definition of failure after therapy, compared to the more vaguely defined failure parameters after RT. Furthermore, overstaging of cT3 PCa ranges from 13 to 27% (pT2).

Recently, long-term follow-up of cT3 PCa treated primarily with a prostatectomy has been published. The majority of patients underwent adjuvant RT and/or HT. 5, 10 and 15-year disease-free survival and disease-specific survival rates were 85%, 73%, and 67% and 95%, 90%, and 79%, respectively [9].

With absent mortality, a perioperative complication rate of 2.5%, and postoperative complication rate of 14.9%, our cT3 population is exposed to an equal risk of complications compared to patients who undergo an RP for cT1 or cT2 tumours.

Furthermore, in our series, functional results in 12 months show total continence (no pad necessary) in 82.9%. Finally, anastomotic stricture was encountered at a rather low rate of 4.2%. Expectedly, potency rates were poor in non-nerve-sparing RP.

Surgical margins after RP are of great importance in progression and oncological outcome. Margin positive status varies between 29% and 60.5% in the corresponding articles. The lowest incidence of positive margins was 29% and was found in a population of predominantly organ-confined PCa (73.7% pT2) .In our series of cT3 PCa, it was 33.2%.

Our present analysis is not devoid of limitations. This is a retrospective analysis of complications and functional results, using data extracted from patients' files. The complications and functional results were compared to data extracted from the literature. Nevertheless, we believe that our analysis has its value in outlining the incidence of complications and the functional results that can be expected after RP for locally advanced PCa. Finally, a significant number of patients received adjuvant or salvage RT and/or HT treatment following surgery, limiting the interpretation of the results regarding the value of surgery in locally advanced PCa. Accepting this limitation, oncologic control with RP as a first step in the treatment of locally advanced PCa is excellent.

CONCLUSION

Significantly many patients with cT3 prostate cancer are overstaged (pT2) in the PSA era. RP, as part of a multimodal treatment strategy for patients with cT3 disease, offers cancer control and survival rates approaching those achieved for cT2 disease. Pathological grade, ploidy and margin status are all significant predictors of outcome after RP. Complications and incontinence rates in patients with cT3 disease mirror those after RP for cT2 disease.

So we can state that with the evidence acquired from the data from literature and with the expertise gained from the surgery, there is no reason why the surgeon cannot propose to the patient, who is fit for surgery with a good life expectancy, surgery as primary treatment for locally advanced prostate cancer disease [2, 3, 4]. The percentage of perioperative complication is also reasonable to justify the proposal for surgery to our patient with some specifics in the surgery stated before. This argument is supported by literature when stating that even after 10 and 15 year follow-up, life expectancy is even better when we compare results with radiotherapy or hormonal treatment [5, 6, 7].

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TRAJTIMI KIRURGJIKAL I KANCERIT TE PROSTATES TE AVANCUAR LOKALISHT

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ABSTRAKT

Hyrje: Kanceri i Avancuar i prostatës lokalisht i referohet T3-T4 klinikisht pa evidencë të metastazave në distancë apo përfshirje të nyjeve limfatike. Në praktikën tonë ne i rekomandojmë rutinë pacientëve tanë prostatektominë radikale retropubike si zgjidhje të parë pacientëve me Kancer të avancuar lokalisht apo atyre me risk të lartë. Gjatë viteve 2007 – 2013 kemi realizuar 47 pacientë me sëmundje të avancuar lokalisht të kancerit të prostatës. Kemi matur komplikacionet perioperative dhe gjithashtu rezultatet funksionale gjatë follow-up-it të pacientit, duke monitorizuar gjithashtu dhe të dhënat onkologjike.

Objektivat: Vlerësimi i rezultateve onkologjike dhe funksionale të kirurgjise së kancerit të avancuar të prostatës duke i krahasuar me ato të sëmundjes së kufizuar brenda glandulës prostatike. Vlerësimi i diskordancave klinike dhe patologjike.

Pacientët dhe metodat: Gjatë viteve 2007-2013 ne vlerësuam 47 pacientë në stad T3, bazuar në ekzaminimin rectal, EKO-n transrektale. Biopsia u realizua duke marrë 12 fragmente me sonde transrektale. Skaneri u krye kur PSA ishte mbi 20ng/dl. Rutinë kemi realizuar limfadenektominë në pacientë me Geason Score > 7 apo me PSA > 10ng/dl. Komplikacionet perioperatore janë vlerësuar, rezultatet funksionale dhe të dhënat onkologjike.

Rezultatet: Asnjë komplikacion serioz gjatë interventit apo pas interventit u vune re. Rrjedhje limfatike u vu re në 6% te rasteve në periudhën postoperatore. Striktura e anastomozës u vu re ne 5% të rasteve duke u zgjidhur me uretrotomi interne. 4% e pacientëve patën nevojë të mbajnë më gjatë kateterin se 3 javë. Infeksionet e plagës u vunë re në 4% të pacientëve. Kontinenca e plotë u rikthye në 79% të pacientëve ndërkohë që potenca seksuale u rikthye vetëm në 5% të pacientëve me procedurë nonnerv –sparing e në 12 % të rasteve me procedurë unilaterale të nerv-sparing. Downstaging nga T3 klinik në T2 patologjik u vu re në 22% të rasteve.

Konkluzione: Eksperienca jonë me pacientët me cT3 tregon se është e mundur të trajtohet kirurgjikalisht kanceri lokalisht i avancuar i prostatës me rezultate onkologjike të përafërta me T2. Ky argument i mbështetur dhe në faktin që kemi gjithnjë alternativë e hormonoterapisë dhe radioterapisë si opsion shtesë. Downstaging u vu re ne 22% të rasteve, duke qenë ky një faktor i rëndësishëm për zgjedhjen e kirurgjisë si opsion primar. Të dhënat tona mbështeten dhe nga literatura, që na tregon se rezultatet 10-15 vjeçare të kirurgjisë radikale, krahasuar me radioterapinë apo dhe hormono-terapinë, janë më të mira se këto të dytat.

Key words: Kanceri i prostatës, kirurgji, komplikimet, down staging.

Original scientific paper

FIBROZA PULMONARE IDIOPATIKE E KOMBINUAR ME EMFIZEMË; NJË SINDROMË E RE

IDIOPATHIC PULMONARY FIBROSIS COMBINED WITH EMPHYSEMA; A NEW SYNDROME

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ABSTRAKT

Sindroma e fibrozës pulmonare të kombinuar me emfizemë (CPFE), është një entitet i ri për të cilën është filluar të flitet vitet e fundit. Karakteristikë është bashkëegzistenca e emfizemës pulmonare në fushat e sipërme pulmonare dhe fibrozës pulmonare idiopatike (IPF) në fushat e poshtme pulmonare në të njëjtin pacient.

Provat funksionale respiratore (PFR) në këta pacientë karakterizohen nga volume pulmonare statike dhe dinamike normale ose lehtësisht të ulura, ndërsa hipoksemia e efortit dhe kapaciteti difuzues për monoksidin e karbonit (Dlco) janë veçanërisht të reduktuara. Faktori etiologjik kryesor është duhanpirja por ende nuk është plotësisht i njohur mekanizmi fispatologjik me anë të të cilit tymi i duhanit shkakton këtë sindromë.

Hipertensioni pulmonar (HTP) është komplikacioni më madhor, dhe përbën faktorin kryesor që luan rol në mortalitet. Diagnoza bazohet në gjetjet radiologjike në tomografinë aksiale me rezolucion të lartë (HRCT toraksi). Prognoza është e keqe. Për terapinë nuk është arritur një konsensus ende në rrethet mjekësore. Për këtë arsye njohja dhe diagnostikimi i hershëm i saj mund të ndihmojnë në gjetjen e rrugëve të reja terapeutike.

Fjalë kyçe: Fibrozë pulmonare idiopatike, Emfizemë pulmonare, Hipertension pulmonar

HISTORIKU

Sindroma e fibrozës pulmonare idiopatike të kombinuar me emfizemë (CPFE) është një entitet i ri i zbuluar vitet e fundit, interesi për të cilën sa vjen e rritet.

Fibroza pulmonare idiopatike (IPF) dhe emfizema pulmonare janë dy patologji të ndryshme nga njëra-tjetra me veçori klinike dhe patologjike specifike që njihen mire nga mjekët pneumologë. IPF është patologjia më e shpeshtë e një grupi të madh sëmundjesh të quajtura sëmundje intersticiale pulmonare (ILD). Karakterizohet nga një prognozë më e keqe krahasuar me intersticiopatitë e tjera, nga mortalitet i lartë dhe mbijetesë rreth 3 vjet nga koha e diagnostikimit (1,2). Emfizema pulmonare është një patologji e njohur dhe e studiuar mirë që prej fillimit të shekullit të XIX-të. Ajo karakterizohet nga zgjerimi jo normal dhe permanent i hapësirave ajrore distalisht bronkioleve terminale dhe destruksioni i mureve të tyre (3,4).

Për herë të parë në literaturë egzistenca e njëkohëshme e IPF-së dhe emfizemës në të njëjtin pacient përmendet në vitin 1990 nga Wiggins et al., të cilët kishin vënë re në një grup pacientësh duhanpires, këto dy patologji bashkëshoqëruese por e përshkruan

këtë gjetje si të rastësishme. Auerbach et Al.. ishte i pari që e përshkroi këtë kombinim jo të rastësishëm, 15 vjet më parë në një studim anatomo-patologjik në 1824 pacientë (5). Në vitin 2005 Grubstein et Al. përveçse bashkëshoqërimit të fibrozës me emfizemën sugjeruan për herë të parë lidhjen e ngushtë të HTP-së te pacientët e studiuar dhe hodhën idenë se duhani ishte një faktor i rëndësishem risku për zhvillimin e tre alterimeve që hasen: emfizemës , fibrozës dhe rimodelimit të vazave të vogla që si rezultat çojnë në zhvillimin e HTP-së (6). Cottin në vitin 2005, ishte i pari autor i cili e përshkroi CPFE-në si entitet më vete, në një grup prej 61 pacientësh. Me këtë gjetje ai tërhoqi vëmendjen e botës shkencore ndaj kësaj nozologjie të re (7).

EPIDEMIOLOGJIA DHE ETIOPATOGENEZA

Prevalenca e CPFE-së nuk është e njohur dhe e përcaktuar ende, megjithatë ajo vlerësohet të zerë rreth 5-10% të rasteve me ILD. Seksi mashkull ka prevalencë të lartë, në më shumë se 95% të rasteve. Kjo shpjegohet me faktin se duhanpirja është më e shpeshtë tek meshkujt në krahasim me femrat megjithatë kjo teori nuk shpjegon atë që jo të gjithë meshkujt duhanpirës vuajnë nga kjo sindromë. Ende nuk është e qartë nëse lezionet emfizematoze dhe fibrotike progresojnë në mënyrë të pavarur nga njëri-tjetri apo njëri rezulton si pasojë e tjetrit, duke qenë se IPF dhe emfizema pulmonare janë dy patologji me veçori klinike dhe patologjike të ndryshme. Në shumicën e rasteve është vënë re që CPFE ndodh në pacientë të njohur me emfizemë pulmonare, në të cilët zhvillohet edhe fibroza pulmonare dhe anasjelltas. Këto dy patologji modifikojnë dekursin natyral të njëra-tjetrës. CPFE meriton termin sindromë duke qenë se ajo paraqitet si grup shenjash dhe simptomash ku çdonjëra prej tyre rrit mundësinë për të egzistuar tjetra. Kjo sindromë prek kryesisht meshkujt > 65 vjeç duhanpirës ose ish duhanpirës të fuqishëm > 40 paketa/vite. Patogeneza e saj është gjithashtu pak e studiuar. Pneumonia intersticiale e zakonshme (UIP) gjendet më shpesh në egzaminimin histopatologjik. Duhanpirja stimulon fibrogenezën që është elementi bazë në patogenezën e IPF-së. Nga ana tjetër emfizema pulmonare raportohet të jetë më e shpeshtë në meshkujt duhanpirës se në femrat duhanpirëse (8,9,23).

Ekspozimi ndaj azbestit dhe pluhurave të mineraleve të tjera është parë se shkakton emfizemë pulmonare. Ndonëse prezenca e emfizemës në azbestozë lidhet me duhanpirjen, njihen edhe raste jo duhanpirës me emfizemë të shoqëruar me azbestozë ose silikozë pulmonare (10). Kjo tregon se emfizema dhe fibroza pulmonare mund të bashkëegzistojnë në një pacient me ose pa praninë e duhanit.Të tjerë faktorë etiologjikë të studjuar, që luajnë rol në zhvillimin e CPFE-së janë : mbishprehja e faktorit të nekrozës tumorale (TNF alfa) dhe faktorit të rritjes së trombociteve beta (PDGF beta). Këta dy faktorë në pulmonet e minjve kanë shkaktuar dilatacion të hapësirave ajrore (emfizemë) dhe fibrozë pulmonare (22,24,25,26). Kohët e fundit është raportuar rasti i një gruaje 32 vjeç, jo duhanpirëse me CPFE dhe të foshnjës së saj 3 muajshe, diagnostikuar me pneumoni intersticiale fibrotike. Nënë e bijë ishin mbartëse të një mutacioni të proteinës C të surfaktantit në genin 14 (SFTPC). Fakti se jo të gjithë duhanpirësit zhvillojnë CPFE dhe rasti i sipërpërmendur mbështesin idenë se edhe faktori genetik luan rol në këtë patogenezë, por nevojiten ende studime të tjera për të shpjeguar këtë fenomen (22). CPFE-në e gjejmë edhe në sëmundjet e indit lidhor ndër to më të shpeshtat përmenden artriti rheumatoid dhe skleroza multiple (11,12,13).

KARAKTERISTIKAT KLINIKE

Klinikisht simptoma më e shpeshtë është dispnea e efortit NYHA (New York Heart Association) III-IV dhe kolla e thatë ose me pak sekrecione. Në egzaminimin objektiv, krepitacionet fine predominojnë në 2/3 inferiore të fushave pulmonare bilaterale, gishtat e tamburit (clubbing) etj.; më të rralla janë: sibilancat, cianoza periorale. HTP është e veçanta e kësaj sindrome. Ai përbën komplikacionin më të rëndë në dekursin natyral të CPFE-së. Pacientët me CPFE kanë risk të lartë për të zhvilluar HTP (50%). Ky risk është më i lartë se ai në IPF ose emfizemë të marrë veçmas. Me përparimin e sëmundjes, si pasojë e rimodelimit të arkitekturës intersticiale dhe të shtratit kapilar vazal ,ulet kapaciteti funksional relativ për shkëmbimin gazor dhe si rrjedhojë ndodh HTP prekapilar. HTP është tregues i prognozës së keqe dhe mortalitetit të lartë në CPFE (14). Në kontrast me ndryshimet e shprehura imazherike në HRCT, në spirometri, kapaciteti vital i sforcuar (FVC), volumi ekspirator i sekondës së parë (FEV1) dhe kapaciteti pulmonar total (TLC) janë në vlera normale ose lehtësisht të reduktuar (15,16). Hipoksemia në këtë sindromë është më e shpeshtë se në emfizemë ose IPF. Ajo është e moderuar dhe

përkeqësohet gjatë efortit. Shkëmbimi i gazeve është i kompromentuar si për shkak të emfizemës (patologji obstruktive) në të cilën ndodh shkatërrimi i indit pulmonar si përgjigje ndaj tymit të duhanit por edhe nga IPF (patologji restriktive) e cila shkakton ulje të kompliancës pulmonare si rrjedhojë e fibrozës dhe ndryshimeve strukturale të indit pulmonar (17-22). Kapaciteti difuzues pulmonar për monoksidin e karbonit (DLco) në pacientët me CPFE është shumë i reduktuar. Ai paraqet një faktor prognostik jo të favorshëm dhe bashkë me FVC-në janë dy parametrat kryesorë që përdoren për të monitoruar ecurinë e sëmundjes (23).

DIAGNOZA

Diagnoza në CPFE bazohet në gjetjet imazherike në HRCT (high-resolution computerised tomography; ose tomografia e kompjuterizuar me rezolucion të lartë) toraksi kombinuar me provat funksionale respiratore dhe repertin klinik të pacientit. Në radiografinë pulmonare vihen re: infiltrime retikulare ose mikronodulare në fushat e poshtme pulmonare, mbiajrosje e fushave të sipërme, sheshim i diafragmave, por radiografia e toraksit nuk konsiderohet egzaminim i besuar për vendosjen e diagnozës së CPFE, Fig 1.

Në HRCT toraksi vihet re: emfizemë centrolobulare dhe/ose paraseptale në lobet e sipërme pulmonare, opacitete subpleurale retikulare, bronkoektazi të traksionit, opacitete "ground glass" dhe "honeycombing". Ky i fundit gjendet më shpesh në pneumoninë intersticiale të zakonshme (UIP) dhe paraqet stadin e fundit të fibrozës pulmonare Fig. 2 (a,b,c). Përvec UIP më rralle hasen edhe lloje të tjera fibroze si psh: pneumonia intersticiale jo specifike (NSIP).

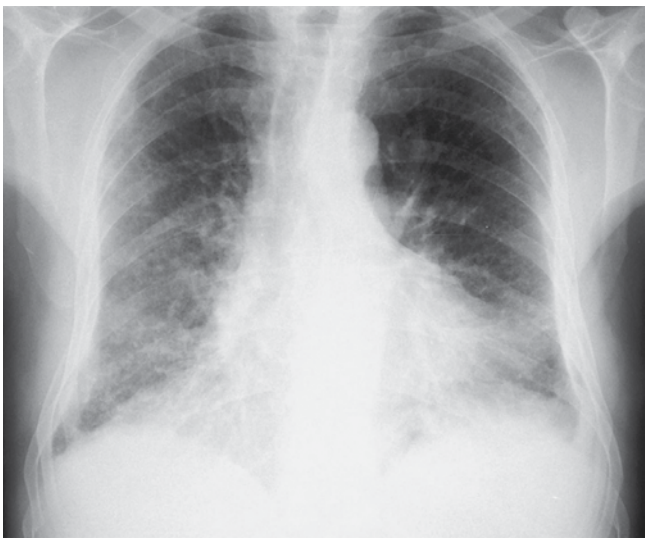


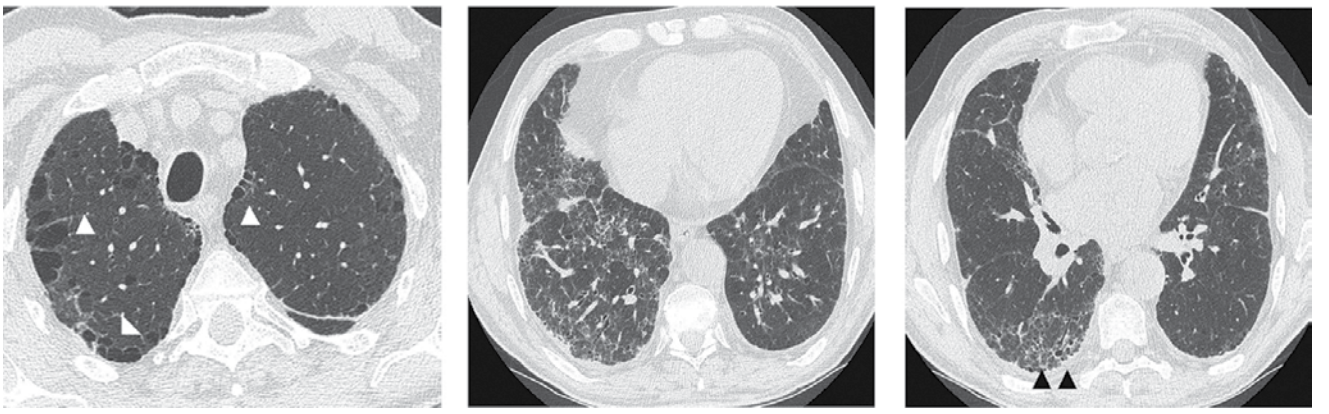
Fig.1 Rö-grafi pulmoni P-A: Pacient mashkull 69 vjeç duhanpirës 35 paketa/vite, i diagnostikuar me CPFE.Vihet re patern intersticial bilateral me infiltrate retikulo-nodulare në të dy bazat pulmonare dhe regjionet subpleurale (fibrozë), mbiajrosje e fushave të sipërme pulmonare (emfizemë).

Spirometria me volume kryesisht në vlera normale, Dlco e ulët dhe hipoxemia në efort te një pacient duhanpirës duhet të ngrejë dyshimin për CPFE. Presioni sistolik në arterien pulmonare (PSAP) ≥ 45 mmHg në ekokardiogramën transtorakale konfirmon prezencën e HTP-së.

KOMPLIKACIONET

Hipertensioni pulmonar është prezent nëse PSAP ≥ 45 mmHg në ekokardiogramën transtorakale. Risku që pacientët me CPFE të zhvillojnë HTP është 50-90% (9). Prezenca e tij është faktor prognostik i keq. Kanceri pulmonar ka gjithashtu një prevalence të lartë te këta pacientë, 42-46%. Tipi histologjik më i shpeshtë është karcinoma me qeliza skuamoze (27, 28). Pacientët me CPFE dhe kancer pulmonar janë duhanpirës të fuqishëm. Këto raste kanë prognozë shumë të keqe. Dëmtimi akut pulmonar (ALI) është një komplikacion tjetër në CPFE; ai ndodh pas rezeksionit kirurgjikal pulmonar .

ALI është më i shpeshtë në pacientët me CPFE krahasuar me ata pacientë që vuajnë nga IPF ose emfizema pulmonare veçmas. Vetë CPFE rrit riskun për dëmtim pulmonar akut.



(a) (b) (c)

Fig 2. HRCT toraksi e pacientit të figurës 1.

(a) Vihet re emfizemë paraseptale, centrolobulare dhe bula subpleurale bilaterale në fushat e sipërme pulmonare.

(b+c) Infiltrime retikulare interstitiale në fushat e mesme dhe të poshtme me trashje të septumeve interlobulare, honeycombing dhe bronkoektazi të traksionit.

TERAPIA

Opsionet terapeutike në CPFE janë të limituara. Mjekimi me kortikosteroidë, imunosupresorë dhe/ose antifibrotikë nuk ka treguar ndonjë përfitim të dukshëm. Duhet inkurajuar ndërprerja e duhanit. Në ata pacientë te të cilët histologjikisht predominon inflamacioni aktiv (ground glass), mund të mendohet përdorimi i imunosupresorëve, por ky mjekim është jo efektiv në pacientët me emfizemë dhe UIP në stad të avancuar (honeycombing) (29). Hipoksemia trajtohet me oksigjeno-terapi. Mjekimi i HTP-së në CPFE nuk ka ende konsensus. Transplanti pulmonar duhet të merret seriozisht në konsideratë te këta pacientë.

KONKLUZIONE

Për CPFE-në ngelet shumë për t'u studiuar. Kjo sindromë është më e shpeshtë se sa mendohet (30%). Prognoza e saj është më e keqe se ajo e IPF-së si patologji më vete. Parametrat funksionalë të ruajtur (spirometria) mund të bëhen shkak për nënvlerësimin e kësaj sindrome. Prezenca e HTP-së është një e dhënë e rëndësishme. Kufiri ndarës ndërmjet IPF-së dhe CPFE-së është ende jo i përcaktuar qartë. Pacientët me CPFE nuk duhet të përfshihen në studimet që bëhen për pacientët e diagnostikuar me IPF ose të paktën të shtresëzohen.

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IDIOPATHIC PULMONARY FIBROSIS COMBINED WITH EMPHYSEMA; A NEW SYNDROME

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SUMMARY

The syndrome of combined pulmonary fibrosis and emphysema (CPFE) is a brand new entity provoking wide discussions in the medical press. Characteristic to the syndrome is the coexistence of lung emphysema in the upper pulmonary fields, and of the idiopathic pulmonary fibrosis in the lower fields, simultaneously at the same patient.

Functional respiratory tests in these patients are typically characterized from static and dynamic lowered volumes, effort hypoxemia and a reduced diffusive capacity of carbon monoxide. The main etiological factor is smoking, although the physio-pathological mechanisms remain still unclear.

Pulmonary hypertension presents a major complication of CPFE, imputed for its role in the mortality of the syndrome. The diagnosis is based in radiological findings, such as high resolution axial tomography. The prognosis is poor, and medical authorities are still far from reaching a consensus regarding the treatment options. Therefore, an early diagnosis might be very important for an otherwise highly invalidating medical pulmonary condition.

Keywords: Idiopathic pulmonary fibrosis, lung emphysema, pulmonary hypertension.

Original scientific paper

СКРИНИНГ ЗА ПРЕМАТУРНА РЕТИНОПАТИЈА ВО РЕПУБЛИКА МАКЕДОНИЈА

SCREENING FOR RETINOPATHY OF PREMATURITY IN REPUBLIC OF MACEDONIA

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АПСТРАКТ

Вовед: Прематурна ретинопатија претставува заболување кое се јавува кај предвремено родени деца и ги зафаќа крвните садови на мрежницата на окото во тек на развојот. Тоа резултира со развој на васкуларни шантови, со неоваскуларизација и во потешките форми, со тракциона аблација на ретина. Целта на ова студија е да се опише воведувањето, резултатите од скринингот и третманот на прематурна ретинопатија во Република Македонија.

Материјал и методи: Се изработи студија на пресек (“cross-sectional”), во која беа вклучени сите новородени со породилна тежина од ≤1500 гр. или помалку и/или родени во 30 гестациска недела или порано во период од Мај, 2009 до Мај, 2014 год. Очното дно на децата беше прегледано со индиректен офталмоскоп во четвртата постнатална недела. Прематурчињата кои развија праговна болест беа третирани со ласерфотокоагулација.

Резултати: Применетиот критериум на скринингот во односот на родилната тежина и гестациската старост вклучува 1630 ризични предвремено родени деца, со идентификација на активен РОП кај 197 прематуруси кои беа третирани со ласерфотокоагулација на двете очи.

Заклучоци: Офталмолошки скрининг претставува базично испитување во клиничкиот пристап на РОП. Добра селекција на деца во неонатолошките единици со висок ризик за појава на РОП и правовремено започнување на офталмолошките прегледи, овозможува правилно спроведување на превенција и лечење.

Клучни зборови: прематурна ретинопатија, скрининг, индиректна офталмоскопија, ласерфотокоагулација.

ВОВЕД

Прематурна ретинопатија или Retinopathy of prematurity-РОП, претставува заболување кое се јавува кај предвремено родени деца и ги зафаќа крвните садови на мрежницата на окото во тек на развојот. Тоа резултира со развој на васкуларни шантови, со неоваскуларизација и во потешките форми, со тракциона аблација на ретина. Развојот на ретинални васкуларни шантови и неоваскуларизацијата при РОП се верува дека се поврзани со локалната исхемија, која е доминантна карактеристика на други пролиферативни ретинопатии како српеста ретинопатија и дијабетична ретинопатија. Единствената специфичност на ROP се однесува на неговата појава само кај прематурни новороденчиња со незрела и некомплетно васкуларизирана мрежница. (1)

Кај предвреме родените деца нормалниот развој на крвните садови на ретината може да биде прекинат, така да периферно поставените делови во тек на својот развој остануваат без васкуларизација. Во деловите на ретина кои се поставени периферно настанува исхемија која стимулира неоваскуларна пролиферација. Развојот на витреоретинална пролиферација и тракциона аблација на ретината на ваква подлога предизвикува траен губиток на функцијата на окото. (2)

За развојот на прематурната ретинопатија одговорни се бројни фактори на ризик кои го попречуваат нормалниот развој на васкуларизацијата на ретината, а меѓу нив најзначајни се: гестациска старост, родилна

тежина, долготрајно давање на вишок кислород и многу други, кои меѓусебно се комбинираат и дополнуваат.

Лекувањето на активниот стадиум е можно со деструкција на аваскуларната ретина со методите на крио или ласерска коагулација која го прекинува развојот и напредувањето на прематурната ретинопатија. (3-4)

Со подигнување на неонаталната нега, овозможено е преживување на децата со ниска гестациска старост и ниска телесна тежина, што ја зголемува инциденцата на прематурна ретинопатија и развивање на тешки форми. (5-6)

Регресија на благите форми на прематурна ретинопатија е возможна преку спроведување на добра контрола и регулација на параметрите на општата состојба на прематурусот.

Превенцијата на прематурна ретинопатија се фокусира на елиминација на факторите на ризик и на офталмолошкиот скрининг.

Мултидисциплинарниот пристап кај прематурна ретинопатија опфаќа општ мониторинг во неонатолошка единица и офталмолошки скрининг за проценка на развиеноста на крвната мрежа на ретината. Прегледот на очното дно со индиректен бинокуларен офталмоскоп и откривање на пореметеноста на развојот на васкуларизацијата во почетните форми, односно во пониските стадиуми на ретинопатијата, овозможува благовремено ефикасно лекување и развој на добра видна функција во иднина. Така правилниот офталмолошки скрининг се поставува како базично испитување во клиничкиот пристап на прематурна ретинопатија, затоа што овозможува правилно и правовремено спроведување на превенција и лекување. (7-8)

И покрај сите напори кои се вложени во превенцијата и лекувањето на прематурна ретинопатија низ петтогодишниот период (2009-2014 год.) на работа и соработка помеѓу Универзитетската Клиника за Очни болести, Единицата за Интензивна Неонатолошка Нега и Терапија при Универзитетската Клиника за Гинекологија и Акушерство и Единицата за Интензивна Неонатолошка Нега и Терапија и Одделот за Неонатологија при Универзитетската Клиника за Педијатрија, ова заболување и понатаму претставува една од водечките причини на слепило кај детската популација. Тоа е и причина за мотивот со овој труд да се осветли проблемот на прематурна ретинопатија во Република Македонија и научно да се обработат и прикажат резултатите од долгогодишното следење на предвремено родените деца и лекување на оваа болест.

Современите истражувања укажуваат на бројните фактори кои имаат влијание на развојот на прематурна ретинопатија, за можноста на контрола и лекување на почетните стадиуми. Истовремено направените анализи на ефикасноста на сложените и скапите хируршки методи на лекување на крајно тешките стадиуми на РОП следени со аблација на ретина и фиброваскуларна организација на стаклестото тело, покажуваат дека ни постигнатите добри анатомски резултати не се пратени со подобрување на видната функција. И покрај напорот кој се вложува во превенцијата и лекувањето на прематурна ретинопатија, ова заболување претставува еден од водечките причинители на слепило кај децата. (9)

Група на офталмолози од повеќе земји во 1988 год. дефинирала класификационен систем на активен ROP, "International Clasification for Retinopathy of Prematurity" (ICROP) или Интернационална Класификација на Прематурна Ретинопатија. Ова преставува основа за контролирани, рандомизирани клинички студии и стандард за офталмолошки скрининг. (10)

Повеќе пилот студии за спроведување на криотерапија претставувале почетна точка за мултицентрично клиничко испитување "Cryoptherapy for Retinopathy of Prematurity (CryoROP). (2) Во оваа студија се прати ефективноста на криотерапијата за редуцирање на лошиот исход на активната ретинопатија. "Laser Therapy for Retinopathy of Prematurity" или "Laser ROP Study" слично на "CryoROP" прати анатомски и функционални резултати на ласерското лекување .

Насоките за примената на суплементарната терапија со кислород ги препорачува клиничката студија "Multicenter Trial of Supplimental Therapeutic Oxygen for Pre-threshold Retinopathy of Prematurity (STOP-ROP). Суплементарната терапија со кислород во лечењето за прв пат е препорачана од Ashton и неговите соработници, како начин на можност за намалување на неоваскуларниот одговор кај прематурната ретинопатија. Phelpsi Rosenbaum и др. покажуваат дека кај мачки со хипероксични индуцирани подрачја

со вазоблитерации, суплементарната терапија со кислород ја намалува ретиналната неоваскуларизација. Овие прелиминарни студии се почетна точка за клиничката студија на STOP-ROP.

ЦЕЛИ НА ТРУДОТ

Примарни цели на овој труд се:

- важноста на спроведувањето на скрининг програмата кај прематурни деца со висок ризик за развој на активна форма на прематурна ретинопатија, за спроведување на соодветно лекување и спречување на понатамошното напредување на патолошкиот процес и
- дефинирање на инклузионите критериуми за ризичната популација на прематуруси која треба да се вклучи во програмата на скрининг на РОП за правовремено откривање на ретинопатијата.

А како секундарни цели на трудот се:

- анализа на влијанието на општите ризик фактори на развојот на прематурна ретинопатија и
- да се даде придонес за развој на стандардни смерници на скринингот кои во иднина ќе бидат применливи за спроведување кај испитуваната популација.

МАТЕРИЈАЛ И МЕТОДИ

Изработена е студија на пресек (“cross-sectional”). Во истражувањето е применет стратифициран примерок каде што основната група е формирана врз основа на критериумите за ризици за развој на ретинопатија кај предвремено родените деца, кои се лекуваат во Единицата за Интензивна Неонатолошка Нега и Терапија при Универзитетската Клиника за Гинекологија и Акушерство, Единицата за Интензивна Неонатолошка Нега и Терапија и Одделот за Неонатологија при Универзитетската Клиника за Педијатрија.

Параметрите на скринингот и селекција на пациенти-критериумите на офталмолошкиот скрининг за прематурна ретинопатија се прифатени според предлогот од страна на Американската Академија на Педијатриска Офталмологија. Селекцијата на скринингот опфаќа предвремено родени деца со телесна тежина при раѓање од ≤1500 гр. и помалку, или гестациска старост од 30 недели и помалку, а добивале кислород, како и прематуруси кои ги преминуваат горенаведените критериуми, но имаат дополнителни ризик фактори во текот на развојот.

Со скринингот се опфатени деца кои се прегледани од Мај, 2009 год. до Мај, 2014 год. Нултиот-првиот офталмолошки преглед беше спроведен во 4-6 недела по раѓањето. Во нултиот офталмолошки преглед од понатамошното следење се исклучувааат децата со правилно развиена крвна мрежа на ретината.

Понатаму се прегледуваат прематуруси каде се прати развојот на крвните садови до самата периферија, обрнувајќи внимание при одстапување во развојот. Кога постои патолошко одстапување и знакови на прематурна ретинопатија се именуваат со стадиум. Придржувајќи се на критериумите на Интернационалната класификација за прематурна ретинопатија (ICROP) за секој преглед во документацијата се внесуваат податоци за локализација на завршетоците на крвните садови, тн. зони и нивниот изглед, спрема озбилноста на стадиумот.

Со секој нареден офталмолошки преглед примерокот се намалува, а целта на детекцијата е активната форма на стадиум 3 на прематурна ретинопатија, чие понатамошно напредување со адекватно лекување, во најголем број може да се спречи.

Во тек на петтогодишниот период со офталмолошки скрининг издвоени се 197 прематуруси со активна форма на ретинопатија од трет степен (threshold retinopathy) и спроведена е ласерфотокоагулацијска деструкција на аваскуларната ретина.

Скринингот беше спроведен за време на престојот на прематурусите во Одделението за Интензивна Неонатална Нега и Терапија при Универзитетската Клиника за Гинекологија и Акушерство или по отпуштањето во Кабинетот за Прематурна Ретинопатија при Универзитетската Клиника за очни болести во Скопје. Прегледот на очното дно е направено во широка зеница. Максимална мидријаза се постигнува со капење на sol. Phenyilephrine 2.5% или sol. Cyclopentolate 0.5% два пати еден час пред прегледот. Прегледот реализиран е со индиректен бинокуларен офталмоскоп и лупа од 28 Д. За подобар преглед на периферните делови на ретина се користи индентатор. Интерпалпебралната рима се држи широко отворена со помош на блефаростат или екартер. Соработката помеѓу персоналот на

педијатрискиот тим и офталмологот овозможува сигурност при одржување на стабилноста на општата здраствена состојба на детето, добар пристап на окото и обезбедува услови за детален преглед на ретината.

Евалвација на скринингот - Во тек на скринингот наодот на очното дно се интерпретира во согласност со Интернационалната класификацијата на прематурна ретинопатија (ICROP). Степенот на прематурна ретинопатија се класифицира според највисокиот степен на промена во окото одделно, кој е регистритан на некој од прегледите, дури иако развојниот стадиум е локализиран во зона III.Специфичните податоци кој се бележат се присуство на дилатирани крвни садови на ретина и степенот на заматување на стаклестото тело. Дилатацијата на крвните садови на ретина се поделени како присутен или одсутен знак плус, а заматувањето на витреус како присуство или одсуство на крв во витреум.

Во зависност од наодот се одредува и терминот на следниот преглед базиран на упатствата на Интернационалната класификација за прематурна ретинопатија. Распространетоста на крвната мрежа, односно локализацијата на завршетоците на крвните садови према Интернационалната класификација за прематурна ретинопатија се обележуваат со римските броеви I, II и III.

Во зона I, крвните садови се шират од дискот на очниот нерв на дијаметар кој е помал од двојната далечина диск-макула. При прегледот, работ на видеокругот на лупа од 28Д се наоѓа на оптичкиот диск и завршетоците на крвните садови внатре васкуларизираната ретина.

Во зона II, крвните садови се шират позади зоната I, но не подалеку од должината на дијаметар до назалниот дел на запчестата линија (orra serata). Транзициона зона е локализирана дел во зона I, а дел во зона II.

Зона III ја претставува темпоралниот дел на периферијата на ретина, надвор од дијаметарот на оддалеченоста на назалниот дел на ора серата.

Во тек на скринингот, потполно развиената крвна мрежа се одбележува со број IV, заради можноста за статистичка обработка.

Степенот на развојот на крвните садови на нивните терминални делови класифициран е према стадиумот дадена од Интернационалната класификација за прематурна ретинопатија, стадиум 1-3, битни за скринингот.

Стадиум 0 се однесува на присуство на неоваскуларизирана ретина на периферија и одбележува состојба на правилно развиени завршетоци на крвните садови, без знаци окарактеризирани во стадиумите 1-3.

Стадиум 1, демаркациона линија представува видлива граница на васкуларизирана од неваскуларизирана ретина. Со ваков наод скринингот продолжува.

Стадиум 2, бедем, каде границата на васкуларизираната од неваскуларизираната ретина почнува да се подигне изнад нивото на ретината. Овој наод бара будно пратење на состојбата на ретината.

Стадиум 3, бедем со пролиферација према витреус, наложува претпазливо пратење на развојот и ширењето на пролиферативниот процес, за правовремено може да се влијае со ласерфотокоагулација кој ја дестроуира исхемичната периферна ретина.

Потполно развиената крвна мрежа, каде крвните садовина ретина досегнуваат до крајната периферија на ретина, циркуларно до ора серата одговара на уреден наод и детето се исклучува од понатамошниот офталмолошки скрининг за РОП, а означен е како стадиум 0, зона IV.

Непотполно развиена мрежа на крвните садови без знаци за ретинопатија е индикација за понатамошно пратење. Интервалот на следните прегледи зависи од зоната каде се наоѓа завршетокот на крвниот знак.

Структура на примерокот –Ризичните предвремено родени деца за офталмолошки скрининг ги издвојуваат педијатрите неонатолози, по следниот критериум:

- Телесна тежина пораѓање (ТТ) ≤1500 гр.; или
- Гестациска возраст (ГС) 30 недели или помала,
- Дејство на други отежнителни услови на развојот или
- Примена на кислород при лечење.

РЕЗУЛТАТИ

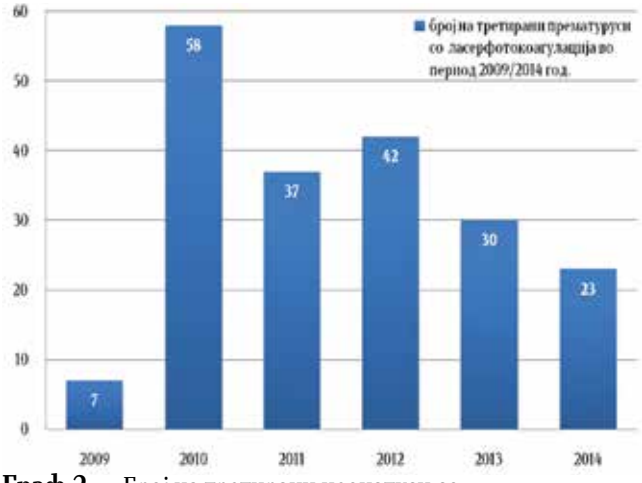
Применетиот инклузионен критериум на скринингот во односот на телесната тежина и гестациската старост вклучува 1630 ризични предвремено родени деца, со идентификација на активен РОП кај 197 прематуруси, што претставува 12.09% и е приближно иста со процентот на третирани прематуруси во европските држави. (Граф.1)

Граф. 1 Прематуруси вклучени во скрининг програмата на прематурна ретинопатија и третирани неонатуси со ласерфотокоагулација кај дијагностициран активен РОП.

Еволутивниот развој на прематурна ретинопатија има свои временски и структурални одредници. Во тек на скринингот пратен е динамизмот на развојот на крвните садови, обрнувајќи внимание на зоната во кој крвните садови се развиваат и состојбата на завршетоците на крвните садови како и нивното понашање во тек на растот.

Кога е дијагностицирана активна ретинопатија – threshold disease, неопходно било активно да се дејствува во рок од 72 часа, односно да се пристапи со деструкција на исхемичната неоваскуларна периферна ретина, се со цел да се спречи понатамошниот тек на пролиферативниот процес кој води према аблација на ретина. Начинот на лекување е само со ласерфотокоагулација со диоден ласер.

Кај 197 прематуруси направено е ласерфотокоагулација во локална анестезија. Во 2009 год. третирани се 7 прематуруси, 2010 год. – 58, 2011 год. – 37, 2012 год. – 42, 2013 год. – 30, додека во 2014 год. третирани биле 23 прематуруси. (Граф.2)



Граф.2 Број на третирани неонатуси со ласерфотокоагулација кај дијагностициран активен РОП во период од 2009/2014 год.

Присуство на хемофталмус заради флоридна форма на прематурна ретинопатија ја оневозможи ласероперацијата на едно око кај едно прематурче. Лекар неонатолог или медицинска сестра од неонатолошките единици беа присутни за време на интервенцијата.

ДИСКУСИЈА

Со предвременото раѓање животните услови се реализираат во динамична средина со променливи параметри. Проблемот кој овде се јавува е незрелоста во регулирање на односите со надворешната средина и специфичностите на потребите.

Согледувањето на сложеноста на проблемот на теоријата на генезата, развојот и напредувањето на прематурна ретинопатија и можноста за превенција, наметнува постојан динамизам на прашања со кои се сретнуваат неонатолози, офталмолози и базични научници.

Во клиничката работа се истакнува превенцијата, која се спроведува во рамките на неонатолошката нега на прематурусите. Примената на кислородот во тек на лекувањето и негата бара постојано мониторирање. Кислородот се опсервира во двојна улога, како фактор за настанување на прематурна ретинопатија и како фактор на нејзина превенција.

Преваленцата на РОП е редуцирана со рестрикцијата на примена на кислородот. Со подобрување на негата се овозможува преживување на децата со мала телесна тежина и ниска гестација, со недоволно развиени системи на органи. Со негата и одржувањето на предвремено родените деца со зголемен збир на фактори на ризик во преживувањето, се зголемува инциденцата на РОП и се зголемува со поместување кон потешките стадиуми.

Базично испитување во клиничкиот пристап на прематурна ретинопатија претставува офталмолошки скрининг. Добрата селекција на децата со висок ризик за појава на прематурна ретинопатија и правовремено започнување на прегледите овозможува шравилно спроведување на превенција и лекување.

Идеална програма за скрининг треба да опфати детекција на сите случаи на прематурна ретинопатија и да ги следи, а истовремено треба да се избегнат непотребните прегледи.

Програмата за скрининг се развива во тесна соработка со педијатар неонатолог и офталмолог.

Високо развиените држави имаат упатства на национален скриниг. Покрај постојаната соработка на неонатолог кој го води мониторингот на општата состојба, критериумите за влез во скрининг програмата може да се прошират. Така, со укажување на присуство и на други можни фактори на ризик, прематурусите со поголема гестација и поголема телесна тежина влегуваат во скрининг.

Стратегија на скринингот кај прематурна ретинопатија се состои во тоа со прегледите на очното дно на прематурчињата да се најдат неправилности на развојот на крвната мрежа, со цел за откривање на активен облик на прематурна ретинопатија и со правовремено лекување да се спречи понатамошниот развој.

Технолошкиот исчекор со поставување на ласерот на индиректен офталмоскоп, овозможува примена на ласер во лекување на активниот стадиум на РОП.

ЗАКЛУЧОЦИ

Прематурна ретинопатија претставува најважен заеднички проблем со кој се соочуваат педијатри и офталмолози и е главна причина за слепило кај деца.

Јасно дефинирани упатства на скринингот и постојан мониторинг на општата состојба претставуваат основни правила за пристап на прематурната ретинопатија. Вредностите на упатствата се општи и временски параметри.

Спрема усвоените критериуми, скринингот е спроведен на 1630 прематуруси.

Скринингот резултираше со откривање на активна прематурна ретинопатија што била и индикација за активно лечење. Кај 197 прематуруси изведена е ласерфотокоагулација.

Тешката општа состојба може да биде причина за касно започнување на скринингот.

Прематурна ретинопатија е зависна од телесната тежина и гестациската возраст. Повеќе е условена од гестациската возраст отколку од телесната тежина при раѓање.

Спрема резултатите на мултипла регресиона анализа должината на давање на кислород се истакнува како значаен фактор во развојот на активната форма на прематурна ретинопатија.

Асистираната механичка вентилација е сигнификантен фактор во тежината на формите на РОП.

Болестите на респираторните органи, интракранијалните крварења како и ацидоза и хиперкапнија во пореметувањата на гасниот статус покажуваат сигнификантно значење во развојот на прематурна ретинопатија

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SCREENING FOR RETINOPATHY OF PREMATURITY IN REPUBLIC OF MACEDONIA

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ABSTRACT

Introduction: Retinopathy of prematurity is a disease occurs in premature infants and affects the retinal vessels during development. The aim of this study is to describe the introduction, the results of screening and treatment for retinopathy of prematurity (ROP) in Republic of Macedonia.

Material and Methods: We used cross-sectional study, which included all infants with birth weight ≤1500gr. and/or born at 30 weeks or earlier from May 2009 to May 2014. Fundus of children was examined with an indirect ophthalmoscope in the fourth postnatal week. Premature babies that developed thresholds disease were treated with laserfotocoagulation.

Results: The applicable criteria of screening in terms of birthweight and gestational age included 1630 preterm children with risk, from witch in 197 infants was identificated active form of retinopathy of prematurity.

Conclusions: Ophthalmic screening presents the basic research into clinical approach for retinopathy of prematurity. Good selection of children in neonatal units with a high risk of retinopathy of prematurity and timely initiation of ophthalmic examinations, allows proper implementation of prevention and treatment.

Key words: retinopathy of prematurity, screening, indirect ophthalmoscope, laserfotocoagulation.

Original scientific paper

PROTOCOLS FOR DETECTION AND PREVENTION OF RhD ALLOIMMUNISATION DURING PREGNANCY

ПРОТОКОЛИ ЗА ДЕТЕКЦИЈА И ПРЕВЕНЦИЈА НА RhD АЛОИМУНИЗАЦИЈАТА ВО ТЕК НА БРЕМЕНОСТА

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ABSTRACT:

Introduction: Mother's alloimmunisation during pregnancy, also known as isoimmunisation, is defined as a presence of irregular Red Blood Cells (RBC's) alloantibodies in blood of pregnant woman that can lead to Hemolytic Disease of the Fetus and Newborn (HDFN) or in severe cases to fetal demise.

Aim: to evaluate the RhD alloimmunisation during pregnancy among women in R. Macedonia and to propose protocols that will improve healthcare and women safety during pregnancy.

Material and method: for 22.009 pregnant women in the period of 2004-2014, were done immunohematology analyses: ABO blood group and Rh type, screening of RBC's alloantibodies, Indirect Antiglobulin Test (IAT) with 5 panels of RBC's antigens, enzyme test (two panels of RBC's antigens), identification of RBC's antibodies (Coombs and enzyme panels), quantification of antibodies and blood group phenotypisation.

Results: total of 3.838 (17.42%) pregnant women were RhD negative. RBC's alloantibodies were detected among 205 women, out of which 169 had sensitization toward RhD antigen and 36 pregnant women had multiple antibodies. The prevalence of allosensibilisation in R. Macedonia is 4.74%; 112 (54.62%) RhD sensitized pregnant women didn't receive antenatal prophylaxis. Symptoms of HBFN didn't show 50.93% of newborns, mild or strong intensity had 36.11% and 12.5% had fetal demise.

Conclusion: The most often reason for RhD sensitization of pregnant women in R. Macedonia is the lack or inappropriate antenatal prophylaxis. It is expected that the wide use of a proposed new protocols will decrease the percentage of women's RhD sensitization and the morbidity and mortality of newborns with HDFN.

Key words: Hemolytic Disease of the Fetus and Newborn (HDFN), Feto - Maternal Hemorragia (FMH), antenatal and postnatal RhD prophylaxis, alloimmunisation.

INTRODUCTION

Mother's alloimmunisation during pregnancy, also known as isoimmunisation, is defined as a presence of irregular Red Blood Cells (RBC's) alloantibodies in blood of pregnant woman that can lead to Hemolytic Disease of the Fetus and Newborn (HDFN) or in severe cases to fetal demise.

The specificity of a blood group is determined by the chemical structure of the antigen determinants that are present in the carbohydrate or protein linked with lipid on the RBC membrane, so called molecule carrier. The blood group antigen can cause immunologic reaction in people that don't have that antigen, producing specific antigen alloantibodies[1].

HDFN begins during intrauterine life, due to presence of IgG antibodies of a pregnant woman against RBC's antigens of the fetus. In most of the cases, HDFN antibodies are connected with D antigen[2] as a result of a higher sensitivity of this antigen compared with other antigens, as well as because the high potential of anti-D antibodies to destroy D- positive fetus RBC's[3,4].

When the antibodies are created and present in a woman's blood, during the time they can become invisible until the new, next contact with antigen. Than, the immune system reacts with increased level of antibodies[5].

Until now, there are over 250 types of identified blood group antigens, together with the corresponding alloantibodies that are divided in 30 different systems, such are: Rhesus (most important antigens are C,c,$C^{W,}$ D, E, e), Kell (with antigens K and κ), Duffy (with the most important antigens Fy^{a} and Fy^{b}), Kidd (antigens Jk^{a} and Jk^{b}) etc[1].

Even though that Rhesus RhD immunoglobulin (RhIG) for prevention of hemolytic disease of the fetus/newborn (HDFN) is widely in use, still, the Rh alloimmunisation remains significant problem in any country.

Around 600-700 new cases of Rh sensitization occur each year in the United Kingdom[6]. It is estimated that about 16-17% of RhD negative women who deliver an RhD positive fetus will become alloimmunised if they don't receive RhIG[7].

There are two main reasons that cause RhD sensitization during pregnancy. First one is missing or inadequate dose of RhIG as antenatal prophylactic therapy. Not all women are treated with anti-D globulin when is needed. The second reason is presence of small, not-detected Feto - Maternal Hemorragia (FMH) during the third semester of pregnancy.

The measurement of fetus erythrocytes in the mother's blood circulation is useful method for estimation of the amount of FMH and adequate RhIG, as well as for good management of feto-maternal RhD incompatibility. The amount of fetus erythrocytes is a vital indicator for determination of therapeutic dose of RhIG and prevention of sensitization of Rh-D negative pregnant woman who carry Rh-D positive fetus[8].

In R. Macedonia, the women's alloimmunisation during pregnancy is important public health problem that require better management.

AIM

The objective of the study is to evaluate the RhD alloimmunisation during pregnancy among women in R. Macedonia and to propose protocols that will improve healthcare and women safety during pregnancy.

MATERIAL AND METHODS

For the purpose of this study were performed immunohematology analyses during the 10 years period (2004-2014), at the Department for immunohematology and antenatal testing at National Institute of Transfusion Medicine in Skopje (NITM).

Retrospective and prospective study methods were used in different stages of study; were analyzed 22.009 blood (serum) samples and gained results from women during their pregnancy and after delivering. For all of them were done laboratory analyses of: ABO blood group and Rh type, screening of RBC's alloantibodies before and after delivering.

After delivery were performed additional tests: Indirect Antiglobulin Test (IAT) with 5 panels of RBC's antigens, enzyme test with two panels of RBC's antigens, identification of RBC's antibodies with Coombs and enzyme panels, quantification of antibodies and blood group phenotypisation of antigens of the mother, father and the newborn, according to detected antibodies.

The structured questionnaire was fill out by each pregnant woman that accepted to participate in the study, by which were provided anamnestic data from respondents about RhD prophylaxis[9].

RESULTS

In the study were included 22.009 pregnant women, out of which 3.838 (17.42%) were RhD negative. RBC's alloantibodies against antibodies of the Rh system were detected among 205 women, with detected 237 alloantibodies, out of which 169 of women had sensitization only toward RhD antigen and 36 pregnant women had multiple antibodies.

In the first phase of data analyze, the prevalence of allosensibilisation in R. Macedonia during pregnancy was 5.34%, with variations in some years between 3.25%-7.34% (table 1). But, later, with deeper analyze of the answers from the questionnaire, with recalculation, this final result was changed to 4.74%. Some of women answered that have received RhIG and some of the results were false positive due to given antenatal prophylaxis.

Table 1 Number of pregnant women and prevalence of sensitized in R. Macedonia (year 2004-2014)

Year	Total number of pregnant women	RhD negative pregnant women	% of RhD negative pregnant women	Anti-D	Prevalence of sensitized (%)	RhIG
2004	1797	364	20,29	11	3.02	14
2005	1635	315	18.98	12	3.80	12
2006	1659	321	19.34	23	7.16	10
2007	2059	317	15.39	12	3.78	12
2008	2118	334	15.76	17	5.08	26
2009	2134	341	15.97	20	5.86	28
2010	2287	422	18.45	28	6.63	15
2011	2078	309	14.87	13	4.20	10
2012	2125	322	15.15	16	5.00	11
2013	2011	369	18.34	12	3.25	11
2014	2106	422	20.03	28	6.63	13
Total	22009	3838	17,42	182	4.74	162

The biggest number of RhD sensitized pregnant women (112 or 54.62%) didn't receive routine antenatal prophylaxis or RhD prophylaxis, especially in cases when there were in any form of risk that contribute to sensitization (ex. after miscarriage). If on that number add the cases with inadequate prophylactic treatment, than the percentage of inappropriate RhD protected pregnant women rise up to 65.35%.

According to gained data from the performed research, the reasons for RhD antigen sensitization that was present among 205 women can be divided into several groups:

- Pregnant women with post-delivery prophylaxis, but without routine antenatal anti-D prophylaxis (AADP), with lack of previous medical history about potential attacks that might cause sensitization during pregnancy (6 women or 2.92%)
- Pregnant women that didn't receive antenatal prophylaxis after confirmed diagnoses of sensitization (34 women or 16.58%)
- Women that didn't receive Antenatal anti-D prophylaxis (AADP) in the previous pregnancies (78 women or 38.04%)
- Women without antenatal and postnatal Rh-D prophylaxis (35 women or 17.07%)
- Sensitized women as a result of inappropriate prophylaxis (22 women or 10.73%)
- Pregnant women that developed sensitization before 28 week of pregnancy (19 women or 9.26%)
- Pregnant women with incomplete medical history (11 women or 5.36%)

By following the healthcare status of pregnant women and later of the newborns of RhD sensitized mothers, was possible to evaluate the clinical outcome of HBFN. Almost half of the newborns (50,93%) didn't show symptoms of HBFN and they didn't receive any therapy. Symptoms with mild or strong intensity of HBFN were present among 36,11% of newborns, followed by phototherapy, exchange-transfusion or pre-term delivery; the rest 12,5% of cases were with registered fetal demise (Table 2).

Table 2. Clinical outcome of newborns delivered by sensitized mothers (year 2004-2014)

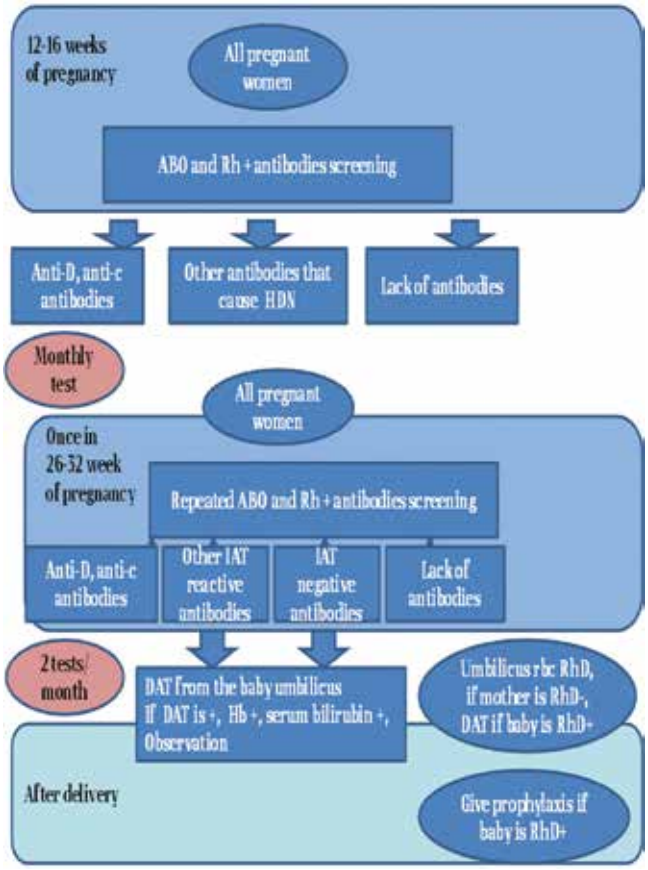
Antibodies	Number of sensitizations	Newborns without therapy	Newborns on phototherapy /exsanguine	Newborns with intrauterine transfusion, hydrops Hb<60g/l
D	182	87 (47.8%)	68 (37.5%)	27 (14.6%)
C	29	20 (69%)	9 (31%)	0
C	1	0	1 (100%)	0
E	4	4 (100%)	0	0
Total	216	111 (50,93%)	78(36.11%)	27 (12.5%)

The sensitization to other antigens of the Rh system, on the second place was against C antigen, in some cases without symptoms, but in other cases with mild or intermediate clinical symptoms of HBFN.

This study during the period of 10 years, accompanied by follow up of the clinical treatment, give the right to the author to conclude that there is a need to revise the current protocols for immunohematology analyses during pregnancy and protocols for RhIG prophylaxis. The proposed new protocols correspond to the newest evidence based medicine practices that are present in developed countries.

The graph 1 represent protocol for immunohematology analyses during pregnancy [10].

Graph 1 Protocol for immunohematology analyses during pregnancy



Protocol for RhIG prophylaxis in the antenatal period

1. Initial blood typing and antibody screening to all pregnant women, during the first trimester of pregnancy, no matter if they are RhD negative or positive. By doing this analysis in the antenatal period, will be achieved:
   - Identification of RhD negative women that are candidates for RhIG prophylaxis
   - Will be discovered alloimmunised women that have to be on a monitoring for HBFN during pregnancy
   - Set up correct and on time diagnosis for HBFN, further observation and appropriate management
   - Identification of ABO blood type of the newborn; in cases of diagnosed symptoms of HBFN the treatment with blood components can start on time
   - To gain time and be ready for fast reaction if there is maternal bleeding during delivery and presence of severe anemia
2. If screening tests are negative, additional control should be done in the period of 26-28 week of pregnancy.
3. When screening tests are positive, but there isn't medical history for RhD prophylactic treatment, it should continue with additional tests for identification and quantification of antierytrocites antibodies.
4. When there is a positive identification of antibodies that cause HBFN with stronger intensity (anti-D, anti-c, anti-K), additional immunohematology laboratory controls are necessary to repeat every 4 weeks until 24 week of pregnancy, after which the level of antibodies have to be controlled every 2 weeks until delivery.
   - For all other antibodies, according to their level, is recommended to make regular immunohematology laboratory controls at every 4 weeks until delivery.
   - During each control of antibodies, it is recommended to do tests screening for presence of additional anti-erythrocytes antibodies.
5. Clinically significant antibodies, are followed by their quantity in serum. If the level is equal or higher than 1:16 for test performed with classic method in tubes or 1:64 with method of micro-agglutination, every increased titer with dilution that is higher than 2 levels should be reported to the obstetrician.
6. In cases when there is a presence of clinically significant antibody, it is necessary to perform blood group phenotyping of biological father, which will help to define whether there is antigen on the fetus erythrocytes. If the biological father doesn't have antigen, there isn't a risk of HBN and no further analyses are needed.
7. If the biological father is a possible carrier of antigen against which is present clinically significant antibody, further tests are needed for detection of fetus alleles, for which determination the best approach is non- invasive method trough plasma analyze of a mother of fetus.
8. In cases with confirmed HBFN, the previous analyses and ABO blood typing help to provide compatible blood for intrauterine transfusion or exchange-transfusion.

Protocol for RhIG prophylaxis in the postnatal period

1. After delivery it is required to make immunohematology test from umbilical blood of a newborn to:
   - Each woman that is RhD negative, but the newborn is RhD positive
   - All newborns that have intensive jaundice and their mothers have a medical history of alloimmunization

2. Newborns that have positive results for Direct Antiglobulin Test (DAT) and don't have clinical signs of HBFN, should be observed at least in the next 5 days and should measure the levels of hemoglobin and serum bilirubin.

Protocol for RhDIG prophylaxis

- RhIG prophylaxis should be given at 26 to 28 week of pregnancy if the woman is RhD negative and with negative anti-D screening. If the test is done before 26 week of pregnancy, it has to be repeated before application of RhIG.
- RhIG should be given if the pregnant woman is Rh negative, antibody screening is positive, but is negative for anti-D.
- Women that are sensitized on D antigen shouldn't receive RhIG.
- RhIG is not recommended if the pregnant woman is RhD negative, but the screening and identification of antibodies are positive on anti-D.
- RhIG is not necessary for pregnant women who are weak D positive
- RhIG should be given to all Rh negative pregnant women that don't have anti-D antibody, within the period of 72 hours after any kind of possible sensitization such are:
  - Pregnancy that is interrupted in >/=13 week
  - Amniocentesis
  - Horion biopsy
- When the woman is D-negative and not sensitized to D and the newborn is also D-negative, there is no need for further tests or RhIG.
- If the mother is D-negative and there is no data about D-sensitization, the newborn is D-positive (including weak D), should do a test for FMH and to estimate the necessary dose of RgIG.
- In cases of prolonged pregnancy and delivery is later that 12 weeks since the last dose of RhIG is given, this preventive RhIG therapy should be repeated.
- When delivery is in the period of 3 weeks after receiving antenatal RhIG, then there is no need of postnatal RhIG, but it is required to measure of FMH, which level should be >15 ml.

For women that are in risk of FMH, there is a need to estimate FMH with qualitative and quantitative methods, especially if there are episodes of repeated bleeding during pregnancy.

The routine screening for excessive FMH during delivery is recommended from:

- American Association of Blood Banks (AABA)[11]
- UK Directives for the use of anti-D immunoglobulin for RhD prophylaxis[12]

FMH should be evaluated for every RhD negative pregnant woman that delivered RhD positive baby. For this purpose is used semi-quantitative method with acid elution, Klickhouer-Betke test. If this test confirm that there is massive bleeding, higher that the "cut off for FMH", than should continue the analysis with other quantitative method (flow citometry) that will evaluate the potentially significance of the FMH[11].

After the 26th week of pregnancy, it is needed to assess the need for additional dose of RhIG for women that have risk or confirmed Feto - Maternal Hemorragia (FMH).

Women that have repeating bleeding during pregnancy, RhIG should receive every 12 weeks adequate level of anti-D, starting to count from the first application of RhIG therapy.

Multiple doses of RhIG are needed if FMH is higher than 15 ml, which is rare during the pregnancy, but more present during delivery.

RhIG >20ml express suppression to 1ml Rh positive erythrocytes. One dose of RhIG of 300µg is enough for suppression of immunological response after exposition of <15 ml. Rh positive erythrocytes. Up to 6 doses of RhIG can be given in the same time, but total dose should be injected not later than 72 hours (3 days).

DISCUSSION AND CONCLUSION

Severe HBN is almost always generated by antigens with protein structure that can be present in the 4th month of pregnancy. The presence of D-antigen can be proven on the erythrocytes membrane even during 5-6 week of pregnancy, which can lead to early primary and specially, secondary immunization of a pregnant woman, by production of anti-erythrocyte's antibodies from the IgG class[13].

Since the year 1960, was introduced postnatal prophylaxis with Rh immunoglobulin's (RhIG). The percentage of RhD aloimmunisation during pregnancy dropped from 14% to 1-2% worldwide. This percentage in a developed countries become even lower, reaching the level of 0.1%, due to implemented additional antenatal prophylaxis in the year 1979[14,15].

The mother's alloimmunisation in Sweden is 0.15%, while 6.2% in Kuwait. The prevalence depends on: time when the screening is performed, the test sensitivity and the population characteristics. In the populations with high obstetric risk, the presence of alloimmunization will be high because the risk factors are directly or indirectly connected with FMH of the women in the past. The antigen distribution has variations in different countries. For example, in the Chinese population RhD immunization is rare, because the prevalence of RhD negative persons is very low (<1%).

The results from this study showed that the most often reason for RhD sensitization of pregnant women in R. Macedonia is the lack or inappropriate antenatal prophylaxis.

The follow up of a confirmed potentially significant FMH is very important issue. In that case, the pregnant woman should be treated with adequate dose of RhIG that will neutralize the fetal cells present in the mother's blood circulation.

One in every 1000 deliveries are associated with excessive FMH. The risk factors can be determined in 50% of cases. Therefore it is important to introduce regular screening for all women to prevent excessive FMH. If there is a confirmed case with excessive maternal bleeding during delivery, for which flow citometry is appropriate and sensitive method that can be used[16].

The prevalence of RhD sensitized women in R. Macedonia is 4.47%, which is twice higher than in developed countries. RhIG prophylaxis is rare and inadequate.

The results of this study confirm the need for implementation of protocols for immunology testing during pregnancy and protocols for RhIG prophylaxis. The management of RhIG prophylaxis can be improved only with team work and better collaboration among specialists in transfusiology, ginecology and pediatry.

The proposed protocols have to be widely used in public and private healthcare organizations that provide healthcare for women and newborn.

It is expected that the permanent and proper use of a proposed new protocols will decrease the percentage of sensitization among pregnant women and will also decrease the morbidity and mortality of newborns with HDFN.

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ПРОТОКОЛИ ЗА ДЕТЕКЦИЈА И ПРЕВЕНЦИЈА НА RHD АЛОИМУНИЗАЦИЈАТА ВО ТЕК НА БРЕМЕНОСТА

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АПСТРАКТ:

Вовед: имунизација на мајката во тек на бременост, позната како алоимунизација се дефинира како присуство на нерегуларни антиеритроцитни алоантитела во крвта на бремената жена, кои можат да предизвикаат Хемолитичка Болест на Фетус и Новородено (ХБФН) и во тешки случаи губење на плодот.

Цел: да се оцени RhD алоимунизацијата кај бремени жени во Р. Македонија и да се предложат протоколи за унапредување на здравствената заштита и безбедноста на жените и плодот во тек на бременост.

Материјал и метод: за 22.009 бремени жени во период од 2004-2014 се направени имунохематолошки анализи: ABO и Rh крвногрупна типизација, скрининг на антиеритроцитни алоантитела, индиректен антиглобулински тест (IAT) со пет панели на еритроцитни антигени, ензимски тест (два панели на еритроцитни антигени), идентификација на антиеритроцитните антитела (Coombs-ов и ензимски панели); квантификација на антителата и крвногрупна фенотипизација.

Резултати: вкупно 3.838 (17.42%) од бремените беа RhD негативни. Еритроцитни алоантитела беа детектирани кај 205 жени, од кои 169 беа кон RhD и 36 жени имаа сензибилизација кон мултипни антитела. Симптоми на ХБФН не покажаа 50.93% од новородените, благи и средно тешки симптоми имаа 36.11% и 12.5% завршија со фетална смрт.

Заклучок: најчеста причина за RhD сензибилизација на бремените во Р. Македонија е недостатокот или несоодветната антенатална профилакса. Се очекува дека широката употреба на предложените нови протоколи ќе ја намалат сензибилизацијата кај бремените и морбидитетот и морталитетот кај новородените.

Клучни зборови: хемолитичка болест на фетус и новородено, фетоматернална хеморагија (FMH), антенатална и постнатална RhD профилакса, алоимунизација.

Original scientific paper

GESTATIONAL DIABETES AS A RISK FACTOR FOR PREECLAMPSIA

DIABETI I SHTATZANISË SI FAKTOR RISKU PËR PREEKLAMPSINË

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ABSTRACT

The frequency of diabetes is 2-3% in pregnant women and 90% of them have gestational diabetes. The frequency of preeclampsia is around 6% in population. Its frequency is significantly much higher in the pregnancies with diabetes and both pathologies are responsible for a high risk of perinatal and maternal morbidity and mortality in the developed countries.

Women with diabetes during their pregnancy have increased risk for preeclampsia, despite other factors.

The Aim of this study was to determine whether GDM increases the risk for preeclampsia independently of other risk factors.

Methods and Materials: We have reviewed all patient files (n=3218) of UHOG "K. Gliozheni" and UHOG "Queen Geraldine" for the period 2005-2012. A case control study was used to investigate the relation between diabetes, as risk factor, during pregnancy and preeclampsia.

Results: GDM occurred in 89 patients (3%) of all pregnancies (n=3218). There was a higher rate of preeclampsia in the GDM group than in the group without GDM (6.1 and 2.8%, respectively).

Conclusion: The patient with diabetes during pregnancy is 2.4 times more likely to develop preeclampsia.

Key words: gestational diabetes, preeclampsia, perinatal mortality.

INTRODUCTION

Reproduction in women with Diabetes Mellitus before the availability of insulin treatment was almost non-existent. When a pregnancy occasionally did occur, it usually ended as a disaster with the death of the mother or infant or in many other cases with the death of both. In 1921, Banting and Best discovered insulin, and it became available as a therapy for the disease[1].

Gestational diabetes mellitus (GDM) is associated with an increased risk of maternal and perinatal short-term and long-term complications[2,3] and together with preeclampsia they compose two of the main pregnancy complications of pregnancy. Hypertensive disorders of pregnancy complicate 5 to 8% of all pregnancies and are the major cause of maternal death[4], accounting for 37% of direct maternal deaths.[5]

The relation between gestational diabetes and preeclampsia is not well understood, but several studies suggest an association between the two diseases. [6, 7]

The rate of preeclampsia is significantly higher in diabetic pregnancies than in pregnancies in the population at large.[8] Several authors have also reported an increase of the frequency in gestational-diabetic pregnancies. [9, 10, 11]

Women with gestational diabetes make up a heterogeneous group in many aspects. For example, they have different grades of impaired glucose metabolism and different times of exposures to the harmful factors. Furthermore, women with gestational diabetes are often at an older age and obese, but there are other factors that may be associated to preeclampsia too.[12]

PE has been frequently reported as a complication of gestational diabetes.[2] Several studies suggest underlying common pathophysiology, including insulin resistance, chronic inflammation and endothelial dysfunction.[13]

Recent studies show an association of PE with altered levels of angiogenic factors, including increased levels of soluble fms-like tyrosine kinase 1 (sFlt1) and reduced levels of placental growth factor (PlGF). PlGF is a placenta-derived angiogenic factor, and sFlt1 is an alternatively spliced circulating form of the VEGF receptor that binds and reduces bioactivity of PlGF. Abnormalities in these circulating factors that regulate angiogenesis have been reported in PE. It is not clear if this is true for women with GDM who develop PE,[12] but the altered anti-angiogenic state in diabetic pregnancies may be one mechanism for the increased risk for PE.[14]

The availability of the Albania Medical Birth Register (MBR) makes it easy to analyze the association between gestational diabetes and preeclampsia and scrutinize the possible influence of several confounding risk factors.

The aim of this study was to determine whether GDM increases the risk for preeclampsia independently of other risk factors.

MATERIALS AND METHODS

We have reviewed 3218 patient files that were in pathology pregnancies clinic of UHOG "K. Gliozheni" and UHOG "Queen Geraldine" for the period 2005-2012.

The study was designed as a case-control study. It was based on the review of medical charts of the subjects. We investigated the relation between diabetes, as risk factor, during pregnancy and preeclampsia.

The cases are women presented with diabetes during pregnancy. Diagnosis is based on the finding of fasting plasma glucose levels higher than 120 mg/dl or postprandial glucose levels higher than 180 mg/dl. We excluded subjects with chronic HTA, chronic renal disease and prior hepatic disease. The cases are patients that have been present in the pregnancy pathology clinic in our hospital from 2005 to 2012.

The control group consists of pregnant women with no diabetes. We excluded subjects with chronic HTA, chronic renal disease and prior hepatic disease. Controls have been present in the department of pregnancy pathology and obstetrics in the same period 2005-2012 (random selection).

STATISTICAL ANALYSIS

The following variables were taken into consideration: Maternal age, residence, education, parity, gestational age, blood glucose level, HbA1c measurement, personal history of diabetes, maternal birth weight, presence of polyhydramnios, and previous history of stillbirth and incidence of preeclampsia.

Data were analyzed using univariate analysis. The variables were divided and organized according to the study objectives. The descriptive analysis of continuous variables consists of the number of observations, mean value, standard deviation, median value and minimal and maximal values.

To explore the distribution of continuous variables, we used standard graphic presentations like the histogram. To explore the distribution of the observations according to the categories, individual and cumulative frequencies were determined.

Bivariate analysis was used to describe and test the association of different variables. Association of categorical variables was analyzed using the $\chi 2$ and Fisher's exact test. The difference between the mean values of the continuous variables according to the categories was analyzed using the Student's test. Confidence intervals were calculated based on the binominal distribution.

To quantify the effect of a variable on another variable we used the Odds homogeneity test. Score's test for odds trend was used to test the association of two variables. To take into consideration the effect of confounding factors (parity, maternal age and maternal birth weight) on the association of diabetes with preeclampsia we used logistic multivariate analysis. Statistical analysis was performed using Intercooled STATA 9.1.

RESULTS

GDM occurred in 89 patients (3%) of all pregnancies (n=3218). There was a higher rate of preeclampsia in the GDM group than in the group without GDM (6.1 and 2.8%, respectively).

The study recruited an equal number of cases and controls (89). The subjects in the case group (pregnant women with gestational diabetes) and the control group, (pregnant women without diabetes) were randomized with no significant differences.

The potential confounders, maternal age, parity, chronic hypertension, were included in the analysis.

It is evident that the majority of the cases reside in urban areas (89%). This finding is consistent with the higher prevalence of diabetes in urban areas.

Another finding is that a greater number of cases result to have attended only the 8-th grade of school compared with the controls (53% vs. 28%). This difference is statistically significant. There was no statistically significant difference of the parity between the two groups. Approximately 87% of the cases have a plasma glucose level higher than normal.

All subjects with preeclampsia are at a gestational age of more than 20 weeks, 21% in the second trimester and 79% in the third trimester.

HbA1c, which is considered a very important indicator of the glucose metabolism was absent for the majority of the subjects (70%).

The average birth weight is significantly different ($p > 0.01$ with the student test) in the case group (3715 g) and in the control group (3242 g).

Stillbirths are reported more often in diabetic subjects with preeclampsia (55%) compared to non-diabetic subjects with preeclampsia (29%).

Polyhydramnios is encountered in 14% of the control group and in 11% of the cases.

HTA is present in 14% of non-diabetic subjects. It means that HTA is not a diagnostic criteria of preeclampsia.

Albuminuria in subjects without preeclampsia occurred in 10-25%.

Preeclampsia in the cases and the controls cases

Preeclampsia is present in 24% of the cases and only 9% of the controls ($p = 0.01$). Diabetic pregnant women are 2.4 times more likely to develop preeclampsia compared with non-diabetic pregnant women (95% confidence interval = 1.2-9).

Table 1. The frequency of preeclampsia in the cases and the controls group

	NO	YES	TOTAL
CASES	65	24	89
	75.95	24.05	100.00
CONTROL CASES	77	12	89
	91.14	8.86	100.00
TOTAL	142	36	178
	83.54	16.46	100.00

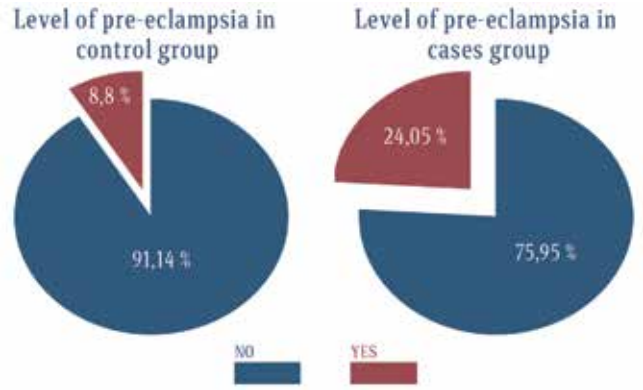

Figure 1. Pregnant women with diabetes are 2.4 times more likely to develop preeclampsia compared to pregnant women without diabetes, for the same parity, age and birth weight.

PREECLAMPSIA AND MATERNAL AGE FACTOR

Subjects with preeclampsia belong to the age-group which is younger than 35 years (79%).

Table 2/a Numbers of births in non-diabetic women (control group)

PREECLAMPSIA	<35	>=35	TOTAL
NO	43	34	77
YES	10	2	12
TOTAL	53	36	89

Table 2/b Numbers of births in non-diabetic women (cases group)

PREECLAMPSIA	<35	>=35	TOTAL
NO	43	22	65
YES	18	6	24
TOTAL	61	28	89

NUMBER OF BIRTHS AND PREECLAMPSIA

If we take into consideration the case of the parity it will be stated that in non-diabetic women (control group), preeclampsia is more frequent in their first or second pregnancy. In diabetic women (cases group), preeclampsia is more frequent in their first pregnancy (42%).

Table 3/a Relation between preeclampsia and parity (control group)

PREECLAMPSIA	0 BIRTH	1 BIRTH	2 BIRTH	3 BIRTH	4 BIRTH	TOTAL
NO	22	22	21	6	6	77
YES	2	7	1	1	1	12
TOTAL	24	29	22	7	7	89

Table 3/b Relation between preeclampsia and parity (cases group)

PREECLAMPSIA	0 BIRTH	1 BIRTH	2 BIRTH	3 BIRTH	4 BIRTH	TOTAL
NO	14	21	19	5	6	65
YES	9	6	5	3	1	24
TOTAL	23	27	24	8	7	89

Preeclampsia is higher in patients without GDM in first pregnancy or second pregnancy, but in patients with GDM the preeclampsia is higher only in the first pregnancy (42%).

DISCUSSION

The result from this population-based study of more than 3200 pregnant women demonstrates that GDM is independently associated with a higher risk for preeclampsia (OR = 3.9).

The relation between the gestational diabetes and preeclampsia is not well understood, 15 however, several studies suggest an association between these diseases.[16]

In a recent study in Finland, Suhonen and Teramo found a combined rate of pregnancy-induced hypertension and preeclampsia that was twice as high in their GDM women compared to women without GDM.[17]

The study showed that fetal cell numbers were indeed elevated in pregnancies with later developed preeclampsia. This indicates that underlying placental disturbances leading to increased fetal cell traffic in preeclampsia occur early in pregnancies which develop preeclampsia.

The lesion implicated in preeclampsia initially only involves fetal/placental compartment, whereas once the symptoms have become visible, the maternal compartment is also affected.[18, 19]

Women with GDM are characterized by increased insulin resistance and/or defective insulin secretion[20]. Studies support an association between preeclampsia and increased insulin resistance. [21] The clinical syndrome of both insulin resistance and essential hypertension has been termed as the Syndrome X by Reaven.[22]

De Fronzo et al. found that hyperinsulinaemia inhibited renal sodium transport in the proximal tubule, reducing sodium excretion. Sodium retention could then result in hypertension.[23]

Anderson et al. noted that insulin resistance was associated with increased plasma norepinephrine levels and increased sympathetic nerve activity, which could raise blood pressure.[24]

Wu et al. reported that insulin enhanced vasoconstriction. Insulin resistance might affect angiogenic pathways. Increased concentrations of the anti-angiogenic protein sFlt-1 and decreased concentrations of pro-angiogenic proteins VEGF and PIGF are thought to damage vascular endothelium and result in clinical preeclampsia.[25]

Thadhani et al. found that the risk for preeclampsia among women with low levels of PIGF was further increased when accompanied by high insulin resistance. They hypothesized that because insulin regulates the expression of genes involved in angiogenesis, deficits in insulin signaling pathways might further disrupt the balance between pro and anti-angiogenic factors, which in turn could increase the risk for developing preeclampsia.[26]

The etiology of preeclampsia is still not clearly established. It probably has a multifactorial etiology and the dysfunction of the vascular endothelium is considered to play a crucial role.[27]

The placenta plays a central role in the pathogenesis of PE. In animal models hyperglycemia increases feto-placental angiogenesis and regulates glucose transporters since the first trimester.[28] Furthermore, hyperglycemia increases capillary permeability through an increased production of nitric oxide and reactive oxygen species. These mechanisms may explain the increased placental and fetal growth observed in pregnant women with diabetes. Increased angiogenesis and endothelial permeability observed in the placenta of pregnant diabetic animals are similar to what is observed in human diabetic retinopathy and nephropathy.

In previous studies investigating the potential value of the first-trimester, maternal biomarkers for early prediction of GDM reported promising results for adiponectin, follistatin-like-3 (FSTL3) and sex hormone-binding globulin (SHBG). [29, 30]

Studies show that screening for GDM can be provided by a combination of maternal characteristics and maternal serum adiponectin and sex hormone-binding globulin (SHBG) levels at 11 to 13 weeks, because the risk of recurrence of GDM, in both studies is very high.[31]

The study also shows that maternal age, residence,

education, parity, hypertension and renal impairment (albuminuria), have an effect on the risk for preeclampsia. All these findings explain the effect of diabetes in pregnancy on the maternal and fetal outcome (the rate of complications in patients with preeclampsia is 15%).

It is evident that women with GDM differ from the background population in factors such as age, BMI, parity, and pre-existing hypertension. These findings are in accordance with other reports.[32, 33]

There are several reasons for observed differences between the GDM and the non-GDM group.

Subjects with preeclampsia belong to the age-group which is younger than 35 years (79%). Age and obesity are well known factors in influencing glucose tolerance.[34] The screening system in which obesity is a reason for performing OGTT, will increase the rate of obesity among women with GDM. This underlines the need to consider the influence of possible confounders.

Goldman et al. found a doubled rate of preeclampsia in GDM women that approached but did not reach statistical significance[35]. They reported a relation between preeclampsia and maternal overweight.

In the literature there are discussions on the threshold values of the plasma glucose levels used for diagnosing diabetes during pregnancy. There are variations of the criteria for performing OGTT, which means that there must be some women with undiagnosed GDM in the "non-GDM" group. In the current study this has resulted in an underestimate level of the presented excess risk of preeclampsia in GDM pregnancies.

Since GDM mothers are characterized by obesity,[36] it is important to consider obesity as a risk factor for preeclampsia in the analysis. A recently published study of risk factors for preeclampsia in quiet a different population of Latin American and Caribbean women supports the finding of GDM as an independent risky factor for preeclampsia.[37]

HbA1c, which is considered an important indicator of the glucose metabolism was absent for the majority of the subjects (70%).

Studies have reported an association between poor glycemic control early in pregnancy and the risk of preeclampsia.[38] In early pregnancy, HbA1c ≥ 8.0% is associated with a significantly increased risk for preeclampsia. Women who developed preeclampsia had significantly higher A1C values before and during the pregnancy. These data suggest that optimal glycemic control both in early stages and throughout the entire pregnancy may reduce the risk for preeclampsia in those women with type 1 diabetes.[39]

The U.K. National Institute for Clinical Excellence recommends that if it is safely achievable, women with diabetes who are planning to become pregnant should aim to maintain their A1C below 6.1%.[40]

The American Diabetes Association recommends that A1C levels should be as close to normal as possible (<7%) in an individual patient before conception is attempted.[41]

Further large cohort studies with a larger data base are needed to establish more clearly the association between diabetes during pregnancy and preeclampsia, as well as other factors that play a role.

As a summary, we may say that the high incidence of preeclampsia in pregnant women with diabetes is not a coincidence.

CONCLUSION

1. The present study has demonstrated an independent and strong significant association of GDM with preeclampsia.
2. This increased preeclampsia rate may contribute to an increased rate of perinatal complications among GDM women.
3. Pregnant women with diabetes are 2.4 times more likely to develop preeclampsia compared to pregnant women without diabetes.
4. All pregnant women should be subject to systematic screening to detect diabetes during pregnancy.
5. Pregnant women diagnosed with diabetes should be followed up for an early diagnosis of preeclampsia.

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DIABETI I SHTATZANISË SI FAKTOR RISKU PËR PREEKLAMPSINË

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ABSTRAKT

Diabeti ndodh në afro 2-3% të shtatzanive dhe 90% e pacienteve kanë diabet të shtatzanisë. Preeclampsia ndodh në afro 6% të popullatës. Shpeshtësia e saj është më e lartë në mënyrë të dukshme në shtatzanitë me diabet dhe të dy patologjitë janë përgjegjëse për një risk të lartë të vdekshmërisë perinatale dhe amëtare në të gjitha vendet e zhvilluara. Gratë me diabet në shtatzani rrisin riskun për preeklampsi pavarsisht prej faktorëve të tjerë.

Qëllimi: Të përcaktojmë nëse diabeti gestacional e rrit riskun për zhvillimin e preeklampsisë pavarsisht faktorëve të tjerë.

Metodat dhe materialet: Janë marrë në shqyrtim të gjitha dosjet e subjekteve të shtruara me diabet gjatë shtatzanisë (n= 3218) në SUOGJ "K. Gliozheni" dhe SUOGJ "Mbreteresha Gerladinë" gjatë periudhes 2005-2012. Në total ishin 89 paciente me diabet në shtatzani. Një studim i tipit rast-kontroll u përdor për të përcaktuar lidhjen ndërmjet diabetit si faktor risku në shfaqen e preeklampsisë.

Rezultatet: Diabeti i shtatzanisë u has vetëm në 89 paciente (3%) nga totali prej 3218. Shpeshtësia e preeklampsisë ne grupin me diabet të shtatzanisë ishte më e lartë se në grupin pa diabet të shtatzanisë. (6.1 dhe 2.8% respektivisht).

Konkluzioni: Subjektet me diabet kanë 2.4 herë më shumë të ngjarë të zhvillojnë Preeklampsi krahasuar me subjektet pa Diabet.

Fjalë kyçe: Diabeti i shtatzanisë, preeklampsia, vdekshmëria perinatale.

Original scientific paper

HOST AND VIRAL FACTORS IMPACT ON VIROLOGICAL RESPONSE IN PATIENTS WITH CHRONIC HEPATITIS C, GENOTYPE 1B TREATED WITH STANDART SCHEME

NDIKIMI I FAKTOREVE TE INDIVIDIT DHE ATYRE VIRALE NE PERGJIGJEN NDAJ MJEKIMIT NE PACIENTET ME HEPATIT KRONIK C, GJENOTIPI 1B ME SKEMEN STANDARTE

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ABSTRACT

Introduction: Chronic hepatitis C (CHC), genotype 1b, represents the majority of cases in our country and the most difficult to treat.

Aim: To asses the impact of host and viral factors on treatment response in these patients

Patients and Methods: We analyzed the data of 60 patients diagnosed with CHC, genotype 1b, treated in UHC "Mother Tereza", Service of Hepatology and Gastroenterology, with Peginterferon (180 µg s.c/week) and Ribavirine (800-1200 mg/day). The duration of treatment was 48-72 weeks according to virological response. Success of treatment or sustained virological response (SVR) was considered the situation with negative HCV RNA (< 50UI/ml) 24 weeks after treatment withdrawal.

Results: From all patients 56 finished the treatment. The SVR rate was 53.5%. Median age of patients who achievied SVR was 40,5 ys/old and Non-SVR was 39.4 ys/old, ($P > 0.05$). Female patients had higher SVR rate (64%) versus males (45%) ($p < 0.05$). Patients with viral load < 800000UI/ml had higher SVR rates than those with baseline viremia >800000UI/ml ($p < 0.01$). SVR rates were 66.7% in the group with BMI < 27 vs 22.2 % in patients with BMI > 27 ($p < 0.0001$).

Conclusions: For genotype 1b in Albania age had not shown influence on SVR rates, while female gender, low baseline viremia, and BMI <27 are positive predictive factors of SVR.

Key words: chronic hepatitis C, genotype1b, treatment response

INTRODUCTION

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide . It is estimated that approximately 130–210 million individuals, i.e. 3% of the world population, are chronically infected with HCV(1). Genotype 1 (subtypes 1a and 1b) is by far the most prevalent genotype worldwide of hepatitis C with a higher prevalence of 1b in Europe and 1a in the US (2). According recent studies HCV genotype 1 comprises 83.4 million cases (46.2% of all HCV cases), approximately one-third of which are in East Asia. Genotype 3 is the next most prevalent globally (54.3 million, 30.1%); genotypes 2, 4, and 6 are responsible for a total 22.8% of all cases; genotype 5 comprises the remaining < 1% (3). The HCV-estimated prevalence in economically developed countries is relatively low with 1%-2% of the adult population whereas 5%-10% in less developed countries (4,5). According studies made by institute of Public Health in Albania and Service of Gastrohepatology genotype 1b is prevalent in Albania and represent nearly 70% of HCV infection, followed by genotype 2 in 24% of cases, genotype 3 nearly 5% and 1% genotype 4 (6).

Acute HCV infection is asymptomatic in 50–90% of cases. An average of 26% of patients with acute hepatitis C (range 20–67%) experience spontaneous clearance of the virus, an event that occurs primarily during the first 3 months after clinical onset of disease. If viremia persists for more than 6 months, chronic disease should be considered (7).

Depending on the presence of co-factors (alcohol consumption, diabetes mellitus, older age of acquisition, HIV or other hepatotropic viruses confection) between 10% and 40% of patients with chronic HCV infection will develop cirrhosis. Death related to the complications of cirrhosis may occur, at an incidence of approximately 4% per year, whereas hepatocarcinoma occurs in this population at an estimated incidence of 1–5% per year (2).

The primary goal of HCV therapy is to cure the infection, which results in eliminating detectable circulating HCV after cessation of treatment. Sustained virological response (SVR) is defined as an undetectable HCV RNA level (<50 IU/ml) 24 weeks after treatment withdrawal. The combination of pegylated interferon (IFN)-a and ribavirin is the approved and well accepted standard-of-care (SoC) for chronic hepatitis C (8,9).

The factors that determine the likelihood of achieving SVR are called predictors of response. They can be classified as viral- factors (like genotype, baseline viremia) or host-related (like age, gender, race, BMI, steatosis, fibrosis etc) or as pre- or on-treatment factors depending on the time point of evaluation.

AIM

To asses the impact of host and viral factors like age, gender, BMI, and baseline viremia in the treatment of patients with Chronic hepatitis C, genotype 1b.

PATIENTS AND METHODS

A total of 60 patients diagnosed with CHC genotype 1b were included in this prospective study during the period 2008-2012. 28 patients (46.7%) were females and 32 (53.3%) males with mean age 40.3 ± 11.3 years old. Chronic HCV infection was defined as both positivity of Anti HCV and serum HCVRNA > six months. The patients included in the study had no absolute contraindication to long acting interferon and ribavirin therapy i.e. uncontrolled depression, psychosis, or epilepsy; uncontrolled autoimmune diseases; cirrhosis (Child–Pugh B7 or more); pregnant women or couples unwilling to comply with adequate contraception; severe concurrent medical disease, such as poorly controlled hypertension, heart failure, poorly controlled diabetes, and chronic obstructive pulmonary disease and also were not included in the study patients with end stage renal disease and hemoglobinopathies. All the patients were treated with Peginterferon alfa-2a (180 µg s.c/week) and Ribavirine 800-1200 mg/day (according to body weight). The duration of treatment varied from 48-72 weeks according to the virological response. The treatment was extended to 72 weeks in slow responders (HCV RNA detectable at week 12 of treatment but undetectable at week 24). The primary end point was SVR defined as undetectable HCVRNA level 24 weeks after the end of treatment. Patients were evaluated at baseline with AST, ALT, GGT, WBC, Hb, PLT, HCVRNA, age, sex, weight, height, and at weeks 4, 12, 24, 48 (and 72 for slow responders) and 24 weeks after end of treatment. We assesed at baseline the weight and height of the patients and calculated BMI according standart formula. Data were evaluated with T test and univariate logistic regression for the impact of age, gender (males vs females) baseline viremia (>800000UI/ml vs <800000UI/ml) and BMI (>27 vs BMI< 27) on SVR rates. P< 0.05 is considered statistically significiant.

RESULTS

From all patients included in the study 56 finished the treatment. In 4 patients the treatment was interrupted because of severe adverse events (intersticial pneumonia, severe thrombocytopenia, depression, hepatic deccompensation). The overall SVR rate was 53.5% (Fig.1).

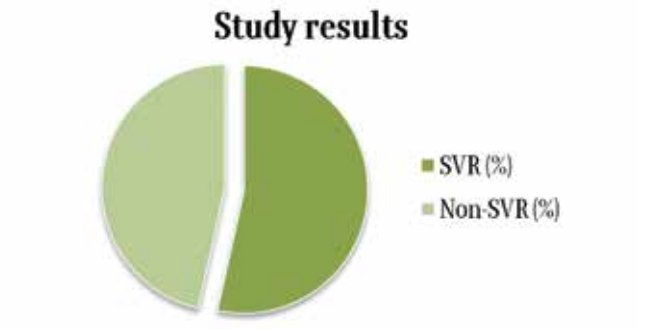

Fig.1: The overall SVR rate in genotype 1b patients treated with peginterferon and ribavirin

Median age of patients who achievied SVR was 40,5 ys/old and for those who had Non-SVR was 39.4 ys/old, without significiant differences between the two groups (Fig.2).

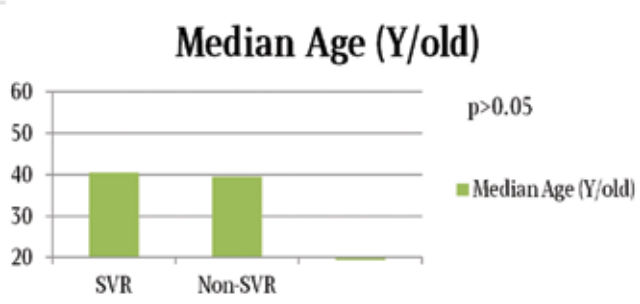

Fig. 2: Age impact on SVR rate in genotype 1b patients treated with standart scheme

Female patients with genotype 1b had higher SVR rate (64%) versus males (45%) ($p < 0.05$). SVR rates were 66.7% in the group of patients with BMI < 27 vs 22.2 % of patients with BMI > 27 with sifnificiant differences between the groups ($p < 0.0001$). Patients with genotype 1b and low viral load at baseline < 800000UI/ml had also higher rates of SVR (68.7%) than those with baseline viremia >800000UI/ml (36.3%) ($p < 0.01$) (Fig 3).

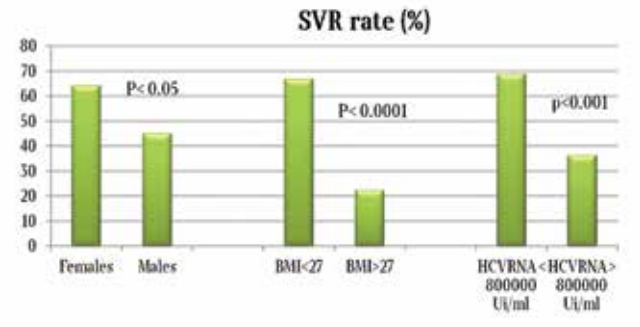

Fig 3: Impact of gender, BMI and HCVRNA at baseline on SVR rates in patients with genotype 1b treated with standart scheme

DISCUSSION

In the pivotal clinical trials for registration of pegylated IFN-a and ribavirin therapy, SVR was achieved in 46%-54% of patients infected with HCV genotype 1 treated with pegylated IFN-a-2a (180 microgram/week) plus weight-based ribavirin (0.8-1.2 g/day) for 48 weeks. According many studies with pegIFN/RBV treatment, SVR rates were 40–50% in genotype 1 and 70–80% in genotypes 2/3-infected patients in western countries (2, 10). Some studies showed that prolonging treatment up to 72 weeks in genotype 1 slow responders (11-13) can increase SVR rates. In our study the SVR rate was 53.5% and importantly we extended the treatment to 72 weeks in slow responders. In genotip 1 patients low baseline HCV RNA level (<600,000–800,000 IU/ml or less) was shown to be an independent predictor of achieving SVR. (14,15). Based on these results, an abbreviated regimen (24-week treatment with pegIFN/RBV) may be indicated for patients with G1 and a low versus high baseline viral load, and undetectable HCV RNA after 4 weeks of treatment. In our study we confirmed that HCVRNA <800 000Ui/ml is a strong predictor factor of SVR. Univariate and multivariate analyses performed in most of the randomized control trials in patients treated with pegIFN/RBV dual therapy showed that younger age significantly correlated with the likelihood of obtaining SVR. Furthermore, higher SVR rates were obtained in patients younger than 40–45 years old (14). In our study age does not seem to effect the treatment. Importantly we analised the group of patients with non-SVR and noticed that 81,7% of patients had positive HCVRNA at week 4. Early viral kinetics are useful in predicting treatment response when treatment has been initiated. With pegIFN/RBV treatment, it was clear that early viral kinetics are the strongest predictor of achieving SVR: obtaining a rapid virologic response (RVR), defined as HCV RNA being undetectable at week 4 of therapy was the strongest predictor of SVR, no matter what adverse baseline predictors may have been present (16). We analised the group with SVR and the result was that 64% of them had RVR (negative HCVRNA at week 4) and 96.7% had C-EVR (negative HCVRNA at week 12 of treatment). In our study age seem to be a positive predictive factor in female patients in which the median age was 40 years old. The favorable therapeutic effect of treatment in females may be related to high levels of estrogen in these women. It has been proposed that estrogen may suppress hepatic fibrosis through an effect that depends on its hepatic tissue receptors, and improve the antiviral therapy (17). A number of studies have found that patients with a higher body weight have reduced response rates following antiviral therapy (18, 19, 20). In our study BMI < 27 is a strong predictor factor for SVR. Treatment failure in obese patients may be due to inappropriate weight based dosing or inadequate drug doses leading to lower serum levels of IFN-a (21) and also increased expression of factors that inhibit interferon signalling may be one important mechanism by which obesity reduces the biological response to IFN-a (19,22,23,24). Another important factor that affect treatment in chronic hepatitis C is adherence of patients to therapy which depends mostly from several adverse events of interferon and ribavirine. Chances of

achieving an SVR significantly decrease when patients receive < 80% of the total dose of peg-IFN and/or < 80% of total ribavirin and/or during < 80% of the total period of treatment (25). In our study we tried to manage accurately the side effects of treatment and only in four cases we interrupted the treatment because of serious adverse events: interstitial pneumonia, severe thrombocytopenia, depression and hepatic deccompensation. In the pegIFN/RBV dual therapy, predictors of response helps the patient and the physician to decide whether or not to start treatment because this therapy is costly and is associated with several side effects and also can help to predict the chance of each patient to respond to the treatment or if the treatment according to these predictors may be extended or shortened. Nowadays where triple therapies and interferon free regimens are present, it is possible, in naive patients, to predict response to dual, triple or other new therapies and choose between them.

CONCLUSIONS

BMI < 27, female gender, low baseline viremia are strong positive predictor factors for SVR during treatment of patients with CHC, genotype 1b in Albania. Optimising weight before treatment is important in order to achieve sustained virological response. Age does not seem to efect SVR rates in CHC genotype 1b patients in Albania. Early viral kinetics during treatment(RVR and C-EVR) are the best predictor of responsevness. Good management of adverse events increases chances of achieving SVR.

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NDIKIMI I FAKTOREVE TE INDIVIDIT DHE ATYRE VIRALE NE PERGJIGJEN NDAJ MJEKIMIT NE PACIENTET ME HEPATIT KRONIK C , GJENOTIPI 1B ME SKEMEN STANDARTE

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ABSTRAKT

Hyrje: Gjenotipi 1b perfaqeson numrin më të madh të rasteve në pacientët me hepatit kronik C dhe njëkohësisht më të vështirin për tu mjekuar.

Qellimi: Vlerësimi i ndikimit te faktorëve individuale dhe virale në përgjigjen ndaj mjekimit në këta pacientë.

Pacientët dhe metodat: U vlerësuan të dhënat e 60 pacientëve me gjenotip 1b, të trajtuar në Shërbimin e Hepatologjisë e Gastroenterologjisë, QSU "Nënë Tereza" me skemen standarte: interferon të pegiluar (180 µg s.c/javë) dhe ribavirin (800-1200 mg/ditë). Zgjatja e mjekimit ishte 48-72 javë mbi bazën e përgjigjes virologjike. Sukses i mjekimit ose përgjigje virologjike e qëndrueshme (SVR) u konsiderua negativizimi i HCVRNA 24 javë pas trajtimit. **Rezultatet:** Nga të gjithë pacientët 56 e përfunduan mjekimin. Shkalla e SVR ishte 53.5%. Mosha mesatare e pacientëve që arritën SVR ishte 40,5vjec dhe jo-SVR 39.4vjec, ($P > 0.05$). Pacientët femra patën shkallë më të lartë të SVR (64%) sesa meshkujt (45%) ($p < 0.05$). Pacientët me baseline HCVRNA < 800000UI/ml patën shkallë më të lartë të SVR sesa ata me HCVRNA >800000UI/ml ($p < 0.01$). Shkalla e SVR në grupin me BMI <27 ishte 66.7% kurse në grupin me BMI >27 ishte 22.2 % ($p < 0.0001$).

Perfundime: Per gjenotipin 1b ne Shqiperi mosha nuk tregoi ndikim te rendesishem ne pergjigjen ndaj mjekimit kurse gjinia femer, HCVRNA e ulët ne baseline, BMI<27 mund te konsiderohen si faktorë parashikues pozitivë në SVR

Fjale kyce: Hepatiti kronik C, gjenotipi 1b, përgjigje ndaj mjekimit

Original scientific paper

A COMPARING THE TREATMENT OF PAIN WITH CONTINUOUS EPIDURAL ANALGESIA VERSUS SYSTEMIC ANALGESIA IN PATIENTS WITH HIP FRACTURE

СПОРЕДБА НА ТРЕТМАНОТ НА БОЛКА СО КОНТИНУИРАНА ЕПИДУРАЛНА АНАЛГЕЗИЈА НАСПРОТИ СИСТЕМСКА АНАЛГЕЗИЈА КАЈ ПАЦИЕНТИ СО СКРШЕНИЦА НА КОЛК

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ABSTRACT

Introduction: The systemic postoperative analgesia is unefficient in most of the patients with hip fracture, which is the reason for pain, especially during leg movement.

The aim of this study was to compare the effect of continuous epidural analgesia versus sistemic analgesia, as a pre- and post operative analgesia in patients with hip fracture.

Methods: Sixty patients with hip fracture were included and were randomly assigned to two groups of 30 patients: SA group –patients with sistemic analgesia; and EDC group - patients with a continuous epidural analgesia. In all patients pain intensity was measured at rest and passive hip flexion by using VDS (0 – 4) in several intervals: 1 and 12h before surgery, after analgesic treatment and 24 and 48 hours after intervention. The motor blockade was measured at the same times only in patients from EDC group, along with the side effects in both groups.

Results: The values of VDS were significantly lower in patients from EDC group versus patients from SA group in rest and movement in all time intervals for $p<0.05$. Motor block was 0 in all patients from EDC group according to modified Bromage score. Registered side effects were sedation, dizziness itching and urine incontinence.

Conclusion: Pain relief in pre- and post operative period has been superior in EDC group versus SA group at rest and movement in patients with hip fracture.

Key words: postoperative analgesia, epidural anesthesia,hip fracture.

INTRODUCTION

Hip fractures occur most commonly in elderly individuals as a result of minimal trauma and vertical falls (1). Hip fractures cause a significant pain in the preoperative and postoperative period, which increases in an attempt to move the injured or operated leg (2). Systemic analgesia as a multimodal analgesia with an opioids, paracetamol and non-steroidal anti-inflammatory drugs is a commonly used method of treating acute pain, as well as postoperative treatment of a hip fracture (3,4). The systematic analgesia in the postoperative period is unsatisfactorily in the majority of hip fracture patients (5). Early mobilization and early commencement of physical therapy are important factors to reduce postoperative morbidity and mortality in elderly patients (6). That is why in this age group of patients an adequate postoperative analgesia is necessary. Uncontrolled acute pain in elderly patients can cause heart, lung and endocrine disorders (7). Trauma and pain induce “a complex response to stress”, which is

characterized by hormonal and inflammatory changes that lead to immunosuppression (8). Effective analgesia in patients greatly modifies the pathophysiological response to stress, prevent or reduce postoperative complications and improves patient recovery (9).

Epidural anesthesia is a central neuraxial block with huge applicative value. As a continuous technique is used as an effective method for postoperative pain relief (10). Epidural anesthesia can be used as sole anesthetic for procedures involving the lower limbs, pelvis, perineum and lower abdomen (11,12). The advantage of epidural anesthesia is the ability to maintain continuous anesthesia after placement of an epidural catheter, thus making it suitable for procedures of long duration (13,14). This feature also enables the use of this technique into the postoperative period for analgesia, using lower concentrations of local anesthetic drugs or in combination with different agents (15). Treatment of pre- and post-operative pain with epidural application of local anesthetic and opioids in patients with hip fracture is essential because, continuous epidural analgesia provides sympatholysis and relieve pain (16,17), and thus reduces the incidence of cardiac and lung complications comparing with systemic opioids administration (18,19).

The aim of this study was to compare the quality of pre- and post operative analgesia with continuous epidural versus sistemic analgesia in patients with hip fracture.

MATERIAL AND METHODS

This study was conducted as a prospective, randomized, controlled clinical study at the University Clinic for Traumatology, Orthopedics, Anesthesia, Reanimation and Intensive Care and the Urgent Center in Skopje, in the period from January 2013 to Mart 2014. Ethical approval was granted by the Clinical Research Ethics Committee of the University Clinic for Traumatology, Orthopedics, Anesthesia, Reanimation and Intensive Care and Urgent Center – Skopje and the Ethics Committee of the Faculty of Medicine – Skopje. Informed consent was obtained from every patient.

Inclusion criteria for the study: the study included 60 patients older than 65 years and ASA II - IV, surgically treated due extracapsular hip fracture (fracture femoris pertrochanterica, fractura femoris subtrochanterica, fractura basocervicalis femoris – for a fixation with DHS or DCS plate).

Exclusion criteria for the study: malignancy; dementia / confusion; history of coagulopathies; local anesthetic allergy or allergy on tramadol and local lumbar infection where block was intended to be performed.

Preoperatively, the following demographic characteristics were registered in all patients: age, gender, body weight (kg), ASA status (classification according to the American Society of Anesthesiologists), duration of surgery, and diagnosis (fractura femoris pertrochanterica, fractura femoris subtrochanterica fractura basocervicalis femoris).

After the admission on traumatology clinic, patients were randomly divided into 2 groups, each one consisting of 30 patients, depending on the method of postoperative analgesia: SA group - patients pre and postoperatively pain-released with sistemic analgesia (niflam 2 x 100 mg/ iv and tramadol 1 mg/kg/iv every 8 h); and EDC group - patients pre- and postoperatively pain-released with continuous epidural analgesia.

In patients randomized to epidural analgesia, an epidural catheter was inserted in the lateral decubitus position into the lumbar epidural space at the L2–L3 or L3–L4 interspace by loss of resistance method. A 3-ml test dose of 0,5% bupivacaine was then administered. This intervention was performed in recovery room and after the ending of the procedure, the patients were transferred to traumatology ward. Pre- and post operatively, pain relief was provided with bupivacaine 0,125% - 5ml/h and fentanyl 3μg/ml. Epidural bupivacaine (0.125%, 5 ml) was administered when pain relief was inadequate (visual descriptive scale score > 1). In patients with sistemic analgesia, 100 mg niflam was administered when VDS > 1 (moderate pain) and if the pain still persisted in the next 30 min. and tramadol 50mg.

Two hours before surgery patients were sedated with 5 mg diazepam. The surgery in patients from SA group was performed in spinal anesthesia with 2.5 to 3 ml 0.5% bupivacaine in L2 - L3 or L3 - L4 – intervertebral space, while, in patients from EDC group in epidural anesthesia by adding intermittently 5ml 0,5% bupivacaine and fentanyl. The surgical anesthesia was considered effective when T10 dermatome was anesthetized. Usually were used 13 – 15 ml bupivacaine 0,5% and fentanyl 0,05 – 0,1 mg. ECG, heart rate, peripheral oxygen saturation, and non-invasive pressure were per operatively routinely monitored. After surgery, patients were transported into the recovery room for 2 hours. Once the patients were pain released, they were transported to the traumatology ward.

The degree of analgesia was monitored pre-operatively 1h and 12h after the administration of the analgesic agent and 24h and 48h post-operatively in patients from both groups and was assessed by using Verbal Descriptive Scale (0 - without pain, 1 - moderate, 2 – moderate to severe, 3 – severe, and 4 - unbearable pain). The degree of analgesia was assessed at rest and during passive flexion of the hip.

The motor blockade was assessed in patients from EDC group in the same time intervals as the degree of analgesia by using a modified Bromage scale (0-3): 0 = no power impairment and able to raise straight leg against resistance; 1 = unable to raise straight leg but able to flex knee; 2 = unable to flex knee but able to move ankle joint; and 3 = unable to move hip, knee, or ankle, no motor activity.

Consecutive side effects (hypotension, nausea, vomiting, sedation, dizziness, hematoma, itching, infection, catheter impassibility, ileus, urine retention and signs of local anesthetic toxicity) were noted, too.

STATISTICAL ANALYSES

Into series with numeric values and homogeneous distribution, the descriptive parameters were assessed, i.e. measures of central tendency (average, standard deviation, minimum and maximum values of the analyzed parameters). Into series with attribute marks, the structural percentages were calculated (relations, proportions). For determination of significant differences, the independent sample tests were utilized, depending on data distribution (Chi-square test, Yates corrected Chi-square test, Fisher exact test, Kolmogorov-Smirnov test, t-test for independent samples, Mann-Whitney U test and the difference between two proportions). Statistically significant and meaningful were values of p <0. 05, and highly significant values of p <0. 01.

RESULTS

Basic demographic characteristics of patients are shown in Table 1.

Tab. 1 Demographical characteristics

	SA	EDC	p level
Gender men/women	20 / 10	25 / 5	0,14
Age (years)	77,63±6,4	80,23±5,2	0,09
Body weight (kg)	67,97 ± 8,6	68 ± 9,1	0,99
ASA status III, IV	20/10	21/9	0,82
Type of fracture pertr/ subtr/basocerv	25/2/3	23/4/3	0,09
Duration of surgery (min)	111,5 ± 11,1	98,67 ± 8,4	0,005

There were no significant differences in distribution of all demographic characteristics between patients in both groups. Both analyzed groups were homogenous considering all demographic characteristics except the surgery duration (Table 1). Pain relief by continuous epidural analgesia is connected with shorter duration of surgery vs. sistemic analgesia because the patients from EDC group were operated under the epidural anesthesia which was already performed, while the patients from SA group were anesthetized with spinal anesthesia which was performed in operating theater. Female respondents dominated in both groups. This was due to the higher incidence of osteoporosis in women than men.

The analgesia degree among respondents at rest as well as during passive hip flexion up to 1 and 12 hours pre operatively after analgesic treatment and 24 and 48 hours post operatively are shown on figure 1 and figure 2. As it can be seen, there is a significant difference in pain relief between both groups at rest and during passive hip flexion at all times, except at 12h after analgesic treatment at rest. Respondents from EDC group had better analgesia versus respondents from SA group, at rest (p<0,05), as well as during passive hip flexion (p<0,01) in all time intervals. Statistical analyses are shown in table 2 and 3.

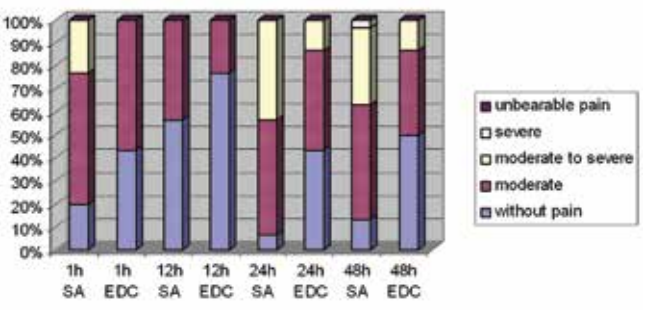

Figure 1. VDS (Verbal descriptive scale) at rest

The analgesia degree among respondents at rest up to 1 and 12 hours pre operatively after analgesic treatment and 24 and 48 hours post operatively.

Table 2. Mann – Whitney U test for VDS at rest

1h	SA vs. EDC	Z=1.92	p=0.044
12h	SA vs. EDC	Z=1.33	P=0.18
24h	SA vs. EDC	Z=3.24	p=0.0011
48h	SA vs. EDC	Z=2,92	p=0.003

Statistical analyses of analgesia degree at rest.

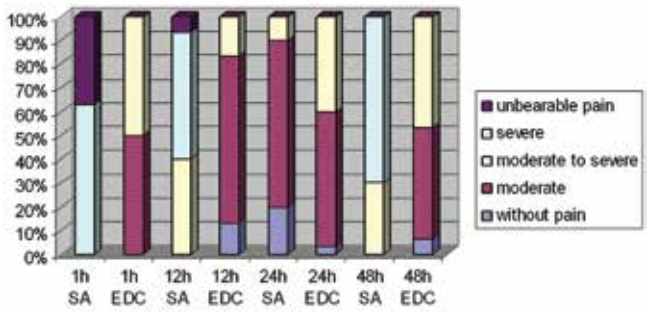

Figure 2. VDS (Verbal descriptive scale) during passive hip flexion

The analgesia degree among respondents during passive hip flexion up to 1 and 12 hours pre operatively after analgesic treatment and 24 and 48 hours post operatively

Table 3. Mann – Whitney U test for VDS during passive hip flexion

1h	SA vs. EDC	Z=6.65	p=0.000
12h	SA vs. EDC	Z=6.21	P=0.000
24h	SA vs. EDC	Z=6.12	P=0.000
48h	SA vs. EDC	Z=5.72	p=0.000

Statistical analyses of analgesia degree during passive hip flexion.

The motor blockade in all patients from EDC group in all four time intervals was 0 = no power impairment and patients were able to raise straight leg against resistance, according to modified Bromage scale.

Certain number of patients provoked unwanted side effects such as sedation, dizziness, itching and urine retention (Figure 4). Itching and urine retention have occurred in 4 (13,3%) respectively 3 (10%) of the patients from EDC group. Sistemic analgesia, significantly more often has resulted in dizziness and sedation ($p < 0.05$) compared to continuous epidural analgesia (table 4).

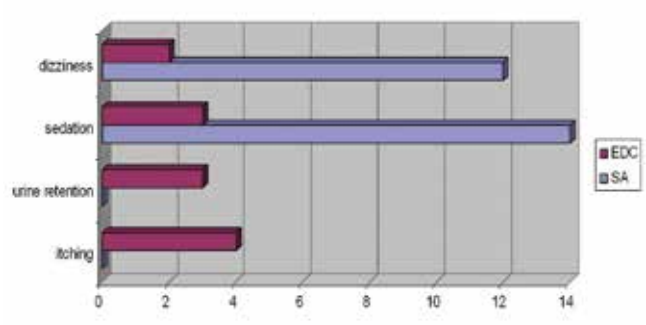

Figure 3. Consecutive side effects

Table 4. Statistical analyses of side effects

	dizziness	sedation
SA group	12 (40%)	14 (46.6%)
EDC group	2 (6,67%)	3 (10%)
Yates corrected Chi-square	2.66	4.2
P	0.04	0.01

DISCUSSION

The results of the study indicate that the continuous epidural analgesia is highly superior versus sistemic analgesia in elderly with hip fracture, at all time intervals at rest, and passive hip flexion. Arnstein (8) emphasizes the need for pain relief to patients, because uncontrolled pain can lead to negative consequences such as the occurrence of cardiac complications in patients with high per operative cardiac risk. Hwang et al (5) found that the patients with a hip fracture who were admitted to the emergency department had often unsatisfactory pain relief. Kehlet and Dahl (6) and Morrison et al (7) indicate the necessity of effective analgesia in patients with a hip fracture and came to the conclusion that in this way, the length of hospital stay is reduced and functional recovery and long-functional outcome of the patients is improved. Superiority of continuous epidural analgesia versus systemic analgesia in elderly patients with hip fracture is proven also in studies of Minville et al (12), Parker et al (14), Block et al (10) and Matot et al (18).

In this research, additional analgesia in both groups of participants was not recorded and statistically analyzed because the patients from two groups received different types of additional analgesia. In patients from EDC group, when they felt moderate pain, as additional analgesia was applied by epidural catheter 5 ml local anesthetic and an opioid, while in patients from SA group was administered Niflam 100 mg, and if the pain still persisted after 30 min. and Tramadol 50 mg. Tramadol was applied intravenously at every 8 hours. This choice for systemic analgesia was made because higher doses of opioids could lead to reduced oxygen saturation and respiratory depression, especially in the elderly (5). This technique of systemic analgesia is used in our institution as standard analgesia and therefore we wanted to compare this standard technique with continuous epidural analgesia.

The examination of the motor blockade of the lower limbs in patients from EDC group showed completely preserved

motor action. This finding as well as highly satisfactory analgesia allows physical rehabilitation in the early post operative period. Simon et al (15) and Block et al (10) as well as the results obtained in our study, found that the placement of an epidural catheter is successful and effective in 100% of respondents and is followed by loss of sensation and preserved motor activity in the lower limbs.

Veering (11), Minville et al (12), Parker et al (14) and Block et al (10) investigated the epidural technique as a choice of anesthesiology technique and postoperative analgesia as well, versus systemic anesthesia and analgesia and at the same time, they assessed the side effects of both techniques of anesthesia and analgesia. The major complication like a systemic toxic effect of local anesthetic was not noted in any patient. The most often registered side effect was hypotension, itching and retention of urine. Veering (11) investigated regional anesthesia in elderly patients and as a negative site of this technique is described the difficulties in performing spinal and epidural anesthesia, especially because of the degenerative changes of the spine that develop over the years. As an unwonted side effect, is hypotension (11), which is more pronounced in a single application of a local anesthetic. According to the results of these studies, in our study the side effects more often occurred in patients with systemic analgesia. Respondents who received continuous epidural analgesia, in rare cases felt dizziness, sedation, urine retention and itching.

In our research, epidural catheter was placed early in the pre operative period, so the patients could receive satisfactory analgesia in pre- operative as well as post operative analgesia. It is still not clear the mechanism by which early administration of epidural analgesia reduces the post operative complications. Although there is little evidence that the stress response leads to increased morbidity, there are a several undesirable physiological effects modulated by the stress response. In several studies such as studies of Christopherson et al (19), Blomberg et al (17) and Yaeger et al (13) is found that stress can lead to increased risk from thrombosis and to increased release of cytokines and neuroendocrine hormones, which can cause vascular thrombosis and cardiac morbidity due to a decrease in the oxygen supply or increased myocardial oxygen demand. Early performed continuous epidural analgesia and local anesthetics and opioids administration, in the post operative period in elderly with much co-morbidity, can lead to the suppression of the stress response, reducing the incidence cardiac morbidity and mortality compared to systemic administration of opioids (9). Norris et al (16) have investigated the impact of continuous epidural anesthesia combined with general anesthesia and postoperative epidural PCA (patient controlled analgesia) versus general anesthesia and postoperative systemic analgesia in patients with abdominal aortic surgery in terms of length of hospital stay and quality of analgesia, and came to the conclusion that epidural anesthesia and analgesia has no advantages or disadvantages versus general anesthesia and analgesia. Unlike Norris et al (16), Yaeger et al (13), who examined the effect of epidural anesthesia, and analgesia versus general anesthesia and systemic analgesia in a high-risk group of surgical patients, found that patients with epidural anesthesia and analgesia have highly significant lower rate postoperative complications, lower incidence of cardiac complications and postoperative infections. Also, in this group of patients were defined decreased cortisol level eliminated in urine versus the group of patients with systemic analgesia and anesthesia.

CONCLUSIONS

Continuous epidural analgesia provides superior and prolonged pre- and post operative analgesia versus sistemic analgesia with less unwonted side effects in elderly patients with hip fracture.

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СПОРЕДБА НА ТРЕТМАНОТ НА БОЛКА СО КОНТИНУИРАНА ЕПИДУРАЛНА АНАЛГЕЗИЈА НАСПРОТИ СИСТЕМСКА АНАЛГЕЗИЈА КАЈ ПАЦИЕНТИ СО СКРШЕНИЦА НА КОЛК

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АПСТРАКТ

Вовед: системската постоперативна аналгезија е незадоволителна кај најголемиот број од пациентите со скршеница на колкот, што е причина за болка, особено при обид за движење на повредената нога.

Целта на оваа студија беше да се спореди влијанието на континуираната епидурална во однос на системската аналгезија, како пред и постоперативна аналгезија кај пациенти со скршеница на колк.

Методи: во оваа студија беа опфатени 60 пациенти со скршеница на колк и беа рандомизирано поделени во 2 групи од 30 пациенти: СА група – пациенти кои примаа системска аналгезија; и ЕДК група – пациенти кои беа обезболувани со континуирана епидурална аналгезија. Кај сите пациенти беше регистриран интензитетот на болката при мирување и при пасивна флексија на колкот, со користење на Вербална дескриптивна скала (ВДС, 0 – 4), во неколку временски интервали: 1 и 12 часа пред оперативниот зафат, после третманот со аналгетик, и 24 и 48 часа после хируршката интервенција. Моторната блокада беше мерена во истите временски интервали само кај пациентите од ЕДК групата, како и несаканите дејства во двете групи.

Резултати: Вредностите на ВДС беа значајно пониски кај пациентите од ЕДК групата наспроти испитаниците од СА групата и при мирување како и при пасивна флексија на колкот во сите временски интервали за $p<0.05$. Моторниот блок беше 0 кај сите пациенти од ЕДК групата во согласност со модифицираниот Bromage скор. Регистрирани несакани дејства беа седација, вртоглавица, чешање и ретенција на урината.

Заклучок: Пред и постоперативното обезболување е супериорно во ЕДК групата наспроти СА групата во мирување и при движење кај пациенти со скршеница на колк.

Клучни зборови: постоперативна аналгезија, епидурална анестезија, скршеница на колк.

Original scientific paper

URINARY STONE DISEASE IN CHILDREN OF ELBASAN - A SINGLE CENTER EXPERIENCE

GURËT E VESHKAVE TEK FEMIJËT E ELBASANIT- EKSPERIENCA E NJË QENDRE

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ABSTRACT

Introduction: Nephrolithiasis is not a rare event in children.It can lead to important consequences such as renal dysfunction and recurrent stones. We aimed to study the incidence, etiology, clinical and biological charachteristics in children with urolithiasis.

Material and methods: From 2003-2014, we studied 94 children (37 girls) with average age 7.9 years old, presented with kidney stone in ultrasonography. Laboratory studies included serum biochemistry, 24 urine volume and electrolites, pH and urine culture. Also data refering to their famile history for urolithiasis, dietary habits and liquid intake were gathered.

Results: The incidence of kidney stones in children is 0.047%, devided in two periods the incidence shows an increase which is 0.045% (2004- 2009) and 0.05% (2009-2014). The M/F ratio is 1.5 :1. The most effected age is above 10 years old (58.5%), but the study showed that above 10 M/F ratio is 1.08:1 . Positive family history for kidney stones is identified in 45% of the total. Urine volume was less that the average in 37 children or 39.4%. Calcium /creatinine ratio average is 2.009 and Sodium/potassium ratio average is 11 in the children with hypercalciuria. Calcic stones are presented in 65 %.

Conclusion: The incidence of kidney stones in children of Elbasan is 0.047% and it is increasing. The most effected age is above 10 years old. Hypercalciuria is an important metabolic cause.

Key words: Nephrolithiases, Calciuria, Metabolism, Incidence

INTRODUCTION

Renal calculoses disease is a veteran, whose clinic is described in the aphorisms of Hippocrates. This pathology represents one of the most widespread diseases in the human race. It is a disease that mainly affects men, and male female ratio varies from 3: 1 to 1: 1.

Some races as for example black, it is not affected. Probability of urinary stone formation is 1-5% in Asia, 5-9% in Europe, 13% in North America, 20% in Saudi Arabia (3.19). The most affected age with renal calculoses peaks at 4 years olders and also teenagers. Kidney stones are aggregate crystals mixed with a protein matrix that causes obstruction of urinary flow and consequently pain, bleeding, and local erosion of renal tissue. (19)

In general crystallization of stone-forming salts owes an abnormal urinary composition which is rich in promoters of crystallization (Calcium Oxalate,uric acid) or poor in crystallization inhibitors (citrate, glycosaminoglycans, kidney proteins such as nefrokalcin, Tamm --Horsfall mucoprotein, uropontine) or both. (2,4,19)

Litogeneses first event is the formation of a microcrystaline, which grows in size and aggregates with crystals of the same nature or with heterogeneous

crystals (ex. phosphate of calcium or urate of sodium). This is the stage of nucleacion which is followed by the second stage or the adhesion of these particles in urinary epitelium and the third stage is the transformation in calcul. (1,3,4).

LITOGENESES

Litogeneses is controlled by three factors:

1. Urine saturation that depends on the concentration or activity of the ions that form calcul. Increasing the concentration of these ions come from increased urinary debit of these substances or by reduction of urinary volume (4,7,9,11).
2. Promoting factors of crystals including:Calcium,Sodium,Oxalate, urate, cysteine, Low urine pH, Tamm - Horsfall protein, Lower urinary flow, Bacterial products.
3. Crystallization inhibitors (1,4,5): They are abundant in urine: They are devided in: organic; Nephrocalcin.Tamm - Horsfall protein ,Urinary prothrombinfragment,Inter α inhibitor,Glycosaminglycans, High urinary flow and inorganic Magnesium , Pyrophosphate , Citrate. Urinary pH also plays an important role in litogeneses. Its lowering favors precipitation of cistine and uric acid. His growth favors precipitation of calcium and phosphates. Urinary pH has an esencial role in inhibitor and promoter interactions. The incidence, composition and clinical characteristics of urinary calcul in children varies from one country to another and from one historical period to another.(2)

PURPOSE OF THE STUDY

1. Study the frequency, distribution and determinants of renal calculose in children of Elbasan.
2. Study the relevant elements of calculose.
3. Study the evolution of the incidence between the two five-year.

MATERIAL AND METHOD

Our study has been extended to 11 years experience at our hospital in children with renal calculosis.

In the period from 2004 to 2014 we examined 94 children, in an average age 7.9, and 37 of them or 45.9% are female. The ratio male/ female is 1.5. In the study were included children who the echography resulted with renal calculosis. 65 children or 70.2% came to the hospital with the followign complaints: hematuri, urinary infection, abdominal pain. 28 children or 29.8% were selected by the routine examination in ultrasonography.

All children underwent laboratory and radiological examinations.

In their blood we examined the electrolytes: calcium, potasium, sodium,blood urea nitrogen, creatinine, uric acid.

For all children urinary volume of last 24 hours was measured and calciuria, creatinuria, natriuria, caliuria, phosphaturia, magnesuria were analysed.

In fresh urine pH was measured and for all urine was conducted the uroculture to isolate the causative microbe of UTI, particularly in cases of repeated UTI

Since there are considerable differences in calcium excretion during 24 hours, for all children the ratio Ca / Cr and the ratio Na / K was calculated.

All children underwent ultrasound where initially renal calculosis was present.

Knowing renal stasis associated with congenital ureteropelvic junction obstruction, can contribute to the formation of stones, all children in addition to the ecography underwent UIV analyses.

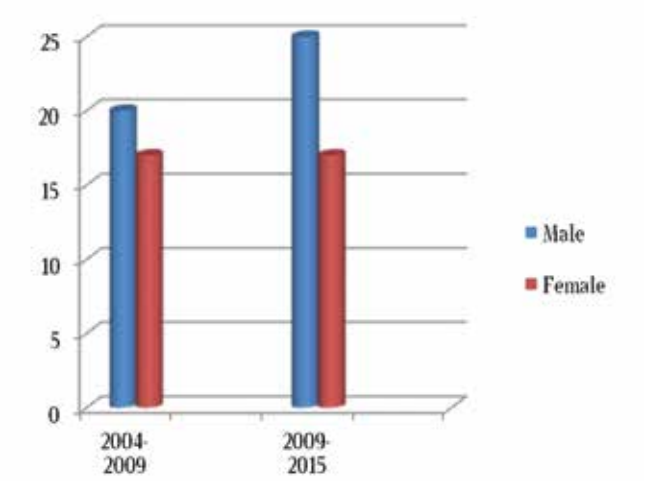
Intravenous urography was performed with contrast uroraphine 60% or 76% based on body weight and age. Through this examination we could search for other calculi, could notice urologic abnormalities, to judge the degree of obstruction and renal damage.

20 of these children did the stone spectral analysis with infrared spectroscopy . The dry stone benefited from litotomia or from his appearance in urine was analyzed by spectroscopy with infrared beam which is useful for the identification of non-crystalline including amorphous substance and metabolites of drugs that are not identified by other techniques . In anamneses all children were evaluated for family antecendente regarding calculosis, the diet, the amount of liquids consumed in 24 hours.

RESULTS

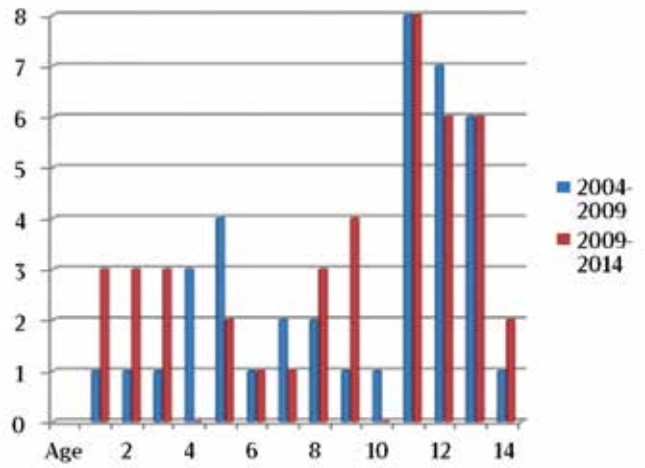
1. The Incidence of renal calculosis in Elbasan district is 0.047%
2. It was observed that children had dietary habits that favor calculoses (pickled vegetables and beans were dominant in their menu)
3. Of the 94 children presented, 37 of them or 39% are female and 57 or 61% male . Male/ female ratio is 1.5.

Male /Female Ratio



4. From the group of children in the study the age over 10 years predominates 58.5%, and the ratio male / female in this age is 1.008: 1

The most effected age

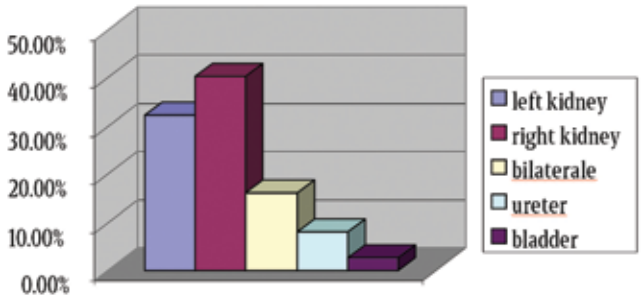


5. Given the anamneses 42 children or 45% have a positive family history for calculoses.
6. 20 cases or 21% are children with positive anamneses of recurrent urinary infections, caused by proteus, E.coli, klebesiella

   All children have a low hydro diet as a result of which the urinary debit of 24 hours is reduced, so the concentration of substances that favor urinary litiases is increased (as urine is oversaturated with these elements).
7. By ultrasonography and intravenous pyelography the stone in 84 children (89.3%) is in the upper urinary apparatus (kidney), in 10 cases or 10.6%, stone is in the lower urinary apparatus (8 in the ureter or 8.3 % and in 2 cases in the bladder or 2.1%).

In children whom the placement of kidney stone is in the kidneys 17 of them or 18% have stones in both kidneys, in 39 cases or 46% placement of the stone is in the right kidney, in 25 cases or 30% placement of the stones is in the left kidney .Ureteral stones and bladder were found in children over 10 years old.

Stone localization



By intravenous urography 12 children resulted with born anatomical defects , which are positive factors for renal calculoses.

(12 cases or 12.7 % with RVU)

14 of the children or 15 % resulted in multiple stones .

80 others or 85 % resulted in only stones .

8 - From laboratory examinations azotemia, creatinemia, natremia, kalemia resulted in the norms.

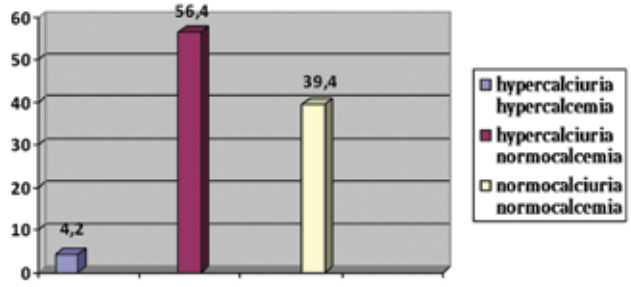
In four cases resulted an increased calcemia (4.2 %) .

From examinations made to the urine of 24 hours 53 children or 56.5 % result in hypercalciuria where 4 of them have simultaneously hypercalcemia .

In 4 children or 4.2% we detected hypercalciuria hypercalcemia.

In 53 children or 56.4% we detected hypercalciuria, normocalcemia.

Normocalciuria normocalcemia is detected in 37 children or 39.4 %



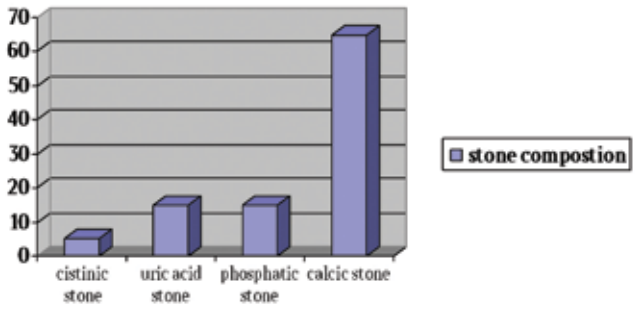
In 100 % of cases the ratio Ca / Cr in urine was higher than the norm (> 0:22), a factor that shows the highest elimination of calcium in urine in favor of ranal calculoses. The average ration Ca / Cr by examinations resulted 2. 009.

In all children caliuria in the urine of 24 hours results below the norms, a factor that shows the poor diets, dehydration (or lower urinary debit) and the tendency to calciuria. The average ratio Na / K resulted in 11. 049 % (norm < 2) , a date that reinforces hypocalciuria .

Ph in fresh urine in 38 children or 40.5 % was above 6.5 which means that calcium lithiases is favored .

In 20 of the cases we did the infrared spectroscopy analysis which showed that the composition of the stone is :

- one case was found cistinic stone (cistinuria) 5 %
- three cases was found uric acid stone containing anhydride (uric acid stone) 15 %
- three cases was found carbapatit stone , struvit (phosphatic stone) 15 %
- five cases was found calcium monohydrate stone + Apatit (phosphocalcic stone) 25 %
- three cases was found calcium dihydrate stone (calcic stone) 15 %
- In five cases calcium monohydrate stone (calcic stone) 25 %



Only in 7 children or 7.4 % examination of the thyroid gland was realized before where PTH was within the norm (for economic reasons other children did not realize this examination).

DISSCUTION

Our study shows that the incidence of renal calculoses in Elbasan District in an 11-year period (2003- 2014) is 0.047%, this figure can not be compared with the data obtained from references because the incidence is calculated for the entire population and not only pediatric (1,2,3,4,19).

Male / female ratio according to our study results 1.5. According to references this ration rangs from 3/1 to 1/1 (2.19).

So male /female ratio in our study is consistent with the male/ female ratio of references.

The predominant age group in our study is over 10 years old in 70% of cases. The most effected ages are 11,12,13 years old. This fact is consistent to some extent with our references as the peak age of calculoses is mentioned the age 4 years and puberty (2).

The study that was done in children with calculoses in our case turns out that they have more than one risk factor that leads to renal lithiasis (19). These includes:

- positive familiarity with calculoses
- diets with much salt and overloaded with calcium products
- low hydro volume consumed in 24 hours due to decreased urinary debit in 24 hours.

  IVU repeated, caused by proteus, E.coli, Klebsiella.

  hypercalcaemia

  hypocalcuria

  Ca / Cr> 0:22 , Na / K> 2(1.2.3.10.14.19)

Positive Familiarity with calculoses is found in 42 cases, or 45% in our study. This factor is positivie in references 3, 5.19. In his article Joel MHTeichman quotes: 55% of those who have recurrent stones have a family history for urolithiases and having that history increases the risk of stone formation.

Diets overloaded with calcium and salt products and low hydro volume consumed during 24 hours observed in children or 51.3% of the calamity which actually almost the same percentage of 59.7% (3.7) because the excess of calcium intake.Alimentary and animal protein which increase bone absorption and lower tubular absorption of calcium (from loads of bringing them acids) increase calciuria.

Roswitha Siener, Natalie Schade, Claudia Nicolay in their article state: A low volume of liquids consumed and greater use of animal protein are indetified as the most important risk of dietary factors.

IVU repeated caused by bacteria Proteus, Klebsiella E.coli that produce characteristic ureazis in phosphate stones which were found as a risk factor for calculoses in 21% of our cases. This fact was found positive but is not shownas a percentage in our results. (1,2,3,4,10)

Cases with hypercalcemia who make up 4.2% in our study are positive factor in calcic calculoses. (1,4,19)

In our study 53 cases or 56.5% of children result with hypocalciuria. The ratio Ca / Cr in urine varies 2.009 and the ratio Na / K varies 11,049 for all children. This three data show hypocalciuria, a fact that is consistent with our references under which hypocalciuria is the cause of renal calculoses in 61% of cases. (19.4)

According to the ultrasound and UIV placing of stones is greater in the upper urinary apparatus, si in kidneys and in all cases we found renal calcic (89.1%). In the right kidney there are 39 cases or 46% and stone setting is bilateral in 18% of cases. This result is consistent in part with references where placement of the stone is more common in the left kidney (2) result which is not consistent with our result and bilateral placement of the stone is 15% (2) approximates the result of our study.

From the spectral analysis of the stones in 65% of cases the stone is calcic so predominant, a result that is consistent with references (1,4,19) where calcic stone occupies 71% of cases. The percentages of other stones which are cistinike 5%, ac.uric 15%, 15% phosphate stones, in each case do not match the references under which uric acid stone occupies 6%, 3% cistinik stone and rock phosphate 20%.

CONCLUSIONS

1. The incidence of renal calculosis in children of Elbasan is 0.047%.
2. The most effected age is above 10 years old.
3. Hypercalciuria is an important metabolic cause.
4. Calcic stones predominate in more than 65 %

RECOMANDATIONS

1. Children diets should be rich and eliminate unilateral diet. Reduce dietary habits rich in animal protein and salt.
2. Increase the amount of liquids consumed during 24 hours.
3. Perform early examination of these children especially in cases where hereditary factor is evident.

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GURËT E VESHKAVE TEK FEMIJËT E ELBASANIT- EKSPERIENCA E NJË QENDRE

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ABSTRAKT

Hyrje: Nefrolitiaza nuk eshte nje ngjarje e rralle tek femijet. Ajo mund te sjelle pasoja te rendesishme si insuficensa renale dhe guret e perseritur. Qellimi yne ishte studimi I incidencës, etiologjise dhe karakteristikave biologjike dhe klinike te femijeve me urolitiaze.

Materiali dhe Metoda: Nga viti 2003 -2014 ne studiuam 94 femije (37 vajza) me moshe mesatare 7.9 vjeç te paraqitur me gure ne ekografi . Studimet laboratorike perfshine analizat biokimike, volumin dhe elektrolitet ne urinen e 24 oreve, pH dhe urokulturen. Gjithashtu u mblodhen te dhëna per histori positive familiare per kalkulozen, zakonet dietike dhe sasine e lengjeve te konsumuara ne 24 ore.

Rezultate: Incidenca e kalkulozes tek femijet eshte 0.047%, e ndare ne dy periudha kohore incidenca paraqet rritje 0.045 % (2004- 2009) dhe 0.05 (2009- 2014). Raporti M/F eshte 1.5 :1. Mosha me e prekur eshte mbi 10 vjeç (58.5%), por studimi tregoi qe mbi 10 vjeç raporti M/F eshte 1.08:1 . 45 % e rasteve ka histori pozitive familjare per kalkulozen. Volumi urines 24 oreshe ishte nen mesatare ne 37 femije ose 39.4.%. Tek keta femije raporti kalçium /kreatinine eshte 2.009 dhe raporti natrium/kalium eshte 11. Guret kalçik perbejne 66 % te rasteve.

Konkluzione: Incidenca e kalkulozes renale tek femijet e Elbasanit 0.047% dhe tregon rritje ne 5-vjeçarin e fundit. Mosha me e prekur eshte mbi 10 vjeç. Shkaku metabolik kryesor eshte Hiperkalçiuria.

Fjalë kyç: Nefrolitiazë, Kalçiuria, Metabolizëm, Incidencë

Original scientific paper

EVALUATION AND MANAGEMENT OF NEONATAL INDIRECT HYPERBILIRUBINEMIA AT THE UNIVERSITY PEDIATRIC CLINIC IN SKOPJE, REPUBLIC OF MACEDONIA

ЕВАЛУАЦИЈА И ТРЕТМАН НА НЕОНАТАЛНА ИНДИРЕКТНА ХИПЕРБИЛИРУБИНЕМИЈА НА УНИВЕРЗИТЕТСКАТА КЛИНИКА ЗА ДЕТСКИ БОЛЕСТИ ВО СКОПЈЕ, РЕПУБЛИКА МАКЕДОНИЈА

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ABSTRACT

Introduction: Neonatal hyperbilirubinemia, defined as a total serum bilirubin level > 86 μmol/L, is a frequent problem affecting approximately 60% of term and 80% of preterm newborns. Clinical challenge is to differentiate between the majority of physiologically jaundiced infants and those with pathological causes, thus to establish appropriate management plan.

Objectives: Purpose of the study was to review evaluation and management of neonatal indirect hyperbilirubinemia at the University Pediatric Clinic Neonatology Department over a two year period.

Methods: Medical records of 284 newborns with indirect hyperbilirubinemia were retrospectively analyzed for history data, clinical presentation, diagnostic procedure and the therapy applied.

Results: Most prevalent was jaundice of undefined etiology (44.37%), followed by neonatal infection, prematurity, hemolysis, and birth trauma. The mean peak serum bilirubin concentration in the undefined etiology group was 333.4±91.1 μmol/l. The peak bilirubin levels and reticulocites in hemolytic jaundice were significantly higher compared to the other etiologies. The first control serum bilirubin level was significantly higher in newborns with hemolysis compared to the groups of premature newborns and jaundice of undefined etiology. Analyzed groups significantly differed according to the day bilirubin reached peak. Most cases were treated with phototherapy, and 2.11% with exchange transfusion.

Conclusions: Hyperbilirubinemia is a frequent pathology at the University Pediatric Clinic-Skopje, R. Macedonia. Most cases are treated with less severe jaundice of undefined etiology. Immediate awareness and management is required for those 15% of infants with hemolytic causes of jaundice that carry a significant risk for early and severe hyperbilirubinemia.

Key words: hyperbilirubinemia, neonate, ABO incompatibility, sepsis, prematurity, G6PD deficiency, evaluation and management, Republic of Macedonia

INTRODUCTION

Neonatal hyperbilirubinemia, defined as a total serum bilirubin level > 5 mg/dl (86 μmol/L), is a frequent problem that affects approximately 60% of term and 80% of preterm babies in the first week of life [1, 2]. About 10% of breastfed babies are still jaundiced at one month of age [1]. Generally it is considered a transitional phenomenon

without noticeable clinical impact, related to hepatic, red cell and gastrointestinal immaturity [1, 3]. However, a dangerous rise of the total serum bilirubin may cause acute bilirubin encephalopathy that frequently evolves into a chronic neurologic condition- kernicterus. Features of the latter include athetoid cerebral palsy, hearing loss, and visual and dental problems [1, 2, 4, 5].

Although both genetic and environmental factors contribute to the development of neonatal hyperbilirubinemia, the importance of genetically determined conditions has been increasingly recognized [6-8].

When serum bilirubin concentrations rise above 17 mg/dl (291 μmol/L) in full-term infants, a pathologic cause of jaundice should be sought [2, 9]. According to the mechanism of accumulation of bilirubin, causes of neonatal indirect hyperbilirubinemia are classified into:

1) bilirubin overproduction that occurs in hemolytic diseases with either positive Coombs test (ABO, Rhesus and minor blood group incompatibilities) or negative Coombs test (red blood cell membrane or enzyme defects, sepsis and some drugs). Bilirubin overload can also be expressed in non-hemolytic diseases like cephalhaemathoma, bruising, central nervous system (CNS) hemorrhage, polycythaemia and impaired gastrointestinal motility [2, 9, 10] and
2) decreased bilirubin conjugation that occurs in physiologic jaundice, Crigler-Najjar syndrome type 1 and 2, Gilbert syndrome, hypothyroidism, breast-milk jaundice and G6PD deficiency. Contrary to traditional considerations that G6PD deficiency associated neonatal hyperbilirubinemia was hemolytic in origin; it was shown that inadequate bilirubin conjugation in the liver was the main component of neonatal jaundice in this group of patients [11, 12].

The third mechanism of jaundice marked by impaired bilirubin excretion causes direct (conjugated) hyperbilirubinemia [2, 9, 10]. Neonatal sepsis can be featured by both indirect and direct hyperbilirubinemia [2].

The laboratory assessment of jaundice depends on the age of the newborn and the clinical presentation of jaundice [4, 13]. Apart from total serum or transcutaneous bilirubin measurement, certain diagnostic tests such as complete blood count and smear, reticulocyte count, ABO blood grouping and Coombs test and end-tidal carbon monoxide (corrected) levels might hasten the etiological diagnosis. Analysis of glucose-6-phosphate dehydrogenase (G6PD) and piruvate kinase deficiencies is considered in cases of positive family history and specific ethnic origin [4, 10]. Treatment options involve phototherapy and exchange transfusion when bilirubin levels exceed gestation and hour specific treatment thresholds [1, 4, 9, 13, 14, 15]. The purpose of the study was to evaluate etiology and management of indirect hyperbilirubinemia at the University Pediatric Clinic in Skopje, R. Macedonia.

METHODS AND MATHERIALS

The study group included 284 newborns who had been admitted to the neonatology department at the University Pediatric Clinic in Skopje with the diagnosis of neonatal indirect hyperbilirubinemia during the period of 2 years (January 2009- December 2010). They represented one quarter of the total number of 1126 hospitalized patients during this period. Medical records were retrospectively analyzed; all data were recorded on standardized questionnaires. Peri/neonatal history data were retrieved as follows: gender, birth weight (BW), birth length (BL), Apgar score (AS), mode of delivery (spontaneous/ cesarean section), day of jaundice emergence, peak bilirubin level and day on which bilirubin reached peak. Medical records were reviewed extensively for the following clinical signs and symptoms: cephalhaemathoma, skin bruising, ecchymoses, lacerations, sepsis, prematurity, hypothyroidism, CNS hemorrhage, intestinal atresia or stenosis, hypertrophyc pyloric stenosis, delayed meconium passage, and Down syndrome [9, 10]. Diagnostic procedure was reviewed; all laboratories and other test were recorded, also the type of therapy applied (phototherapy and/or exchange transfusion). The following tests were taken into consideration: full blood count and smear, hemoglobin and hematocrit levels, reticulocite count, serum levels of total, indirect and direct bilirubin, serum aminotransferases- aspartat transaminase (AST) and alanin transaminase (ALT), G6PD quantitative test, maternal and neonatal blood groups, direct antiglobulin (Coombs) test, C-reactive protein (CRP), and results of blood, cerebrospinal fluid and other cultures, thyroid screening test and/or thyroxin and thyroid stimulating hormone results as well as ultrasonography of CNS and radiograms [1, 2, 4, 9, 10].

Nine groups of clinical presentation of jaundice were differentiated: 1. ABO incompatibility, 2. Rhesus (Rh) incompatibility, 3. Cephalhaemathoma, bruising 4. Sepsis, 5. Prematurity, 6. Intracranial hemorrhage, 7. Hemolysis (abnormal peripheral smear, elevated reticulocite count, neither ABO nor Rh incompatibility), 8. Down syndrome

and 9. Undefined. Etiology of sepsis was assigned to newborns with a positive blood/ cerebrospinal fluid culture or positive CRP and clinical signs of infection requiring a course of antibiotic therapy. Newborns with sepsis and elevated direct bilirubin levels > 2 mg/dl (34μmol/l) or > 20% of total serum bilirubin level were excluded from the study [2].

Prematurity-associated jaundice was considered in newborns of less than 37 weeks gestational age and absence of other obvious causes of jaundice. Birth trauma was manifested with cephahaemathoma and bruising. Undefined etiology included: exaggerated physiological jaundice, early and late onset breast-milk jaundice [2, 9], and no identifiable etiology.

Full blood count was analyzed using the Sysmex K-4500 automated hematology analyzer (Minesota, USA); light microscopy was involved when analyzing blood smear and reticulocites. Total serum bilirubin and fractions were obtained using photometric chemistry analyzer Kodak Ectachem 250 (Rochester, NY) [16]. G6PD activity in erythrocytes was determined spectrophotometricaly by measuring the rate of absorbance change at 340 nm, due to the reduction of nicotinamide adenine dinucleotide phosphate (NADP) to NADPH when a sample was incubated with G6P (Humananalyser 3000, Germany). G6PD activity was calculated in relation to erythrocyte count. Commercially available kits (AMS U.K. Ltd, East Sussex, U.K.) were used. Values of 245 - 299 mU/109 erythrocytes were considered normal. The results were interpreted as percentage of the normal G6PD activity [17, 18].

Statistical analyses were performed using the statistical package Statistical Package for the Social Sciences (SPSS) 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were presented with absolute numbers and percentages whereas quantitative variables were presented with mean, standard deviation, minimum, maximum, median and rang. Testing of significance between groups regarding the analyzed parameters was performed with: Kruskal-Wallis test, Mann-Whitney U test, and Analysis of Variance.The result was considered significant if probability value (p) was <0.05 and <0.01 for high significance.

The study has been approved by an institutional Ethics Committee in accordance with the Declaration of Helsinki.

RESULTS

The subject group included 284 patients treated with indirect hyperbilirubinemia in a two year period, of which 172 (60.56%) boys and 112 (39.44%) girls. Most prevalent was jaundice of undefined etiology (44.37%), followed by neonatal infection (19.37%), prematurity (15.85%), ABO incompatibility (8.45%), Rh incompatibility (5.63%), cephalhaematoma and bruising due to birth trauma (2.82%), intracranial hemorrhage (2.46%), hemolysis (neither ABO nor Rh incompatibility) (0,35%) and Down syndrome (0,70%) (Table 1.).

Table 1. Causes of neonatal indirect hyperbilirubinemia.

Etiology	Number	Percentage (%)
Undefined etiology	126	44.37
Neonatal infection	55	19.37
Prematurity	45	15.85
ABO incompatibility	24	8.45
Rh incompatibility	16	5.63
Cephalhaematoma and bruising due to birth trauma	8	2.82
Intracranial hemorrhage	7	2.46
Hemolysis (neither ABO nor Rh incompatibility)	1	0.35
Down syndrome	2	0.70
Total	284	100

We did not find any cases of hypothyroidism, intestinal atresia or stenosis, hypertrophyc pyloric stenosis, delayed meconium passage, polycythaemia and G6PD deficiency.

The basic perinatal characteristics of the group of patients with hyperbilirubinemia are presented in Table 2.

Table 2. Basic perinatal characteristics of the hyperbilirubinemia group.

	Mean	Min	Max	M	Interquartile range
Age	11.5±9.5	1	50	8	5-15
GW	38.1±2.3	28	42	39	37-40
BW	3028.9± 599.1	1000	4500	3100	2625-3450
BL	49.3± 2.8	37	56	50	48-51

Min- Minimum; Max- Maximum; M- Median; GW- Gestation weeks; BW- Birth weight; BL- Birth length

In 44.37% of cases etiology could not be determined. When analyzing the general characteristics of this group of patients, they were found to be near term or term newborns with median (interquartile range) age

of presentation of jaundice at day 3 (3-4). They were mostly delivered spontaneously (90.47%) with normal birth parameters (BW and BL) and did not suffer major perinatal asphyxia (Table 3.).

Table 3. Basic characteristics of the undefined etiology group.

	Mean	Min	Max	M	Interqurtile range
Age	4±2.5	2	14	3	3-4
GW	39±1.2	37	42	39	38-40
BW	3247.1± 437.4	2200	4500	3245	2980-3500
BL	50.2± 1.8	46	56	50	49-51
Mode of delivery	N	%			
Spontaneous	114	90.47			
CS	9	7.14			
Vacuum extraction	2	1.59			
Forceps	1	0.8			
Perinatal asphyxia	N	%			
No	109	86.51			
AS 7	16	12.7			
AS 4-6	1	0.79			

Min- Minimum;Max- Maximum;M- Median; GW- Gestation weeks; BW- Birth weight; BL- Birth length; CS- Cesarean section; AS – Apgar score

In the undefined etiology group, the peak bilirubine level was registered at median (interquartile range) day 9 (6-17). The median (interquartile range) of the peak bilirubin level was 324 (270-394) μmol/l with a mean peak serum bilirubin concentration of 333.4±91.1 μmol/l.

For the purpose of statistical analyses different presentations of hyperbilirubinemia were grouped into five etiological groups as follows:

1. Hemolytic etiology of jaundice including ABO incompatibility, Rh incompatibility, and hemolysis (neither ABO nor Rh incompatibility)
2. Neonatal infection/sepsis
3. Prematurity
4. Hematomas (cephalhaemathoma, bruising, intracranial hemorrhage) and
5. Undefined etiology

Following laboratory parameters were analyzed:

Peak bilirubin level

Mean peak bilirubin levels in newborns with jaundice showed high statistical correlation to the etiological cause of jaundice. Mean peak bilirubin levels in newborns with hemolysis (group 1) were statistically significantly higher than levels in the groups with neonatal infection, prematurity and hematomas (groups 2, 3 and 4) (Table 4).

Table 4. Peak bilirubin level (μmol/l) Mean peak bilirubin levels in group 1 were statistically significantly higher than levels in the groups 2, 3, and 4.

Etiology groups	Mean	N	SD	p
1. Hemolysis	379.75	41	133.55	
2. Neonatal infection	315.23	55	106.15	0.015
3. Prematurity	299.80	45	81.40	0.002
4. Hematomas	291.73	15	90.46	0.03
5. Undefined	333.44	126	91.11	NS

N- number of patients; SD- standard deviation; p- probability value; NS- not significant

Day of bilirubin peak

Analyzed groups of newborns with jaundice showed high statistically significant difference according to the day when bilirubin level reached peak. Differences were marked between the third group in comparison to groups 1, 2 and 4, as well as between groups 2 and 5 (Kruskal-Wallis test: H (4, N= 282) =28.84943 p=.0000; 1/3 p=0.01; 1/5 p=0.04; 2/3 p=0.00005; 2/5 p=0.005; 3/4 p=0.0008) signifying earlier bilirubin peak in hemolysis, infection and cephalhaemathoma/bruising compared to prematurity.

First control bilirubin

The first control serum bilirubin level was significantly higher in newborns with hemolysis compared to the levels determined in the groups of premature newborns and jaundice of undefined etiology (Table 5.).

Table 5. First control bilirubin (μmol/l) The first control serum bilirubin level was significantly higher in newborns of group 1 compared to groups 3 and 5.

Etiology groups	Mean	N	SD	p
1. Hemolysis	274.20	40	124.85	
2. Neonatal infection	242.77	45	99.26	NS
3. Prematurity	190.04	41	61.37	0.000258
4. Hematomas	212.42	14	79.32	NS
5. Undefined	227.39	112	80.68	0.038

N- number of patients;SD- standard deviation;p- probability value;NS- not significant

Second control bilirubin

Analyzed groups of newborns showed statistically insignificant differences in the second control bilirubin measurement.

Amynotransferases- AST and ALT

Levels of hepatic transaminases were not found to depend significantly on the etiology of jaundice.

Hemoglobin (Hb)

Mean hemoglobin levels showed marked statistical differences among the five analyzed groups of newborns. Post hoc analysis confirmed with high statistical significance higher mean values of this parameter in the group of infection compared to the hemolysis group (p=0.01) and compared to the group of premature newborns (p=0.001). Also statistically significant higher levels were noted in the group of newborns with undefined etiology compared to the premature newborns (p=0.036) (Table 6.).

Erythrocytes (Er)

Different etiological groups of jaundice showed high statistically significant difference regarding the mean erythrocyte levels. Newborns with undefined etiology had significantly higher erythrocyte levels compared to hemolytic etiology (p=0.017), also high statistically significant difference compared to the premature newborns (p=0.0008). Newborns of group 2 showed high statistical differences compared to groups 1 and 3 (Table 6.).

Hematocrit (Hct)

Mean hematocrit levels depended significantly on the etiology of hyperbilirubinemia. Highest mean values of this parameter in newborns with infection were significantly higher than the hemolytic group (p=0.016) and highly significantly higher compared to the prematurity group (p=0.001). Newborns of group 3 have markedly lower levels of hematocrit compared to group 5 (p=0.03) (Table 6.).

Table 6. Hematological parameters in neonatal hyperbilirubinemia

	Varaible (mean±SD)	Groups 1-5				
		Hemolysis	Infection	Prematurity	Hematomas	Undefined
	Hb (g/l)	155.02±30.26	173.03±24.45	152.02±29.38	168.26±23.93	165.35±26.46
Post hoc Tukey HSD test: significant at p < .05	1		0.01			
	2	0.01		0.001		
	3		0.001			0.036
	4					
	5			0.036		
	Er (x1012)	4.29±0.77	4.82±0.60	4.21±0.73	4.62±0.71	4.66±0.63
Post hoc Tukey HSD test: significant at p < .05	1		0.001			0.017
	2	0.001		0.00006		
	3		0.00006			0.0008
	4					
	5	0.017		0.0008		
	Hct (%)	41.35±8.99	46.24±6.61	40,47±8.18	46.02±8.36	44.26±7.19
Post hoc Tukey HSD test: significant at p < .05	1		0.016			
	2	0.016		0.001		
	3		0.001			0.033
	4					
	5			0.033		

Hb- hemoglobin ; Er- erythrocytes ; Hct- hematocrit

Reticulocites (Ret)

Reticulocite count differed highly significantly between etiology groups. Significant differences were noticeable between the first in comparison to the 2, 3, and 4th group, as well as between newborns of the 2 and 3rd group (Kruskal-Wallis test: H (4, N=281) =33.92498 p=0.0000; 1/2 *p=0.000001; 1/3 *p=0.014; 1/4 *p=0.008; 1/5 *p=0.0026; 2/3 *p=0.00017 *p Mann-Whitney U Test) (Figure1).

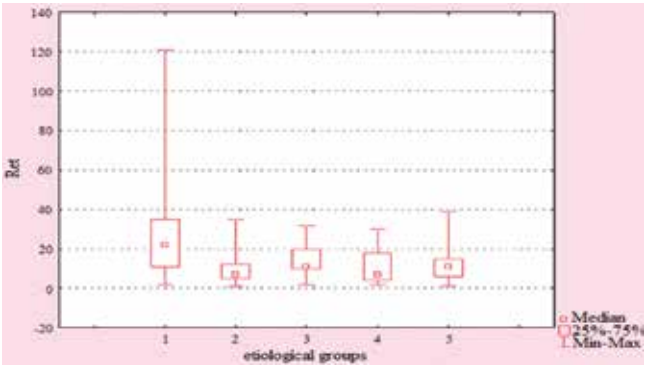

Figure 1. Reticulocite count in hyperbilirubinemia groups.

Treatment of jaundice was performed according to current protocols with phototherapy/ and or exchange transfusion [1, 4, 9, 13, 14, 15, 19, 20, 21]. The vast majority of cases (97.89%) were managed conventionally using double surface (overhead and underneath) blue light phototherapy lamps at wave length of 460 nm. Six patients (2.11%) were treated with exchange transfusion (ECT) out of which 4 (66.67%) patients presented with ABO incompatibility, and 2 (33.33%) with Rh incompatibility. All exchange transfusion cases were Coombs positive. The peak bilirubine level was registered at median (interquartile range) day 1.5 (1-2), with a mean peak serum bilirubin concentration of 461.4±118.8 μmol/l.

DISCUSSION

We found a high percentage of jaundice of undefined etiology (44.37%). In another study a clear higher prevalence of undetermined etiology (75.8%) was reported [10]. The etiology could not be determined in 65.6% of cases admitted for treatment of extreme hyperbilirubinemia at the NICU in southern Turkey [22]. Davutoğlu M et al. report of 11 cases of unknown etiology in a group of 79 ECT cases (13.9%) [23]. In contrast, we did not find undefined etiology among our ECT cases. It could be assumed that the diverse prevalence of "undefined etiology" is due to the different classifications of the causes of neonatal jaundice on one hand, and on the other hand, the different levels of TSB taken into consideration (pathologic or extreme). According to our study, an undefined etiology definition applied for the cases where despite intensive workout, no identifiable cause or contributing factor for jaundice could be found. When selecting these cases carefully we obtained a rather homogenous group of clinically stable patients with normal birth parameters that required treatment with photoherapy. We can speculate an imbalance between bilirubin production and conjugation to be the concept of jaundice in this group since no history, clinical and laboratory data exist to indicate another mechanism of jaundice [24]. We found statistically significant higher levels of haematological parameters (Er, Hb and Hct) in this group compared to the group of premature newborns and significantly higher erythrocyte levels compared to hemolytic etiology. A controversy represented the prematurity- associated jaundice. Premature newborns, due to physiological characteristics, and associated risk factors are more prone to development of pronounced and prolonged jaundice [25]. Also, there is a paucity of evidence-based data on the safe treatment thresholds in this group [26, 27]. Bilirubin neurotoxicity has unequivocally been associated with prematurity alone; the presence of a concurrent neonatal disease and the use of total parenteral nutrition or drugs that alter bilirubin-binding properties are considered additional factors that potentiate the risk of neurotoxicity. Clinical manifestations of acute bilirubin encephalopathy in preterm infants are often more subtle than those of term infants [28-30]. For all these reasons, we stratified prematurity as a distinct entity; contrary to assignment of these patients into the "undetermined etiology" performed by other authors [10]. We have shown slower increase towards the peak bilirubin level in the group of premature newborns compared to groups of hemolysis, hemathomas and infection. With regard to the levels of Er, Hb and Hct in premature newborns, we have shown them to be statistically significantly lower than the groups of undefined etiology and infection. We did not find any cases of hypothyroidism, intestinal atresia or stenosis, hypertrophyc pyloric stenosis, delayed meconium passage, and polycythaemia. However, we did find 2 cases (0.7%) of jaundice associated with Down syndrome. We did not find cases of G6PD deficiency in the studied group. In a previous study a prevalence of 1.02% among Macedonians and 6.63% in Romanies on the territory of Skopje has been shown [31]. Although no cases of G6PD deficiency were found in the analyzed group, the year of 2009 was important for the introduction of a new quantitative assay for G6PD detection, thereby overcoming the uncertainties connected with the previously used qualitative method. Numbers of studies recommend quantitative testing for G6PD deficiency, thereby avoiding patients with partial G6PD deficiency to be missed [32, 33]. The physiologic polycythaemia of the neonatal period accounts for as much as 1/3 higher levels of G6PD in this period [33]. In cases with borderline low normal result and specific ethnic origin, it is reasonable to schedule another subsequent test. We developed a so called group of patients with hemathomas, encompassing patient with extra-vascular collections of blood where an increased bilirubin load is presumed to be the fundamental mechanism of hyperbilirubinemia [2, 9, 10, 25]. We did not find statistically significant haematological correlations between this group and the other 4 groups of patients. Sepsis is a known perinatal risk factor for both unconjugated and conjugated jaundice [2, 9, 25]; it is also listed as a risk factor for hyperbilirubinemia neurotoxicity [34]. Analysis of prevalence rates showed varying importance of infection in various

world regions. In Africa infection was associated with over 13.9% of all cases of hyperbilirubinaemia or kernicterus. In Asia the prevalence rates of infection-associated hyperbilirubinemia ranged from 9.7% to 31.2% and in Europe and North America infection was implicated in 14.3% of kernicterus cases [1]. The group of infection- associated indirect hyperbilirubinemia is represented with 19.37% in our study. This might be an overrepresentation due to the fact that not only culture positive cases were included, but also newborns with clinical or biochemical markers of sepsis. We could not reliably discriminate between culture positive and culture negative cases for several reasons. First of all, newborns are being sent to our department from maternity hospitals all over the country for further treatment in cases of emerging sepsis. Often antibiotic therapy is immediately initiated, but in some occasions blood culture is not taken in the referring hospital. These cases are sometimes culture negative despite obvious clinical signs of sepsis. On the other end of the scale are cases of suspected neonatal infection that received a course of antibiotic therapy until negative blood culture was obtained. Therefore we used the terminology "infection" rather than "sepsis" for more accurate reflection on this group of patients. We showed statistically significant higher levels of hematological parameters (Er, Hb and Hct) in this group compared to the hemolytic group and the premature newborns. The fifth group of patients included cases of Rh or ABO isoimmunisation termed hemolytic according to the nature of the disease process. According to the last update on management of newborn infants ≥35 weeks' gestation, isoimmune hemolytic disease is considered an important risk factor for both severe hyperbilirubinemia and bilirubin neurotoxicity [34]. It has been postulated that synergistic effect of DAT positive isoimmune hemolytic disease and severe hyperbilirubinemia potentiate bilirubin-induced neurotoxicity [35]. In a Turkish study, 19 out of 93 (20.43%) extreme hyperbilirubinemia patients were isoimmunised [22]. Two other studies reported ABO isoimmunization as the most common cause of hyperbilirubinemia requiring ECT, reported rates were 38% and 27.8% respectively [23, 36]. In our study ABO incompatibility was represented with 8.45%, and Rh incompatibility with 5.63% of all hyperbilirubinemia cases. We also discovered one patient with hemolysis that could not be assigned to either ABO or Rh incompatibility. When all hemolytic cases were pooled together, the percentage increased to 14.43%. In the group of hemolytic etiology we found statistically significant higher peak bilirubin levels compared to the groups of neonatal infection, prematurity and hematomas. Also statistically significant difference was found on the second bilirubin measurement in hemolytic etiology compared to prematurity and undefined etiology. This fact points out a slower decrease of bilirubin levels under phototherapy in hemolysis compared to undefined etiology (statistical significance changed from non-significant to significant). Six Coombs positive ABO/Rh incompatibility patients (2.11%) were treated with exchange transfusion, the remaining majority of cases (97.89%) were managed conventionally.

The major limitation of the study is its analytical retrospective design. Our hospital is a tertiary level residency teaching institution. All patients were examined on a daily basis by attending clinicians and residents. All medical records were written thoroughly and reviewed carefully.

CONCLUSIONS

Hyperbilirubinemia is a frequent pathology at the University Pediatric Clinic-Skopje, R. Macedonia. Most cases are treated with less severe jaundice of undefined etiology. Immediate awareness and management is required for those 15% of infants with hemolytic causes of jaundice that carry a significant risk for early and severe hyperbilirubinemia.

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Figure legends.-Figure 1. Graphical illustration of significantly higher levels of reticulocites in group 1 (hemolysis) compared to groups 2 (infection), 3 (prematurity), and 4 (hematomas), as well as in group 3 compared to group 2.

ЕВАЛУАЦИЈА И ТРЕТМАН НА НЕОНАТАЛНА ИНДИРЕКТНА ХИПЕРБИЛИРУБИНЕМИЈА НА УНИВЕРЗИТЕТСКАТА КЛИНИКА ЗА ДЕТСКИ БОЛЕСТИ ВО СКОПЈЕ, РЕПУБЛИКА МАКЕДОНИЈА

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АПСТРАКТ

Вовед: Неонаталната хипербилирубинемија дефинирана како ниво на серумски билирубин > 86 μmol/L е чест проблем кој се среќава кај околу 60% од терминските и 80% од предтерминските новороденчиња. Клинички предизвик е да се диференцира меѓу мнозинството новороденчиња со физиолошка жолтица и оние со патолошки причини за да се воспостави соодветен план за третман.

Цели: Цел на студијата е осврт кон евалуацијата и третманот на неонатална индиректна хипербилирубинемија во двегодишен период на одделот за неонатологија при Универзитетската Клиника за детски болести.

Методи: Историите на болест на 284 новороденчиња со индиректна хипербилирубинемија ретроспективно беа анализирани за следните параметри: анамнестички податоци, клиничка презентација, дијагностичка процедура и применета терапија.

Резултати: Најзастапена беше жолтицата со недефинирана етиологија (44.37%), следена со неонатална инфекција, прематуритет, хемолиза и родилна траума. Средната концентрација на серумски билирубин во групата на недефинирана етиологија беше 333.4±91.1 μmol/l. Највисоката концентрација на билирубин и ретикулоцити кај хемолитичката жолтица беа сигнификантно повисоки во споредба со другите етиологии. Првиот контролен серумски билирубин беше сигнификантно повисок кај новороденчиња со хемолиза во споредба со групите на прематурни новородени и недефинирана етиологија на жолтицата. Анализираните групи сигнификантно се разликуваа според денот на кој билирубинот достигнува пик. Најголемиот број новороденчиња беа третирани со фототерапија, а кај 2.11% беше изведена ексангвинотрансфузија.

Заклучоци: Хипербилирубинемијата е честа патологија на Универзитетската Клиника за детски болести-Скопје, Р. Македонија. Повеќето случаи се третираат со умерена жолтица од необјаснета етиологија. Непосредна свесност и брз третман е потребен кај околу 15% новороденчиња со хемолитички причини за жолтицата кои носат значаен ризик за рана и тешка хипербилирубинемија.

Key words: хипербилирубинемија, новородено, АВО инкомпатибилија, сепса, прематуритет, G6PD дефицит, евалуација и третман, Република Македонија

Original scientific paper

ВКУПНИ ХИДРОПЕРОКСИДИ – МАРКЕР ЗА ЛИПИДНА ПЕРОКСИДАЦИЈА КАЈ КОРОНАРНА АРТЕРИСКА БОЛЕСТ

TOTAL HYDROPEROXIDES – A MARKER OF LIPID PEROXIDATION AT CORONARY ARTERY DISEASE

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АПСТРАКТ

Вовед: Оксидативниот стрес придонесува во развојот на атеросклерозата и доведува до нестабилност на плаката во васкуларниот sид. Серумските биомаркери на липидна пероксидација, како што се хидропероксидите, може да претставуваат независен индикатор за ризик кај пациентите со коронарна артериска болест (КАБ).

Цел: Да се испита дали постои разлика во концентрацијата на хидропероксидите во плазмата, помеѓу пациенти со коронарна артериска болест и здрави крводарители.

Материјал и методи: Испитувањето претставува пресечна студија во која се вклучени 300 пациенти, поделени во две групи: пациенти со акутна коронарна артериска болест и хронична (исхемична) болест на срцето, со соодветни подгрупи. Примероците се обработувани во биохемиската лабораторија при што е користен фотометриски тест за квантитативно определување на вкупните хидропероксиди во крвна плазма, а за интерпретација на резултатите се користени стандардни референтни вредности.

Резултати: Добиените резултати укажуваат на статистички значајна разлика во однос на средните вредности на концентрацијата на хидропероксидите кај испитаниците со и без коронарна артериска болест, но непостои статистички значајна разлика меѓу испитаниците со акутна и со хронична коронарна артериска болест, ниту пак меѓу формираните подгрупи на пациенти.

Заклучок: Резултатите укажуваат на зголемено ниво на вкупните хидропероксиди во крвната плазма кај пациенти со коронарна артериска болест што укажува на постоње на редокс дисбаланс во споредба со здравите пациенти. Потребно е, во иднина, овие анализи да се користат како дел од панелот на веќе познати и/или нови биомаркери со цел соодветно да се делува кон превенција или одреден третман при лекувањето на пациентите со КАБ.

Клучни зборови: вкупни хидропероксиди, оксидативен стрес, коронарна артериска болест.

ВОВЕД

Современ концепт на атеросклероза

Атеросклерозата е прогресивна системска болест која генерално се карактеризира со акумулација на липиди, фиброзни елементи и воспалителни клетки и молекули, најчесто во големите и средно еластични мускулни артерии, кои можат да доведат до исхемија на срцето, мозокот и/или екстремитетите што на крај ќе резултира со инфаркт.

Современиот концепт за патогенеза на процесот на атеросклероза започнува со ендотелна повреда или дисфункција која се карактеризира со зголемена ендотелна пермеабилност и таложење на циркулирачкиот LDL (low density lipoprotein) од вонклеточниот матрикс во интимата на крвниот сад. LDL се акумулира на местото на ендотелната лезија, при што настанува процес на негова оксидација како резултат на нивната интеракција со реактивните кислородни слободни радикали (ROS) со што започнува акутна воспалителна реакција на артерискиот ѕид. Ендотелната повреда најверојатно е предизвикана од оксидираниот LDL (ox-LDL), како и од страна на физички, хемиски фактори и/или инфекција. Оваа лезија предизвикува зголемување на бројот на проинфламаторни молекули, молекули на адхезија, како што се P-селектин, хемотактичните фактори и фактори на раст. Ова доведува до адхезија, активирање и прикачување на моноцитите и Т-лимфоцити на ендотелните клетки. Моноцитите ги ингестираат липопротеините и преминуваат во макрофаги, макрофагите произведуваат ROS, кои го оксидираат LDL, кои пак, превземени од страна на макрофагите формираат "пенести клетки". Пенестите клетки лачат повеќе фактори за раст кои индуцираат непречена миграција на мускулните клетки во интимата и нивна пролиферација и доведуваат до формирање на фиброзна плоча. Подоцна, може да дојде до калцификација на плочата што ќе доведе до стабилизација на плаката. Плаките кои не се калцифицирани се нестабилни и кај нив фиброзните плочи може да руптурираат и да формират тромби, процес наречен атеротромбоза. Ова е хроничен процес кој вклучува формација на тромб богат со тромбоцити во атеросклеротичните артерии.Овој процес може да доведе до разни клинички консеквенции како ангина пекторис, транзиторни исхемични атаки, прогресивна клаудикација, а во крајна линија може да доведе до оклузија на крвните садови, што ќе резултира со миокарден инфаркт, исхемичен мозочен удар и васкуларна смрт (1).

Оксидативен стрес

Во секој организам постојано постои рамнотежа помеѓу про-оксиданти и антиоксиданти. Ова рамнотежа е многу важна за одржување на виталните клеточни функции (2-4). Секое нарушувањето на оваа рамнотежа кое ќе доведе до зголемување на про-оксиданти во однос на концетрацијата на антиоксидантите се дефинира како оксидативен стрес (5) кој настанува како последица на аеробниот живот и ќе доведе до оксидативно оштетување на биолошките цели (targets) како што се: липидите, нуклеинските киселини и протеините.

Слободните радикали се високо реактивни и се способни за оштетување скоро на сите видови на биомолекули (протеини, липиди, јаглехидрати и нуклеински киселини). Слободните радикали произведуваат низа на други слободни радикали од биолошките соединенија кои продолжуваат како верижна реакција. Оксидативен стрес може да се појави кога во клетката не можат адекватно да се уништат вишокот на формираните слободни радикали. (6) Овие слободни радикали може да ги оштетат клеточните мембрани и липопротеини преку процес наречен како липидна пероксидацијата.

Неодамнешните докази укажуваат на тоа дека циркулирачките липидни хидропероксиди играат клучна улога во развојот на атерогенезата (7-9), а со тоа и во развојот на коронарна срцева болест, единствена најчеста причина за смрт во САД и западниот свет. Липидната пероксидација иницира серија на настани ин витро, кои на крајот доведуваат до подобрено навлегување на липопротеини со ниска густина во макрофагите и формирање на пенести клетки, една од најраните атеросклеротични лезии во артериската интима. Деталните познавања на механизмите на формирање и распаѓање на липидните хидропероксиди во крвта на човечката плазма може да се покажат како корисни во разбирањето и превенцијата на атеросклерозата. Исто така, елиминирањето на липидните хидропероксиди во плазмата пред тие да поминат во периферните ткива може да има големо влијание врз различните други болести поврзани со оксидативниот стрес.

Со оглед на централната улога на плазмата во транспортот и судбината на липидите, а со тоа и на потенцијалните липидни хидропероксиди, малку се знае за можното формирање на липидните хидропероксиди во плазмата и релативниот придонес на различни ендогени антиоксиданти во спречување на штетата од липидната пероксидација. Исто така, судбината на липидните хидропероксиди кои еднаш се формирале во плазмата или се превземени во неа и можното вклучување на различни антиоксиданти, се главно неистражени. Поради ова, целта на нашата студија беше да се оцени и спореди нивото

на хидропероксидите, како маркери на липидна пероксидација, кај пациенти со КАБ и контролните здрави пациенти (10).

ЦЕЛИ

Целите на ова истражување се:

- Да се утврди дали постои разлика во концентрацијата на хидропероксидите во плазмата, како маркери за липидна пероксидација, помеѓу пациентите со коронарна артериска болест и здравите крводарители.
- Да се утврди дали постои разлика помеѓу двете групи на пациенти: со акутна коронарна болест и хронична (исхемична) болест на срцето.
- Да се утврди дали постои статистички значајни разлики во концентрацијата на хидропероксидите помеѓу подгрупите во една група, формирани во зависност од анамнестичките податоци, физикалниот преглед, лабораториските анализи и неинвазивните дијагностички методи, и тоа:
  - Во групата на пациенти со акутна коронарна артериска болест меѓу пациентите со акутен миокарден инфаркт со СТ-сегмент елевација, со акутен миокарден инфаркт без СТ-сегмент елевација и со нестабилна ангина пекторис.
  - Во групата на пациенти со хронична (исхемична) болест на срцето меѓу пациентите по прележан миокарден инфаркт, кај пациенти по миокардна реваскуларизација со перкутани коронарни интервенции и/или коронарна бајпас хирургија и други реваскуларизациони процедури и кај пациенти со асимптоматска КАБ.

МАТЕРИЈАЛ И МЕТОДИ

Трудот претставува трансверзална (пресечна) студија која е спроведена на Клиника за кардиологија-Скопје, во периодот од 01-ви ноември 2013 до 31-ви март 2014 година. Во студијата беа вклучени 300 пациенти со коронарна артериска болест (КАБ).

1. Пациентите со работна дијагноза за Акутна коронарна артериска болест (Акутен коронарен синдром), кои беа примени во единица за интензивна нега беа вклучени во студијата, вкупно 187 пациенти. Врз основа на неинвазивни методи (електрокардиограм, ехокардиографија) и лабораториски анализи (маркери на некроза: миоглобин, тропонин, креатинин киназа – СК-МВ) беа поделени во соодветни подгрупи:

1а. Акутен миокарден инфаркт со СТ-сегмент елевација (СТЕМИ), вкупно 83 (44,4%) пациенти

1б. Акутен миокарден инфаркт без СТ-сегмент елевација (НСТЕМИ), вкупно 14 (7,5%) пациенти

1в. Нестабилна ангина пекторис (АПНС), вкупно 90 (48,1%) пациенти

2. Пациентите со потврдена коронарна артериска болест беа селектирани, рандомизирани во тек на нивните редовни контроли и во студијата беа вклучени оние пациенти кои ги исполнуваат кристериумите за хронична коронарна артериска болест: Симптомите да се стабилни во последните 60дена; Во тој период да нема промена во честоста, траењето, провоцирачките фактори; Да нема доказ за неодамнешна миокардна повреда. Групата на пациенти со хронична коронарна (исхемична) болест на срцето, вкупно 113 пациенти, беа поделени во следните подгрупи:

2а. Пациенти по прележан миокарден инфаркт (St.post MI), вкупно 76 (67,3%)

2б. Пациенти по миокардна реваскуларизација со перкутани коронарни интервенции и/или коронарна бајпас хирургија и други реваскуларизациони процедури (St.post PKI/CABG), вкупно 25 (22,1%)

2в. Пациенти со асимтоматска КАБ, вкупно 12 (10,6%)

Контролната група се 30 физичко и ментално здрави крводарители, со отсуство на било каков вид на акутно и/или хронично заболување, кои во тек на истражувањето дарувале крв во РЕ Трансфузилогија – Штип.

Специфични критериуми за исклучување од студијата беа сите оние пациенти кои дадоа податок за примена на антиоксиданти и витамини и други медикаменти кои влијаат врз липидната пероксидација и антиоксидантниот статус.

Сите испитаници вклучени во студијата беа информирани за целта на истражувањето и дадоа писмена согласност за учество во студијата пред собирањето на примероците на крв.

Протокол и собирање на примероци

Примероци на крв беа собрани со венопунктура од пациентите и беа обработени во Биохемиската

лабораторија на Факултетот за Медицински науки, при Универзитет "Гоце Делчев" во Штип. Примероци на полна крв беа собрани со венопунктура од сите испитаници, во епрувети кои содржат EDTA како антикоагуланс. Крвта беше центрифугирана на 10.000 g во тек на 5 минути и температура од 4ºC. Супернатантите беа одвоени во епрувети и чувани на температура од -70ºC се до моментот на анализирање (11).

Принцип на PerOx тест

Беше користен фотометриски тест систем за квантитативно определување на вкупните хидропероксиди во ЕДТА плазма (12).

Одредувањето на хидропероксиди се врши од страна на реакција на пероксидаза со пероксидите во примерокот проследено со конверзија на 3,3,5,5-Тетраметилбензидин (TMB) во обоен производ. По додавање на реагенсот за прекинување на реакцијата, абсорбанцата беше мерена на 450 nm со читач на микротитерски плочки (12). Концентрацијата на хидропероксиди беше изразувана како CARR U.

Статистички метод

Сите податоци од интерес за изработка на трудот се табеларно и графички прикажани; Кај сериите со нумерички белези, дистрибуцијата на податоците е тестирана со Test for normality: Kolmogorov-Smirnov test, Lilliefors-test и Shapiro-Wilks W test; Нумеричките серии се анализирани со помош на мерките на централна тенденција (просек) и мерките на дисперзија (стандардна девијација);

Тестирање на значајност на разликите меѓу две аритметички средини кај независните примероци (помеѓу групите) е направено со непараметарскиот Mann-Whitney U Test (постои неправилна дистрибуција);

Тестирање на значајност на разлики помеѓу три аритметички средини кај независните примероци е направено со анализа на варијанса (ANOVA). За сигнификантни се сметани сите оние резултати каде вредноста на $p < 0,05$.

РЕЗУЛТАТИ

Во нашето истражување беа вклучени вкупно 300 пациенти со коронарна артериска болест (КАБ). Од нив 187 (62.3%) пациенти беа со дијагноза акутна коронарна артериска болест и 113 (37,7%) пациенти со хронична исхемична болест на срцето.

Со цел да испитаме дали постои разлика во концентрацијата на хидропероксидите (ХП), како маркери за липидна пероксидација, најнапред ја одредивме средната концентрација во плазмата на хидропероксидите и тоа, кај пациентите со КАБ и кај пациенти без КАБ (здрави крводарители).

Табела бр. 1. Средни вредности на концентрацијата на хидропероксидите кај двете испитувани групи (пациенти со КАБ и здрави крводарители)

Испитувани групи	Број на испитаници (N)	Просечна вредност на ХП (CARR U)	СД	Ниво на значајност (p)
Пациенти со КАБ	(N=300)	282,7	73,87	Z = 3,606 p = 0,00031
Пациенти без КАБ (Здрави крводарители)	(N=30)	238,5	63,91	

Врз основа на податоците од табела бр.1 може да се види дека средната вредност на концентрацијата кај пациените со КАБ изнесува 282,7 CARR U, а кај здравите пациенти без КАБ изнесува CARR U.

Статистичката анализа на овие податоци покажа дека постои статистички значајна разлика во однос на средните вредности на концентрацијата на хидропероксидите кај испитаниците со и без КАБ.

Анализата покажува дека концентрацијата на хидропероксидите е поголема кај пациентите со КАБ во споредба со здравите крводарители.

Нашиот понатамошен интерес беше да се утврди дали постои разлика во нивото на хидропероксидите, помеѓу пациентите со акутна коронарна болест и хронична (исхемична) болест на срцето. Со таа цел, направивме анализа на средните концентрации на хидропероксиди помеѓу овие две групи.

Табела бр. 2. Средни вредности на концентрацијата на хидропероксидите кај испитаниците со акутна (КАБ) и хронична исхемична болест

Испитувани групи	Број на испитаници	%	Просечна вредност на ХП (CARR U)	СД	ниво на значајност (p)
Акутна КАБ	N=187	62,3	285,6	73,12	Z = 0,826 p = 0,4083
Хронична исхемична болест	N=113	37,7	277,9	75,17	

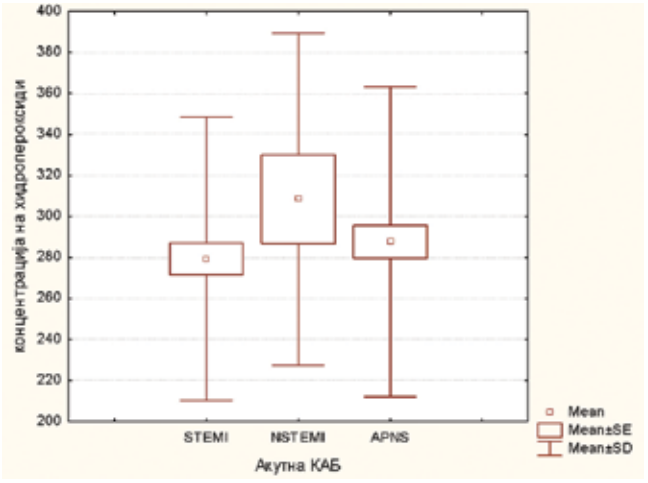
Од табела бр.2 може да се види дека средната вредност на концентрацијата на пероксидите кај пациентите со акутна КАБ изнесува 285,6 CARR U, а кај пациентите со хронична исхемична болест изнесува CARR U.

Статистичката анализа на добиените вредности укажуваат дека непостои статистички значајна разлика во однос на средните вредности на концентрацијата на хидропероксидите кај пациентите со акутна КАБ и со хронична исхемична болест на срце.

Со цел да видиме дали постои значајна разлика во концетрацијата на хидропероксидите помеѓу пациентите со акутна КАБ, ги анализиравме средните концентрации меѓу пациентите со акутен миокарден инфаркт со СТ-сегмент елевација (STEMI), акутен миокарден инфаркт без СТ-сегмент елевација (NSTEMI) и со нестабилна ангина пекторис (APNS).

Табела бр. 3. Средни вредности на концентрацијата на хидропероксидите помеѓу пациентите со акутна КАБ

Акутна КАБ	Број на испитаници	%	Просечна вредност на ХП (CARR U)	СД	ANOVA
STEMI	N=83	44,4	279,4	68,98	F = 1,024 p = 0,3609
NSTEMI	N=14,	7,5	308,5	80,92	
APNS	N=90	48,1	287,7	75,56	



Графикон бр.3. Средни вредности на концентрацијата на хидропероксидите помеѓу пациентите со акутна КАБ

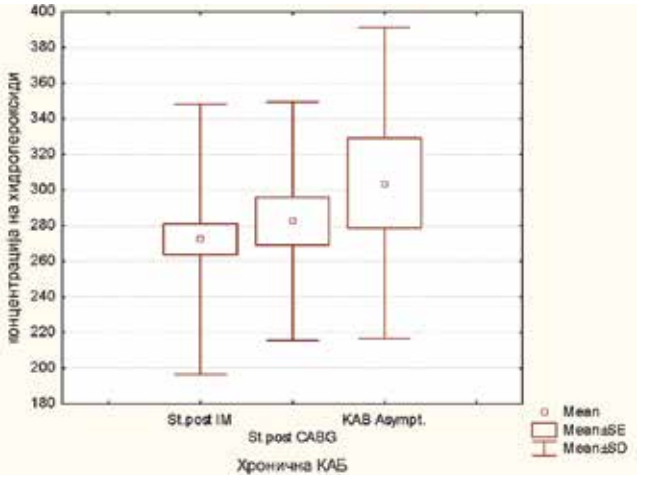
Од табела бр.3 и графикон бр.3 се гледа дека средните концентрации на хидропероксиди меѓу пациентите со акутна КАБ се разликуваат, при што највисоки вредности од 308,5 CARR U кај пациентите со NSTEMI, кај пациентите со APNS 287,7 CARR U, а најниски вредности од 279,4 CARR U се регистрирани кај пациентите со STEMI.

Понатамошната статистичка анализа на податоците покажува дека не постои статистички значајна разлика во однос на средните вредности на концентрацијата на хидропероксидите помеѓу испитаниците во групата на акутна КАБ: меѓу STEMI, NSTEMI и APNS.

Со цел да испитаме дали постои разлика во концетрацијата на хидропероксидите помеѓу пациентите со хронична исхемична болест, ги анализиравме средните вредности меѓу пациентите по прележан миокарден инфаркт (St.post IM), кај пациентите кои имале миокардна реваскуларизација со перкутани коронарни интервенции и/или коронарна бајпас хирургија и други реваскуларизациони процедури (St.post PKI/CABG), и кај пациентите со асимптоматска КАБ).

Табела бр. 4. Средни вредности на концентрацијата на хидропероксидите меѓу пациентите со хронична исхемична болест

Хронична исхемична болест	Број на испитаници	%	Просечна вредност на ХП (CARR U)	СД	ANOVA
St. post IM	N=76	67,3	272,3	75,76	F = 0,970 p = 0,3821
St. post PKI/ CABG	N=25	22,1	282,4	66,95	
Асимптоматска КАБ	N=12	10,6	303,9	87,32	



Графикон бр.4. Средни вредности на концентрацијата на хидропероксидите меѓу пациентите со хронична исхемична болест

Од табела бр.4 и графикон бр.4 се гледа дека средните концентрации на хидропероксидите меѓу пациентите со хронична (исхемична) болест на срце се разликуваат, при што највисоки вредности од 303,9 CARR U се регистрирани кај пациентите со асимптоматска КАБ, кај пациентите по миокардна реваскуларизација со перкутана коронарна интервенција и/или коронарна бајпас хирургија изнесува 282,4 CARR U, а најниски вредности од 272,3 CARR U кај пациентите по прележан миокарден инфаркт.

Статистичката анализа на податоците покажува дека не постои статистички значајна разлика во однос на средните вредности на концентрацијата на хидропероксидите помеѓу испитаниците по прележан МИ, по миокардна реваскуларизација со ПКИ и/или коронарна бајпас хирургија и асимптоматска КАБ, од групата на хронична болест на срце.

ДИСКУСИЈА И ЗАКЛУЧОК

Теоријата дека оксидативниот стрес и ендогеното создавање на токсични продукти како што се кислородните слободни радикали имаат важна улога во развојот на атерогенезата и болестите поврзани со тој процес, како што е коронарната артериска болест, добива се повеќе приврзаници во современата научна литература (13). Во последните години, постои зголемен интерес за проучување на улогата на липидната пероксидација кај пациентите со коронарни васкуларни болести (14).

Студијата на Oen LII et al. докажала дека пости значително зголемување на нивото на липидни пероксиди кај пациенти кои страдаат од коронарна срцева болест во однос на контролната група на пациенти (15). Студијата на Dincic et al. покажала докази за зголемото ниво на слободни радикали кај пациенти со срцева исхемија во однос на контролните субјекти (16). Други студии испитувале и други биомаркери, на пример студијата на Khan et al. (17) покажала значителна врска помеѓу покачено ниво на малонилалдехидот (како краен производ од липидната пероксидација) и коронарната артериска болест. Зголемено ниво на малонилалдехид укажуваат на зголемување на нивото на производството на реактивните кислородни слободните радикали (ROS), што укажува на нивната можна улога во атерогенезата, што доведува до коронарна артериска болест. Студијата на Walter et al. (18) каде серумските нивоа на малониалдехид биле мерени како реактивни супстанции на тиобарбитурната киселина (TBARS) докажала дека се силен предиктивен фактор за кардиоваскуларни настани кај пациенти со стабилна коронарна артериска болест, независно од традиционалните фактори на ризик и воспалителни маркери. Во последниве години, оксидација на полинезаситените масни киселини во плазма е постулат да биде критичен чекор во развојот атеросклерозата. Тогаш следење на липидите пероксидацијата треба да биде корисен индикатор за ризикот и прогресијата на болеста. Липидната пероксидација на полинезаситените масни киселини, F2-изопростаните, се корисни биомаркери, кои потенцијално би можеле да се користат како индикатори на коронарна срцева болест било објавено во студијата на Davies et al. (19)

Од големиот број на студии, јасно произлегува и добро е дефинираната критичната улогата на оксидативниот стрес во развојот на атерогенезата. Затоа, развојот на технички лесни и сигурни методи за евалуација на оксидативниот стрес во клинички испитувања е особено важно. Современите пристапи вклучуваат мерење на стабилни производи, како што се серумски липидни хидропероксиди (производи на липидната пероксидација), плазма малонилалдехид (краен производ на липидна пероксидација) или урина (наместо плазма) F2-изопростани (производ од пероксидиција на фосфолипиди врзани за арахидонската киселина). Мерењето на циркулирачките биомаркери на оксидативниот стрес е предизвик, бидејќи повеќето од нив се покажа дека имаат предвидувачка вредност во кардиоваскуларните болести, иако нивното вистинско биолошко значење сеуште е нејасно.

Во оваа студија беа користени само вкупните хидропероксиди, како биомаркери за липидната пероксидација кај пациентите со КАБ. Потребно е, во иднина, овие анализи да се користат како дел од панелот на познати биомаркери и нови биомаркери и заедно со други клинички наоди, како и одредување на концентрацијата на антиоксидантите, да се дојде до поцелосен увид во оценка на оксидативниот статус, со цел соодветно да се делува кон превенција или одреден третман при лекувањето на пациентите со КАБ.

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TOTAL HYDROPEROXIDES – A MARKER OF LIPID PEROXIDATION AT CORONARY ARTERY DISEASE

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ABSTRACT

Introduction: The oxidative stress contributes for the development of the atherosclerosis and leads to instability of the plaque in the vascular wall. The serum biomarkers of lipid peroxidation, such as hydroperoxides, may represent an independent indicator of risk for patients with coronary artery disease (CAD).

Goal: To be examined if there is a difference in the concentration of the hydroperoxides in the plasma, among the patients with a coronary artery disease and healthy blood donors.

Material and methods: The examination represents a cross – sectional study involving 300 patients, divided in two groups: patients with an acute coronary artery disease and a chronic (ischemic) heart disease, divided into appropriate subgroups.The specimens processed in the biochemistry laboratory and it was used photometric test for quantitative determination of the total hydroperoxides in blood plasma and for an interpretation of the results standard reference values are used.

Results: The results indicate statistically significant difference regarding the mean values of the concentration of the hydroperoxides at the patients with and without coronary artery disease, but does not exist statistically important difference between those with an acute and with a chronic coronary artery disease, nor among the subgroups of patients formed.

Conclusion: The results of the performed research indicate to an increased level of the total hydroperoxides in the blood plasma at the patients with a coronary artery disease that indicates an existence of a redox imbalance compared with healthy patients. It is necessary, in future, these analyses to be used as a part of the panel of already known and/or new biomarkers with a goal appropriately to act toward the prevention or a certain treatment when curing patients with CAD.

Key words: total hydroperoxides, oxidative stress, coronary artery disease

Original scientific paper

ASSOCIATION OF PROGNOSTIC FACTORS WITH OVERALL SURVIVAL IN MYELODYSPLASTIC SYNDROMES: A COHORT STUDY

ПОВРЗАНОСТ НА ПРОГНОСТИЧКИТЕ ФАКТОРИ СО ПРЕЖИВУВАЊЕТО КАЈ МИЕЛОДИСПЛАСТИЧНИТЕ СИНДРОМИ: СТУДИЈА НА КОХОРТА

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ABSTRACT

Background: Myelodysplastic syndromes (MDS) are heterogeneous disorders in terms of clinical presentation, laboratory findings and life expectancies. A lot of studies have been conducted to determine factors that can refine the prediction of prognosis in MDS.

Aim: Our aim was to evaluate which prognostic factors had an impact on overall survival (OS) in MDS.

Methods: we conducted retrospective cohort study of 154 adult patients (81 male, 73 female) with MDS who presented to the University Clinic of Hematology, Ss Cyril and Methodius University, Skopje, Macedonia, from January 2011 to June 2014. Data on demographics, FAB classification, treatment and outcome were collected.

Results: Age and gender had no influence on OS (p=.80847 and p=.974895, respectfully). Different FAB subtypes had an impact on OS (p = .00757). Bone marrow (BM) blast percentage correlated significantly with OS (p= .028026). Hemoglobin, platelet count and absolute neutrophil count (ANC) did not influence OS (p=. 179970, p= .386355 and p= .972602, respectfully). Transfusion did not influence OS (p= .445856). Albumins had no impact on OS (p=.559900). Lactate dehydrogenase (LDH) and comorbidities influenced OS (p= .018895 and p= .02278, respectfully). Leukemic transformation was noticed in 7 (4.5%) patients. Mortality was 35.1%.

Conclusions: FAB subtypes, BM blast percentage, LDH and comorbidities are independent predictors on OS and should be considered for future revisions of International Prognostic Scoring System in order to refine the prediction of prognosis in MDS.

Key words: myelodysplastic syndromes, overall survival, prognostic factors

INTRODUCTION

Myelodysplastic syndromes (MDS) comprise a group of clonal hematopoietic stem-cell disorders, characterized by ineffective hematopoiesis and peripheral cytopenias, heterogeneous clinical presentation, laboratory findings and life expectancies ranging from a few months to several years.[1,2] Disease characteristics and outcomes are defined by FAB and WHO classification. Prognosis is defined by IPSS and R-IPSS score.[3] Overall survival (OS) is important for both the patients and their physicians. Accurate prediction of a patient's prognosis is useful to define the risk posed by the disease. For that reason it is of great importance to know the impact of some prognostic factors on OS. Some of them are already included in IPSS and R-IPSS - BM blast cell count, peripheral cytopenias and cytogenetics. There are a lot of studies trying to define other prognostic factors: age[4,5,6,7,8], gender[4,7,8], FAB subtypes[9], RBC transfusion dependence[10,11], ferritin[12,13,14,15,16], albumins[18], LDH[17], mutations[19,20,21] and co-morbidities.[1] Diagnosis requires BM examination, cytogenetic and lately molecular studies. The consensual

minimum criteria for diagnosis are presence of erythroid, granulocyte or megakaryocyte dysplasia in 10% or more informative cells.[22] The incidence of MDS increases with age.[4,5,6,7,23] Age had a significant effect on OS - the older the age, the worse the prognosis. The impact of gender on OS was observed in several studies. The incidence of MDS is higher in males than in females (1.5 - 2 to 1). Males had worse prognosis.[4,7] FAB subtypes can worsen prognosis in MDS, with differences among subtypes.[9] BM blast count showed a significant predictive value on OS.[23] More than 5% blasts in BM were considered as a bad prognostic factor for OS.[24,25] Cytopenias did not reach statistical significance in OS.[23] The occurrence of anemia (hemoglobin < 10 g/dl) or thrombocytopenia (platelets < 100×10^9 /l) was associated with a higher risk for OS. A lower absolute neutrophil count (< 1.8×10^9/l) did not significantly affect OS.[7] Red blood cell (RBC) transfusions are commonly used therapy for symptomatic anemia. Transfusion dependence is defined by the MDS International Study Group (2000) as requiring transfusion of at least one RBC unit at 8 weeks for 4 months.[9] Transfusion-dependent patients had shorter survival rate than those who received less than 18 units of blood over a period of 36 months.[26] Serum ferritin level ≥500 μg/l at diagnosis was a strong independent predictor of survival. Serum ferritin significantly correlated with OS in Chinese patients.[12] Lactate dehydrogenase (LDH) should be recognized as a prognostic factor in MDS.[17] One German study pointed out the correlation between LDH level and OS.[21] Serum albumin is an independent prognostic factor that influences OS.[18] Recurrent chromosomal abnormalities have been identified in 40–70% of the 'de novo' MDS and 95% of secondary MDS. Favorable prognostic markers according to IPSS include: a normal karyotype, 5q- as an isolated anomaly, 20q- as an isolated anomaly and -Y chromosome. Karyotype findings associated with poor prognosis include complex karyotype and chromosome 7 abnormalities. Other cytogenetic abnormalities confer an intermediate prognosis.[27,28] The abnormal karyotype correlates with poor prognosis and shorter OS.[19,29] Somatic mutations are identified in more than 70% of MDS patients, including more of them with normal karyotype. They are major predictors of the clinical phenotype, and could also be predictors of prognosis.[19,20,21] The incidence of MDS increases with age and so does the prevalence of co-morbidities. About 50% of MDS patients have one or more co-morbidities. They are independent predictors in MDS.[1]

The aim of this study was to evaluate the influence of some prognostic factors in MDS (like age, gender, FAB subtypes, BM blast percentage, cytopenias, transfusion dependence, serum levels of ferritin, lactate dehydrogenase and albumin, comorbidities and specific karyotype abnormalities) on OS.

MATERIAL AND METHODS

Study setting and study subjects: We conducted a retrospective cohort study that included 154 adult patients with MDS who presented to the University Clinic of Hematology, Ss Cyril and Methodius University, Skopje, Macedonia, from January 2011 to June 2014. Observation time was 42 months. In addition to demographic data, we collected information on each patient's date of presentation and date of death/last follow-up. FAB classification, treatment and outcome were also obtained. This study was approved by the Ethical Board of the University and the procedures followed were in accordance with the Helsinki Declaration of 1975, revised in 2000.

Patients were evaluated for clinical and hematologic features at diagnosis and leukemic transformation. We evaluated some parameters that could influence OS: age, gender, BM blast percentage, red blood cell (RBC) transfusion dependence, serum levels of hemoglobin, ferritin, LDH and albumin as well as specific karyotype abnormalities. Most patients (pts) received supportive care: transfusion of RBC units and platelets, red cell and granulocyte growth factors - 23 pts (14.9%), corticosteroids, iron chelatation therapy - 7 pts (4.5%), chemotherapy -10 pts (6.5%), 1 patient (0.6%) was treated with azacytidine and 3 patients (1.9%) underwent allogeneic transplantation. Leukemic transformation was noticed in 7 patients (4.5%). Mortality was 35.1% (54 patients). Infectious and hemorrhagic complications as well as BM failure were considered causes of MDS-related deaths.

Statistical analysis: Descriptive statistics of the study population, including means (with corresponding standard deviations), medians (with corresponding ranges) and proportions, were computed. Differences among variables were evaluated by the Chi-square test. The determinations of correlations between different variables was based on the Pearson correlation coefficient and a certain correlation was considered statistically significant if $p < 0.05$. OS was calculated in months from day of presentation to the time of death

/ time of last visit. Observations were censored for patients at the last follow-up date. The probabilities of OS were estimated using Kaplan and Meier method. Cox proportional hazards regression models were used to assess the association between prognostic factors and OS. The statistical analyses were carried out using statistical package STATISTICA 8.0.

RESULTS

A total of 154 adult patients were included in this cohort study. OS was 13.1 months. (Figure 1) Median age at presentation was 65,8 years (SD 14.96) (range 17 to 89 years). The correlation between OS as a dependent variable and age as an independent variable was not statistically significant (p=.80847). When patients were divided in five groups: the first ≤ 50 years (26 patients) - OS 13.6 months (SD 9.36), the second 51-60 years (13 patients) - OS 13.7 months (SD 8.48), the third 61-70 years (35 patients) - OS 13.8 months (SD 11.32), the forth 71-80 years (55 patients) - OS 13.5 months (SD 11.19) and the fifth >80 years (24 patients) - OS 9.9 months (SD 9.93), but the differences in OS among groups were not statistically significant (p = .49751). When patients were divided in two groups, OS in the first group ≤ 65 years (60 patients) was 13.4 months (SD 9.18) and in the second group >65 years (93 patients) - 12.8 months (SD 11.29), showing no significant difference (p = .15760). Surviving at 42 months in the first group was 77.5% and in the second 90.7%.

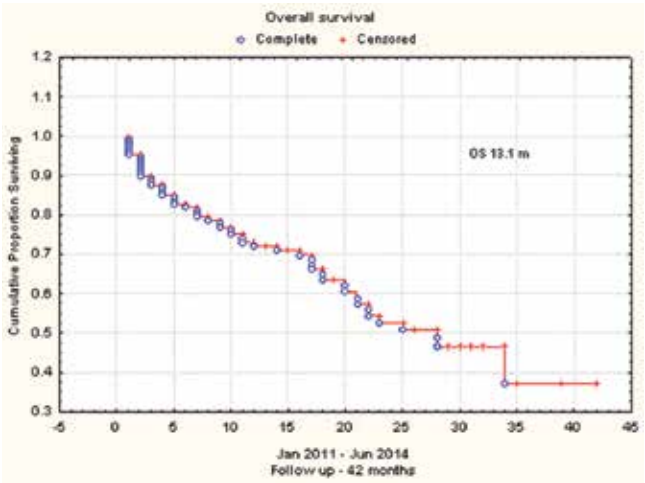

Figure 1. OS in the cohort followed for 42 months.

In this cohort 81 patients (52.6%) were male and 73 (47.4%) female. Male to female ratio was 1,11 to 1. Males had better OS than females - 13.0 (SD 10.62) versus 12.9 months (SD 10.37), being not significant (p = .44569). Surviving at 46 months was 82.4% for males and 83.1% for females. The correlation between OS and gender was not significant (p=.974895).

The correlation between OS and FAB subtypes was not significant (p= .231835). According to the FAB classification patients were classified as follows: 108 patients as having refractory anemia (RA)- 70%, 3 patients - RA with ringed sideroblasts (RARS) - 2%, 26 patients - RA with excess of blasts (RAEB) - 17%, 5 patients - RAEB in transformation (RAEB-T) - 6%, 9 patients - chronic myelomonocytic leukemia (CMML) - 3% and 3 patients - secondary MDS (MDSs) – 2%. (Figure 2)

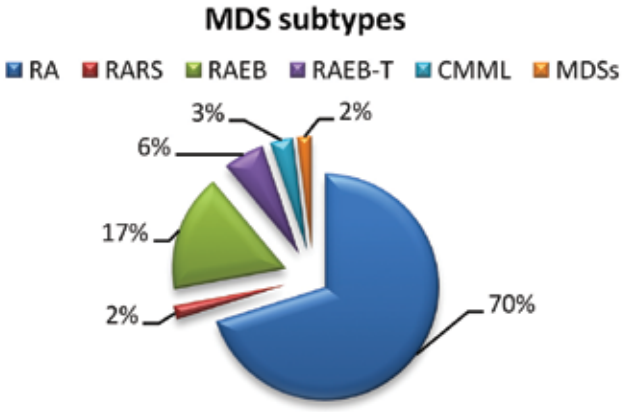

Figure 2. Distribution of FAB subtipes in percentage.

OS in patients with RA was 13.9 months (SD 10.75), with RARS - 7.0 months (SD 10.39), with RAEB - 9.3 months (SD 9.16), with RAEB-T - 7.8 months (SD 7.05), with CMML - 15.0 months (SD 8.23) and with MDSs - 18.0 months (SD 16.52), and the differences in OS were significant (p = .01133). (Figure 3)

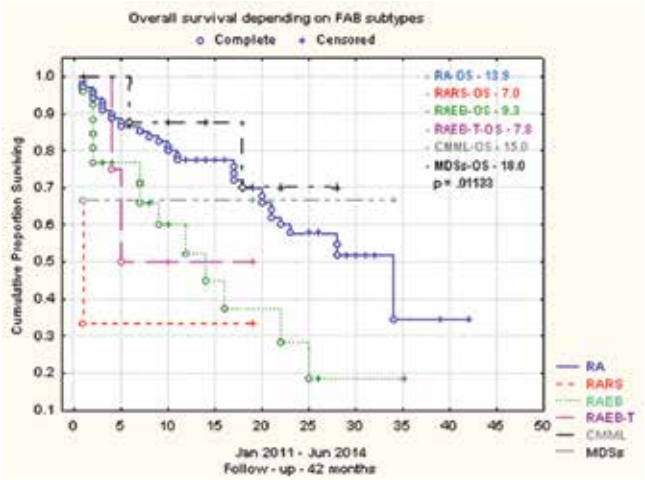

Figure 3. Differences in OS among FAB subtypes

The correlation between OS and BM blast percentage was statistically significant (p= .028026). Mean BM blast percentage was 6.3% (SD 6.72). OS in the group with <5% blasts (114 patients) was 14.4 months (SD 10.78), in the group with blasts 5-10% (15 patients) - 9.9 months (SD9.87), with blasts 11-20% (18 patients) - 8.5 months (SD 7.85) and in the group with 21-30% blasts (7 patients) - 8.3 months (SD 7.61), the differences being significant (p = .00757). (Figure 4)

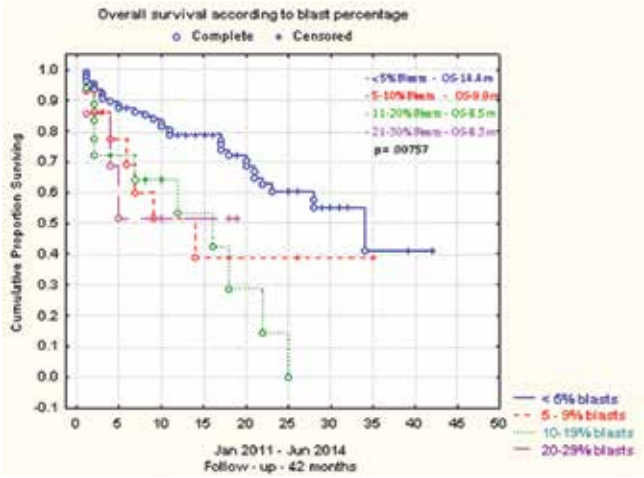

Figure 4. Differences in OS according to the blast percentage

The correlation between OS and hemoglobin was not statistically significant (p= .179970). Mean hemoglobin (Hb) level in our cohort was 8.61g/dl (SD 24.42) (range 4.1-15.0 g/dl). The patients were divided in three categories according to the severity of anemia: severe anemia (Hb <8.0 g/dl), moderate anemia (Hb 8.0-10.0 g/dl) and patients with Hb >10.0 g/dl. OS in the group with Hb >10.0 g/dl (63 patients) was 15.4 months (10.76), in the group with Hb 8.0-10.0 g/dl (51 patients) - 11.5 months (SD 8.87) and in the group with Hb <10.0g/dl (36 patients) – 15.8 months (SD 11.99), the differences being not significant (p = . 24980).

The correlation between OS and hemoglobin was statistically significant (p= .386355). Mean platelet count was 136.8×10^9/l (SD 122.82) (range 3-629). Patients were divided in two groups: the first with platelet count $<100\times10^9$/l (80 patients) - OS – 12.0 months (SD 9.57) and the second with platelet count $>100\times10^9$ /l (72 patients) - OS – 14.1 months (SD 11.46), the differences being not significant (p = .20496).

The correlation between OS and ANC was not statistically significant (p= .972602). Mean ANC was ANC 3042 cells/mm3 (SD 4.29) (range 200 – 34800 cells/mm3. Patients were divided in three groups according to the ANC: the first with ANC < 500 cells/mm3 (12 patients) - OS – 12.2 months (SD 9.79), the second with ANC - 500-1000 cells/mm3 (20 patients) - OS – 13.2 months (SD 9.87) and the third with ANC >1000 cells/mm3 (120 patients) - OS – 13.0 months (SD 10.77), the differences being not significant (p = .79375).

Mean level of serum ferritin in our group was 758.6µg/L (SD 841.96) (range 10.0-3940.0). The group with ferritin <500 µg/l (19 patients) had OS 9.4 months (SD 10.48) and the group with ferritin >500 µg /l (12 patients) had OS 16.7 months (SD 10.65), without significant differences in OS (p = .84758).

The correlation between OS and transfusion dependence was not statistically significant (p= .445856). Mean transfused RBC units were 11.6 (SD 15.09) (range 1-87). OS in the group without RBC (56 patients) was 12.0 months (SD 10.69), in the group that received ≤ 18 RBC (78 patients) - 11.8 months (SD 10.24) and the group that received >18 RBC (20 patients) - 20.4 months (SD7.75), being not statistically significant (p = .38876).

The correlation between OS and albumin was not statistically significant (p=.559900). Mean albumin level in our cohort was 39.3g/l (SD 6.24) (range 21-49). The differences in OS were statistically significant (p = .00316) among the three groups with different albumin levels: the first with albumins <35 g/l (11 patients) - OS – 8.8 months (SD 9.79), the second with albumins 35-40g/l (14 patients) - OS – 13.7 months (SD 9.87) and the third with albumins >40 g/L (26 patients) - OS – 13.6 months (SD 10.77). (Figure 5)

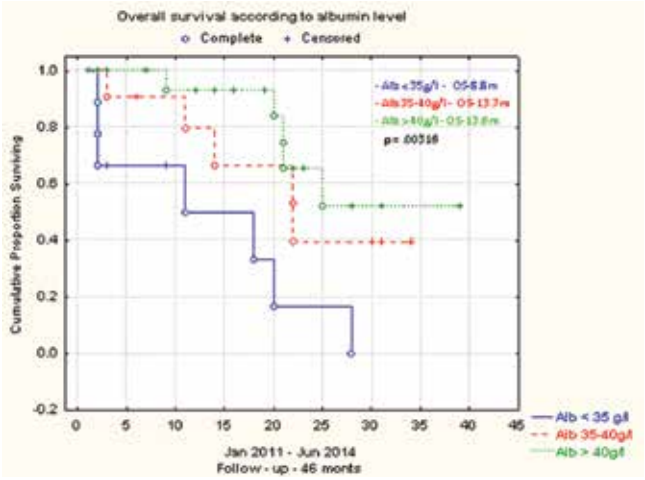

Figure 5. Differences in OS according to the albumin level

The correlation between OS and LDH was statistically significant (p= .018895). Mean serum level of LDH was 829.9 IU/l (SD 907.25) (range 217-5790). There was no significance in OS (p = .18757) between the two groups: the first with LDH<423IU/l (73 patients) - OS 15.7 months (SD 12.00) and the second with LDH>423 IU/l (54 patients) - OS 10.7 months (SD 8.54).

Comorbidities as an independent variable had significant impact on OS (p = .00386). The difference in OS in the two groups was also significant (p = .02278) (Figure 4): the first with no comorbidities (126 patients) -OS 13.3 months (SD 10.28) and the second with comorbidities (27 patients) - OS 11.6 months (SD 11.59).

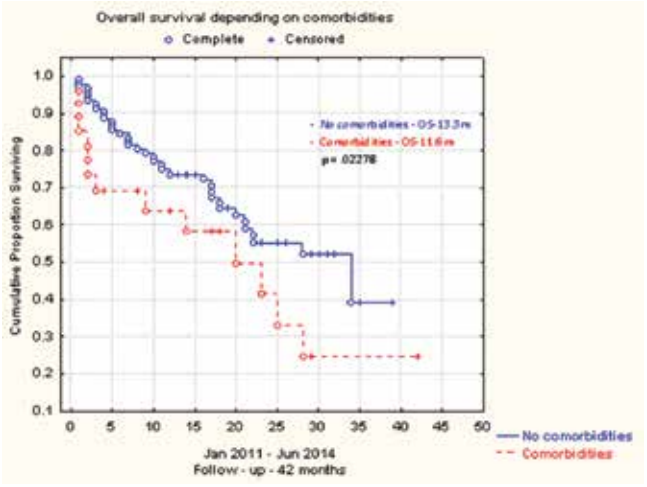

Figure 6. Differences in OS according to comorbidities

The correlation of joint effect of multiple variables (age, sex, FAB subtypes, BM blast percentage, hemoglobin, platelets, ANC, RBC transfusion, ferritin, albumin, LDH and comorbidities) on OS was statistically significant (p= .01357).

We were able to perform cytogenetic analysis only in 6 patients: 3 had normal karyotype, one had +8, one - inv16 and one – inv9 and inv13. Due to the small number of patients survival curves are not presented.

DISCUSSION

Our results considering age (65.8 years) correspond with those in the literature.[8] Age did not affect OS neither as a whole nor stratified by subgroups, similar with some studies[23]. Considering gender, men had slightly better OS than women, not corresponding with the data in the literature[4,7]. FAB subtypes had a significant effect on OS. The worst results were observed in RAEB-T, than in RAEB, RARS, RA and CMML subtype, similar with those in the literature.[9] OS correlated inversely with BM blast percentage, showed also in other studies.[24,25] Hemoglobin as a whole and stratified into subgroups did not show any impact on OS.[23] We could not demonstrate an impact of platelet count on OS. Also, prognostic significance of ANC was not demonstrated in our cohort.[7] Serum ferritin level ≥500 µg/l at diagnosis was a strong independent predictor of survival[12], although it was not the case in our cohort. Transfusion dependence is an independent prognostic factor for bad prognosis[15], although in our group the impact on OS was not significant. LDH is a factor sited as having predictive value[17], also proved in our cohort. Albumin is an independent prognostic factor in MDS patients[8], but, in our group it had not significant impact on OS. Comorbidities were an independent prognostic factor for OS, which corresponds with data from the literature.[1] Cardiac diseases were the most frequent comorbidities. In our cohort only 6 patients were analyzed for cytogenetic abnormalities, three of them with good prognosis (normal cytogenetics) and three of them (+8, inv16 and inv9; inv13) with intermediate prognosis.

We can conclude that beside BM blast percentage, FAB subtypes, LDH and comorbidities are independent prognostic factors for OS in MDS. This should be proved in larger cohort studies and later proposed to be considered for future revisions of IPSS in order to refine the prediction of prognosis in MDS.

Limitations in our study include retrospective analysis, insufficient data on cytogenetic analysis and impossibility to stratify patients according to IPSS score, lack of data on some variables that probably reflected on the results, making them different than those cited in the literature.

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ПОВРЗАНОСТ НА ПРОГНОСТИЧКИТЕ ФАКТОРИ СО ПРЕЖИВУВАЊЕТО КАЈ МИЕЛОДИСПЛАСТИЧНИТЕ СИНДРОМИ: СТУДИЈА НА КОХОРТА

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АПСТРАКТ

Вовед: Миелодиспластичните синдроми (МДС) се хетерогена група на заболувања во однос на клиничката слика, лабораториските наоди и очекуваните преживувања. Многу студии се превземени со цел да се одредат факторите кои можат да ги прецизираат предвидувањата на прогнозата за МДС.

Цели: Целта на оваа студија беше да се евалуираат прогностичките фактори кои имаат влијание врз преживувањето кај МДС.

Методи: ова е ретроспективна анализа на кохорта од 154 адултни пациенти (81 маж, 73 жени) со МДС дијагностицирани на Универзитетската клиника за хематологија, Универзитет „Св.Кирил и Методиј“, Скопје, Македонија, во периодот од јануари 2011 до јуни 2014 година. Собрани се демографски податоци, како и податоци за ФАБ поттиповите, третманот на пациентите и исходот од терапијата.

Резултати: Возраста и полот немаа влијание на преживувањето (p=.80847 и p=.974895, соодветно). Различните ФАБ поттипови имаа влијание врз преживувањето (p = .00757). Процентот на бласти во коскена срцевина (КС) корелираше значајно со преживувањето (p= .028026). Хемоглобинот, бројот на тромбоцитите и апсолутниот број на неутрофили (АБН) не влијаеа на преживувањето (p=. 179970, p= .386355 и p= .972602, соодветно). Трансфузиите не влијаеа на преживувањето (p= .445856), како ни албумините (p=.559900). Лактат дехидрогеназата (ЛДХ) и коморбидитетите влијаеа на преживувањето (p= .018895 и p = .02278, соодветно). Леукемична трансформација беше нотирана кај 7 (4.5%) пациенти. Морталитетот беше 35.1%.

Заклучок: ФАБ поттиповите, процентот на бласти во КС, ЛДХ, и коморбидитетите се независен предиктор за преживувањето и би требало да се земат во предвид при следни ревизии на Интернационалниот прогностички скоринг систем со цел да се рафинираат предвидувањата за прогнозата на МДС

Key words: миелодиспластичнен синдроми, прогностички фактори, преживување.

Original scientific paper

ПРОЦЕНКА НА РИЗИК ОД ПОЈАВА НА МАСОВНИ МЕДИЦИНСКИ ИНЦИДЕНТИ СО ХБИР АГЕНСИ ВО РЕПУБЛИКА МАКЕДОНИЈА

INCIDENT RISK ASSESSMENT OF MAJOR MEDICAL INCIDENTS WITH CBR AGENTS IN THE REPUBLIC OF MACEDONIA

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РЕЗИМЕ

Вовед: Се почестите закани од хемиски, биолошки и радиолошки агенси изнудуваат потреба од изработување на стратегија за превенција, детекција, ублажување на ефектот и подготвеност за брз и ефективен медицински одговор.

Цел: Основна цел на студијата е проценка на ризикот од масовни инциденти со ХБиР агенси во Р. Македонија и евалуација на системот за подготвеност и одговор на овој вид на закана по здравјето на населението.

Материјал и методи: Проценката на ризик од појава на масовни медицински инциденти со ХБиР агенси во Р. Македонија во овој труд ќе се одреди преку алгоритамска анализа на епидемијата на грип со вирусот A/H1N1 (пандемиски грип) 2009/2010 година , користејќи ја прилагодената метода на Cardona и сор., која за прв пат е употребена 2003 година.

Заклучок: ДДИ (Дизастер дефицит индекс) на РМ од 0,4, споредено со останатите држави, спаѓа во редот на држави со доволен човечки, економски и управувачки капацитет за одговор при масовни инциденти со ХБиР агенси. Комплементарниот ДДИ од 0,95 укажува дека издвоените 0,005% финансиски средства од републичкиот буџет се недоволни да ги покријат евентуалните загуби при овој вид на катастрофи.

Клучни зборови: ХБиР агенси, индикатори за проценка на ризик и подготвеност за одговор на катастрофи, медицина на катастрофи (disaster medicine).

ВОВЕД

Медицината на масовни повреди и кризни состојби (Disaster Medicine) е медицинска гранка која се занимава со подготовка на медицинскиот персонал и организирање на сите расположиви капацитети и ресурси на државата со цел навремен и адекватен медицински одговор при разни инциденти придружени со масовно нарушување на здравјето на населението.

Управувањето со масовните медицински инциденти предизвикани од ХБиР агенси директно се потпира на подготвеноста на здравствениот и јавно-здравствениот сектор – од детекција на настанот, идентификација на агенсот, лабораториска контрола, тријажа на повредените и/или заболените, медицински транспорт, прехоспитала и хоспитална грижа и медицинска рехабилитација.

Денес хемиските, биолошките и радиолошките катастрофи и инциденти опфаќаат значаен сегмент од целокупниот ризик по здравјето на населението во целиот свет. Човештвото се наоѓа под постојана закана од разни видови на токсични материи, микроорганизми и радиоактивни материјали. Истите можат да бидат ослободени и да предизвикаат големи човечки

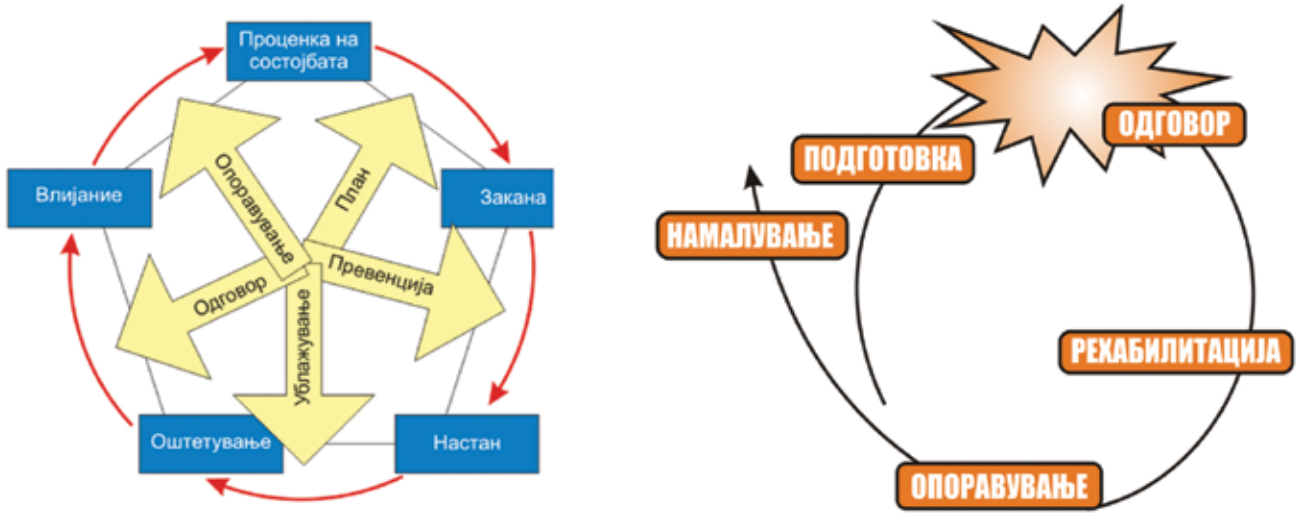
и материјални загуби во случаи на: технолошки/индустриски хаварии, природни катастрофи, воени дејствија, професионална изложеност или тероризам. Масовните човечки и материјални загуби кои настанаа во последниве две декади, како: хаваријата на нуклеарните централи на Фукушима , радиолошките катастрофи во Чернобил 1986 и Мајпури – Њу Делхи 2010, терористичкиот напад со гас Сарин во Токио, терористичките закани со сомнителни пратки контаминирани со спори на антракс во 2001, инцидентот 9/11 во Њу Јорк, контаминацијата на челик со Cobalt-60, користење на Polonium-210 како отров од страна на разузнавачките служби, контаминирањето на млекото со melamin, пандемијата на грип со вирусот A/H1N1 и др., укажуваат на итна потреба од специфична подготовка за превенција и одговор на здравствените системи, како основа за спасување на што поголем број на човечки животи и намалување на економските последици. (1,2,3)

Секоја земја мора да има соодветни системи за справување со катастрофите, а принциите на кои тие ќе се темелат се утврдени со соодветни меѓународни правила. Целта за нивното воспоставување е превенција на штетните последици и сочувување на човечките животи на локално и на меѓународно ниво. Водечкиот документ кој го утврдува Светската здравствена организација и претставува обврска за сите земји членки на СЗО е Меѓународниот здравствен правилник, кој во претходната негова верзија се однесуваше на следење и известување само на заразните болести со висок потенцијал за морбидитет, морталитет и ширење. (4,5,6). Ревизијата на Меѓународниот здравствен правилник од 2007 година (МЗП, 2007) обврзува на потреба за известување за сите настани кои ја загрозуваат националната и/или меѓународната заедница и бараат ангажирање на техничка и друга помош. Примената на овој правилник е обврска и за Република Македонија, па тоа не става пред нов предизвик за воспоставување на систем за следење и известување, но и за соодветно планирање и подготвеност за одговор на заканите и катастрофите.

Управувањето со катастрофите ги опфаќа следните фази:

- Проценка на состојбата,
- Предвидување на заканата,
- Подготовка и превенција,
- Управување со настанот,
- Одговор,
- Опоравување и
- Пост-дизастер евалуација/ревизија

Фазите во развојот на постапките што се неопходни за успешно управување и справување со катастрофите шематски се прикажани на приказ бр.1:



Приказ бр.1 – Фази во развојот на постапките за успешно управување и справување со масовни медицински инциденти

Правилната проценка на степенот на ризик од појава на масовен медицински инцидент со ХБиР агенси е основен предуслов за пристапување кон подготовка на хоспиталниот и нехоспитален систем во една држава, со цел намалување или минимизирање на последиците од истиот. (4)

Во досегашната пракса, проценката на ризик од појава на масовни медицински инциденти се одредуваше преку дескриптивна анализа на параметрите добиени од некоја претходна катастрофа или настан во кој бил регистриран голем број на заболени или повредени лица.

Индикаторите кои досега се користеа во вообичаената пракса и кои беа цел на дескриптивна анализа, се претставени во табела бр.1.

Табела бр.1. – Дескриптивни индикатори за проценка на подготвеност

Основни Индикатори	"Клучни Елементи" потребни за есенцијална припрема на здравствниот систем при медицински катастрофи и инциденти
Раководење	Национална легална рамка за мултисекторно управување при справување со масивни инциденти, Национален програм за здравствено управување при итни ситуации Институционален пристап на организирање на здравствениот систем во услови на масовни инциденти, Програмски компоненти на здравствениот програм за справување со итни состојби
Здравствени ресурси	Човечки ресурси за справување при медицински катастрофи и масовни инциденти
Медицински средства, вакцини и технологија	Медицински материјали и опрема за адекватен одговор при масовни повредени и заболени , која е на располагање
Здравствена информација	Системи на информативно управување кои се користени за намалување на ризикот и за адекватна медицинска подготовка Системи на информативно управување кои се користат за итен медицински одговор и опоравување Недостатоци во комуникација
Здравствено финансирање	Национални и субнационални стратегии за здравствена подготовка
Оперативност и ефикасност	Расположиви капацитети и можности Организирање на систем на служба за итна медицинска помош при катастрофи и масовни инциденти Организирање на хоспитално згрижување при масовни повреди Логистика и оперативна способност на службите за поддршка при масовни инциденти

Со цел да се избегне или намали субјективната компонента при користењето на дескриптивната анализа на параметрите при проценката на степенот на ризик и степенот на подготвеност на една држава за адекватно и навремено справување со појавата на масовните медицински катастрофи, Cardona и сор., развија нова т.н. алгоритамска методологија, која се базира на обработка на објективни односно егзактни параметри поврзани со вонредните медицински настани (9).

При тоа целиот овој систем на проценка се состои од одредување на 4 главни индикатори (индекси) и тоа:

1. **Дизастер дефицит индекс (ДДИ)**

   ДДИ = ПВЗ загуби (потврдени вкупни загуби од инцидентот) / Предвидени финансиски средства за вонредни настани

2. **Локален дизастер индекс (ЛДИ)**

   ЛДИ = ЛДИ(починати) + ЛДИ(афектирани) + ЛДИ(финансиска загуба)

3. **Превалентен дефицит индекс (ПДИ)**

   ПДИ = ПДИ(изложеност) + ПДИ(осетливост) + ПДИ(отпорност)

4. **Индекс на управување со ризик од појава на масовен медицински инцидент (ИУР)**

   ИУК =ИУКри + ИУКрр + ИУКум + ИУКфп / 4

   - РИ – идентификација на ризикот од појава на масовен медицински инцидент
   - РР – редукција (намалување) на ризикот
   - УМ – управување со масовниот медицински инцидент
   - ФП – финансиска поддршка

1. **Дизастер дефицит индекс (ДДИ),** го одредува ризикот на една држава од макроекономски и финансиски аспект во случај на катастрофа. Тој се користи за проценување на критичниот ефект за време на изложеноста на државата од инцидентот, како и за проценка на нејзините финансиски способности за покривање на настанатите штети. Истиот се одредува како број на проценети евентуални загуби поделен со предвидените годишни финансиски средства за таа намена во една држава:

$$ДДИ = \frac{\text{ПВЗ загуби (потврдени вкупни загуби од инцидентот)}}{\text{Предвидени финансиски средства за вонредни настани}}$$

Комплементарниот дизастер дефицит индекс - ДДИ' го прикажува односот помеѓу предвидените средства кои државата ги одредува на годишно ниво за покривање на евентуални загуби од масовни медицински инциденти и реално потрошените средства за таа намена кои се прикажани на крајот од испитуваната календарска година. На тој начин овој индекс дава конкретни насоки за правилно и адекватно планирање на средствата кои треба една држава да ги одвојува за покривање на загубите од вонредни настани поврзани со масовни заболени или повредени.

$$ДДИ' = \frac{\text{Одвоени средства за медицински масовни инциденти за една година}}{\text{Прикажани годишни расходи за вонредни настани за таа година}}$$

2. **Локален дефицит индекс (ЛДИ),** дава приказ на социјалната, економска и здравствена вулнерабилност на населението во одредени региони во државата, кои се изложени на чести и повторувачки медицински инциденти со ХБиР агенси. Овој индекс ја презентира просторната варијабилност и дисперзија на ризикот од мали и рекурентни вонредни настани во една држава.

ЛДИ се одредува како сума од три локални суб-индикатори кои се калкулирани врз база на податоци дадени за бројот на мртви – К, бројот на луѓето афектирани во настанот – А и вкупните финансиски загуби – L :

ЛДИ = ЛДИК + ЛДИА + ЛДИL

Локалниот дефицит индекс (ЛДИ) се одредува врз основа на податоци добиени од претходно настанати инциденти (9).

ЦЕЛИ НА ТРУДОТ

1. Изработка на методологија за алгоритамски пристап за проценка на степенот на ризик од појава на масовен медицински инцидент со ХБиР агенси и проценка на степенот на подготвеност за управување со истиот преку користење на соодветни индикатори.
2. Проценка на степенот на ризик од појава на масовен медицински инцидент од ХБиР агенси во Р. Македонија, преку индикаторите : ДДИ (дизастер дефицит индекс), ДДИ' (комплементарен дизастер дефицит индекс), ЛДИ (локален дизастер индекс) и ЛДИ' (комплементарен локален дизастер индекс), користејќи ги параметрите од пандемијата на грип со вирусот A/H1N1, во Р. Македонија во 2009 година.

МАТЕРИЈАЛ И МЕТОДИ

Проценката на ризик од појава на масовен медицински инцидент со ХБиР агенси и вулнерабилноста на населението, се направи преку ретроспективна анализа на епидемијата на грип со вирусот A/H1N1 (пандемиски грип), која во рамките на пандемијата ја зафати и Република Македонија, во периодот од 40-тата недела во 2009 година до 5-тата недела во 2010 година. При тоа добиените податоци математички се обработија по модифицираната методата на Cardona и сор., со употреба на специфични индикатори на ризик.

Индикаторите за евалуација при изработка на трудот се собраа, анализираа и обработија во просториите на Институтот за превентивна медицина во Скопје.

Методи на истражување

Методи за проценка на ризикот од масовни инциденти - индикатори на ризик

Во истражувањето како индикатори за проценка на степенот на ризик од масовни инциденти со ХБиР агенси во Р. Македонија се користени и статистички обработени 2 од 4-те т.н. главни "индикатори на ризик" и еден комплементарен индекс и тоа:

1. Дизастер дефицит индекс (ДДИ)

   ДДИ = ПВЗзагуби (потврдени вкупни загуби од инцидентот) / Предвидени финансиски средства за вонредни настани
2. Комплементарен дизастер дефицит индекс – ДДИ'

$$ДДИ' = \frac{\text{Очекувани годишни трошоци}}{\text{Потврдени годишни расходи}}$$

3. Локален дизастер индекс (ЛДИ)

   ЛДИ = ЛДИ(починати) + ЛДИ(афектирани) + ЛДИ (финансиска загуба)

РЕЗУЛТАТИ:

- -Република Македонија во 2009 година за вонредни настани предвидела вкупно X_2 милиони денари од државниот буџетот кој изнесувал X_1 милијарди денари или 0,005%. Од овие средства: на ЦУК (Центарот за управување со кризи) му доделила

X_3 денари или X_4 евра, што изнесува 0,001% од вкупниот буџет, а на Дирекцијата за заштита и спасување X_5 денари или X_6 евра т.е. 0,004% од буџетот.

$$ДДИ = \frac{X_1 \text{ евра}}{X_2 \text{ евра}} = 0,4$$

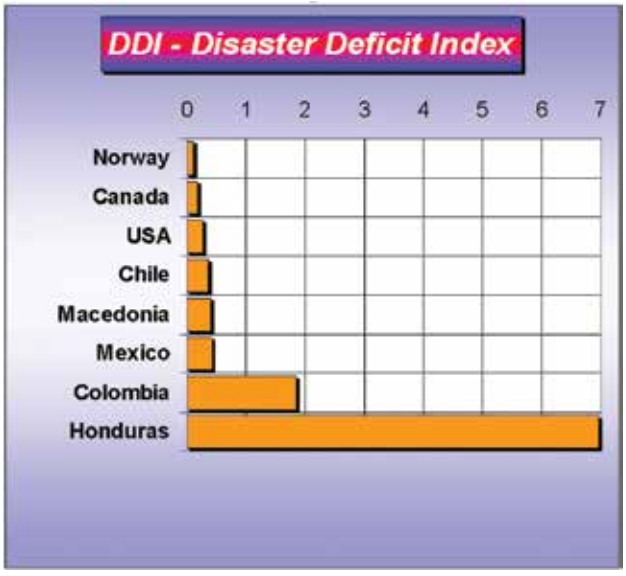
- -На крајот на годината ЦУК прикажал вкупен расход од X_7 денари (плус дополнителни X_8 и X_9 денари) или вкупно X_{10} денари, а Дирекцијата за заштита и спасување прикажала вкупен расход од X_{11} денари односно X_{12} евра.

Овие податоци беа користени за пресметување на комплементарниот дизастер дефицит индекс (ДДИ') за Р. Македонија за 2009 година. Од пресметка произлегува дека:

$$ДДИ' = \frac{X_2 \text{ евра}}{X_{13} \text{ евра}} = 0,95$$

Дизастер дефицит индексот во повекето земји во развој се движи од 0,37 во Чиле до 6,96 во Хондурас. Во европските земји и САД овој индекс се движи помеѓу 0,11 во Скандинавските земји и 0,80 во земјите на Југоисточна Европа. Вредностите на ДДИ од 0,4 и ДДИ' од 0,95 добиени во текот на нашето истражување покажуваат дека Р. Македонија спаѓа меѓу државите која има макроекономски и финансиски капацитет да се справи со можни масовни медицински инциденти со ХБиР агенси. (Приказ бр.2)

Приказ бр.2 Вредности на ДДИ на Р. Македонија во споредба со други држави



Проценка на Локален Дизастер Индекс (ЛДИ)

За време на пандемијата 2009 година, Р. Македонија ги претрпела следните човечки и материјални загуби:

ЛДИ = 32 (починати) + 51599 (афектирани) + 4 357 682 евра (загуба)

Анализирајќи ја епидемијата на грип со A/H1N1 во 2009/10 година во Р. Македонија гледано по региони , истражувањето ни ги стави на располагање следните податоци:

ЛДИ$_А$ - според бројот на заболени на прво место бил градот Скопје со 16.314 (31,6%), а потоа следат: Куманово 6.439 (12,5%), Прилеп 3.701 (7,2%), Струмица 3.242 (6,3%), Тетово 3.142 (6,1%) и Битола 3.064 (5,9%).

ЛДИ$_К$ - застапеноста на смртноста од инцидентот по региони била следната:

Скопје 15, Тетово 4, Кочани 3, Битола 2, Куманово 2, Кручево 1, Велес 1, Охрид 1, Струмица 1 Богданци 1 и Д. Хисар 1 починат.

ЛДИ$_л$ - најголеми финансиски загуби се регистрирани во градот Скопје со проценети најмалку 2.075.843 евра, а потоа следат општините: Куманово со 819.318 евра, Прилеп со 47.092 евра, Струмица со 41.252 евра, Тетово со 39.979 евра итн.

Податоците укажуваат дека најголема концентрација на афектирани и починати, како и најголеми финансиски загуби во Република Македонија треба да се очекуваат во Скопје и поголемите градови и тоа пред се поради поголемата концентрација на населението.

Табела бр. 2 Преглед на број на афектирани , починати и вкупни финансиски загуби од пандемскиот грип 2009 година по општини

Општина	Бр. на афектирани	Бр. на починати	Финансиски загуби во евра
Скопје	16 314 (31,6%)	15	2 075 843
Куманово	6439 (12,5%)	2	819 318
Прилеп	3701 (7,2%)	0	47 092
Струмица	3242 (6,3%)	1	41 252
Тетово	3142 (6,1%)	4	39 979
Битола	3064 (5,9%)	2	38 528

ДИСКУСИЈА:

Вообичаено секоја година во Република Македонија се јавуваат во просек околу 24 118 случаи на грип (меѓу 20356 и 27000). Справувањето со овој просечен број на заболени не бара дополнителни финансиски средства, ниту вонредно ангажирање на поголем број медицински персонал.

Користејќи ги достапните и релевантни податоци за состојбата за време на пандемскиот грип со вирусот А/H1N1, а со цел да се пресмета ДДИ (дизастер дефицит индексот на Р. Македонија) утврдени беа следните состојби:

- во периодот од 40-тата недела 2009 до 5-тата недела 2010 година во Р. Македонија регистрирани биле вкупно 51.599 случаи на лабораториски докажан грип со вирусот А/H1N1,
- регистрираниот морбидитет од ова заболување изнесувал 252,9/10000 жители,
- од вкупниот број на случаи во 2009 година биле регистрирани 45.681 болен, што претставува највисок број на заболени за истиот период во последните 30 години.

Во продолжение е направена проценка на дополнителното финансиско оптеретување за нашата земја како последица на потребата за справување со пандемискиот грип. Пандемскиот грип 2009 година, вонредно ја оптеретил Р. Македонија со најмалку 267.135.930,00 денари или 5.225.489,00 евра, при што:

- за вонредни прегледи биле потрошени 35.631.180,00 денари или 581.259,00 евра (според ФЗО цената на еден преглед во 2009 година изнесувал 780 денари , односно 45681x780ден.= 35 631 180ден),
- за болничко лекување на 3.195 хоспитализирани, биле потрошени 59.107.500,00 ден или 964.230,00 евра (3.195 пациенти x 1850 ден./болнички ден), при е земено дека просечното лекување на секој пациент траело по 10 денови.просечно 10 дневно лекување),
- за вакцини против свински грип потрошени биле вкупно 225.584.000,00 денари или 3. 680.000,00 евра (при тоа вакцинирани биле 17.000 лица а 75000 вакцини останале неискористени поради поминат рок на траење во 2011 година).

При пресметување на ДДИ и Комплементарниот ДДИ за Р Македонија, калкулацијата податоците е изведена во однос на делот од државниот буџет за 2009 година, наменет за овој вид на настани, а кој изнесувал 0,005%. (Висината на средствата е прикажана со X вредности поради заштита на податоци)

ЗАКЛУЧОК:

1. Воведувањето на т.н. "систем на индикатори" овозможува:
   а) Алгоритамска презентацијата на податоците за потенцијалниот ризик од масовни инциденти со ХБиР агенси.
   б) идентификација на вулнерабилноста и управувачките капацитети на здравствените системи и
   в) размена на технички информации помеѓу јавните здравствени системи, управните органи и носителите на економска и финансиска поддршка во државата.
2. Во споредба со поголемиот број на држави во светот, Република Македонија со вредност на ДДИ од 0,4 спаѓа во редот на држави кои располагаат со доволен економски, управувачки и човечки потенцијал за адекватно планирање и справување со масовни медицински инциденти со ХБиР агенси.
3. Диспропорцијата меѓу дизастер дефицит индексот (ДДИ) кој изнесува 0,4 и комплементарниот дизастер дефицит индекс (ДДИ') кој изнесува 0,95 укажува дека издвојувањето на 0,005% од вкупниот буџет на државата за оваа намена би можел да биде недоволен за покривање на евентуалните загуби при оваков вид на катастрофи.

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INCIDENT RISK ASSESSMENT OF MAJOR MEDICAL INCIDENTS WITH CBR AGENTS IN THE REPUBLIC OF MACEDONIA

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SUMMARY

Introduction: The persistent threats of major medical incidents with chemical, biological and radiological agents elicit need for preparation of strategy for prevention, detection, effect mitigation and preparedness for fast and effective medical response.

Aim: The basic goal of the study is risk assessment of major incidents with CBR agents in the Republic of Macedonia and evaluation of the system and its preparedness for response from this kind of threat for the public health.

Material and methods: The risk assessment of major incidents with CBR agents in the Republic of Macedonia in this study will be determined with algorithm analysis of the epidemic with A/H1N1 virus (pandemic flu), 2009/10, using the adjusted method of Cardona and associates, which was applied for the first time in 2003.

Results: DDI (Disaster Deficit Index) of the R of M of 0,4, compared with other countries, is considered as country with sufficient human, economical and governing capacities for respond to major medical incidents with CBR agents. DDI' (Complementary Disaster Deficit Index) of 0,95 shows that 0,005% of the finances of the state budget are not sufficient to cover the possible lost from this kind of catastrophe.

Key words: CBR agents, risk assessment indicators, indicators for assessment of preparedness for response to disaster, disaster medicine,

Original scientific paper

THE PILOT STUDY ABOUT DENTAL CARIES EXPERIENCE AMONG 15-YEARS OLD (SECONDARY SCHOOL) CHILDREN IN THE SOUTHEAST REGION OF THE REPUBLIC OF MACEDONIA

ПИЛОТ СТУДИЈА ЗА ЗАСТАПЕНОСТА НА ДЕНТАЛНИОТ КАРИЕС КАЈ 15-ГОДИШНИТЕ АДОЛЕСЦЕНТИ ОД ЈУГОИСТОЧНИОТ РЕГИОН НА РЕПУБЛИКА МАКЕДОНИЈА

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ABSTRACT

Aim: The aim of this study was to assess dental caries in 15-year-old children attending regular public secondary school in Strumica.

Methods: The study was conducted during 2013 year for adolescents aged 15. In this cross-sectional study, secondary school children from first grades (N=90) were selected from one Secondary School in Strumica. Participants dental status was evaluated using the 1997 World Health Organization caries diagnostic criteria for Decayed, Missing or Filled Teeth (DMFT) by 2 calibrated examiners. P value ≤0.05 was considered statistically significant.

Results: The total number of children in the sample was 90, comprising 32 (35.56 %) females and 58 (64.44 %) males. The mean DMFT was 2.8444, with standard deviation (SD) of 3.2148 and 95% confidence interval (CI) of 2.1711-3.5178. Significant caries (SiC) index was 6.33. The prevalence of caries-free children was 26.67 %. The percentage of untreated caries or the ration of D/DMFT was 0.5586 (55.86 %).

Conclusions: The present study provides some evidence of low caries prevalence of 15 aged adolescents from southeast region of our country. Incorporating of the other schools from different parts of the Southeast region have to be done in the future.

Key Words: Caries, caries prevalence, DMFT index, Macedonia, school children.

INTRODUCTION

Decrease in dental caries in the world has occurred together with a skewed distribution of caries prevalence, with a small part of the population concentrating care or need for dental treatment (1).Due to this skewed distribution, a new index called significant Caries Index (SiC) was introduced in 2000, to focus attention to those individuals with higher caries indexes in the population studied (1, 2).

Figure 1

Figure 2

The Southeast Region (Figure 1) is located in the extreme southeast part of the country and comprises the Strumica-Radovish and Gevgelija-Valandovo basins, the Strumica River valley and the lower course of the Vardar River. In 2011, 8.4% of the total population in the Republic of Macedonia lived in this region. The region covers 10.9% of the total land area of the country and has a population density of 63.2 people per km^2. The extensive hydrographic network, the great number of sunny days, the climate and the favorable pedologic conditions characterize the region as predominantly agricultural. The large-scale production of high-quality early vegetables, fruits and industrial crops enable the development of the canning and food processing industry, for which this region is renowned. In recent years, there has been an increasing trend in tourism, shown by the increased number of accommodation facilities, tourists and nights spent in the region. This is mostly due to the revitalization of the Dojran Lake and its exploitation for tourism. Another specific feature of the region is that in 2011, compared to the other regions, it had the highest activity and employment rates (71.0 and 64.4, respectively) and the lowest unemployment rate (9.3) (3).

The current population of the Southeastern Statistical Region is 171.416 citizens, according to the last population census in 2002. The largest ethnic group in the Southeast region are the Macedonians 90.4%, Turks 7.4%, Serbs 0.7% and others 1.5% (Figure2).

In the Republic of Macedonia, a system for monitoring and registration of dental caries exists, but the statistics is not coordinated with that of the European Union and the WHO and the existing legal obligations are not respected. For that reason, database with relevant statistical indicators (DMFT) do not exist[4].

However, epidemiological data representing oral health status, particularly referring to dental caries among Macedonian school children are still insufficient and incomplete.

WHO recommends performing oral health epidemiological studies in certain key age groups: adolescents from 12 and 15 years old and in children 5 to 6 are two of these. From an epidemiological point of view, dental caries is widely disseminated across the world and may be considered a public health problem in Macedonia. It results from differences between normal interactions of the teeth surface, microbial biofilm, oral hygiene and dietary habits, and still equally affects individuals of all ages (5). Some reports have identified different socioeconomic and sociodemographic variables associated with caries, such as age (6, 7, 8) and being female (9, 10).

Diverse strategies have been carried out to bring under control the dental caries problem, mainly by means of fluoridation in its various approaches (11,12).

The objective of the present study was to expand the information with regard to adolescent oral health by evaluating experience, prevalence, and severity of dental caries in adolescents (15-years old) from Southeast region of the Republic of Macedonia.

AIM

The aim of this study was to assess the dental caries prevalence and experience of 15-year-old secondary school children within the Southeast Region of the Republic of Macedonia and evaluate how their disease pattern is related to variables, such as gender, rural-urban areas of the population.

METHODS

The sample for the present cross-sectional study was 90 school children from four classes of first grades (electrical technicians, transport and shipping technicians, electromechanical technicians and traffic technicians) attending secondary municipality school "Nikola Karev" in Strumica. Based on the information from the Macedonian Institute of Statistics [13] there are approximately 6790 children attending regular secondary schools in this region. In the municipality Strumica live 54 676 inhabitants. In the municipality of Strumica, three secondary schools exist in which 3807 pupils attend the schools.

Written permission was obtained from the Regional Education Authority and parents or guardians of the pupils. Permission for the study was obtained from the school authorities, who sought and obtained consent from the parents of the children concerned.

It was decided to use cluster sampling because it was more economical and achievable within the constraints of resources and finance. Four classes of children in the secondary municipality school "Nikola Karev" were included in the study. Ethical approval was obtained from the Ministry of Health.

The study was conducted over a period of one month in April 2013.Data were collected by means of clinical examinations in daylight using plain dental mirrors and probe, which took place in separate room with the subject seated on the dental chair.

Inclusion criteria for dental caries were diagnosed clinically and detected as visually apparent cavitations, discolorations of the enamel and/or visually diagnosed recurrent caries lesions. No radiographs were taken at that stage. Clinically acquired data was stored for each patient separately. DMFT scores were evaluated according to the WHO criteria (5). The following criteria also included D component for untreated caries, M for teeth which were missing due to caries, and F for fillings that were present at the time of examination. Caries prevalence was classified according to a scale as an indicator of oral health, DMFT 0 to 1.1 (very low prevalence); DMFT 1.2 to 2.6 (low prevalence); DMFT 2.7 to 4.4 (moderate prevalence); DMFT 4.5 to 6.5 (high prevalence) and DMFT>6.6 (very high prevalence).

Children from first grades of secondary schools are around 15 years old. At this age the permanent teeth have been exposed to the oral environment for 3-9 years. The assessment of caries prevalence is therefore often more meaningful than at 12 years of age. Oral exams

were performed by two examiners, who were previously trained and standardized. WHO's criteria for detection of caries were employed (kappa interexaminer =0.93; intraexaminer =0.98). Two calibrated dental examiners conducted the dental examination and the clinical part of the form was filled in by two other trained dentists (kappa values for inter-examiner reliability was 0.93). World Health Organization 1997 [5] caries diagnostic criteria were followed. The DMFT, Decayed, Missed, or Filled Surfaces (DMFS) and SiC indices were used to evaluate children dental caries experience. A new index called the 'Significant Caries Index' (SiC) was recently proposed by the World Health Organization (WHO) to draw attention to those individuals with the highest caries scores in each population [1, 2 Bratthall].This index is calculated as of the DMFT scores (mean decayed, missing, and filled teeth) and the third of the population with higher DMFT scores are the bases to calculate SiC (2).

STATISTICAL ANALYSIS

Simple descriptive statistical tests were used in the form of percentage and frequency distribution. For statistical analysis of DMFT scores to access the oral health among secondary school children, the R software environment for statistical computing was used (http://www.r-project.org/).

One way analysis of variance (ANOVA) was used to find the difference in mean DMFT between sex groups and area groups. Kruskal-Wallis rank sum test was used to find the difference in mean DMFT of the children living in different cities.

RESULTS

Statistical data that was collected were from secondary school children in the Southeast Region of the Republic

of Macedonia. For each child following data was recorded: age, sex (male or female), ethnic group, area (urban or rural), city/village, number of decayed teeth (DT), number of missing teeth (MT) and number of filled teeth (FT). Then, the DMFT score, the sum of DT, MT and FT, was calculated and recorded for each child. The size of the statistical sample was 90. In table 1 and 2, the distribution of individuals in studied sample is given.

The mean value of the DMFT index for the whole sample is 2.844 , with standard deviation (SD) of 3.214, and 95% confidence interval (CI) of 2.1711 - 3.5178. In the whole sample, 24 (26.67%) % of the individuals were caries free (DMFT=0). As a complement of the mean DMFT value, for the whole sample, the SiC index of 6.33 was calculated.

In Figure 3, the distribution of DMFT score is given. The Shapiro-Wilk test for normality was performed, and the hypothesis that the data is normally distributed is rejected with p-value 4.677e-10 << 0.05.In Figure 4, the boxplot of DMFT score in the whole sample is given, showing the range, quartiles and outliers.

The mean DMFT index with SD and 95% CI were calculated for each group (according to sex orientation and area of living) and these results are reported in Table 3. Kruskal-Wallis rank sum test is a nonparametric test, so the normality of data is not necessary. With this test the equality of medians is tested, and it achieves its best performance for sample sizes 5 and larger. There are not statistically significant differences between DMFT medians for individuals who live in Strumica and Radovis, with p-value = 0.3633 > 0.05 (Table 4).Distributions of DMFT scores for some of the groups are illustrated by the boxplots (Figure 5 and 6).

One way Analysis of Variance (ANOVA) was performed to see if there are differences in mean DMFT index between the groups, and corresponding p-values are reported in Table 3.One way analysis of variance (ANOVA) with p-value = 0.7667 > 0.05, show that there are not statistically significant differences among males and females (Table 3 and Figure 5).

While, one way analysis of variance (ANOVA) with p-value = 0.2834 > 0.05, show that there are not statistically significant differences between mean DMFT scores for individuals who live in urban and rural area (Table 3 and Figure 6).

The DMFT components, DT, MT and FT, were also analyzed. The frequencies, mean values, SD's and 95% CT's are reported in Table 5 and Figure 7.

DISCUSSION

Data about oral health in adolescents is sparse in the scientific literature, not only in Macedonia but also in general (11). In this context, one contribution of the present findings is to help fill the existing information gap for this age group. First, we found that caries prevalence was close to 75 percent in this population – that is,three out of every four adolescents had at least one tooth decayed.

This prevalence (73.33 percent), the DMFT index (2.8444 ± 3.2148) and the SiC (6.33) observed in 15-year-old adolescents were lower than those reported in the other studies from Balkan countries-for example, the findings reported by Markovic et al (14). Among 15-year-olds from Bosnia and Herzegovina, the DMFT was 7.6 (SD ± 4.1), SiC was 9.2 (SD ± 1.2), and filled teeth constituted the major part of the index. In the study from Lalić M et al.(15) conducted in Belgrade, the capital of Serbia, DMFT index of 15-year old children was 5.84.

Following WHO methodology made it possible to compare our findings with other national surveys.The first nationwide survey according to WHO standards on the prevalence of dental caries from this region (the region of former Yugoslavia) was carried out in 1986 (16). Results showed the prevalence of dental caries in the Yugoslav child population to be very high, with a mean DMFT for 12-year-olds of 6.1 and 9.6 for 15-year-olds(16Vrbic,Vulovic). Slovenia was the only former Yugoslav country where a remarkable decrease in caries prevalence was recorded (17).

In the analytical study of Nishi et al. published in 2002, all the country except three (Bolivia, Costa Rica and Honduras) has DMFT mean values less than 3.Only Jamaica, Senegal and Sweden showed SiC indices that were less than 3 DMFT(1).

The SiC is part of DMFT, calculated on one third of population with the highest caries scores and it is always higher than DMFT. In general, the greater the mean DMFT a country has, the greater the SiC index (1). Some other studies reported average DMFT score in the group of 15 years old subjects 1.8 in Germany (18), 3.19 in Greece (19), 4.3 in Slovenia (17), and 6.6 in Bosnia (20).

In the investigation conducted from May 2003 to May 2004, Ambarkova et al. (21) studied the fluoride concentration in the sources of drinking water in 92 localities from Macedonia. Optimal fluorine contents was found in the tap water from village Kolešino, and

suboptimal in the villages Balinci, Marvinci, Brajkovci, Murtino and Pirava. Unfortunately, our study did not include students who were born in these villages, except one student from Murtino.

Since health promotion activities in Macedonia are not systematically and consistently implemented, and the health care system is oriented toward treatment rather than prevention of oral diseases, DMFT score in 15 year-old adolescents of 2.8 is not so worse.

However the value of 2.8 DMFT for15 year old children from Strumica is even better than DMFT value find by Oulis et al. in Greece, but worse than the value of DMFT estimated in Germany by Schiffner et al (18). This region of our country is economically more developed compared to other regions. Strumica is the main agricultural center in the Republic of Macedonia, with good developed food industry, textile factories and a developed domestic and international trade network. This is due to its location and favorable climate. Strumica is the largest city in the eastern Republic of Macedonia, near the Novo Selo-Petrich border crossing with Bulgaria. Relatively good oral health of adolescents from this region and DMFT index of 2.84 maybe is due to their adequate attitudes and habits.

In Central and Eastern European countries, increased prevalence of dental caries in school children and adolescents is associated with inconsistent implementation of preventive measures and lack of organized health promotion activities (22).

CONCLUSIONS:

The prevalence of dental caries in secondary school children from Strumica was 73.33%. The mean DMFT was 2.844 ± 3.214. Significant caries (SiC) index was 6.33. The prevalence of caries free children was 26.67 %.

The present study provides some evidence of low caries prevalence of 15 aged adolescents from southeast region of our country. Incorporating of the other schools from different parts of the Southeast region have to be done in the future.

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Table 1. Distribution of individuals in studied sample (gender, area).

Area \ Sex	Male	Female	Total
Urban	31(34,44%)	9 (10%)	40 (44,44%)
Rural	27(30%)	23 (25,55%)	50 (55,56%)
Total	58 (64,44%)	32 (35,56%)	90 (100%)

Table 2. Distribution of individuals in studied sample (city/village of living ,ethnic affiliation).

City/Village of living \ ethnic affiliation	Macedonians	Turks	Total
Strumica	31 (34.44 %)	2 (2.22 %)	33 (54, 33%)
Radoviš	6 (6.67 %)	0 (0%)	6 (11, 19%)
Vasilevo	3 (3.33 %)	0 (0%)	3(10, 24%)
Novo Selo	4 (4.44 %)	0 (0%)	4(3, 15%)
Kukliš	3 (3.33 %)	0 (0%)	3 (3.33 %)
Bansko	3 (3.33 %)	0 (0%)	3 (3.33 %)
Vladevci	3 (3.33 %)	0 (0%)	3 (3.33%)
Gradošorci	0 (0 %)	1 (1.11 %)	1 (1.11 %)
Ilovica	3 (3.33 %)	0 (0%)	3 (3.33%)
Others	31(34.44 %)	0 (0%)	31 (21, 26%)
Total	87 (96.67 %)	3 (3.33 %)	90 (100%)

Table 3. Caries free individuals, DMFT scores and equality tests for mean DMFT index

	caries free	DMFT Mean (SD)	DMFT 95% CI	p-value
whole sample	24 (26.67%)	2.844 (3.214)	2.1711-3.5178	
sex groups				
male	15 (25.86%)	2.913 (3.516)	1.9894-3.8382	0.7667
female	9 (28.12%)	2.719 (2.630)	1.7704-3.6671	
area groups				
urban area	11 (27.50%)	3.275 (3.9677)	2.0061-4.5439	0.2834
rural area	13 (26.00%)	2.500 (2.443)	1.8056-3.1944	

Table 4 Caries free individuals, DMFT scores and equality tests for mean DMFT index (city/villages)

		DMFT				
	caries free	Mean (SD)	95%CI	DMFT median	95%CI for DMFT median with Wilcoxon signed rank test	p-value
city/village of living						
Strumica	10 (30.30%)	2.848 (3.073)	1.759-3.938	2.00	2.000001 - 5.000031	0.3633
Radoviš	6 (6.67%)	5.833 (7.278)		4.00	1 - 20	

Table 5. DT, MT, FT frequencies and scores for the whole sample

	frequency	Mean (SD)	95% CI
DT	55.86%	1.589 (2.565)	1.052-2.126
MT	9.37%	0.267 (0.699)	0.120-0.413
FT	34.77%	0.989 (1.821)	0.608-1.370

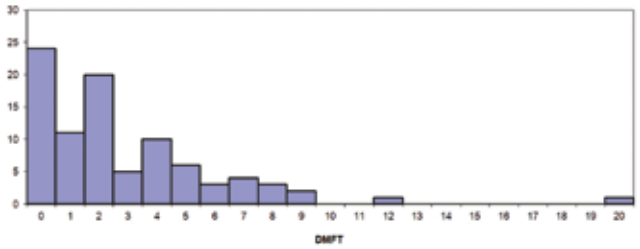

Figure 3. Distribution of DMFT score in the whole sample

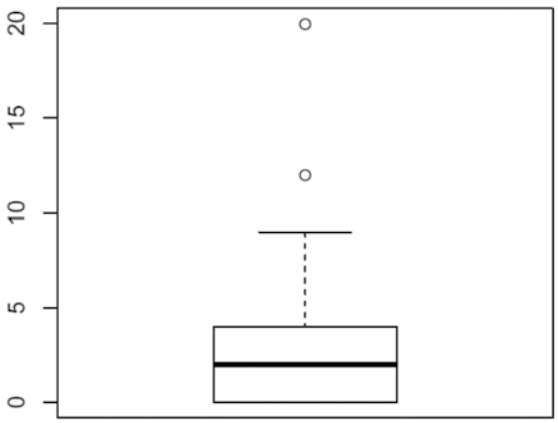

Figure 4. Boxplot of DMFT score in the whole sample.

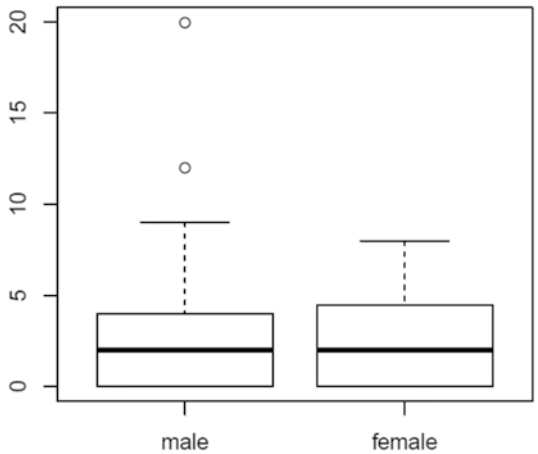

Figure 5. Boxplots of DMFT score for sex groups.

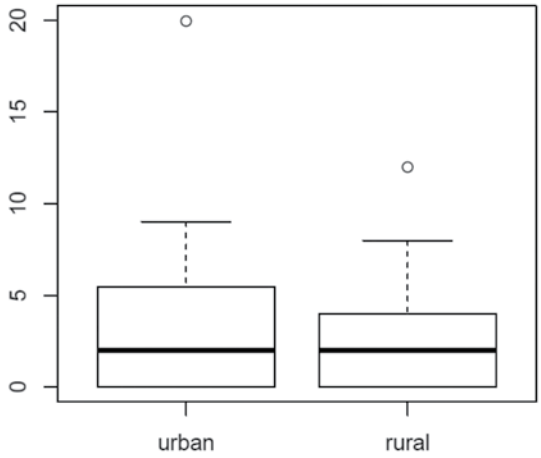

Figure 6. Boxplots of DMFT score for area groups.

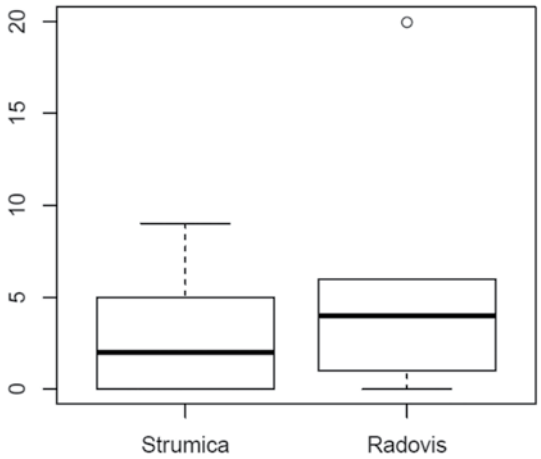

Figure 7. Boxplots of DMFT score for Strumica and Radovis.

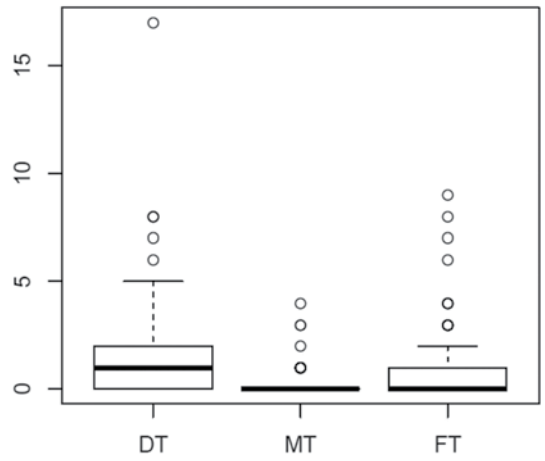

Figure 8. Boxplots of DT, MT and FT score in the whole sample.

ПИЛОТ СТУДИЈА ЗА ЗАСТАПЕНОСТА НА ДЕНТАЛНИОТ КАРИЕС КАЈ 15-ГОДИШНИТЕ АДОЛЕСЦЕНТИ ОД ЈУГОИСТОЧНИОТ РЕГИОН НА РЕПУБЛИКА МАКЕДОНИЈА

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АБСТРАКТ

Цел на оваа студија е да се одреди застапеноста на денталниот кариес кај 15-годишни деца кои ги посетуваат редовните јавни училишта во Струмица.

Методи: Испитувањето е спроведено во текот на 2013 година кај адолесценти од 15 години. Кај оваа на напречен пресек студија, учениците од средното училиште од прва година (N=90) беа селектирани од едно средно училиште од Струмица. Денталниот статус на учесниците во испитувањето се одредуваше со користење на дијагностичките критериуми на Светската Здравствена Организација за кариесот, преку кариозните, екстрахираните и пломбираните заби (КЕП) од 1997 година, од страна на двајца калибрирани испитувачи. П вредноста ≤ 0.05 се сметаше за статистички значајна.

Резултати:Вкупниот број на децата во примерокот беше 90, сочинувајќи 32 (35.56%) деца од женски и 58 (64.44%) деца од машки пол. Средната вредност на КЕП индексот изнесуваше 2.8444, со стандардна девијација (SD) од 3.2148 и 95% интервал на доверба (CI) од 2.1711- 3.5178. Сигнификантниот кариес индекс (SiC) изнесуваше 6.33.Застапеноста на децата без кариес беше 26.67%. Процентот на заби со нетретиран кариес или односот помеѓу забите со кариес и вкупниот КЕП изнесуваше 0.5586 (55.86 %).

Клучни зборови: кариес, преваленција на кариес, КЕП индекс, Македонија, училишни деца.

Original scientific paper

EFFECT OF SYNBIOTIC SOYMILK ON INTESTINAL MICROBIOTA AND LIPID PROFILE IN ADULT SPONTANEOUSLY HYPERTENSIVE RATS

ВЛИЈАНИЕ НА ФЕРМЕНТИРАНО СОЈА МЛЕКО НА ЦРЕВНАТА МИКРОФЛОРА И ЛИПИДЕН ПРОФИЛ КАЈ СПОНТАНО ХИПЕРТЕНЗИВНИ СТАОРЦИ

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ABSTRACT

The aim of the study was to examine the influence of a new synbiotic fermented soymilk on microbiota and lipid profile in rats. In addition body weight, and stool consistency were also investigated.

Material and methods: Soy milk fortified with prebiotic (Synergy1) was fermented with probiotic L casei-01. The viable L casei-01 counts in fermented end product were 11.49±0.13 log10 cfu mL-1. 1 ml of synbiotic fermented soymilk was administered daily to six months old male spontaneously hypertensive rats (SHR's). After 4 weeks treatment, jejunal, illeal, colon and fecal samples were analyzed for Lactobacillus spp, E coli, Enterococcus spp and Staphylococcus spp viable counts. Cholesterol, triglycerides and HDL concentrations in blood samples were determined.

Results: The significantly higher viable Lactobacillus spp counts followed with significantly decreased E coli and Enterococcus spp counts in all samples were observed in treated vs. control group. Staphylococcus spp counts were significantly decreased in colon samples. The difference in lipide profile was insignificant.

In conclusion, synbiotic fermented soymilk significantly improved the composition of the intestinal microbiota in rats. The lipid profile of healthy adult spontaneously hypertensive rats was not altered.

Key words: L. casei, Synergy 1, spontaneously hypertensive rats, intestinal microbiora, lipid profile

INTRODUCTION

Intestinal microbial ecosystem comprised of various bacteria with diverse metabolic capacity influence the health status of the host. There is a complex relationship between diet and intestinal microflora. Expanding interest in healthier diet challenged researchers to design functional food, food that not only provide basic nutrition, but also has the ability to provide health benefit effect. Some of health claims are prevention of chronic diseases such as GI disorders, cardiovascular disease, cancer, osteoporosis and healthier aging (1).

Examples of functional ingredients which can be incorporated in food products to obtain functional foods are probiotics and prebiotics i.e. synbiotics. Probiotics are defined by FAO/WHO (2002) as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (2). Probiotic bacteria yield the health

benefits due to their interactions with the microbiota in gastrointestinal tract (3). However, insufficient viability and survival of these bacteria in the food product and during the transit in the upper intestine remains a problem, which can be solved by adding a prebiotic. Prebiotics acting as a support to the probiotic growth contribute to increased number of live probiotic cells and potentiate their effects in the delivery matrix as well in the gut. "A prebiotic is a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well-being and health" (4). Utilization of prebiotics is strain specific and proper choice of propre mixture in functional food development is essential. According to our previous study, oligofructose - enriched inulin (Synergy 1) is considered as favorable prebiotic for the synbiotic mixture (5), thus for the preparing of our functional soymilk, this prebiotic was chosen.

Various dietary strategies based on probiotic interventions have been proposed after establishing strong relationship between diet, gut microbiota and risk factors for cardiovascular disease (obesity, hypertension, dislipidemia) (6, 7). WHO alert that, by 2030, cardiovascular diseases (CVD) will be the leading cause of death in the world (8). Elevated serum cholesterol level is a risk factor for CVD. Many researches claimed that probiotic Lactobacillus can lower serum cholesterol level of humans and animals (9). However, there are still controversial reports owing to the differences among probiotic strains used in the studies, combinations of probiotics and prebiotics to develop a synbiotic formulations and in vitro laboratory conditions which not always reflect the indigenous conditions of the in vivo systems (10).

In addition, in functional food development, important input has the food product which is used as delivery matrix for probiotic/synbiotic. Soybean-based foods are of great interest since 1999, when U. S. Food and Drug Administration approved indication of soy consumption in lowering the risk of CVD (11). Soymilk has several nutritional advantages over cow's milk such as reduced level of cholesterol, saturated fat, and is lactose free product (12). Due to these properties, usage of soymilk is favorable for the consumers who are at risk of CVD or lactose intolerant people. In addition, among a wide variety of soy-based food products, soymilk is considered as the most acceptable product for the consumers with specific dietary and health concerns.

The prepared synbiotic soymilk product in our study may be applied in individuals who are at risk of CVD. The probiotic L. casei possesses proven health effects (13). The prebiotic effect of the inulin and oligosaccharides are also confirmed in the literature (14). However, any new synbiotic mixture and delivery matrix used have to be separately evaluated due to the specific substrate- and strain-dependent effects. Namely, the effects of a probiotic/synbiotic have to be demonstrated in appropriate in vivo studies and approved in a view of the dosage regimen, duration of the treatment, host benefits and safety of consumption.

The aim of this study was to evaluate the effect of L. casei-01 fermented soy milk fortified with Synergy 1 on intestinal microbiota and lipide profile of spontaneously hypertensive rats. For this aim, rats were administered by synbiotic enriched fermented soy milk with high viable level of L. casei-01 during 4 weeks.

MATERIAL AND METHODS

Animals and facility

The study was conducted on male SHR/NCrl rats originate from Charles River Laboratories Inc., Germany. The experiments were performed in an accredited establishment (number 11-4888/3; animal facility of the Medical Faculty, UKIM, Skopje, Macedonia) according to guidelines of the Macedonian government. The environmental conditions were carefully controlled: temperature (22 ± 1°C), humidity (approximately 50%) and 12:12 h light:dark schedule (07.00-19.00). The animals were supplied with water and commercial rat chow (a mixture of 20% protein–complete mixture for laboratory rats, Veterinary Institute, Subotica, Serbia) ad libitum. Animal handling met the national regulatory guidelines on proper care and use of laboratory animals and was approved (approval No 02-1392/1) by Food and Veterinary agency of Macedonia (the competent authority in Macedonia).

Study design

Six months old male SHR rats (n=20) were randomly divided into 2 groups, control group (K) receiving saline solution and F group treated with fermented soymilk. All animals had free access to commercial rat chow and water throughout the study. The animal received 1ml of experimental diet daily, by gastric intubations (Feeding needle-16 Gauge/75mm long, FST - Fine Science Tools, Germany).

The duration of the experiment was 4 weeks. At the end of the treatment rats were sacrificed by an ether anesthesia. Blood was collected from abdominal aorta and analyzed the same day. Ten cm of the proximal jejunum, 10 cm of the terminal ileum and colon of rats were cut off. For the microbiological analysis the intestinal content was collected by gentle squeezing. The samples of each group were pooled, weighted and placed in fecal containers. The samples were plated on selective media within 2 hours of the collection procedure.

Fermentation of soymilk

Preparation and optimization of synbiotic fermented soy milk is completely explained in previous study (5). Briefly, commercial (cholesterol, lactose and gluten free) soymilk (Valsoia Original – VALSOIA SpA, Italy) was fortified with 1.5 % w/v prebiotic, oligofructose-enriched inulin (Synergy-1, Orafti® Synergy 1, Orafti-Rue L. Maréchal, Tienen, Belgium). The mixture was heat treated in a water bath at 90°C for 30 min, then cooled to 37°C and aseptically inoculated with L. casei-01 (FD-DVS/ Lactobacillus casei-01 nu-trish, Chr. Hansen, Hoersholm, Denmark). The fermented soymilk end-product contained 11.49±0.13 log10cfu/ml L casei-01. During the experiment, the synbiotic fermented soy milk was stored at the refrigerated conditions. The viable L. casei-01 counts were stable during storage of two weeks. However, every week new batch was prepared.

Bacterial analysis

Isolation and enumeration of target microorganismus

For the purpose to determinate the viable counts of the microorganisms studied, the surface-spread method on selective media was used. Quantitative microbiological analyses were done in triplicates. The samples were homogenized in normal saline using hand-held glass homogenizer, filtered through sterile gauze and serially diluted. The volume of 0.1 ml of subsequent 10-fold serial dilutions was transferred to Petri plate. Culture media and incubation conditions are summarized in Tab 1.

Table 1. The selective media and incubation conditions for targeted bacteria.

Lactobacillus spp	MRS agar (deMan, Rogosa and Sharpe, Oxoid LTD,Hampshire, England)	37 °C/72h Anaerobicaly (GasPak System)
Staphylococcus spp	Baird Parker agar (Oxoid LTD,Hampshire, England)	37 °C/48h Aerobically
Enterococcus spp	Slanetz Bartley agar (Oxoid LTD,Hampshire, England)	37 °C/48h Aerobically
E coli	Chromocult® Coliform Agar (Merck KGaA 64271 Darmstadt, Germany)	37 °C/24h Aerobically

For enumeration of viable counts, plates containing 25-250 colonies were considered. Results are expressed as log10 cfu g -1 wet feces and intestinal content.

Lipid profile

The serum samples were analyzed for total cholesterol, high density lipoprotein (HDL) and triglycerides using a ChemWell® Automated Chemistry Analyzer (Chem Well; Awareness Technology, USA). The results are expressed in mmol/l.

Statistical analysis

The results obtained are presented as means ± SD. Differences were determined by using pared Student t-test. Probability level of $p<0.05$ was used as a significant difference.

RESULTS

Counts of viable Lactobacillus spp

Viable counts of Lactobacillus spp in different intestinal compartments extracted from control and treated rats are comparitively given at Fig. 1.

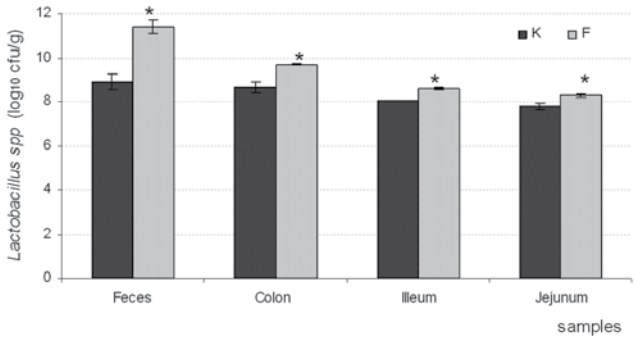

Figure 1. Effect of synbiotic fermented soymilk on viable Lactobacillus spp counts in different intestinal compartments. All results are expressed as mean ±SD of 10 rats. *Significant when $p<0.05$. K, control rats; F, treated rats.

Fig. 1 apparently shows the difference of the total lactobacilli counts in the samples taken from different intestinal compartments of the control and treated rats. The samples were collected at the end of the treatment. The observed values in feces, colon, ileum and jejunum samples in treated vs. control rats were 11.4±0.3, 9.7±0.01, 8.6±0.07, 8.3±0.1 vs. 8.9±0.4, 8.6±0.25, 8.06±0.02, 7.8±0.14 log10 cfu/ml, respectively.

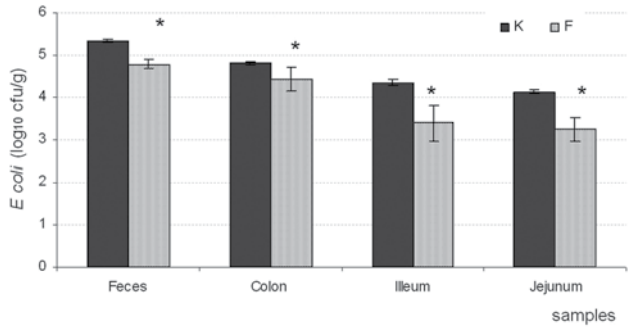

Figure 2. Effect of synbiotic fermented soymilk on viable E coli counts in different intestinal compartments. All results are expressed as mean ±SD of 10 rats. *Significant when p<0.05. K, control rats; F, treated rats.

On Fig. 2 are shown values for E coli counts after 4 weeks treatment in feces, colon, ileum and jejunum samples for treated vs. control group: 4.8±0.1, 4.4±0.3, 3.4±0.43, 3.3±0.28 vs. 5.3±0.05, 4.8±0.03, 4.4±0.08, 4.13±0.06 log 10 cfu/ml, respectively.

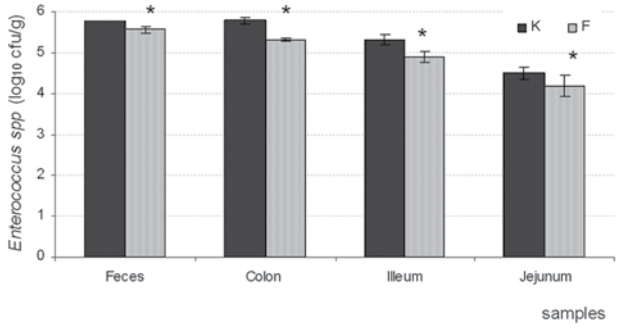

Figure 3. Effect of synbiotic fermented soymilk on viable Enterococcus spp counts in different intestinal compartments. All results are expressed as mean ±SD of 10 rats. *Significant when p<0.05. K, control rats; F, treated rats.

Values in Fig. 3 represent the changes in Enterococcus spp counts in feces, colon, ileum and jejunum samples for treated vs. control group: 5.56±0.06, 5.33±0.03, 4.9±0.14, 4.18±0.24 vs. 5.78±0.01, 5.8±0.08, 5.3±0.14, 4.5±0.14 log10 cfu/ml, respectively.

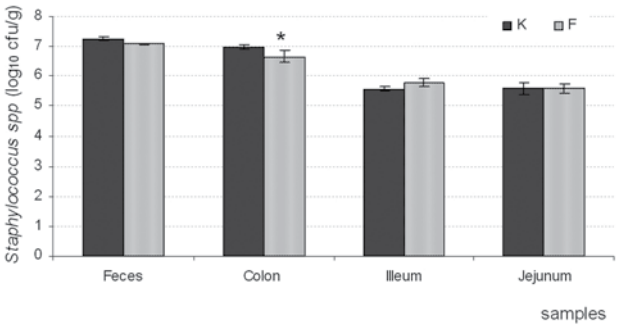

Figure 4. Effect of synbiotic fermented soymilk on viable Staphylococcus spp counts in different intestinal compartments. All results are expressed as mean mean ±SD of 10 rats. *Significant when p<0.05.

The changes in Staphylococcus spp counts are shown in Fig. 4. The observed values in feces, colon, ileum and jejunum samples for treated vs. control group were: 7.1±0.02, 6.66±0.2, 5.64±0.3, 5.58±0.17 vs. 7.25 ±0.06, 6.97±0.06, 5.57±0.07, 5.6±0.2 log10 cfu/ml, respectively.

Changes in lipid profile in serum of SHR after 4 weeks treatment are shown in Fig. 5.

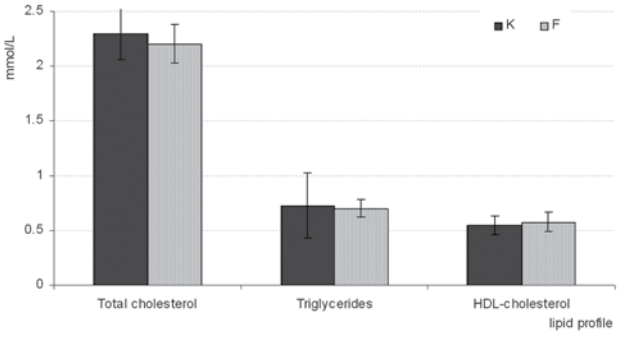

Figure 5. Effect of synbiotic fermented soymilk on total cholesterol, triglyceride and HDL-cholesterol values. All results are expressed as mean ±SD of 10 rats. *Significant when p<0.05.

The observed values in treated vs. control SHR's for the total cholesterol, triglycerides and HDL-cholesterol in serum, were 2.2±0.18, 0.58±0.09 and 0.7±0.08mmol/L vs. 2.29±0.2, 0.55±0.08 and 0.73±0.18mmol/L respectively. There was not a significant difference among groups.

DISCUSSION

The aim of the study was to investigate the ability of the high viable level of L casei-01 administered daily in fermented soy milk to modulate the intestinal microbiota in the gut of SHR's. The 4 week oral gavage treatment with probiotic dose of 11.49±0.13 log10 cfu mL-1 has shown changes in viable cell counts of Lactobacillus spp, E. coli, Enterococcus and Staphylococcus. According to the findings that fecal samples do not reflect the microbiota of the small bowel and are not adequate to assess probiotic colonization (15), we have also performed the analysis of the colon, ileum and jejunum samples.

After 4 weeks treatment with synbiotic fermented soymilk, the lactobacilli counts were significantly increased not only in fecal and colon samples, but in ileum and jejunum as well (Fig. 1). Obtained results are in agreement with report of Minelli et al. (2004), who observed a stimulatory effect of the consumption of milk fermented with L casei on lactobacilli in rats (16). The obtained results in this study strengthened the claims that L casei survives transit through the gut when consumed in fermented milk diets and reach the colon in sufficient number to exert the beneficial effects (17).

On the other hand, claims based on in vivo and in vitro studies in respect to the ability of L casei to colonize the rat's jejunum and ileum are inconsistent. The variations of the results obtained in different studies are attributed to different L casei strains used, as well as different inoculum and delivery matrix. For example, the adhesion of L. casei strains to mouse ileal epithelial cells was studied in vitro. Lactobacillus casei CRL 431 and other L. casei strains isolated from humans showed good ability to adhere to exfoliated ileal epithelial cells, while L. casei isolated from dairy source did not (18). Furthermore, the adhesion ability of Lactobacillus casei ATCC 393 was evaluated in vivo on Wistar rats. The rats treated for 7 days shoved higher values (≥6 log cfu/g) in colon and cecum than rats with single oral administration (5 log cfu/g). The adhesion in jejunum and ileum was significantly lower (≤3 logCFU/g). This indicated that adhesion is targeted process. In addition, the harsh environment in ileum and jejunum contribute to lower adhesion (19). The 4 weeks treatment conducted in our study comprising a L. casei-01 dose of 11.49 log10 cfu/ml per day significantly increased the viable cell counts of Lactobacillus spp in jejunum and ileum of SHR's.

As we expected, the E coli counts were significantly reduced in all examined samples (Fig. 2). The effect of lactobacilli on coliforms is known for years. One of the proven mechanisms of action is competitive colonization (a process that has been demonstrated in vitro) (20). Furthermore, Worametrachanon et al. (2014) performed the quantitative polymerase chain reaction analysis and demonstrated that L casei-01 increased the lactobacilli counts in colon, while decreased the number of coliforms. In this study, a simulator of the human intestinal microbial ecosystem was used (21).

While Ning Xie et al. (2011), reported that enterococci were not affected by lactobacilli treatment, Manley et al. (2007) demonstrated a significant reduction in the detection of Vancomycin-resistant Enterococcus (VRE) in fecal specimens of patients receiving a probiotic yoghurt containing Lactobacillus rhamnosus GG (LGG) (22, 23). L casei-01, the commercial name for L. paracasei sp paracasei used in our synbiotic mixture, significantly reduced Enterococcus spp counts not only in feces, but in all examined GIT compartments (Fig. 3).

Staphylococcus spp counts were significantly decreased in colon samples (Fig. 4). The lowering effect was consistent with anti-staphylococcal activity of L. paracasei sp paracasei confirmed by in vitro and in vivo studies (24).

It is known that as a consequence of harsh environment in GI tract, the viability of probiotic cells is reduced. Furthermore, there are claims that in order to achieve significant health effects, probiotic should be provided at a minimum concentration of 106 cfu/g, while FAO/WHO (2002) recommended effective dosage for probiotic consumption to be 108 – 1011 cfu/g daily (6, 2). Taking this into consideration, we fortified the soy milk by the probiotic inoculum to reach the highest recommended dose of 1011 cfu/ml. The obtained results have shown that the dose was high enough for L casei-01 to exert its beneficial effects on the targeted bacteria in the treated rats.

The effects that we have observed can be explained by direct influence of L. casei-01 on the total number of lactobacilli, and the competitive effect on the potentially harmful bacteria. On the other hand, bioactive peptides in fermented milk exert their antibacterial effects as well. Also, the short-chain fatty acids produced during the fermentation of oligofructose and inulin mixture (Synergy1) may contribute to the beneficial effects observed. These findings were confirmed by in vitro studies, too. Namely, Kingwatee et al. 2014 reported that L casei-01 after fermentation of 24 h in lychee juice enriched with inulin significantly enhanced the

growth of the colon lactobacilli and bifidobacteria, while suppressed the growth of harmful microbes including fecal coliforms, and total anaerobic bacteria (25).

Various studies have shown that probiotics could lower the cholesterol. Several mechanisms have been proposed via control of cholesterol metabolism. The suggested mechanisms are removal the cholesterol by assimilation (26, 27), lowering the absorption from the small intestine by binding the cholesterol and bile acids to cell surface (28) and the effects of bacterial bile-salt hydrolaze (BSH) activity (29). To evaluate the cholesterol-lowering effect of L. casei-01 we previously performed in vitro experiment. The results showed significant cholesterol assimilation. Although the BSH activity in vitro was insignificant, we presumed that the probiotic still has an ability to decrease the cholesterol level in vivo (30). The values observed for total cholesterol in treated rats were lower than in control rats but the differences were not significant. The synbiotic fermented soymilk has shown no significant effect on triglyceride and HDL values, either (Fig 5). In some of the experiments that have provided the evidence to support the roles of probiotics and synbiotics in improving the lipid profiles, the subjects (animals or humans) were treated at least 6 weeks. For example, male Sprague-Dawley rats aged 5 weeks were treated with diet in which 20% of the diet was replaced by soy yogurt (lactic acid fermented soymilk) for 7 weeks. At the end of treatment the level of plasma cholesterol was significantly reduced (31). Furthermore, a variety of studies were conducted on subjects with altered lipid status due to high –carbohydrate or high –lipid diets (32). Results from experiment on male Wistar rats fed with cholesterol-enriched diet with L. casei ASCC 292, FOS, and maltodextrin, ad libitum for 6 weeks, showed significantly lower total cholesterol and triglyceride levels compared with the control rats fed with high-cholesterol diet (33).

SH rats included in this study were healthy and were not challenged to high fat, high carbohydrate diets or any cause of dislipidemia. They had no access to synbiotic product ad libitum and the duration of treatment was 4 weeks. Further studies are needed to evaluate the appropriate dosage of the synbiotic fermented soymilk and duration of treatment for beneficial effect on lipid profile in intact adult SH rats.

In conclusion, Lactobacillus casei-01 fermented soymilk fortified with prebiotic Synergy 1, beneficially modified the intestinal microbiota in 6 month old spontaneously hypertensive rats. The applied 4 week treatment exerted no effect on lipid profile of rats.

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ВЛИЈАНИЕ НА ФЕРМЕНТИРАНО СОЈА МЛЕКО НА ЦРЕВНАТА МИКРОФЛОРА И ЛИПИДЕН ПРОФИЛ КАЈ СПОНТАНО ХИПЕРТЕНЗИВНИ СТАОРЦИ

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АБСТРАКТ

Цел на оваа студија беше да се процени влијанието на ново синбиотско ферментирано соино млеко на цревната микрофлора и липиден профил кај возрасни спонтано хипертензивни стаорци.

Материјал и методи: Соино млеко збогатено со пребиотик (Synergy1) беше ферментирано со пробиотик L casei-01. Бројот на вијабилни L casei-01 во финалниот продукт изнесуваше 11.49 ±0.13 log10 cfu ml-1. Машки спонтано хипертензивни стаорци (СХС) на возраст од 6 месеци беа третирани со 1 мл/ден од ферментираното соино млеко. По третман од 4 недели, вкупен број на виабилни Lactobacillus spp, E coli, Enterococcus spp, и Staphylococcus spp беа анализирани во примероци од јејунум , илеум, колон и фецес. Концентрациите на вкупниот холестерол, триглицеридите и ХДЛ-холестерол беа определувани во серум.

Резултати: Во сите анализирани примероци, забележан е сигнификантно повисок број на Lactobacillus spp а намален број на E coli и Enterococcus spp. Вкупниот број на Staphylococcus spp беше значајно намален во примероци од колон. Разликите во липидниот профил не беа значајни.

Заклучок: синбиотско ферментирано соино млеко сигнификантно ја подобри цревната микрофлората кај СХС. Липидниот профил на стаорците не беше променет по третман од 4 недели.

Клучни зборови: L casei, Synergy1, спонтано хипертензивни стаорци, цревна микрофлората, липиден профил.

APENDEKTOMIA LAPAROSKOPIKE NË TRETMANIN E APENDICITIT AKUT

LAPAROSCOPIC APPENDECTOMY FOR THE TRETMENT OF ACUTE APPENDICITIS

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ABSTRACTI

Hyrje. Prerja kirurgjike laparoskopike minimizon traumat operative pa ndonjë shenjë të dukshme. Ndryshe nga apendektomia e hapur, kirurgjialaparoskopike është e fokusuarnëminimizimine traumavekirurgjikedhe përmirësimin eefekteve estetike. Metoda e prezantuar është pjesë e trendit të ri në kirurgjinë laparoskopike.Prerja kirurgjike laparoskopike minimizon traumat operative dhe mundëson procedurat kirurgjike pa ndonjë shenjë të dukshme. Këtu prezentojm rastin e appendicitit akut dhe intervenimin me metodën laparoscopice që është përdorur në appendectomy Qasja laparaskopike për appendectomi bëhet me dy metoda: 1.Metoda laparoscopike me tri porta dhe 2. Prerje të vetme kirurgjike laparoscopike(SILS).

Qëllimi i punimit: Është prezantim i një ndërhyrjeje kirurgjike laparoskopike të apendicitit akut për herë të parë te një paciente në Spitalin Rajonal të Gjilanit.

Prezantim rasti: Procedura është bërë përmes tri porteve. Vendosim CO2 me presion 12mmHg dhe fitojmë hapësirën intraperitoneale. Kapet appendixi, ku bëhet kauterizimi dhe bëhet prerja e mesoapendixit. Pasi të vërtetohet se nuk ka gjakderdhje vazhdohet me ligim të appendixit me endoloop vajkril 2.0 dhe prehet appendixi i cili nxirret jashtë.

Konkluzion: Prerja me tri porta e kirurgjisë laparoskopike te apendiciti është përfituese për pacientët, për shkak të kozmetikës dhe zvogëlimit të traumave postoperative, si dhe zvogëlimit të dhembjes postoperative, që mundësojnë kthimin e shpejtë në punë dhe aftësimin fizik. Procedura kryhet nga kirurgët me përvojë në laparoskopi.

Fjalë çelës: Apendektomia, laparoskopia, tri porta

HYRJA

Apendektominë laparoskopike, i pari e përshkroi Semm më 1983 (1). Pier dhe Al. më 1991 paraqitën studimin krahasues të një apendektomie laparoskopike dhe një apendektomi të hapur, duke raportuar avantazhet (2,3. Ideja për kirurgjinë laparoskopike është që traumat kirurgjike të jenë minimale kirurgjike; qëndrimi në spital të jetë sa më i shkurtër; të ketë sa më pak dhembje postoperative; kthim më i shpejtë në aktivitetet e përditshme; rezultati më i mirë kozmetik. Këto kanë bërë që kirurgjia laparoskopike për apendicitin akut të jetë shumë tërheqës. (9,10,15). Laparoskopia ka dëshmuar se mund tëkrahasohet mekirurgjinë e hapur nëmenaxhimin e të dyja sëmundjeve beninjedhemalinje (4,5,7). Tani, teknikat miniinvazivefilluantë çmohenngapacientëtdhekirurgët, ku nëdisa raste janëbërë metodatë zgjedhjes (10).

Në ditët esotme, aplikohen 2metodalaparoskopike

1. *Metoda laparoskopkie me tri porta dhe*
2. *Metoda me prerje të vetme kirurgjike laparoskopike të apendektomisë (SILS)(11,15).*

Aktualisht, edhe pse nuk ka konsensus lidhur me superioritetin e qasjes laparoskopike mbi teknikën konvencionale, ekzistojnë prirje drejt shfrytëzimit më të madh të apendektomisë laparoskopike (15,17). Në bazë të një studimi, 758 pacientë iu nënshtruan apendektomisë

për apendicit akut, gjatë periudhës së studimit 5-vjeçar. 271 ose 36 %, prej tyre kishin apendektomi të hapur, ndërkaq 487 ose 64 % kishin apendektomi laparoskopike [3]. Konvertimi nga intervenimi laparoskopik në intervenim të hapur ishte e nevojshme për 28 pacientë ose 2,7 %) (7).

QËLLIMI I PUNIMIT

Është prezantim i një ndërhyrjeje kirurgjike me metodën laparoskopike të apendicitit akut, për herë të parë te një paciente, në Spitalin Rajonal të Gjilanit. Qëllimi ynë është që të shikohet dobia e apendektomisë laparoskopike, duke krahasuar me metodën konvencionale të kryera në Spitalin Rajonal të Gjilanit dhe shqyrtimin me autorët e qendrave të tjera.

RAPORTI MBI RASTIN

Pacientja ishte pranuar si rast urgjent nga emergjenca, me dhimbje barkut në pjesën inguinale djathtas, nauze, temperaturë, plogështi. Ekzaminimet fizike në palpacion sipërfaqësor dhe të thellë dhimbjet ishin shumë të shprehura, me shenja të Blumbergut, Rowsingu pozitiv, raportet laboratorike me vlera të rritura. Është bërë echo e abdomenit, rtg nativ i abdomenit. Pas njoftimit të pacientes me teknikën e sugjeruar dhe marrjes së pëlqimit të saj, ajo u kualifikua për ndërhyrje kirurgjike laparoskopike, e cila u krye në Departamentin e Kirurgjisë së Përgjithshme në Spitalin Rajonal të Gjilanit.

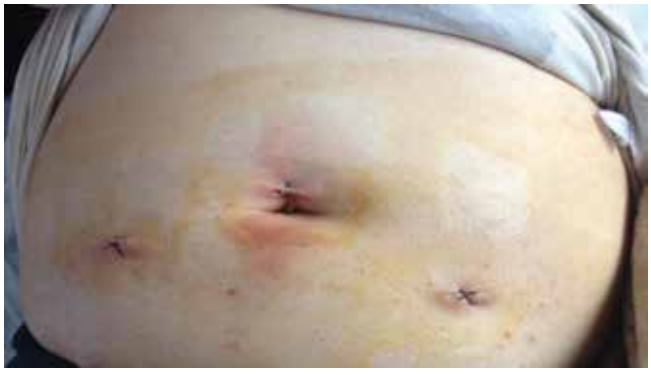

Fig.1 Trivendete portave

TEKNIKA KIRURGJIKALE

Procedura është bërë përmes tri porteve (fig. 1).Një portë në prerjen 10 mm, në regjionin *supra umbilikal* dhe dy nga 5mm të bëra në një distancë në mes 1/3 e jashtme të djathtë, në mes të *umbilikusit* dhe *spina iliaka anterior superior* dhe tjetra në 1/3 e brendshme të vijes *umbilicus-SIAS*. Procedura ka filluar me vendosjen e pacientes në pozitë të pjerrtë në shpinë, në këndin 20 shkallë. Vendoset trokari 10 mm dhe dioksidi i karbonit, i cili nuk e kaluar presionin 12 mm/Hg dhe fitojmë pneumoperitoneumin. Dy portat hyrëse 5 mm vendosen, siç theksua më lart dhe fitojmë hapësirën ekzistuese intraperitoneale. Pozita e tillë mundëson që laku i zorrëve të ngritet lart dhe të mundësojë që të shihet më qartë. Largohet një pjesë e omentumit, ku kemi një pamje të qartë të *appendixit*, i cili ishte me ndryshime gangrenose (fig. 2). Hapi i parë ishte identifikimi i *appendixit*, meson e appendixit dhe cecumin. Pastaj kapet appendixi (fig. 3) dhe bëhet kauterizimi dhe prerja e *mesoapendixit*, ku pas vërtetimit se nuk ka gjakderdhje vazhdohet me ligim të *appendixit* me *endoloop vajkril* 2.0 (fig. 4) dhe prehet appendixi (fig. 5). Për shkak të mundësisë së ndonjë infeksioni futet në qese dhe nxirret jashtë. Shpërlahet kaviteti abdominal me tretje fiziologjike. Pasi është kontrolluar hemostaza, largohen portat dhe mbyllen me penj të absorbueshëm 3.0. Operacioni është proceduar pa komplikime dhe ka zgjatur 30 minuta.

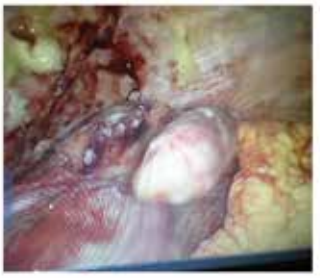

Fig 2 Appendiciti ac. gangrenos

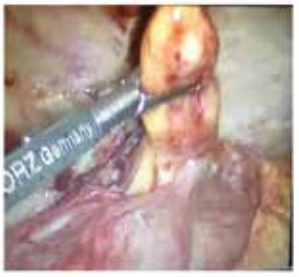

Fig 3 Kapja e appendiksit

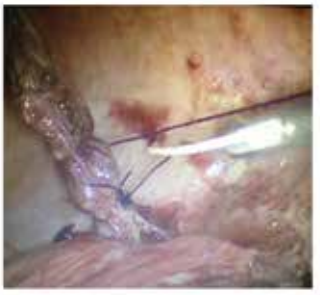

Fig.4 Ligimi me endoloop

Fig. 5 Prerja e Appendicitit

Shërimi postoperativ ishte pa komplikime. Pacientja është liruar nga spitali,pas48orëve, me gjendje të përgjithshme të mirë dhe është rekomanduar të vijëpërkontroll. Tre muajpasprocedurëspacientja nuk ka raportuar për ndonjë sëmundje apogjendje tëkeqe dhe nuk është vërejtur cikatrix idukshëm.

DISKUTIMI

Laparoskopia ka bërë një revolucion dhe ka ndryshuar kirurgjinë e përgjithshme. Apendiksi akut është kusht që kërkon urgjencë [18]. Edhe pse kanë kaluar më shumë se 20 vjet nga futja e apendektomisë laparoskopike, nuk ka konsensus mbi avantazhet dhe disavantazhet e saj, në krahasim me teknikën konvencionale. Studimet e fundit kanë treguar avantazhe të konsiderueshme të apendektomisë laparoskopike, në lidhje me kohëzgjatjen e qëndrimit në spital; dhembjen postoperative dhe komplikacionet infektive [5,8,12,14].Papërvoja e kirurgut në teknikë të re mund të kontribuojë në kohëzgjatjen e operacionit [16-18]. Disa studime kanë raportuar më pak dhimbje në 48 h pas apendektomisë laparoskopike [20]. Normat e përgjithshme të komplikimeve sillen 5,7 % për apendektominë e hapur dhe 3 % për apendektominë laparoskopike [13-15]. Apendiksi i komplikuar fillimisht është konsideruat si një kundërindikacion për apendektominë laparoskopike [19,20]. Megjithatë, studimet e fundit kanë treguar se qasja laparoskopike në sëmundje të komplikuar është e mundshme dhe madje mund të jetë superiore ndaj qasjes konvencionale [6,7,10].Ndërhyrja laparoskopike, e cila mundëson shërim të shpejtë, si dhe rezultate të mira kozmetike është avantazh i padiskutueshëm në laparoskopi. Apendektomia laparoskopike kryhet përmes tri prerjeve. Mundësitë për të observuar patologjitë brenda zgavrës së abdomenit, vizuelizimin dhe patologjitë e hershme, në anën tjetër janë të padiskutueshme avantazhet e kësaj metode(15,18). Në laparoskopi, pozicionimi, distanca dhe këndinë mes portaveveçe veç janëjashtë zakonishttë rëndësi shme,sepse pengon dukshëmmanovrimin e instrumenteve, porgjithashtu sjellëpërplasje meinstru mentin optik. Këtojanë vështirësitë teknike, të cilatzvogëlohenme përvojëne kirurgut (12,14) . Instrumentet erejalaparoskopi kejanë të njohuranë treg dhe sëshpejtiprerja metriporta laparoskopike do të ketë aplikimmëtëgjerë edhenëtrevattona, kurezultatet kozmetikedo tëjenëtënjë rëndësietë madhe, me gjithë vësh tirësitë teknike që mund të dekurajojnë kirurgët. Përfitimi kozmetik është i vërejtur: sidoqoftëimbetet pacientit ta vlerësojë, passhërimit dhe uljessëdhembjeve postoperative dhe komplikimeve, në krahasim me metodën konvencionale. Në bazë të një studimi, 758 pacientë iu nënshtruan apendektomisë për apendicit akut, gjatë periudhës së studimit 5-vjeçar. 271 ose 36 %, prej tyre kishin apendektomi të hapur, ndërkaq 487 ose 64 % kishin apendektomi laparoskopike [3]. Konvertimi nga intervenimi laparoskopik në intervenim të hapur ishte e nevojshme për 28 pacientë ose 2,7 %) [7].Nga kjo dhe nga shumë punime të autorëve të tjerë, del se apendektomia laparoskopike është në rritje. Përvoja e kirurgut dhe pajisjet që janë në dispozicion, e bën që apendektomia laparoskopike është e sigurt dhe po aq efikase në krahasim me teknikën konvencionale. Zgjedhja e procedurës do të bazohet në preferencat e kirurgut dhe të pacientit. Studimet shtesë priten t'japinpërgjigje këtyrepyetjeve.

KONKLUDIMET

1. Prerja me tri porta e kirurgjisë laparoskopike te appendixiti është përfituese për pacienten, për shkak të kozmetikës së mirë dhe zvogëlimit të traumave postoperative që mundësojnë një shërim më të shpejtë.
2. Pasi janë disa vështirësi teknike, procedura duhet të kryhet nga kirurgët që kanë përvojë në laparoskopi.
3. Zvogëlimi i dhembjes postoperative.
4. Mundësia e kthimit të shpejt në punë dhe aftësimi fizik.
5. Kostoja.
6. Mundësia e identifikimit të elementeve të rëndësishme gjatë operacionit është shumë e kufizuar tek teknika e vjetër.
7. Mundësia e dëmtimit të elementeve të rëndësishme gjatë operacionit është shumë më e madhe tek teknika e vjetër.
8. Koha e zgjatjes së operacionit është shumë më e gjatë se me teknikën e re.
9. Dehiscenca e plagës është e mundshme vetëm tek teknika e vjetër.
10. Infeksionet e plagëve janë në përqindje shumë më të lartë tek teknika e vjetër.

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LAPAROSCOPIC APPENDECTOMY FOR THE TRETMENT OF ACUTE APPENDICITIS

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SUMMARY

Introduction: Laparoscopic surgical cutting minimizes operative trauma without any visible sign. Unlike appendectomy open, laparoscopic surgery is focused on minimizing surgical traumas and improving the aesthetic effects. The method presented is part of a new trend in laparoscopic surgery.

The purpose is: The presentation of a surgical intervention to laparoscopic appendicitis to an acute patient at Regional Hospital in Gjilan.

Case report: procedure was done through three ports. We put CO2 with pressure 12mmHg and we obtain intraperitoneal space. The appendix is held while cauterization is being done and we cut the mesoappendix. After it is confirmed that there is no bleeding we continue with ligation of appendix with endoloop krill oil 2.0 and the appendix is cut and pulled out.

Conclusion: Cutting through three ports in the appendix laparoscopic surgery for the patients is a beneficiary because of the cosmetic and reducing post-operative traumas, post-operative pain reduce, and the possibility of returning to work sooner and physical activity. The procedure is done by experienced surgeons in the field of laparoscopy.

Keywords: Appendectomy, laparoscopies, three ports

SITUS AMBIGUS I SHOQËRUAR ME FORMË TË RËNDË TË ANOMILSË NË ZEMËR

SITUS AMBIGUS ASSOCIATED WITH COMPLEX CONGENITAL HEART DISEASE

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ABSTRAKT

Anomalitë e lindura të zemrës (ALZ) lajmërohen me një përqindje shumë më të lartë te malpozicioni i organeve torako-abdominale. Qasja segmento-sekuenciale në diagnostikimin e anomalive të lindura të zemrës dhe përcaktimi i pozicionit të organeve torako-abdominale është baza e ekzaminimit dhe përcaktimit të pozicionit normal prej atij abnormal. Në këtë artikull ne kemi përshkruar një të porsalindur me izomerizëm të djathtë dhe ALZ komplekse, me dominim të atresionit të arteries pulmonare dhe prezencën e vetëm një ventrikuli. Rasti i ynë është nga shumë aspekte i veçantë dhe i cili, përpos izomerizmit të djathtë dhe prezencës së mëlçisë në të dy anët, ka edhe një seri ta anomalive që rrallë mund të shihen në një fëmijë. Përkundër kompleksitetit anomalia mirë tolerohet gjatë shtatzënisë falë.

Fajlët kyçe: right isomerism, congenital heart defect, pulmonary atresia, univentriclar heart,

HYRJA

Qasja segmento-sekuenciale në diagnostikimin e anomalive të lindura të zemrës dhe përcaktimi i pozicionit të organeve torako-abdominale është baza e ekzaminimit dhe përcaktimit të pozicionit normal prej atij abnormal. Në këtë drejtim ekzistojnë ndarja themelore në situs solitus, i cili e përshkruan pozicionin normal të organeve torako-abdominale dhe situs inversus me dy mundësi kryesore të paraqitjes: izomerizmi i djathtë dhe i majtë dhe forma e pa klasifikuar, si formë shumë e rrallë. Anomalitë e lindura të zemrës (ALZ) lajmërohen me një përqindje shumë më të lartë te malpozicioni i organeve torako-abdominale. (1,2) Njëkohësisht, malpozicioni e përkeqson prognozen kirurgjike të ALZ. Në këtë artikull ne kemi përshkruar një të porsalindur me izomerizëm të djathtë dhe ALZ komplekse, me dominim të atresionit të arteries pulmonare dhe prezencën e vetëm një ventrikuli. (3)

PREZANTIMI I RASTIT

Fëmija i parë, nga shtatzënia e parë, rregullisht e kontrolluar nga obstetri dhe nuk është regjistruar ndonjë anomali. Lindja është në termin, në lindore rajonale, me PT=3200g, Appgar-score 7, 8/10. Në ditën e dytë të jetës regjistrohet cianoza qendrore; me pulsoksimetri regjistrohet saturim i ultë i cili nuk përmirësohet me dhënien e oksigjenit shtesë. Fëmija transferohët në Klinikën e Neonatologjisë në Prishtinë pëfr ekzaminim në drejtim të përcaktimit të etiologjisë të cianozës qendrore.

Radiografia e organeve torako-abdominale konfirmon indeks të ruajtur kardio-torakal, me redukim të vizatimit bronko-vaskular. Sileta e zemrës është e pozicionuar më majë në të djathtë (dextrocardia), mediastinumi është i ngushtuar, me hark të aortës në të djathtë. Regjistrohet hije hiperekogjene e mëlçisë e cila shtrihet në të dy anët e abdomenit kurse hija e lukthit është në pozicion qendror.

Elektrokardiograma prezanton P negative në D1, me shenja të hipertrofisë së ventrikulit të djathtë.

Ekzaminimi ekokardiografik: Zemra është në situs inversus (dextrocardia). Derdhja e venave është në rregull. Dominon ana e djathtë e zemrës. Septumi interatrial në pjesën e mesme e ka nje defekt me diametër deri 4mm, me qarkullim majtas-djathtas dhe pa rëndësi hemodinamike. Në pjesën e poshtme të septumit interatrial regjistrohet edhe një defekt i cili shtrihet edhe në pjesën e valvulave atrioventrikulare (AV) me qarkullim bidirekcional. Regjistrohet vetëm një valvulë atrioventrukulare e cila morfologjikisht i takon valvulës trikuspidale, me qarkullim laminar anterograd dhe regurgjitim mesotelesistolik, me disa vrushkuj, me shpejtësi sistemike dhe i cili mund të kuantifikohet me ¼+. Regjistrohet vetëm një ventrikul, morfologjikisht i djathtë, me kontraktilitet të ruajtur. Ventrikuli tjetër (i majti) është hipoplastik dhe plotësisht afunksional. Prej ventrikulit funksional, para dhe majtas del aorta, me diameter deri 10.2mm, trivelare, me separim të mirë sistolik dhe qarkullim laminar anterogtrad kurse në diastolë manifeston koaptim të mirë. Harku është i djathtë, në rregull, me qarkullim laminar. Mungon AP, e cila është e pozicionuar prapa dhe djathtas, trungu është me diametër deri 6mm, degët nga 4.3mm, me qarkullim i cili vjen prej duktusit arterial. Regjistrohen edhe disa komunikime restriktive aorto-pulmonare. Perikardi eshtë i lirë. Nuk regjistrohen çrregullime të ritmit të zemrës.

Diagnoza përfundimtare: Situs inversus - dextrocardia. Right isomerism. Atrial septal defect typ II restricitiva. Complet canalis atrioventricularis. Common atrioventricular valvae. Atresio valvulae mitralis. Hypoplasio left ventricle. Single ventricle (right). D-Transposistio of the great arteries. Atresio arteriae pulmonalis. Right aortic arch. Ductus arteriosus persistens. MAPCA.

Ekzaminimi ekosonografik i abdomenit: Mëlçia shtrihet në të dy anët e abdomenit, me ekogjenitet në rregull. Regjistrohet lieni i cili është në anën e majtë të abdomenit kurse lukthi është në pozicion qendror. Tjerat organe parenkimatoze të abdomenit janë në rregull.

Fëmija, në konsultim me mjekët nga Italia, transferohet në Institutin "Gianina Gaslini" në Xhenovë, ku bëhet kateterizimi diagnostik dhe intervenimi paliativ kirurgjikal i formës cavo-pulmonary shunt - bidirectional Glenn dhe, pas stabilizimit të gjendjës, kthehet në Kosovë deri në intervenimin e ardhshëm. Fëmija ka rritje dhe zhvillim në rregull, me SPO2 deri 92%, me air të dhomës.

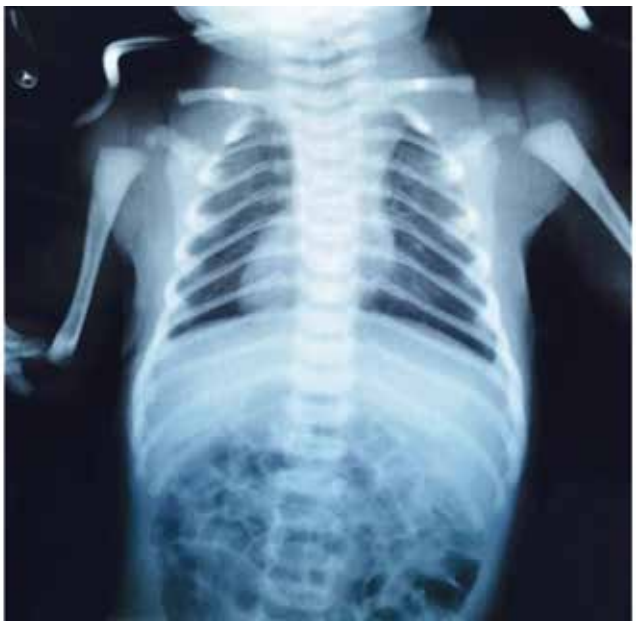

Fig. 1 Zemra është në anën e djathtë, hija e mëlçsië shtrihet në të dy anët e abdomenit kurse lukthi është në pozicionin qendror

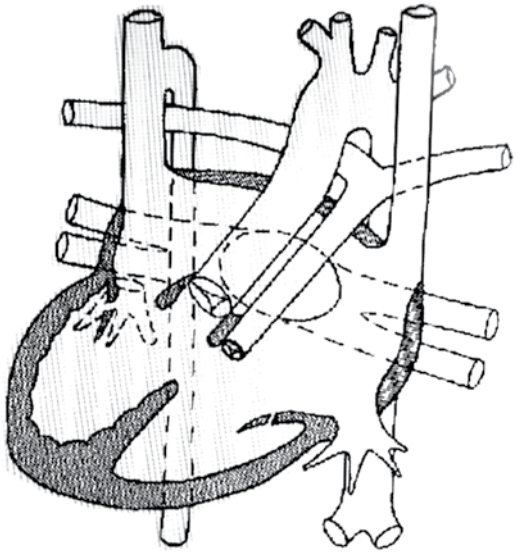

Fig.2. Kardiogrami te rasti i ynë

DISKUTIMI

Gjatë ekzaminimit segmento-sekuencial me qëllim të diagnostikimit të ALZ, të propozuar nga çifti i patologëve amerikan Stella dhe Robert Van Praagh, përcaktimi i pozicionit të organeve torako-abdominale është pjesa obligative gjatë ekzaminimit dhe ka rëndësi të madhe në diagnostikimin përfundimtar si dhe prognozën e ALZ (2,4).

Fjala heterotaxy ka përardhje nga fjala greke hetero – i ndryshëm dhe taxy aranzhimi – pozicionimi dhe përdoret edhe si heterotaksia e organeve ose sindroma e heterotaksisë ku e definon aranzhimin – pozicionimin abnormal të organeve torako-abdominale në raport me prerjen sagjitale të trupit të njeriut. Isomerism - te pacientet me heterotaksi humbet asimetria normale e organeve torako – abdominale duke e manifestuar në shkallë të ndryshme asimetrinë e organeve dhe enëve të gjakut. Fjala "isomerism", poashtu ka përardhje nga fjala greke (iso - i barabartë dhe meros - pjesë) dhe më së miri analizohet me ekzaminimin ekokardiografik të apendiksit të atriumeve (5,6).

Situs solitus paraqet pozicionin normal të organeve torako-abdominale të cilin e gjejmë te shumica e popullatës. Kjo nënkupton pozicionin bilateral të organeve në proporcion më trupin e njeriut dhe pozicionin e atriumeve në proporcion me zemrën. Përpos pozicionit normal ekzistojnë edhe pozicionet abnormale ku organet janë të vendosura "si në pasqyrë" ose izomerizmi i djathtë ose i majtë (7,8,9).

Izomerizmi i djathtë veçohet me "djathtësinë" e dyanshme ku në dy anët mushkëritë janë me tre lobe dhe bronket adekuate. Aorta descendente dhe vena cava inferior (VCI) janë në të njëjtën anë të abdomenit, në anën e djathtë apo të majtë, ku VCI është në pozicion anterior. Lukthi mund të jetë në anën e djathtë apo të majtë por në shumicën e rasteve është në pozicion qendror (në 80 % të rasteve zemra dhe lukthi janë në të njëjtën anë). Intestinumi është në malrotacion kurse në pozicionin qendror është mëlçia me lobe simetrike. Shpretka ose mungon (asplenia) ose gjenden "ujëdhesa" të saj të dislokuara në abdomen.

Izomerizmi është në shkallë të lartë i shoqëruar me ALZ, prej formave të lehta deri te ato më komplekse. Duke filluar prej konektimit të venave pulmonare, pasi që të dy atriumet janë të djathta, deri të dalja e enëve të mëdha të gjakut, regjistrohet nje laramani komplekse e ALZ, të cilat gjatë diagnostikimit kërkojnë një qasje të kujdesshme, duke e zvogëluar në minimum mundësinë e gabimeve në diagnostikim (11,12,13).

Rasti i ynë është nga shumë aspekte i veçantë dhe i cili, përpos izomerizmit të djathtë dhe prezencës së mëlçisë në të dy anët, ka edhe një seri ta anomalive që rrallë mund të shihen në një fëmijë. Përkundër kompleksitetit anomalia mirë tolerohet gjatë shtatzënisë falë komunikimeve të cilat ekzistojnë në jetën fetale (ductus arteriosus, ductus venosis dhe foramen ovale). Anomalia mund të diagnostikohet edhe në periudhen fetale por, në rastin tonë, përkundër disa ekzaminimeve ekosonografike nga obstetri, nuk është regjistruar dhe nuk është dyshuar për te.

Edhe në ditet e para të jetës, për shkak të kompleksitetit dhe qarkullimit specifik i cili zhvillohet te ku kompleks i anomalive, klinikisht anomalia mund të mos regjistrohet. Cianoza qendrore të fëmija klinikisht i shëndoshë, dhe e cila nuk përmirësohet me dhenien e oksigjenit, është shenjë kruciale për neonatologun të dyshoj dhe të filloj me ekzaminime shtesë për mundësinë e ekzistimit të ALZ ose për elimimin e saj.

Ekzaminimet ekokardiografike në periudhen antenatale dhe pas lindjes janë vendimtare , përzgjedhëse dhe mjaft sensitive në diagnostikimin përfundimtar dhe të cilat, më të dhëna te sakta imazherike, mundësojnë intervenimin kirurgjikal, pa diagnostikim invasiv. Të dhënat ekokardiografike, të fituara gjatë kzaminimit ekokardiografik transtorakal në Institucionin tone, kan qenë të mjaftueshmë për prezantim dhë dërgim të fëmijës jashtë vendit për intervenim kirurgjikal. Të njëjtat kanë mjaftuar edhe për ndëhyrje kirurgjike paliative.

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SITUS AMBIGUS ASSOCIATED WITH COMPLEX CONGENITAL HEART DISEASE

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ABSTRACT

Congenital heart abnormalities (CHA) announced with a much higher percentage of malposition of thoracic-abdominal organs. Segmental-sequential approach in the diagnosis of congenital heart and determination of position in thoracic-abdominal organs is the basis of the examination and determination of normal position from the abnormal. In this article we describe a new-born with right isomerisation and CHA complex with domination of atresia of the pulmonary artery and the presence of only one ventricle. Our case is in many aspects unique and which, apart right isomerisation and the presence of the liver on both sides, there are also a series of anomalies that can rarely be seen in a child. Despite the complexity during the pregnancy, the anomaly is well tolerated.

Key words right isomerism, congenital heart defect, pulmonary atresia, univentriclar heart,

ADVANTAGES OF STERRAD 100s STERILIZATION SYSTEM COMPARED TO GAS PLASMA STERILIZATION SYSTEM

PËRPARËSITË E STERRAD 100S SISTEMIT TË STERILIZIMIT KRAHASUAR ME PLAZMA SISTEMIN GAZOR TË STERILIZIMIT

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ABSTRACT

With advantages in surgical techniques, a large number of innovative and equally expensive instruments are being used. As the number of different surgical instruments being used is increasing and the increasing surgical activities per day, so the need of fast and new way of sterilization is also increased.

We compared 100 sterilization cycle of STERRAD with 100 traditional sterilization methods cycles in several fields of interest: 1) time of lasting of sterilization; 2) guarantee for sterility of sterilized instruments, 3) temperature used during the process of sterilization; 4) toxicity for the personal using these systems; 5) types of instruments that can be sterilized and damage of instruments being used in the process of sterilization.

Regarding all of the data presented we strongly recommend use of STERRAD Low Temperature Sterilization System.

Key words: Sterrad, low temperature sterilization, optical instruments, urology.

INTRODUCTION

With advantages in surgical techniques , a large number of innovative and equally expensive instruments are being used. Also, the surgical loads are increasing leading to a need for faster turn around time of instruments. In order to get the maximum out of these instruments,we use STERRAD* Low Temperature Hydrogen Peroxide Gas Plasma Sterilization System. STERRAD* is a low temperature hydrogen peroxide gas plasma sterilization system – the most advanced LTS technology developed by Advanced Sterilization Products in 1993, the technology has over 7000 installations worldwide, more than 3500 of which are in the United States of America.[1]

MATERIALS AND METHODS

We compared 100 sterilization cycle of STERRAD with 100 traditional sterilization methods cycles in several fields of interest: 1) time of lasting of sterilization; 2) guarantee for sterility of sterilized instruments, 3) temperature used during the process of sterilization; 4) toxicity for the personal using these systems; 5) types of instruments that can be sterilized and damage of instruments being used in the process of sterilization. We compared 100 different types of instruments and surgical materials sterilized in old Plasma sterilization system compared to new STERRAD low temperature sterilization system.

RESULTS

Regarding the timing of sterilization in the traditional sterilization methods cycle's sterilization lasted approximately two and a half hours, compared with new STERRAD system in which the sterilization process lasted only 55 minutes. The STERRAD* system produces only water vapor and oxygen as the by-products of the one hour sterilization cycle. Hence, there is absolutely no need for aeration time and the instruments can be used immediately after completion of the cycle.[2] Also,

there are cuts in the surgical inventory costs. With the STERRAD*, the faster cycle of only one hour time allows faster turnover of instruments. As the same instruments are available in a much shorter period of time, inventory costs are cut drastically

Sterility3 of the instruments sterilized in the new STERRAD system was completely fullfield in 99 of 100 instruments examined. Sterility of the instruments sterilized with the traditional methods was fullfield in 92 of 100 instruments examined.

Temperature used in the new STERRAD system was 50°C, compared with 120°C in the traditional plasma sterilization system.

Toxicity didn't occur in the new STERRAD system, compared to plasma sterilization system which in 2 of 100 examined cycles, personal who carried out sterilization reported significant numbers of skin allergic reactions and respiratory track problems.

We used all possible surgical materials and instruments4, such as, microsurgical instruments and most delicate optic instruments (gastroscopes, bronchoscopes, cystoscopes, colonoscopies, hysteroscopes, choledochoscopes) for endoscopic and laparoscopic surgical intervention as well as cameras necessary for this kind of procedures. With STERRAD system damage of instruments occurred in only one in 100 tested instruments. Regarding surgical materials like abdominal drains or staplers, there are was no damage even after multiple resterilizations. Compared to this, the traditional method of autoclaving, resulted in damage of 2 cystoscope optics and blurred vision in one colonoscope. Plastic surgical materials were unfit for sterilization regarding high temperature of the process.

DISCUSSION

We grouped all our discussion and world literature experience and we will explain differences in the following discussion.

STERRAD Low Temperature Sterilisation System is not harmful to human health , because it uses Hydrogen Peroxide plasma , instead of Ethylene Oxide used in Old High Temperature system, which is shown to have following acute and chronic health effects: EtO gas is classified as a known carcinogen by the National Toxicology Program (United States) and as Category 1 (carcinogen to humans) by the International Agency for Research on Cancer (IARC) and as a potential carcinogen by OSHA and by ACGIH. Also, EtO is a probable teratogen and may pose reproductive hazards to humans.Also it is well known and proven that EtO may damage the central nervous system, kidneys, liver and may cause cataracts through continuous exposure.

Besides negative effects of Old High Temperature System on human health, which I discussed previously, now I wish to stress negative effects of this system to the surgical instruments and materials. By many studies it has been shown that it EtO sterilizes wet plastic tubing. EtO reacts with water to form Ethylene glycol which is a human toxin and less than 100ml are needed to kill a human. That doesn't happen using STERRAD Low Temperature Sterilisation System because Hydrogen peroxide plasma prevents the sterilization of wet instruments which ensures adherence to best practices in sterilization. On contrary STERRAD System Hydrogen peroxide plasma does not react with PVC. Other negetive feature of this Old High Temperature System is also damaging of human health in means of NIOSH recommends an exposure limit of not more than 1 ppm based on the fact that EtO is carcinogenic, mutagenic and teratogenic, negative effects on human reproductive system. With TERRAD system studies show that all of this effects are avoided, because The Permissible Exposure Limit set for Hydrogen Peroxide by NIOSH is 1 ppm based on the risk of irritation.

I want to stess that there are a lot of scientific evidence that all of these health problem of Old High Temperature System can be simly caused by it's chemical composition of Ethylene oxide is a gas which gives poisonous by-products of Ethylene oxide, ethylene glycol and Ethylene Chlorohydrin. It is avoided in STERRAD System because Hydrogen peroxide plasma recombines to form non-toxic by products of oxygen and water vapour.

Newest scientific recearsch discover one more positive characteristic of STERRAD Low Temperature Sterilisation System Minimum of 12 hours aeration is required to eliminate the toxic gases that have been absorbed by the materials which are sterilized, which doesn't happen in New STERRAD system because Aeration is not required as there are no toxic by-products of the sterilization process.

CONCLUSION

Regarding all of the data mentioned above we strongly recommend use of STERRAD Low Temperature Sterilization System.

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PËRPARËSITË E STERRAD 100S SISTEMIT TË STERILIZIMIT KRAHASUAR ME PLAZMA SISTEMIN GAZOR TË STERILIZIMIT

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REZYME

Me përparimin e teknikave kirurgjikale, dita-ditës shtohet numri i instrumenteve inovative dhe po aq të shtrenjta. Sikurse numri i ndryshëm i instrumenteve kirurgjikale në përdorim ashtu edhe numri i aktiviteteve kirurgjikale ditore shënojnë tendencë rritjeje, gjithashtu edhe nevoja për mënyrë të re dhe të shpejtë të sterilizimit është rritur.

Kemi krahasuar 100 cikle sterilizimi të STERRAD me 100 cikle të metodave tradicionale të sterilizimit në disa fusha me interes: 1) kohëzgjatja e sterilizimit; 2) garancioni për sterilitetin e instrumeneteve të sterilizuara; 3) temperatura e përdorur gjatë procesit të sterilizimit; 4) toksiciteti për personelin të cilët i përdorin këto sisteme; 5) llojet e instrumenteve të cilat mund të sterilizohen dhe dëmtimi i instrumenteve të përdorura në procesin e sterilizimit.

Lidhur me të gjitha të dhënat e lartpërmendura rekomandojmë përdorimin e STERRAD Sistem Sterilizimi me Temperature të Ulët.

Fjalë kyç: Sterrad, sterilizim në temperaturë të ulët, instrumente optike, urologji.

ВЛОШУВАЊЕ НА КЛИНИЧКАТА СЛИКА НА ПАРКИНСОНОВАТА БОЛЕСТ ПРИ ПОДОЛГОТРАЕН ТРЕТМАН СО ЛЕВО-ДОПА

WORSENING OF THE CLINICAL PICTURE OF THE PARKINSON'S DISEASE BY LONGER LASTING TREATMENT WITH LEVO DOPA

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РЕЗИМЕ

Лево-допата (ЛД) преставува златен стандард во терапија на Паркинсоновата болест (ПБ). Се смета дека лекот може да го забрза процесот на невродегенерација и да доведе до забрзување на токот и еволуцијата на болеста. Беа испитани 30 пациенти (24 мажи и 6 жени), кои се лекувале на одделот за екстрапирамидни заболувања при Универзитетската Клиника за Неврологија- Скопје (УКНС). Во студијата беа вклучени пациенти кои се третирани со ЛД повеќе од 5 години. На сите пациенти им се извршени: комплетен невролошки статус, неврофизиолошки испитувања, невропсихолошки тестови и невроимејџинг техники. Кај пациентите беа регистрирани: wearing off и on-off fenomen, двофазни дикинезии, немоторни симптоми, намален и флуктуирачки моторен одговор на терапија.

Пациентите имаа двофазни дискинезии, немоторни промени во психичката сфера, намален и флуктуирачки моторен одговор на терапијата со лево допа и секако намалена контрола врз моторните и немоторните симптоми. Кај 30 од болните се регистрираше постепен губиток на ефикасноста на лекот, со повторна појава и влошување на симптомите на Паркинсоновата болест, за околу 40%. Кај 23.3 % болни беше регистриран wearing off феноменот, а кај 27% пациенти беше присутен on-off феноменот. Кај еден пациент се појавија двофазни дискинезии. КТМ и НМР кај сите пациенти беа неспецифично променети. ЕЕГ-то беше уреден кај 77%, а кај останатите болни неспецифично променето. ВЕП покажа пролонгирана латенца на P100 бранот кај 83% болни на двете очи, а кај 2 (6.6%) пациенти, латенцата беше пролонгирана на едното око. СЕП беше уреден кај 77% болни, а кај 17% беше со пролонгирана латенца на спиноградот, а кај двајца (6.6%) пациенти беа пролонгирани латенците на кортикалните одговори.

Клучни точки: леводопа, дискинезии, немоторни симптоми

ВОВЕД

Познато е дека леводопата (ЛД) (L-dihidroksifenilalanin) терапијата преставува сеуште златен стандард во терапијата на болните од ПБ. ЛД терапијата преставува субституциона терапија на допаминот, кој како што е познато недостасува или е во голема количина намален кај болните од ПБ. Допаминот сам по себе нема својство да ја минува хематоенцефалната бариера и како таков доколку се даде чист допамин тој нема да стигне во мозокот и да делува. Затоа постои овој препарат кој преставува аминокиселина која преставува прекурсор на допаминот, која има особина поради својата биохемиска структура а ја минува ова хематоенецефална бариера и од крвта да стигне во мозокот, каде се конвертира во допамин и на тој начин делува во самиот мозок, како субституција на недостаточниот допамин. Овој лек се комбинира со инхибитор на периферниот декарбоксилазен ензим, кој во крвта го разградува леводопат препаратот, па така што и покрај ова особина тој ќе биде разграден во крвта од овој ензим и поради ова препаратот мора да се комбинира со овој инхибитор на ензимот периферна декарбоксилаза. Инхибиторот може да е различен како на пример карбидопа или пак бенсеразид. Но, подолготрајниот третман со овој лек, во просек околу

три до пет години од првичната примена на овој лек може да даде несакани ефекти од терапијата.

Тие несакани ефекти се најчесто појавата на дискинезиите претежно од типот на груб тремор и хореатични движења, особено познатата утринска дистонија како еден од wearing off феномените, on-off феноменот, која што преставува флуктуација на моторниот одговор поради губиток на рамномерната контрола врз моторните симптоми на болеста и која може да се манифестира со појава на нагол freezing феномен кога пациентот е како здрвен со акинезија и кога одеднаш преминува во фазата при што одеднаш се јавуваат груби хореатични движења, како и дистонични спори движења кои го оневозможуваат нормалното функционирање на болните. Можна е и појавата на бројни психички пореметувања од типот на параноидни психози, понекогаш силна агитација пропратена и со делиуриум и конфузија и бројни халуцинации, како и особено изразен страв во вечерните часови (pavor nocturnum).

Поради сето ова во последно време се повеќе се доведува во прашање дали навистина овој лек е златен стандард во терапијата на оваа болест или пак тој можеби сам по себе го забрзува процесот на невродегенерација на болеста и всушност доведува до забрзување на токот и еволуцијата на болеста и само по себе влошување на веќе постоечките симптоми. ЛД препаратот во терапијата на почетниот стадиум дава спектакуларен ефект во подобрување на симптомите на болеста но не влијае на самата постоечка патологија на болеста и дури се смета дека може да ја влоши и забрза веќе постоечката патологија на оваа болест и дури се смета дека може да ја влоши и забрза веќе постоешката патологија на оваа болест и дури се смета дека може да ја влоши и забрза веќе постоечката патологија на ова болест. Терапијата со лекот повеќе од пет години е поврзна и со зголемена токсичност и губиток на ефикасноста, а појавата на дискинезиите сеуште во доволна мерка не е разјаснета. Меѓу почестите несакани ефекти се и peak off dose дискинезијата и wearing off ефектот наречен end of dose dyskinesia. Wearing off најчесто се манифестира и со утринска дистонија, а може често и појавата на akinesia paradoksika поради нагол уплив на допамин во мозокот. Од останатите појави треба да ги спомнеме и двофазните дискинезии.

ЦЕЛ НА ТРУДОТ

Целта на трдот е да се прикажат негативните ефекти од ЛД терапијата во предолг временски интервал кај пациентите со ПБ.

МАТЕРИЈАЛ И МЕТОДИ

Беа испитани 30 пациенти (24 мажи и 6 жени) кои се повеќе години лекувани на одделот за екстрапирамидни заболувања при ЈЗУ Универзитетска Клиника за Неврологија-Скопје. Во студијата беа вклучени пациенти кои се третирани со ЛД повеќе од 5 години. Пациентите се на возраст од 58 до 76 годишна возраст. Пациентите се со средно времетраење на болеста од 7 години, а лекувани се со ЛД просечно 6 години. Сите пациенти боледуваат од ПБ.

Кај пациентите беше извршен детален невролошки преглед, од неврофизиолошките испитувања беа направени електроенцефалографија (ЕЕГ), евоцирани потенцијали, и тоа визуелните и соматосензорните евоцирани потенцијали (ВЕП и СЕП), беа направени батерија на невропсихолошки тестови и тоа мини ментал тестпт (ММСЕ), Весклеров тест за интилигенција, Рејов тест, Рej-Остерит комплексна фигура, Хуперов тест за визуелна ориентација, Бостонски тест и Минесота мултифазен инвентар на личноста како и невроимејџинг техниките, компјутеризирана томографија на мозок (КТМ) и нуклеарна магнетна резонанца на мозок (НМР).

ЕЕГ-то се изведува на 18 канален Галилео апарат во четри стандардни монтажи при што електродите се поставени на черепот по 10-20 интернационалниот SI стандарден систем . ВЕП (визуелни евоцирани потенцијали) се врши со помош на апаратот за визуелни потенцијали “TÖNNIS” со визулна “Heizif-shift” стимулација по стандардизирана техника. СЕП (соматосензорни евоцирани потенцијали) се изведува на истиот апарат за евоцирани потенцијали при што се врши дразба на nervus medianus и nervus tibialis.

Кај пациентите беа регистрирани wearing off и on-off феноменот со присутните дискинезии, двофазни дискинезии, немоторни промени во психичката сфера, намален и флуктуирачки моторен одговор на терапијата со ЛД и секако намалена контрола врз моторните но и немоторните симптоми кај ПБ.

Дискинезиите беа проценувани со помош на Abnormaly involuntary movement scale –AIMS.

РЕЗУЛТАТИ

Пациентите кои се на долготрајна терапија со ЛД беа опсервирани во период од 6 години. Кај 30 од болните се регистрираше постепен губиток на ефикасноста на лекот, со повторна појава и влошување на симптомите на ПБ за околу 40%. Кај 23.3% болни беа регистрирани и психички промени од кои кај еден маж се регистрираа симптоми на параноидна психоза, со халуцинации кои после еден период на прекин на терапијата од две недели и повторно воспоставување на лекот во мали дози, симптомите се повлекоа. Кај останатите болни чест симптом беше појавата на депресијата, инсомнијата, а кај еден болен кои беше на високи дози на субституционене лек се јави конфузност и краткотрајна делирантна состојба која се повлече по прекинот на терапијата.

Кај 40% пациенти беше регистриран wearing off феноменот, а кај 27% пациенти беше присутен on-off феноменот. Кај 23% од пациентите со wearing off се појави влошување на треморот со појава на груб тремор во мир и при движење со појава и на ригор со чувство на здрвеност, кај 10% се појави постурална нестабилност со губиток на рамнотежата поради кои одот беше скоро невозможен, а тешка брадикинезија кај 27% од болните. Кај еден пациент се појавија и немоторни симптоми со потешкотии во говорот и абнормални нелагодности, како и болки, а кај еден пациент се регистрираше и појава на утринска офф дистонија со потешкотии при станувањето од креветот наутро. Дистонијата беше изразена на стопалата, која после половина час од давањето на наредната ЛД таблета исчезна. Тешка брадикинезија до акинезија особено беше изразена во утринските часови, пред пациентите да ја испијат првата доза на ЛД препаратот. Анамнестички 5 (16.6%) пациенти даваат податок дека поволниот ефект од ЛД лекот им трае околу три, а кај 3 (10%) до пет часа. Најчесто последната вечерна доза ја земаа околу 22 и 23 часот, па наутро при будење имаа потешкотии при станување од креветот со изразена моторна успореност, а кај еден пациент и појава на акинезија веднаш по будењето.

Кај еден пациент дискинезиите се појавија после само девет месеци од почетокот на терапијата со ЛД. Кај еден пациент се појавија двофазни дискинезии при кои околу половина час по давањето на лекот се појавија груби дистонични движења на нозете кои слабо реагираа на терапија со амантадин сулфат., во траење од 40 мин, после што следеше период од час и половина кога беше во добра on фаза за да на крај од дозата на ЛД “end of doses” повторно се појавија дистоничните движења во траење од околу 20 минути, за потоа повторно да се јават знаците на ПБ.

Кај 30% од пациентите со on-off симптомите во off фаза беа со појава на акинизија и потоа во on фаза со нагла појава на груби хореатични движења кај 27% со ригор, а кај еден пациент се појави груб тремор наместо хореа.

КТМ и НМР кај сите пациенти беа неспецифично променети при што се покажа глобална кортикална мозочна атрофија кај 90% од пациентите, а кај двајца беа најдени и дифузни васкуаропатски промени на крвните садови во белата маса.

ЕЕГ-то беше кај 77% уредно, а кај останатите болни, неспецифично променето со присуство ма тета ритам, и кај двајцата пациенти со васкуларопатски промени и со високоволтиран алфа основен мозочен ритам. Кај еден од пациентите кои имаше и почетни дементни промени спориот тета ритам беше поназначен, мономорфен со средна волтажа. ВЕП-от покажа пролонгирана латенца на П100 бранот кај 83% болни на двете очи, а кај 2 (6.6%) пациенти латенцата беше пролонгирана на едното око. СЕП-от беше уреден кај 77% болни, а кај 17% беше со пролонгирана латенца на спинограмот поради лумбоишиалгија и полидископатија која беше присутна како коморбидитет, а кај двајца пациенти беа пролонгирани латенците на кортикалните одговори.

ДИСКУСИЈА

ЛД сеуште преставува златен стандард во терапијата на ПБ. Меѓутоа после давање на лекот во подолг временски период од околу 3 до 5 години, и со самото напредување на ова хронична болест се јавуваат компликации од лекот, дискинезии предизвикани од лекот, како и појава на автономни, сензитивни болни и психички немоторни симптоми предизвикани од употреба на лекот. Промените се јавуваат поради промени во самата фармакодинамика на лекот и прогресивното оштетување на базалните ганглии и нивните патишта како и екцесивната стимулација на допаминските рецептори. Најчести компликации се моторните флуктуации како што се wearing off, нагли непредвидливи off феномени, леводопа индуцираната дискинезија, on-off флуктуациите, појавата на хореатични, дистонични движења и миоклонус кои се јавуваат особено при употреба на високи дози на ЛД лекот, како и off дистонијата и двофазните дискинезии,

кои се јавуваат при подолготраен третман со пониски дози на ЛД. ЛД индуцираните компликации се резултат на повремено давање на ЛД таблетарна терапија при која се врши хронична, но повремена стимулација на постсинаптичките допамински рецептори, за разлика од континуираната стимулација на допаминските рецептори со овој лек кои даваат помалку индуцирани дискинезии. Појавата на компликациите во голема мерка е и во корелација со самото напредување на болеста, но тоа не е секогаш правило. Тоа особено се однесува за пациентите со јувенилен паркинсонизам и оние со автозомно рецесивна форма на ПБ, каде што појавата на моторните компликации од употребата на овој лек може да се појават и на самиот почеток од болеста.

Се рапортира во литературата за ризикот од појавата на ЛД индуцираните дискинезии и генетските варијации во допаминскиот рецепторен ген (DRD2), допаминскиот транспортер и опоидниот рецептор (OPRM1), полиморфизам во BDNF генот и А-алелот на COMT полиморфизмот. АА генотипот за DRD 3 корелира со ризикот од развој на дифазната дискинезија, но не и на peak дозната дискинезија, а алелниот полиморфизам во HOMER 1 генот, кои го кодира постсинаптичкиот протеин одговорен за синаптичкиот пластицитет и сигналната трансдукција на глутаматот е асоцирана со ниска преваленција на дискинезија кај ПБ (1).

Кај нашите пациенти со wearing off најчеста манифестација беше појавата на тешка брадикинезија до акинезија особено изразена во утринските часови, пред да ја земат првата таблетарна доза на ЛД препаратот. Анамнестички дава податок дека поволниот ефект од ЛД лекот им трае околу 3 до 5 часа. Најчесто последната вечерна доза ја земаа околу 22 и 23 часот, па наутро при будење имаа потешкотии при станување од кревет со изразена моторна успореност, а кај некој и појава на акинезија веднаш по будењето. Најчеста моторна компликација кај нашите пациенти беа on-off флуктуациите, при кои пациентите во on периодот имаа хиперкинетски движења, најчесто од типот на груби хореатични движења, при што за краток период одеднаш влегуваа во off фаза со појавата на акинезија и freezing феноменот. Најчеста дискинезија кај нашите пациенти беше хореата, а поретко дистонијата. Дискинезиите беа најмногу застапени во форма на peak of dose дискинезии, кога концентрацијата на ЛД беше највисока. При давањето на пониски дози на ЛД забележавме дека дискинезиите се јавуваат при крајот на дејството на ЛД кога и нејзината концентрација е најниска. Најчеста компликации при ЛД терапијата во ниски дози во кои размакот на временскиот период во давањето на наредната доза беше поголема појавата на двофазни дискинезии. Таа најчесто се манифестира со дистонија, после која следи подобрување па повторно дистонија. Слично на нашите наоди и горенаведените авторки наведуваат дека двофазните дискинезии почесто се јавуваат кај мажи со ран почеток на ПБ и рани моторни компликации.

Долготрајната терапија со ЛД може да има токсичен ефект и да ја забрза невроналната дегенерација предизвикувајќи формирање на цитотоксични слободни радикали и други оксидативни токсични видови и хроничниот третман е асоциран со развој на моторни компликации кои се извор на инвалидитет кои се извор на инвалидитет кај некои пациенти со ПБ. Се укажува на фактот дека ЛД може да биде токсичен врз допаминските неврони и може да ја забрза прогресијата на болеста. ЛД која во мозокот се конвертира во допамин во тек на оксидативниот метаболизам формира хидроген пероксид (H2O2), кои се отстрануваат со глутатионот (GSH) во нормални услови, но тој е редуциран кај болни со ПБ и тогаш се водород пероксидот (H2O2) влегува во интеракција со железниот јон Fe++ и формира високо реактивен и цитотоксичен слободен хидроксилен OH радикал во согласност со фентоновата реакција. ЛД ја намалува и конверзијата на токсичните видови на алфа синуклеин протофибрилите и ја блокира Chaperone посредуваната автофагија (2).

Несомнено е дека ЛД терапијата во почеток на болеста доведува до подобрување на симптомите за околу 70-80% од нелекуваните болни. Тој терапевтски ефект опадна кај нашите болни за околу 40%, после 3-5 години од пероралната терапија со овој лек. Особено ефикасноста беше опаднатa кај оние болни кој беа на високи и временски давани почести дози на овој лек. Се јавуваат психички промени, па дури и психотични манифестации, кои беа поизразени кај пациентите кои имаа знаци на деменција и оние кај кои невропсихолошките тестови покажаа глобални когнитивни нарушувања. Најчести психички манифестации се халуцинациите, инсомнијата па се до ноќните кошмари, параноидно интерпретативниот синдром и конфузно психотичните состојби.

Халуцинациите се најчесто идни, а поретко аудитивни, а може дури и почесто да се јават и при употреба на амантадин сулфат и особено антихолинергиците во постарата возрасна група на пациенти. *Wearing off* феноменот е последица на дегенерација на висок процент ма допаминските неврони и поради тоа најчесто е присутен кај болните со напредната форма на ПБ.

On off феноменот во суштина преставува феномен или состојба на нагла промена од состојба на добро контролиран паркинсонизам во состојба на нагло потенцирање и влошување на симптомите со појава особено на тешка акинезија со неможност за започнување на иницијативата во движењето, појавата на груб тремор и особено груби хореатични движења кога пациентот е во on кој настанува нагло, кога еден пациент кој е неподвижен во акинезија, одеднаш почнува да манифестира груби хиперкинетски најчесто хореатични движења. Овој феномен се споредува со неизменично палење и гасење на светлото. Од останатите дискинезии како што беше наведено се јавуваат но поретко дистонијата, тиковите, миоклонусот, бализмот, а особено неволни движења во лингво-фацио-букалната мускулатура. Треба да се истакне и проблемот при појавата на двофазните дискинезии кои преставуваат терапевтски проблем поради нивната слаба реактибилност на терапијата, особено со Амантадин сулфат и апоморфинот, кои се употребуваат во терапија на дискинезиите, особено во напредната фаза кај ПБ. Овие дискинезии се јавуваат особено при хируршки интервенции во предел на таламусот, како на пример таламотомијата, како и при длабока мозочна стимулација (ДБС) во таламичната регија и најчесто се јавуваат во нозете со појава на тешки балистички движења, после што настанува период на подобрување за да повторно при крајот на терапевтското дејство на дозата повторно нагло се појавата и престануваат со потполна појава на знаците на паркинсонизмот. Постојат и пароксизмакни дискинезии познати како уо-уо феноменот кои се јавуваат особено кај болните кои во напредната фаза на болеста подолго време се лекуваат со високи дози на ЛД и се одликуваат со нагли преоди од состојба на неподвижност во состојба на изразени дискинезии. Миоклонусот се јавувана нозете, најчесто навечер и честопати заедно со нарушување на сонот и останатите психички немоторни симптоми. Од автономните симптоми во off периодот најчесто се јавува терморегулаторна дисфункција, кризи на интензивно потење и сфинктерни дисфункции како што е уринарната ургентност за мокрење и уринарна инконтиненција. Во склоп на сензитивните симптоми секако треба да се спомене и појавата на болка, особено појавата на силните дистонични болни спазми во стопалата.

ЗАКЛУЧОК

Долготрајната интермитента допаминска стимулација на постсинаптичките допаминергични рецептори при перорална терапија со таблети ЛД предизвикува несакани ефекти. Најчести несакани ефекти се on-off феноменот, wearing off, ослабени терапевтски одговори и дискинезии. Кај сите испитаници настана повторна појава на симптомите на ПБ, како и нивно влошување.

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WORSENING OF THE CLINICAL PICTURE OF THE PARKINSON'S DISEASE BY LONGER LASTING TREATMENT WITH LEVO DOPA

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ABSTRACT

Levo-dopa(LD) is a golden standard in therapy of Parkinson`s disease (PD). It is considered that the medication can accelerate the process of neurodegeneration and can lead to acceleration of the disease course and the evolution of the disease. Therty patients were investigated (24 men and 6 women) which many years are treated at the movement disorders department by University Neurology Clinic- Skopje (UNCS). In the study were included patients who are treated with LD more than 5 years. To all the patients were made: complete neurological status,neurophysiologic investigations, neuropsychologic tests and neuroimaging techniques. The patients had diphasic dyskinesias,nonmotor changes in th psychological sphere,decreased an fluctuated motor response at the therapy with levo dopa and of course decreased control on the motor and nonmotor symptoms. At 30 of the patients it was registrated gradual loss of the efficacy of the medication, with repeated occurrence and worsening of the symptoms of Parkinson`s disease, for about 40 %. In 23,3 % of patients wearing off phenomenon was registrated, and at 27% of patients on-off phenomenon was presented. In one patient diphasic dyskinesias occurred. CT scan and MRI in all patients were nonspecific changed. EEG was normal in 77% and in the rest of the patients was nonspecific changed. VEP showed prolonged latency at P100 wave in 83% of the patients in both eyes and in 2 (6,6%) patients the latency was prolonged on one eye. SEP was normal in 77% of patients and in 17% was with prolonged latency of the spinogram, while in two(6,6%) patients the latencies of the cortical response were prolonged.

Key words: levodopa, dyskinesias, nonmotor symptoms

TRAJTIMI I DEPRESIONIT MADHOR PËRMES SEKS TERAPISË

TREATMENT OF MAJOR DEPRESSION THROUGH SEX THERAPY

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ABSTRAKTI

Njerëzit ndjejnë depresion kur dështojnë në arritjen e një qëllimi, kur u vdes një njeri i afërt, kur kanë probleme financiare, sociale e më së shumti kur kanë probleme emocionale e që lidhen kryesisht me probleme seksuale dhe ato në çift. Në rangimin e simptomave vegjetative të depresionit zvogëlimi i libidos rangohet si i pari i pasuar pastaj me simptome të ndryshimit në peshë, anoreksi, pagjumësi dhe çrregullim të ciklit menstrual. Trajtimi bashkëkohor i depresionit madhor është intergrativ (psikoterapi dhe farmakoterapi). Terapia e seksit është krijuar për të ndryshuar disa struktura të sjelljes seksuale. Që të kihet një funksionim i mirë seksual (që nga ana e tij ndikon në rritjen e kohezivitetit dhe kënaqësisë në marrëdhënie), individi duhet të jetë i lirë jo vetëm nga ndjesitë negative por edhe nga kontrolli i tepërt konjitiv. Terapistët e REBT (Rational emotive behavior therapy) që në shqip nënkupton terapinë racionale emotive të sjelljes, bëjnë një dallim të qartë mes pakënaqësisë në çift dhe shqetësimeve në çift. Pakënaqësia në çift ndodh kur një ose të dy partnerët nuk marrin aq sa do të donin nga partneri tjetër dhe /ose nga marrëdhënia intime. Shqetësimet në çift shfaqen kur një ose të dy partnerët shqetësohen emocionalisht nga këto pakënaqësi. Si përfundim mund të thuhet se terapia e seksit me gjasa është terapi e funksionimit disa planësh: në të njëjtën kohë identifikon, vlerëson, modifikon, ndryshon dhe integron problematikën në marrëdhënien në çift dhe atë të vetë çrregullimit.

Fjalët Kyçe: depresioni madhor, seks terapia, psikoterapia

HYRJE

Njerëzit ndjejnë depresion kur dështojnë në arritjen e një qëllimi, kur u vdes një njeri i afërt, kur kanë probleme financiare, sociale e më së shumti kur kanë probleme emocionale e që lidhen kryesisht me probleme seksuale dhe ato në çift.

Depresioni madhor ndodh kur një individ provon një ose më shumë episode depresioni madhor, simptoma kryesore e të cilit është ajo e një gjendjeje shpirtërore të rënë dhe humbje e interesit për aktivitete normale. Simptoma të tjera mund të përfshijnë prishjen e gjumit, këputjen, rënien në peshë, ndjenjën e fajit të kotë, ndjenjë e të ndierit i pavlefshëm, paaftësi për t'u përqendruar, mendime rreth vdekjes dhe vetëvrasjes. Këto simptoma shfaqen të paktën për një periudhë dy javore. Personat që vuajnë nga depresioni madhor e përshkruajnë veten si të trishtuar dhe të pashpresë. Ndodh që ata nuk gjejnë motiv për të vazhduar jetën dhe përpiqen të vrasin veten (1). Depresioni madhor zakonisht fillon në moshën e pjekurisë së hershme, por episode të depresionit madhor mund të shfaqen në çdo moshë, duke përfshirë edhe fëmijërinë. Një episod i depresionit madhor zgjat të paktën gjashtë muaj, por mund të shkojë edhe një vit, madje edhe më tepër. Sipas OBSH depresioni rangohet i katërti në listën e problemeve urgjente që atakon më shumë femrat se meshkujt, paraqitet kryesisht në moshën 20-50 vjeçare dhe është më i shpesht te personat që nuk kanë raporte të mira interpersonale dhe te të divorcuarit (2).

Në rangimin e simptomave vegjetative të depresionit zvogëlimi i libidos rangohet si i pari i pasuar pastaj me simptome të ndryshimit në peshë, anoreksi, pagjumësi dhe çrregullim të ciklit menstrual, (3). Edhe në rastin e përshkrimit të faktorëve të rrezikut

për depresionin pas faktorit gjenetik dhe tiparit të personalitetit vjen gjendja civile e që si pasojë e problemeve në martesës dhe divorcit mund të paraqiten nivele të ulta dhe të larta depresive.

Problemet seksuale gjithnjë kanë qenë bazë e çrregullimeve të shumta në jetën e njeriut duke paraqitur shenja të pakënaqësisë dhe prishjes së balancit neurologjik dhe emotiv te individi ashtu edhe te partneri i tij dhe rrethi ku ai jeton dhe vepron.

Deri ne gjysmën e shekullit të XX nuk ka patur një qasje të mirëfilltë dhe shkencore që kishte si qëllim trajtimin e problemeve seksuale e që do mundësonin zgjedhjen e problemeve dhe sëmundjeve tjera në mesin e të cilave janë edhe sëmundjet shpirtërore.

Në linjën e këtyre që u thanë më lartë vendoset fokusimi mbi tipologjinë alternative të terapisë së seksit si mënyrë e re e ridemensionimit funksional të individit brenda sigurisë së tij, rritje e brendshme dhe mbështetje e rregullit parimor të familjes dhe mirëqenies së individit brenda fushëveprimit të tij..

QËLLIMI I PUNIMIT

Qëllimi kryesor i këtij punimi ka qenë përmbledhja me kujdes e informatave shkencore që kanë të bëjnë më terapinë e seksit si metodë për trajtim të depresionit në mënyrë që profesionistët të kenë një mundësi për ndryshim të qasjes ndaj kësaj kategorie kurse qëllimi tjetër ishte dhënia e informatave për lexuesit e thjeshtë dhe ata që kanë nevojë për përmirësimin e gjendjes së tyre shpirtërore përmes disa këshillave të thjeshta e praktike.

METODOLOGJIA

Një përmbledhje sistematike e të dhënave dhe informatave nga punimet origjinale kërkuese shkencore të përzgjedhura në mënyrë selektive dhe rigoroze duke ndjekur metodën shkencore të vlerësimit të balancuar të studimeve kërkimore origjinale.

Kërkimet janë bërë duke hulumtuar nëpër bazën e të dhënave kompjuterike, duke përdor njohuritë personale nga kjo fushë, duke kontrolluar listën e referimeve në artikuj të ndryshëm të botuar në zhurnalë shkencore dhe dukë bërë një kërkim manual në zhurnalët kyç të fushës së terapisë së seksit dhe depresionit.

SHTRIRJA E PROBLEMIT

Trajtimi bashkëkohor i depresionit madhor është integrativ (psikoterapi dhe farmakoterapi).

Si farmakoterapi mund të përdoren një numër i antidepresantëve të tipologjive të ndryshme:

Frenuesit e rikapjes selektive të serotoninit (SSRI), Frenuesit e rikapjes se Norepinefrinës dhe Dopaminës (NDRI), Antidepresantët atipik - triciklik dhe frenuesit e Monoamine-Oxidazës (2).

Trajtimi Psikoterapeutik dha Alternativ.

Studimet kanë raportuar disa tipe të psikoterapisë si efektive për depresionin:

Terapia Konjitive –Behaviorale (CBT) është më e përdorshmja. Ajo ndihmon në identifikimin e besimeve negative dhe sjelljeve dhe i zëvendëson ato me të tjera të shëndetshme dhe pozitive. Parimi bazë është se janë mendimet tona që përcaktojnë sesi ndihemi dhe sillemi. Ne mund të ndryshojmë mënyrën e të menduarit dhe të sjellurit kësisoj.

Terapia Elektokonvulsive (ECT): Përshkimi i rrymave elektrike në tru mendohet se ndikon në nivelet e neurotrasmetueseve. Jep efekte të menjëhershme lehtësuese edhe të simptomave më rezistente të depresionit. Efekti anësor më i zakonshëm është konfuzioni, ndonjëherë humbje e kujtesës.

Terapia Hormonale. Studimi i Serotoninit, Progresteronit dhe Estrogenit në gratë në periudhë menopauzale me depresion, pa përdorimin e antidepresantëve, vërtetuan praninë e gjendjeve depresive si pasojë e mungesës nën nivel të këtyre hormoneve. (Anrdrew Herzog 2010). Kjo procedurë e re e trajtimit të depresionit është mjaft premtuese (4).

Seks terapia sikundër e njohur sot, është themeluar nga Matsers and Johnson(1970) që publikuan për herë të parë një metodë të re terapeutike ndaj revolucionarizimit të problemeve seksuale për profesionistët e shëndetit . Përtej faktorëve intrapsikikë, për Masters dhe Johnson (1970) janë shkaqet sociale dhe konjitive ato që shkaktojnë problemet seksuale, (5). Në të njëjtën linjë, Helen Kaplan (1974) përpunoi versionin e saj të terapisë së re të seksit, e parë si një urë integrative mes psikanalizës tradicionale dhe teknikave bashkëkohore behaviorale (6).

Studiuesit dhe një mini kërkim në fushën e klinikës shqiptare nga Ejona Icka, psikologe, tentojnë të hedhin dritë mbi kuptimin e faktorëve psikologjik dhe fizik që ndikojnë në ndryshimet e interesit seksual.

Burrat e moshuar dhe gratë në periudha postmenopausale, duan të ndjejnë kënaqësi të njëjtë seksuale si do çift i ri. Ata që mbijetojnë ndaj traumave, qoftë neurologjike, apo të shtëpisë duan të rimarrin kënaqësinë e jetës seksuale aktive. Pjesa më e madhe e studiuesve klinik bien dakord se klima e tashme kulturore inkurajon interes aktiv ndaj seksit, edhe nëse normat kulturore dhe (mbase) ato shtetërore publike nuk nxisin shumë atë (lirinë seksuale). Praktika e terapisë së seksit është e lidhur ngushtë me seksologjinë si shkencë.

Terapia e re e seksit sipas Masters dhe Johnson (1970) përfshinte punën afat-shkurtër por intensive me çiftin (terapinë e përbashkët), me një çift terapistësh (një mashkull dhe një femër). Ndërhyrja konsistonte në ushtrime behaviorale të drejtpërdrejta, terapinë konjitive-behaviorale të çiftit (Kilmann,Boland, Norton, Davidson & Caid 1986; Hawton 1992; Teifer 1994;Leiblum &Rosen 1995). Ekzistojnë disa metoda të trajtimit me seks terapi:

Metoda Masters-Johnson: Trajtimi fillon me procedurat e vlerësimit (ekzaminimi fizik dhe intervistat) me terapistin. Ditën e tretë, terapisti takon çiftin për të diskutuar rezultatet e vlerësimit dhe parashkrimin e plan-trajtimit.

Metoda Kaplan: Ndihmon partnerët në arritjen e qëllimeve të tyre seksuale në kohën më të shkurtër të mundshme. Seancat mbahen një ose dy herë në javë teksa partnerët praktikojnë edhe në shtëpi.

Metoda PLISSIT (Annon 1976): Ky model parashtron për të katërt fazat e teknika të veçanta: Faza e parë e trajtimit: Lejimi i informimit që i mundëson klientit të dijë parametrat dhe sqarojë shqetësimet dhe problematikat që ka. Faza e dytë e trajtimit: Informimi i kufizuar. Dhënia e informacionit specifik faktik në lidhje me shqetësimin kryesor të klienti. Faza e tretë e trajtimit: Sugjerime specifike në lidhje me çështjet kyçe të nxjerra në terapi. Faza e katërt e trajtimit: Terapia intensive, që në P-LI-SS-IT shihet si trajtim individual i orientuar dhe i standardizuar.

DISKUTIMI

Krejt ky zhvillimi në fushën e terapisë së seksit na vë përballë sfidave dhe çështjeve të tjera të gjëra: Çfarë është një çrregullim seksual? Sa e rëndësishme është prania e distresit (stresit negativ) në konsideratën diagnostike? Cilat janë trajtimet e duhura? A është REBT terapia më e mirë ndaj problematikave që shoqërojnë seksin? Cilat janë pritshtmëritë e një trajtimi të mirë? Cili përcakton suksesin e trajtimit, terapisti apo pacienti? si vlerësohet suksesi i terapisë (ndjesitë e kënaqësisë, intimiteti) (7).

Terapia e seksit është krijuar për të ndryshuar disa struktura të sjelljes seksuale. Masters dhe Johnson i dhanë një dimension të ri më terapinë e seksit. Që të kihet një funksionim i mirë seksual (që nga ana e tij ndikon në rritjen e kohezivitetit dhe kënaqësisë në marrëdhënie), individi duhet të jetë i lirë jo vetëm nga ndjesitë negative por edhe nga kontrolli i tepërt konjitiv.

Në shoqërinë shqiptare të ardhur nga një sistem besimi i plotë ku marrëdhënia intime dhe ajo seksuale në veçanti nuk konsideroheshin te denja për diskutim të gjerë, dhe ku jo rrallë çifti fshihte dhe i nënshtrohej fatit të vet dhe ku shpesh marrëdhënia në çift kthehej në tipike shoqërore, seksi ka qenë tabu e mendimit dhe i frenuar në komunikim e përditshëm. Ende sot (ku në fakt figura e psikologut këshillues të çiftit dhe seksit është figurë e menduar), shoqëria parapëlqen të stërmundohet vetë për të gjetur një zgjidhje të problemeve-shpesh zgjidhje irracionale të mbivendosura-duke përforcuar negativisht negativen e marrëdhënies. Në shoqërinë tonë represimi seksual, shumë prej problematikave seksaule dhe atyre të çiftit janë pasojë e informacionit të pakët, keqpërceptimeve dhe miteve të përhapura rreth fantazisë, klimaksit të përbashkët etj (8).

Seks-Terapia – REBT (Terapia emotive behaviorale racionale), ka marr një zhvillim të dukshëm kohet e fundit. Një pikë e fortë e REBT është pozicioni që ajo bart ndaj zemërimit dhe reagimeve të dhunshme në marrëdhëniet intime. Terapistët e REBT bëjnë një dallim të qartë mes pakënaqësisë në çift dhe shqetësimeve në çift. Pakënaqësia në çift ndodh kur një ose të dy partnerët nuk marrin aq sa do të donin nga partneri tjetër dhe /ose nga marrëdhënia intime. Shqetësimet në çift shfaqen kur një ose të dy partnerët shqetësohen emocionalisht nga këto pakënaqësi. Kësisoj ata përjetojnë ankth, zemërim, lëndim, depresion, turp, ndjenjë faji dhe xhelozi-emocione që ndërhyjnë në komunikimin konstruktiv, zgjidhjen e problemeve dhe proceset e negocimit që ndihmojnë në zgjidhjen e pakënaqësive në çift. Kur një ose të dy partnerët janë të shqetësuar emocionalisht, ata vihen në situate vet-mbrojtëse që përforcojnë shqetësimin në çift. Teoria REBT postulon se nëse çiftet kanë një komunikim

konstruktiv, aftësinë pro-zgjidhëse dhe të negocimit, çiftet mund të zgjidhin vetë problemet e pakënaqësisë. Kur ata nuk i posedojnë këto aftësi, fokusi i terapisë është t'i trajtojë dhe përdorë këto aftësi. Kur çiftet janë në stadin e marrëdhënies së shqetësuar, derisa problemet e tyre të zgjidhen, shfaqja e problemeve në marrëdhënie është prezente pavarësisht aftësive komunikuese të partnerëve (10, 11, 12 ,13).

PËRFUNDIME

Depresioni Madhor, është pasojë e faktorëve multindërvepruesbiologjikë-konjitivë-emocional-social. Tendenca e shfaqjes u atribuohet kushteve fizike dhe psikologjike që me gjasa e kthejnë ndikimin e disa faktorëve në ndikim sistemi. Një përforcim mendor negativ sjell një sjellje negative dhe emocionalitet negativ. Zhbërja e tyre është atributi primar i terapisë CBT.

Terapia e seksit me gjasa është terapi e funksionimit disa planësh: në të njëjtën kohë identifikon, vlerëson, modifikon, ndryshon dhe integron problematikën në marrëdhënien në çift dhe atë të vetë çrregullimit.

Nëse Depresioni Madhor trajtohet me seks-terapi (REBT), përpos trajtimit specifik të çrregullimit, mund të trajtohet edhe dimensionaliteti i tij duke ndryshuar mendimin (irracional-racional); duke përforcuar strategjinë e të menduarit pozitiv dhe duke e trajnuar këtë përforcim për përdorim të jetës së përditshme.

Terapia REBT është terapi integrative e së ardhmes e cila pak ose aspak njihet në klinikën shqiptare. Nëse në perspektivën tonë diagnostike marrim në konsideratë këtë terapi, atëherë ne mund përfitojmë si në koston neto dhe atë oportune, ulim njëkohësisht koston humane të përdorimit farmakoterapik, dhe japim një dimension të ri trajtimit të përgjithshëm psiko-social në shërbim të sigurisë së qenies. Përfitohet kësisoj edhe në nivel sistemi!

REKOMANDIME

Aftësimi dhe përgatitja e stafit profesional të Psikologut të seksit, standardizimi kurrikular dhe njësimi i procedimeve bashkëkohore të kërkimit - diagnozës dhe trajtimit alternativ të çrregullimit të Depresionit Unipolar përmes terapisë shumëdimensionale të Seksit.

Përpjekje maksimale për promovimin e terapisë së seksit si metodë për trajtimin e depresionit në masën që ajo të jetë e kuptueshme për profesionistët dhe ata që vuajnë nga depresioni.

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TREATMENT OF MAJOR DEPRESSION THROUGH SEX THERAPY

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ABSTRACT

People feel mild depression when fail to achieve a goal, when a family close member dead when they social and financial problems and mostly when they have emotional problems mainly related to sexual and relationship problems. In the ranking of vegetative symptoms of depression, reduction of libido is ranked as the first, followed then by symptoms of change in weight, anorexia, insomnia and menstrual cycle disorder. Contemporary treatment of major depression is integrative (psychotherapy and pharmacotherapy). Sex therapy is designed to change certain structures sexual behavior. To have a good sexual function (which increases the cohesiveness and relationship satisfaction), the individual must be free not only from negative feelings but also by excessive cognitive control. REBT (Rationale Emotive Behavioral Therapy) therapists make a clear distinction between dissatisfaction and concern inside the couple. Couple dissatisfaction occurs when one or both partners do not take as much as they would like from the other partner and / or intimate relationship. Couple Concerns arise when one or both partners worry emotionally from this disappointment. In conclusion it can be said that sex therapy is probably some faceted operation therapy, at the same time identifies, evaluates, modifies, alters and integrates issues in relation to the couple and disorder itself.

Keywords: major depression, sex therapy, psychotherapy

VOLUNTEER MEDICAL MISSION "AMERICAN WOMEN'S HOSPITALS" IN MACEDONIA AND KOSOVO DURING AND IMMEDIATELY THE GREAT WAR

ДОБРОВОЛНА МЕДИЦИНСКА МИСИЈА ,, "AMERICAN WOMEN'S HOSPITALS" ВО МАКЕДОНИЈА И КОСОВО ЗА И НЕПОСРЕДНО ПОСЛЕ ПРВАТА СВЕТСКА ВОЈНА

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ABSTRACT

This paper generally is about the difficult period for Macedonia and Kosovo dating back in time of the First World War and the years right away it. Actually, that is the period when this territory was under occupation of the Allied and Central army for about four years. Also, in the same time the life of the people became unbearably tough due to the pressure for the daily requisitions for food, livestock, housing and forced work for those who were capable of working.

The presence of the international sanitary missions in The Kingdom of Serbia during the Great War and several years afterwards was welcomed and necessary. The Great War that brought great sufferings, did not only changed the world forever, but also put the international solidarity on a test and without it the number of the victims from the epidemic and pandemic diseases, famine and poverty would be more tragic and bigger.

The international sanitary missions represented a huge saviour and one of them belong to the mission 'Hospitals of the American women' and its director, the legendary d-r Eta Grey. They give the population enormous healthy-social protection at times when was decisive whether to be or not.

Purpose of the paper: The purpose of this paper is to present the role of the international solidarity of the "American Women Hospitals" mission in providing medical prevention in during the hard years after the First World War.

For writing this paper it was used historical-researching method while the subject of research is the problem with the chronological order and analysis of the researched material. Except the written material it is used photo-documentation, reports, letters, working reports and newspaper articles

Key words: Macedonia, Kosovo, First World War, hospitals, contagious diseases, sanitary missions.

Introduction

With the First World War which started in 1914 and lasted until 1918, it also started the biggest and the hardest military discord in the history of the mankind. There were 60 million mobilized people, 15 million people were dead and 20 million wounded people only in Europe. Moreover, one third of the Serbian population has died together with Kosovo and Macedonia and shortly after the war, 500 000 children were left parentless as well.

In the period from 1912 to 1918, three wars occurred on the Macedonian territory in its ethnic borders. Firstly, the First Balkan War occurred which was followed by the Second Balkan War and afterwards without time

breaks, the First World War started together with all the disasters and misfortunes which were brought by the bloody conflicts of the world's great powers and their struggle for world domination and colonial empires.

Namely, the First World War as a global armed conflict was centered among several fronts and many continents. One of them or the Southern Front was spread on the Macedonian territory and therefore, it was also called as Macedonian Front.

This war has caused far-reaching political, social and civilization changes in the history of the Balkans and the other European nations. Before the First World War, there was no war which has altered the European map such dramatically as the World War I.

In that time, trough the territory of Macedonia and Kosovo went by a variety of troops from the entire world such as: the Austrians, British troops, the Australians, Albanians, the Americans, Bulgarians, Russians, Croatians, Dalmatians, Germans, French troops, Greeks, Turkish troops, Senegalese and many other various colonial armies. What is more, they also destroyed all the property owned by the people living in those regions. As passing through the populated areas, they used to remove the windows, doors and other type of carpentry in order to satisfy the needs of their camps. Consequently, the houses remained in miserable condition due to their similarity with skeletons.

Finally, the Macedonian Front stopped to exist at the end of September in 1918 with the victory of the Triple Entente. The first days after the end of the Great War were outstanding and extremely difficult for the people in Vardar Macedonia and Kosovo.

What is more, during the war and immediately after it, numerous charitable organizations with their hard work saved lives of many unfortunate people including thousands of children in their toughest moments.

More specifically, on the territory of Macedonia and Kosovo during the war, the care for the sick and injured people was in the hands of the following organizations: the English mission - The Serbian Relief Fund-SRF, Scottish women's hospitals-SWH, and after the war, the care was taken by the American mission - The American Women's Hospitals – AWH and the American Red Cross which actually is the subject of this paper.

The end of the First World War the founders of the mission "Hospitals of American women" meant only the end of military operations, but not the end of the diseases, poverty and hunger. The necessity of medical care in the post-war years in the Balkans was more than necessary because of the presence of typhoid fever, influenza, malaria, tuberculosis, venereal diseases, pneumonia, smallpox, cholera, various leather, surgical and ophthalmic diseases.

American Women's Hospitals Hospitals physicians, nurses and chauffeurs,before leaving for Europe

TWO ELMIRA DOCTORS BORN WOMEN WHO PROVIDED CARE FOR REFUGEES

During and after the World War I the doctors Regina Flood Keyes and her cousin Frances M. Flood[1], both natives of Elmira, were the first to serve in an American Woman's Hospital uniform. They were provided with uniforms in December 1917 and accredited to the American Red Cross for duty near the Salonika front. On the invitation of Colonel Jourdan, medical officer of the Seventeenth Colonial Division, French Troops, Dr. Keyes, with all the supplies she could muster, she served in the medical corps on the Salonica front during the offensive of the Allied forces in 1918.

Eventually, they opened a hospital in Vodena, Greece. This hospital was a refuge to Serbian and other displaced persons as well as to sick and helpless Greek villagers.

In addition to the care of inpatients, about 3,000 visits were recorded monthly in the outpatient department. Dr. Keyes and Dr. Flood, with two American nurses and a corps of local assistants were on double duty most of the time.[2]

Dr. Keyes was the director and surgeon of the hospital that held 60 beds. In addition to the wounds from the war, they were faced with epidemics of the deadly typhus fever. Dr. Flood dealt with the non-surgical cases which included typhus and the infamous influenza epidemic that cost so many lives in 1918. During the influenza epidemic they treated Greek, French and Serbian soldiers as well as the refugees.

Dr. Regina Flood Keyes

Dr. Frances Mabel Flood Heath

In the Balkan Peninsula there was no plan which involved transportation that worked out according to schedule, and if supplies were not forthcoming it was necessary to improvise substitutes. Submarine activities in the Mediterranean sea prevented the delivery of equipment for the Vodena Hospital. Fortunately, Dr. Keyes was well supplied with instruments, and, with the aid of carpenters, thinners, and whitewashers, the hospital, which had been opened some time before in a Turkish schoolhouse, was renovated and put in working order. Dispensaries were opened in connection to this hospital and Dr. Keyes, Dr. Flood, and their two American nurses, with a staff of native assistants, were kept busy from dawn until dark during 1918. About three thousand treatments were given monthly in these dispensaries, and the hospital was a haven of refuge for the desperately ill. The Balkans had never been well supplied with physicians, and many of those who had practiced in that country lost their lives during the Balkan and World wars.[3] For these reasons there was a large number of neglected surgical diseases, and great was

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Hospitals & Colleges

American Women's Hospitals

Reconstruction Committee of the Medical Women's National Association
Headquarters, 637 Madison Ave., New York

SPLENDID WORK DONE BY WOMEN DOCTORS OF THE A. W. H. IN SERBIA DURING DISASTER AT MONASTIR

THE work done by medical women through the American Women's Hospitals is one of those great pieces of work which is so quietly done that only through a great disaster, or some occurrence quite out of the ordinary course of events, is its greatness recognized even by those who are really interested. This was shown recently when the splendid work of American women physicians at the time of the Monastir disaster was given great publicity by the Associated Press in every country of the world. We reprint from the New York Times some of the work done by members of our own Association, which thrill us with appreciation of the splendid worth of these women who have been giving all their time and energy to these countries which have so sadly needed them, and in this last disaster the only source of relief was this American Women's Hospital, founded by American women physicians and supported by America:

BELGRADE, April 20 (by the Associated Press). —Four hundred carloads of ammunition and high explosives stored near the railroad station at Monastir, Southern Serbia, exploded April 21st, at noon, killing hundreds of persons, including more than 400 soldiers, wounding thousands and virtually destroying the heart of the city. One-half of the city's population of 50,000 was rendered homeless. The disaster takes on the proportions of one of the greatest catastrophes in history.

The victims were mostly children and soldiers. A church in which the children were worshipping collapsed under the detonation, while the barracks in which 1,800 soldiers were having lunch was destroyed. Property worth millions was destroyed.

Immediately after the explosion fire broke out in various parts of the city. The panic-stricken inhabitants fled to the nearby woods and mountains, from which they watched their homes burn. All telegraphic and telephonic communication from Monastir with the outside world was cut off. The first news of the disaster reached Belgrade from refugees who managed to reach Prilep, thirty miles northwest of Monastir. Several Serbian relief units were immediately organized and started for Monastir.

Six American women doctors of the American Woman's Hospital at Veles left there for Monastir as soon as news of the explosion was received. They were headed by Dr. Esther Lovejoy, of Richmond, Va. They expected to negotiate the fifty miles of bad roads over the mountains to Monastir and reach the stricken city this evening.

Mrs. William Brewster, of New York City, who conducted an American missionary school in the center of Monastir, has not been heard from since the explosion.

King Alexander has sent a message of sympathy to the victims, and the government is dispatching a large sum of money for the immediate relief of the homeless.

It is impossible to estimate the total number of persons killed, but several hundred were wounded, many of them hopelessly. Great numbers of the injured have been removed to the American hospital founded by Dr. Regina Flood Keyes, of Buffalo, N. Y., which, somewhat removed from the scene of the explosion, escaped with slight damage.

Relief workers from the American Women's Hospital at Veles arrived last night, bringing cots, blankets and medicines. H. H. Reeder, Jr., of New York City, acting director of the American Relief Commission in Belgrade, is hurrying to Monastir with physicians, nurses and medicines. He will take charge of the relief work.

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the joy among those with bona fide operative disorders, because, with only fifty hospital beds, the preference was given to such cases. "There is some soul of goodness in things evil," and a hernia, cured by an operation, which incidentally provided a patient with food and a bed for three weeks, or a month, was not altogether bad in a country where food and beds were daily problems of vital importance. This was the only hospital in Vodena at that time where major operations were performed. There was a large variety of cases, and of nationalities-Albanians, Dalmatians, Greeks, Macedonians, Romanians, Serbians and Turks.

When the Serbian refugees returned to their country after the Armistice in 1918, after the war was over, the Vodena Hospital was transferred to Monastir, and the two doctors ran a hospital in Monastir.[4] There were present large numbers of war prisoners, returning from Bulgaria,who were suffering from typhus.

An anti-insect campaign was conducted in this hospital with the result that insect-borne diseases were reduced to a minimum and the place became widely known as the Flyless Hospital of the Balkans.

Insects have had an enormous influence in the history of the Balkans and other parts of the world. Flies, lice, fleas, gnats and mosquitoes are among the greatest enemies of mankind. They are allies of war and famine, retainers of pestilence, carrying typhoid, typhus, sand fly fever, tuberculosis, malaria and many other forms of disease. They worked there under very difficult conditions. They had no coal for heat and very little wood. Food was also very scarce. The hospital was one of the few buildings left standing in the city after the war.[5]

Dr. Etta Gray, of Los Angeles, President of the Medical Women's National Association, was sent to the Balkans as organizer and director of the work of the Association in that country. She was young, strong, a well-trained physician and surgeon, with a gift of the uncommon quality known as common sense.[6]

Dr. Gray made a careful survey of the country. The seemingly neediest section was finally found in Macedonian Serbia and Kosovo, and the announcement of her intention to establish a medical service in the district, with a central hospital and headquarters at Veles, was received with pathetic expressions of gratitude and a organizations had surveyed that field, but had gone away and never returned. The buildings for headquarters and a central hospital, granted by the local government,

Dr. Gray and Mrs. Cruikshank, of the American Women's Hospitals, at Veles, Serbia

registered seven years' warfare. They were without windows, doors and woodwork, but the damage was not all due to explosives. Troops and refugees passing to and fro after military victories, or defeats, destroy all movable property. The doors and other woodwork of houses were used to keep their camp fires burning. This accounted thousands of skeletons of houses in the Balkans and near eastern countries.[7]

When the matter of location was definitely decided, Dr. Gray went to Belgrade to complete arrangements. The government agreed to transport hospital supplies and personnel of the Association, without charge, wherever trains were running.

With several carloads of such material, Dr. Gray returned to Veles about the middle of November, 1919, and with the help of Dr. Laura Myers and Miss Freda Frost the central hospital and headquarters for Serbia (Macedonia and Kosovo) were opened at that town, in the heart of a desert of destitution and utter wretchedness. This place was rarely visited by travellers. Practically the only contacts for almost three years were contacts with the sick and

hungry, and the variety of life was made up largely of variety in diseases, some of which were experienced personally by the head of the hospital service and her assistants in that district.

Headquarters might have been opened in the nearest large city, or in the capital of the country, but Dr. Gray had a fine sense of the fitness of things, and from her standpoint it was not fit that the head of a hospital service should live in safety and comfort while her staff lived in danger and discomfort. Besides, the object of the American Women's Hospitals was to care for the sick among those in greatest need, incidentally to carry on a health educational service, and to do as much as possible with the funds contributed for the purpose. Headquarters at Belgrade would have been advantageous in some respects, but the cost would have reduced the work in the field.

Getting the headquarters and personnel house in order at Veles was no small job. The court was cleared of debris and cleaned to its bedrock of cobblestones. The building was scrubbed, fumigated and whitewashed, a water supply provided, and shower baths improvised by the ingenious use of Standard Oil cans. Iron beds were set up, prim as Priscilla, their four little feet resting in milk cans with an inch of Creso solution.

Weeks before the hospital was opened, the sick began to apply for admission. A temporary clinic and dressing station was arranged to care for those suffering from painful minor ailments.

In one report, dated from December 13, 1919, Dr. Gray wrote: „ Before moving into the house, the patients began to come and they were coming in increasing numbers . . . . Such pitiful sights!-people with neglected sores and wounds who had had no treatment whatever for weeks. Terrible infections of all sorts and appalling eye diseases. It was terrible to look into the upturned faces of human beings who were sightless from neglect and to know that proper care at the right time would have had saved them. There were a large number of tubercular cases, and many undernourished children ready to develop the disease. Their parents were told to feed them, but they didn't have the food. We should put in a feeding station for these sick children and we should have soon had a large number of day boarders.

A great many surgical cases were seen at the clinic every day, but nothing could be done to help these people until the hospital was ready to receive them.....“

Chronic surgical cases had been accumulating in that district for years and all kinds of hernias resulted, some of which were of enormous size, containing part of the abdominal viscera. Without treatment these unfortunate people got worse or died. If the rupture was small and an intestinal loop became strangulated, the victim suffered agony and died promptly. But where strangulation did not occur, the abdominal contents escaped, little by little, through the opening, and the hernia increased in size month after month and year after year.

Dr. Gray, in her surgical cap and gown, with a choice selection of scalpels, forceps, scissors, needles and thread, bandages and anæsthetics, was a popular lady with the hernia brotherhood. One after another they came to be operated upon and sometimes sat in the court for a week waiting for a bed.

„ It is further said in Etha Gray report that for seven years, beginning from 1912, this town and the surrounding country had been the theatre of the military activities of three wars, and at the time hospital personnel arrived on the scene the town might more appropriately have been called Ichabod. The first and second Balkan Wars were closely followed by the World War, and for this section of the earth's surface it was a World War in all the horror of actual experience. During the years of these three wars, soldiers from far and near, friend and foe, occupied this territory in turn. In alphabetical order there were Albanians, Americans, Australians, Austrians, British, Bulgarians, Cretans, Croatians, Dalmatians, French, Germans, Greeks, Senegalese, Turks, and Satan only knows how many others.

Wherever soldiers occupy a country they leave their blood not only on the battlefields but in the veins of the population for ultimate good or harm, according to its quality. In some of the Macedonian towns which were very completely occupied by the Central and other forces, the evidence of this occupation could be seen in ruined buildings and in striking types of fair children here and there.“

Plans for development of a chain of hospitals and dispensaries in Macedonian Serbia and Kosovo were subject of the rapidly changing conditions of a country recovering after years of warfare and enemy occupation.

Permanent hospitals had been opened at Monastir by Serbian agencies, and the urgent need at that point had been relieved, but at Strumica and Prilep no provision for the sick had been made.

Transport of the wounded and sick people from home to hospital

Plans for development of a chain of hospitals and dispensaries in Macedonian Serbia and Kosovo were subject of the rapidly changing conditions of a country recovering after years of warfare and enemy occupation. Permanent hospitals had been opened at Monastir by Serbian agencies, and the urgent need at that point had been relieved, but at Strumica and Prilep no provision for the sick had been made.

Dr. Toggnazzini with patient in Pristina hospital

The work of the AWH mission in Southern Serbia increased rapidly, and by the end of 1920 thousands of cases were being reported monthly. Dr. Lilla Ridout had been placed in charge of the hospital at Prelip; Dr. Mary Elliott of Chicago was head of the Strumica Hospital, and Dr. Irene Tognazzini was running the Pristina Hospital with the help of two American nurses.

In connection with our hospitals, outlying clinics were conducted at Giljiane, Podujevo, Gratchnitza, Frisovitch and Urasavitch by Dr. Ellen Cover and Miss Nora Hollway.

The hospitals, clinics, dispensaries, and distributing stations for clothing were in full swing Serbia in August, 1921.[8]

Under the direction of Dr. Gray, assisted by Drs. Hazel D. Dr.Bonness, May T. Stout, Marguerite White, Mary N. Bercea and Miss Freda Frost, head nurse and general supervisor, with a corps of American nurses, Veles became an important medical centre, especially for surgical work and children's diseases. Patients came from all directions, sometimes walking for miles and reaching the hospital in a state of complete exhaustion.

There was a report of one boy who walked fifteen days slowly leading his sister, who could not see, to the eye clinic. Many of the sick and disabled came in ox-carts, or on donkeys, and those who could not afford to pay for lodgings at the world's worst hotels sat outside the hospital walls and waited until beds were vacated.

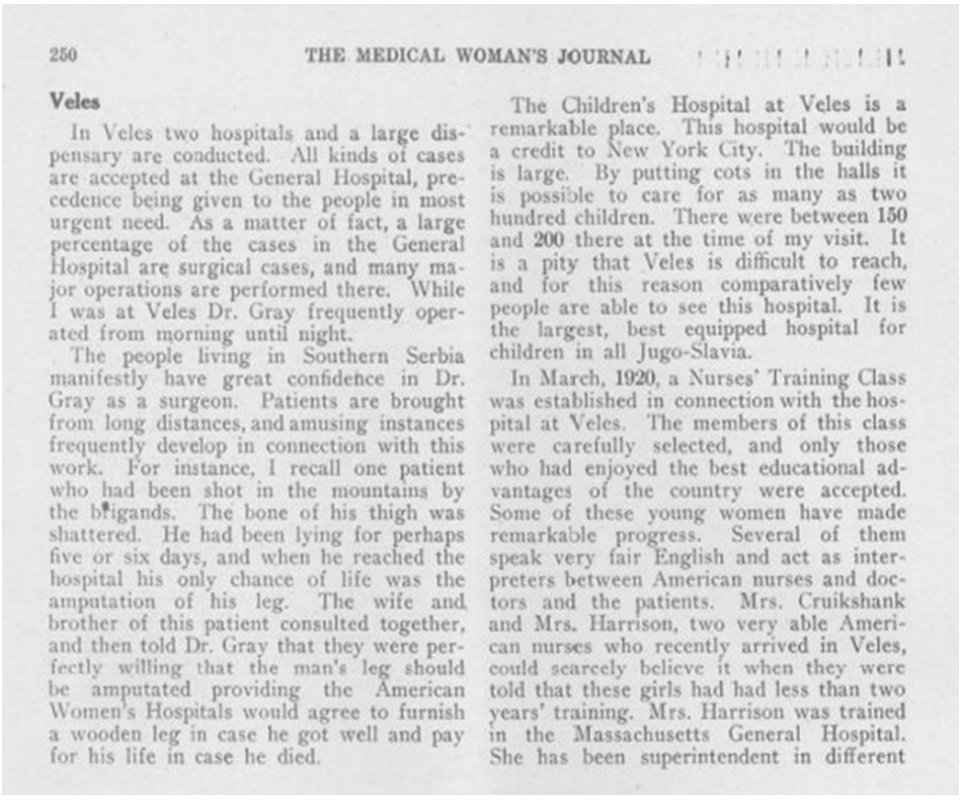
A great many surgical cases were seen at the clinic every day, but nothing could be done to help these people until the hospital was ready to receive them. Before moving into the house, the patients began to come and they were coming in increasing numbers . . . . Such pitiful sights !---people with neglected sores and wounds who had had no treatment whatever for weeks. Terrible infections of all sorts and appalling eye diseases. It was terrible to look into the upturned faces of human beings who were sightless from neglect and to know that proper care at the right time would have had saved them. There were a large number of tubercular cases, and many undernourished children ready to develop the disease. Their parents were told to feed them, but they didn't have the food. We should put in a feeding station for these sick children and we should have soon had a large number of day boarders.[9]

Dr. Mary Elliott Dr. Lilla Ridout Dr. Irene Tognazzini

Dr. Gray, in her surgical cap and gown, with a choice selection of scalpels, forceps, scissors, needles and thread, bandages and anæsthetics, was a popular lady with the hernia brotherhood. One after another they came to be operated upon and sometimes sat in the court for a week waiting for a bed.

The story of the Children's Hospital at Veles is the best and brightest page of the history of the work in Serbia. When countries declare war, they declare war chiefly on their children. These little ones are not killed with shot and shell---nothing so merciful. Famine and pestilence are their portion. They die slowly from diseases incident to malnutrition. Maimed and suffering, many of those who were hard to kill came to the Children's Hospital on the hill with bone, joint and glandular disorders resulting from protracted undernourishment.

Hospital physicians had been trained in America, where most people had enough to eat all the time, and they were amazed to see children with seemingly incurable diseases begin to get well as soon as they got half a chance. The following is taken from a letter received from Dr. Gray in the spring of 1921: There were about 160 children and they were able to take at least 30 more. They came from all over Serbia, but most of them from Macedonia, where there was the greatest need . . . It would have been a pity to close, for they did not know what to do with those pathetic little children. There was a lot of Pott's disease, and tuberculosis of the joints, and those cases were doing so well.



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Veles

In Veles two hospitals and a large dispensary are conducted. All kinds of cases are accepted at the General Hospital, precedence being given to the people in most urgent need. As a matter of fact, a large percentage of the cases in the General Hospital are surgical cases, and many major operations are performed there. While I was at Veles Dr. Gray frequently operated from morning until night.

The people living in Southern Serbia manifestly have great confidence in Dr. Gray as a surgeon. Patients are brought from long distances, and amusing instances frequently develop in connection with this work. For instance, I recall one patient who had been shot in the mountains by the brigands. The bone of his thigh was shattered. He had been lying for perhaps five or six days, and when he reached the hospital his only chance of life was the amputation of his leg. The wife and brother of this patient consulted together, and then told Dr. Gray that they were perfectly willing that the man's leg should be amputated providing the American Women's Hospitals would agree to furnish a wooden leg in case he got well and pay for his life in case he died.

The Children's Hospital at Veles is a remarkable place. This hospital would be a credit to New York City. The building is large. By putting cots in the halls it is possible to care for as many as two hundred children. There were between 150 and 200 there at the time of my visit. It is a pity that Veles is difficult to reach, and for this reason comparatively few people are able to see this hospital. It is the largest, best equipped hospital for children in all Jugo-Slavia.

In March, 1920, a Nurses' Training Class was established in connection with the hospital at Veles. The members of this class were carefully selected, and only those who had enjoyed the best educational advantages of the country were accepted. Some of these young women have made remarkable progress. Several of them speak very fair English and act as interpreters between American nurses and doctors and the patients. Mrs. Cruikshank and Mrs. Harrison, two very able American nurses who recently arrived in Veles, could scarcely believe it when they were told that these girls had had less than two years' training. Mrs. Harrison was trained in the Massachusetts General Hospital. She has been superintendent in different

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In home visits

They improved more rapidly than such cases do at home, and it was a great gratification to watch them day after day. The poorest, skinniest little things came in, and as soon as they got proper food and care, they gain so fast. These little patients had all been kept in close quarters, and at first their mothers strongly objected to their sleeping out of doors. It was useless to argue with them. The improved condition of the children soon silenced their objections. They had good food, clean beds, warm clothing, playthings, a wonderful sun court, and a Christmas tree with presents at the proper season.

Dr. May T. Stout, oculist and a group of cataract patients. Over four hundred operations were performed in our Serbian hospitals for the relief of blindness due to cataract during the years 1920-22.

SPECIAL CLINIC FOR CATARACT AND OTHER EYE DISEASES

Patients with appalling eye diseases were among the first to appeal for help when the clinics opened in Serbia. There had never been an oculist in the country, and cataract cases had accumulated. People do not die of cataract. They gradually go blind while remaining in good physical health. The fact that this condition is curable adds greatly to the tragedy of it when it is impossible to get proper treatment.

One of the most tragic views was the black hair and white eyes. In Macedonian Serbia and Kosovo, a large number of people had black hair and white eyes, and many of them sat in darkness day after day by the wayside begging like blind Bartimaeus. Ages of disappointment had not destroyed their hope and faith. They, too, believed in miracles, and their prayer was always the same: “Lord, that I might receive my sight.”

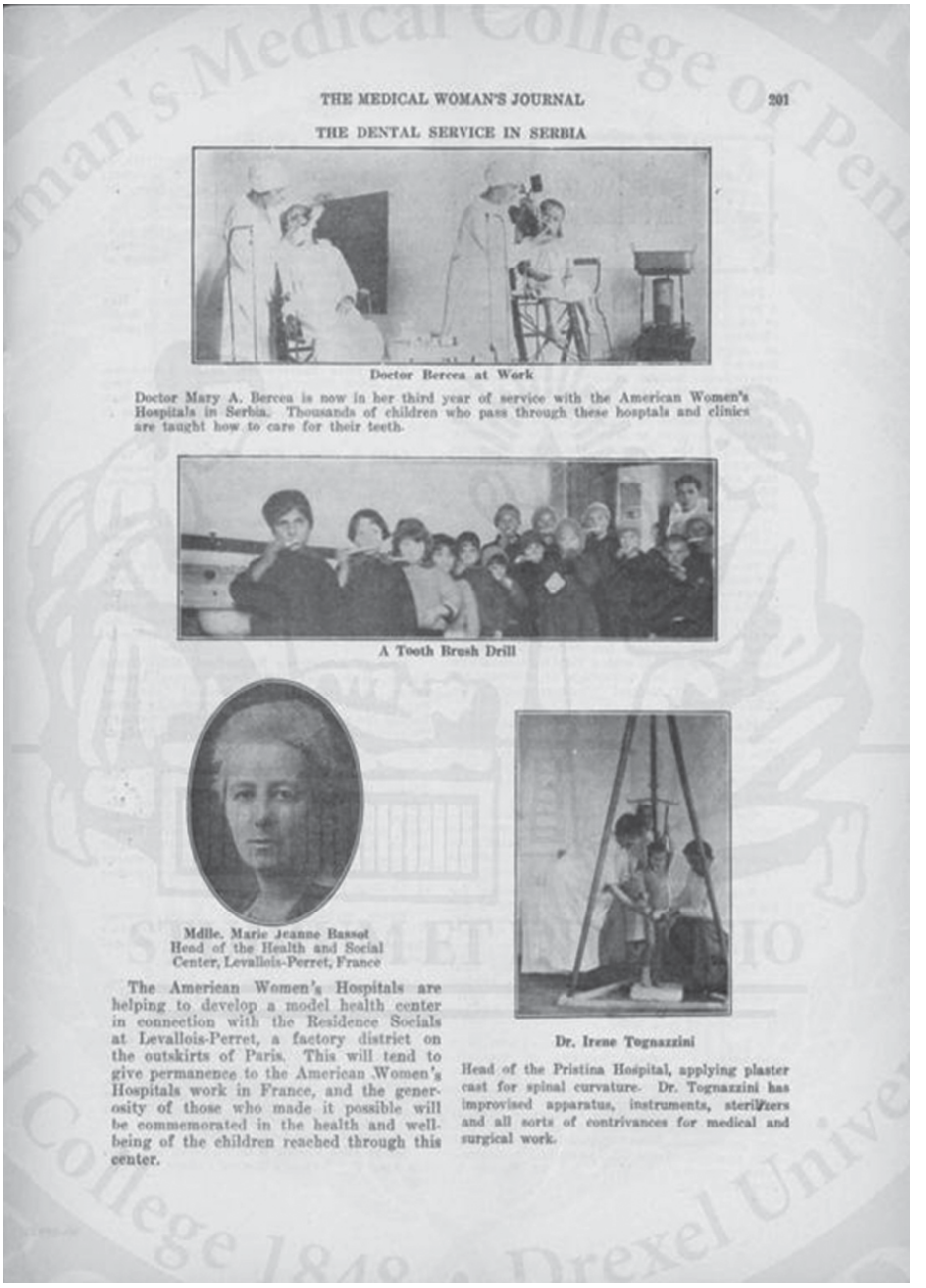
And in the district round about Veles, this prayer was answered. A woman was sent from America who could give them back their sight. And the man with the greatest faith came first. A slight but skilful operation was performed, and after a few days, the light which had been shut away for so many years reached his centre of vision and he could see. The story of this seeming miracle was passed from person to person. The blind came in increasing numbers, and over four hundred were operated upon for cataract and their sight restored.

The emergency nature of the American Women’s Hospitals’ service in different countries has precluded the possibility of keeping complete records. The available reports, covering about two-thirds of the work actually done in Serbia, show that 3,996 eye and ear cases were cared for, and that 1,068 operations were performed for the relief of eye diseases.[10]

DENTAL PROTECTION OF THE ARMY AND POPULATION IN MACEDONIA AND KOSOVO IN ORGANIZATION OF THE AWH MISSION

Dr. Mary N. Bercea was the head of the dental work. She was the only dentist in the Veles district. Children were preferred patients at the dental clinic, but young soldiers, especially officers, appreciated the value of good teeth, and there was always a waiting list of such men, and a long line of other people, including Turkish women wearing black tcharchaffs and heavy veils.[11]

Dental laboratory in Prilep, 1919, in which war prisoners worked



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THE DENTAL SERVICE IN SERBIA

Doctor Bercea at Work

Doctor Mary A. Bercea is now in her third year of service with the American Women's Hospitals in Serbia. Thousands of children who pass through these hosptals and clinics are taught how to care for their teeth.

A Tooth Brush Drill

Mdlle. Marie Jeanne Bassot
Head of the Health and Social Center, Levallois-Perret, France

The American Women's Hospitals are helping to develop a model health center in connection with the Residence Socials at Levallois-Perret, a factory district on the outskirts of Paris. This will tend to give permanence to the American Women's Hospitals work in France, and the generosity of those who made it possible will be commemorated in the health and well-being of the children reached through this center.

Dr. Irene Tognazzini

Head of the Pristina Hospital, applying plaster cast for spinal curvature. Dr. Tognazzini has improvised apparatus, instruments, sterilizers and all sorts of contrivances for medical and surgical work.

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Evangeline Cavan, M.D.
Child Welfare Assoc

Dr.Mary A.Vercea, head of the W.H. dental service, Veles 1919-22Welfare Assoc

Dr.May T.Stout, oculist with the A.W.H. in Serbia 1920-1922

TRAINING FOR MEDICAL NURSES FROM MACEDONIA ORGANIZED BY THE AWH MISSION 1920

From the beginning of the work in Southern Serbia, nurses were trained to take care of the sick. This plan conserved the funds and gave the work a permanent value. A large number of young women applied for service in the hospitals, and the best educated and most intelligent were selected.

Eight years of warfare had left most of them so poor that they were without shoes. These girls were grateful for food and clothing, and particularly for instruction. Nurses' training was an innovation. There was a strong prejudice against nursing, due to a Mohammedan point of view, and to the social status of women in that country who served in hospitals. This attitude was modified in regard to the hospitals of the Association for the reason that a measure of chaperonage was afforded which protected the reputations of the girls in our service, to the end that their matrimonial prospects were not jeopardized.

Ella W. Harrison, R. N., with Serbian student nurses

Miss Lucy Morhous was the head of our first nurses' training class, which was started in Veles in January, 1920. The student nurses were not up to the standard of that time American student nurses, but they were up to the standard of student nurses at the time of the beginning of nurses' training in the United States as a nationwide educational movement. Some of these young women displayed remarkable aptitude, and in a short time learned to take orders in English and to care for minor cases. A picture of Miss Morhous and her class of nurses was sent.

There were fourteen of them and they looked so well in their blue dresses and white aprons. They had been in training a little over a month, and they do practically all the routine work in the dispensary and hospital, under the supervision of American nurses.

The training class grew with the hospital and dispensary service. Mrs. Ella WT. Harrison was sent to Veles in February 1921, as general supervisor, and Mrs. Marian P. Cruikshank went out as Dr. Gray's

surgical nurse, and took over the surgical training of the student nurses. On account of exceptional ability, some of these girls were sent to Belgrade when the Government training school for nurses was established, and the first probationer accepted at Veles Hospital without shoes on her feet, was one of the leading pioneer trained nurses in Serbia at that time.

From the beginning to the end of the service in Serbia the American Red Cross was generous in gifts of supplies, in many instances delivering carloads of material at headquarters of the Association, and relieving it the cost and responsibility of transportation. Without this help, it would have been impossible for the American Women's Hospitals to have functioned so promptly and effectively.

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   Dr. Flood met her husband to be, Alfred Heath, in England and settled in Elmira after the war. In 1923 Dr. Flood-Heath died following an appendicitis operation. She was survived by her husband and infant daughter. In 1928 her daughter, then aged 5, received her mother's war honors. Little Miss Marjorie Louise Heath received the Order of St. Sava by direction of King Alexander of Yugoslavia. Sadly little Marjorie succumbed to pneumonia just two years after she received the medal for her mother. (Source: Flood family biographical file).
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ДОБРОВОЛНА МЕДИЦИНСКА МИСИЈА ,, "AMERICAN WOMEN'S HOSPITALS" ВО МАКЕДОНИЈА И КОСОВО ЗА И НЕПОСРЕДНО ПОСЛЕ ПРВАТА СВЕТСКА ВОЈНА

Јосимовска в.

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Апстракт

Трудот обработува еден тежок период за Македонија и Косово од Првата светска војна и годините непосредно после неа. Тоа е времето кога оваа територија во период од четири години, била под окупација на Сојузничките и Централната армија. Овде животот под притисок на секојдневните реквизиции на храна, добиток, покуќнина и принудна работа на се што било работоспособно, станал неподнослив тежок.

Присуството на меѓународните санитарни мисии во Кралството на Србија за време на Големата војна и неколку години потоа било за поздравување и повеќе од потребно. Големата војна која донела големи страдања, го променила не само светот но ја ставила на тест и меѓународната солидарност, без која бројот на жртвите од болести, глад и сиромаштија би бил потрагичен и поголем. Меѓународните санитарни мисии претставувале огромен спасител, а еден од нив припаѓаат на мисијата Болниците од американските жени" и нејзин директор, легендарниот д-р ЕТА Грej. Тие даваат на населението огромна здравено социјална заштита во време кога било во прашање да се биде или не.

Клучни зборови: Македонија, Косово, Прва светска војна, болници, заразни болести, санитетски мисии.

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Revista është organ i "Shoqatës së Mjekëve Shqiptarë në Maqedoni."

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Ju lutemi përdoreni madhësinë standarde të punimit në format: *Word për Windows*, Times New Roman 12.

Dorëshkrimet dërgohen në format elektronik, qoftë me

CD ose përmes e-mailit tek Kryeredaktori,
Prof. Dr. Azis K. Pollozhani,
Zyra e Redaksisë, rr. 50 Divizija, No 6, 1000
Shkup, apo në
e-mail: medicus.shmshm@gmail.com

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Revista do të **njoftojë pranimin** e artikullit tuaj brenda shtatë ditësh dhe do t'ju bëjë me dije se kur do të informoheni për vendimin e këshillit redaktues.

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These guidelines are in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (The complete document appears at www.icmje.org)

Medicus is an international journal of that publishes papers from all areas of medical research. Furthermore, the journal indends to bring educational material of high quality to its members for continuous medical education (CME), by publishing original research, professional and review papers, case reports, brief communications, literature summary articles and editorials.

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Please use standard-sized paper and submit your article in the following formate: Word for Windows, Times New Roman 12.

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Numri i faqeve (përfshirë tabelat dhe/ose figurat/ ilustrimet) varet nga lloji i artikullit:

punim origjinal hulumtues –deri ne12 faqe dhe jo më shumë se 6 tabela dhe/ose grafikone/fotografi;

punim profesional ose punim revyal – deri ne 8 faqe dhe jo më shumë se 4 tabela dhe/ose figura/imazhe;

prezantim rasti apo kumtesë e shkurtër – deri 6 faqe dhe maksimum 3 tabela dhe/ose figura/imazhe.

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Së bashku me dorëshkrimin, dorëzoni një faqe me **titullin** e artikullit; **emrin/at e autorit/ve**, duke përfshirë emrin me jo më shumë se dy tituj shkencor; emrin e departamentit dhe institucionit në të cilin është bërë punimi; institucioni ku punon (për secilin autor); si dhe emri dhe adresa e autorit të cilit do ti adresohen kërkesat nga ana e Redaksisë (shihni Informacionet plotësuese për autorët)

Abstrakti duhet te jete me jo më shumë se 250 fjalë. Duhet të konsistojë në katër paragrafë, i klasifikuar në Hyrje, Metodat, Rezultatet dhe Diskutimi (Përfundimet). Ato duhet të përshkruhen shkurt, respektivisht, problem qenësor i studimit, se si është kryer studimi, rezultatet e fituara, dhe perfundimi.

Tabelat, figurat dhe legjendat (shihni Informacionet plotësuese për autorët)

Fjalët kyqe -Tri deri pesë flaje apo fraza te shkurtëra duhet t'i shtohen pjesës së fundme të faqes së abstraktit.

Citatet e referencave në tekst duhet fillimisht të jenë nga revistat e indeksuara në **PubMed**. Stili i referencave që kërkohet nga Medicus është i formatit Vancouver (shihni Informacionet plotësuese për autorët).

Shkurtimet (**akronimet**) përdoren për njësitë matëse, kurse në raste tjera kur përmendet për herë të parë, ai duhet të jetë i sqaruar me fjalën bazë bashkangjitur.

Për të gjitha barnat duhet të përdoren **emrat gjenerik** ndërkombëtar. Nëse në hulumtim janë të përdorura brendet e patentuara, përfshini emrin e brendit në kllapa në paragrafin e Metodave.

Dorëshkrimi i dërguar tek botuesi duhet të shënohet nga autorët , nëse janë në seksionin e "punimeve origjinale shkencore" apo në pjeset tjera përmbajtesore të revistës.

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The number of pages (including tables and/or figures/ illustrations) is dependent upon the type of the article:

original research paper - up to 12 pages and no more than 6 tables and / or graphs / pictures;

professional or review paper - up to 8 pages and no more than 4 tables and / or figures / images;

case report or brief communication - up to 6 pages and a maximum of 3 tables and / or figures/images.

Leter up to 2 pages

With the manuscript, provide a page giving the title of the paper; the name(s) of the author(s), including the first name(s) and no more than two graduate degrees; the name of the department and institution in which the work was done; the institutional affiliation of each author; and the name and address of the author to whom reprint requests should be addressed. (see Additional Information for Authors)

Provide an **abstract** of not more than 250 words. It should consist of four paragraphs, labeled Backround, Methods, Results and Conclusions. They should briefly describe, respectively, the problem being in the study, how the study was performed, the salient results, and what the authors conclude from the results.

Tables, figures and legends (see Additional Information for Authors)

Three to five **key words** or short phrases should be added to the bottom of the abstract page.

Quotations of references in the text should primarily be from journals indexed in **PubMed** which have proven their significance. The style of references required by **Medicus** is the Vancouver format (see Additional Information for Authors).

Except for units of measurement, abbreviations are discouraged. The first time an abbreviation appears it should be preceded by the words for which it stands.

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All manuscript sent to the editor should be noted by the authors whether they are meant for the "original research papers" section or the rest of the journal's content.

The authors receive two copies of the relevant issue.

Informacione plotësuese për autorët

I. Faqja e parë – *ballina*: Duhet të përmbajë: (a) titullin e punimit, të shkurtër, por informativ; (b) emri, inicialet e emrit të mesëm dhe mbiemrit të secilit autor; (c) institucioni; (d) emri i departamentit që i atribuohet punës shkencore; (e) emri dhe adresa e autorit për t'iu përgjigjur në lidhje me dorëshkrimin; (f) burimi/përkrahja në formë të granteve, paisjeve, barnave dhe në përgjithësi.

II. Faqja e dytë – *abstrakti dhe fjalët kyqe*: Abstrakti duhet të shkruhet me maksimum prej 150 fjalësh për abstraktet e pastrukturuara, dhe me 250 fjalë për abstraktet e strukturuara (pjesët përmbajtësore: objekti/ete studimit ose hulumtimit, procedurat bazë, siç është përzgjedhja e subjekteve apo kafshët laboratorike, metodat vrojtuese dhe analitike, pastaj, rezultatet/gjetjet përfundimtare (të dhënat dhe rëndësia e tyre statistikore, nëse është e mundur), dhe konkluzionet kryesore. Vini theksin mbi aspektet e reja dhe të rëndësishme të studimit apo vrojtimit. Nën abstraktin indentifikoni dhe shkruani fjalët kyqe: 3-5 fjalë apo fraza të shkurtëra që do të ndihmojnë në paisjen me tregues të punimit dhe publikimit të abstraktit. Përdorni terme nga lista e Index Medikus për Nëntituj Mjekësor (Medical Sub-Headings [MeSH]); nëse nuk ka term të përshtatshëm në MeSH për disa terme të reja, mund të përdorni termet e dhëna.

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1. Hyrja: Krijoni një kontekst apo prapavijë(trualli) të studimit (që në fakt është natyra e problemit dhe rëndësia e tij). Për të bërë këtë duhet të bëni një hulumtim të literaturës – duke kërkuar, gjetur dhe lexuar punimet përkatëse, që duhet të jenë si referencë në dorëshkrimin tuaj. Sqaroni hipotezat tuaja dhe planifikoni t'i testoni ato, si dhe përshkruani qëllimet tuaja. Kini qëndrim të qartë se çka prisni të gjeni dhe arsyet që ju udhëhoqën tek hipotezat që keni krijuar. Objekti i hulumtimit më së shpeshti fokusohet kur parashtrohet si pyetje. Mos përfshini të dhëna apo rezultate nga puna që do të raportohet.

2. Metodat & Materialet: Ky paragraf duhet të përfshijë atë informacion që ishte në dispozicion në kohën që plani apo protokoli i studimit po shkruhej. Të gjitha informacionet e marra gjatë studimit i takojnë paragrafit të Rezultateve.

Përshkruani përzgjedhjen tuaj të pjesëmarrësve së vrojtimit ose eksperimentit (pacientët ose kafshët laboratorike, përfshirë kontrollat) qartë, duke përfshirë kriteret e përshtatshme (inkluzive) dhe përjashtuese (ekskluzive).

Parimi udhëheqës duhet të jetë i qartë se si dhe pse studimi është bërë në një mënyrë të caktuar. Jepni detaje të mjaftueshme për metodat, mjetet dhe materialet (jepni emrin dhe adresën e prodhuesit në kllapa), dhe procedurat për të lejuar të tjerët të kuptojnë dhe riprodhojnë rezultatet tuaja.

Nëse një metodë e caktuar që është përdorur është e njohur, atëherë nuk është e nevojshme të jepet përshkrim komplet i saj. Mund t'i referoheni punimit në të cilin së pari herë është përshkruar dhe të

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II. Second page - *abstract and keywords*: The abstract should be written with a maximum of 150 words for unstructured abstracts and 250 words for structured abstracts (containing parts: objective(s) of study or research, basic procedures, such as selection of subjects or laboratory animals, observational and analytical methods, then, the main findings/results (data and their statistical significance, if possible), and the main conclusions. Emphasize the new and important aspects of the study or observation.

Below the abstract identify and write the keywords: 35 words or short phrases that will assist in indexing the paper and publication of the abstract.

Use terms from the list of Index Medicus for Medical Sub-Headings (MeSH); if there is no appropriate MeSH term for some newly introduced terms, we can use the given terms.

III. Third and further pages – *full text of the article*: The full text of research or observational articles should normally be, but not necessarily, divided into sections with the following headings: introduction, material and methods, results and discussion.

1. Introduction: Provide a context or background for the study (that is, the nature of the problem and its significance). To do this you must complete a literature review – searching for, finding and reading relevant papers, which must be referenced in your manuscript. Explain your hypotheses and the plan to test them, and describe your aims. Clearly state what you expect to find and the reasoning that led you to the hypotheses that you have made. The research objective is often more sharply focused when stated as a question. Do not include data or conclusions from the work being reported.

2. Methods & Material: This section should include only information that was available at the time the plan or protocol for the study was being written. All information obtained during the study belongs in the Results section.

Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria.The guiding principle should be clarity about how and why a study was done in a particular way.

Give sufficient details of the methods, apparatus and materials (give the manufacturer's name and address in parentheses), and procedures to allow others to understand and reproduce your results.

If a particular method used is well known then there is no need to give a complete description. You can reference the paper in

përmendni ndonjë modifikim/ndryshim që keni bërë. Jepni arsyet për përdorimin e tyre dhe vlerësoni kufizimet e tyre. Në fund, përshkruani se si i keni analizuar të dhënat tuaja, duke përfshirë metodat statistikore dhe pakon programore që keni përdorur.

Autorët e doreshkrimeve të rishqyrtuara duhet të përfshijnë një paragraf që përshkruajnë metodat që kanë përdorur për lokalizimin, përzgjedhjen, ekstrahimin dhe sintetizimin e të dhënave. Përdorni formën joveprore të foljes, në vetën e tretë, kur dokumentoni metodat, gjë që do të fokusonte vëmendjen e lexuesit tek puna që është bërë e jo tek hulumtuesi (P.sh. Janë marrë, janë realizuar, janë prezantuar etj.)

2. a) Statistikat: Përshkruani metodat statistikore me detaje të mjaftueshme për t'ia mundësuar një lexuesi me njohje në atë fushë t'i qaset të dhënave origjinale për të verifikuar rezultatet e raportuara. Kur është e mundur, përcaktoni sasinë e zbulimeve dhe prezantoni ato me indikatorë përkatës të gabimeve në matje apo pasiguri (siç janë inter-valet e besueshmërisë). Evitoni mbështetjen vetëm në testet statistikore të hipotezave, siç janë vlerat p, që dështojnë të transmetojnë informacion të rëndësishëm mbi madhësinë e efektit. Jepni detaje rreth përzgjedhjes së rasteve (randomizimi) dhe përshkruani metodat dhe sukseset e vro¬jtimit gjatë realizimit të studimeve të verbuara. Definoni termet statis¬tikore, shkurtesat dhe më së shumti simbolet. Specifikoni programin kompjuterik që është përdorur.

3. Rezultatet: Ky paragraf duhet t'i bëjë gjetjet tuaja të qarta. Prezantoni rezultatet tuaja në rend logjik në tekst, tabela dhe ilustrime, duke dhënë së pari rezultatet kryesore ose më të rëndësishme. Mos i përsërisni të gjitha të dhënat në tabela apo ilustrime, në tekst. Nënvizoni ose përm-bledhni shkurtimisht vetëm vrojtimet më të rëndësishme.

Kur të dhënat përmblidhen në paragrafin e Rezultateve, jepni rezultate numerike jo vetëm si derivate (për shembull, përqindja) por gjithashtu si numra absolut nga të cilët derivatet janë llogaritur, dhe specifikoni metodat statistikore që janë përdorur për t'i analizuar ato.

Kufizoni tabelat dhe figurat në aq sa janë të nevojshme për të sqaruar argumentin e punimit dhe për të vlerësuar të dhënat ndihmëse. Duke përdorur grafikonet për të reprezentuar të dhënat tuaja si alternativë e tabelave, do të rrisë kuptueshmërinë e lexuesit. Mos i dyfishoni të dhënat në grafikone dhe tabela. Duhet të jeni të qartë se cili lloj i grafikoneve është i përshtatshëm për informacionet tuaja. Për shembull, për të reprezentuar korelimin mes dy ndryshoreve, preferohet grafiku vijëzor, krahasuar me grafikun rrethor apo në formë shtyllash.

Sa i përket të gjitha paragrafeve, qartësia dhe të qënit i thuktë është kyçe. Mos prezantoni të njëjtat të dhëna më shumë se një herë. Kufizojeni veten në të dhënat që ndihmojnë në adresimin e hipotezave tuaja. Kjo është e rëndësishme edhe nëse të dhënat i aprovojnë ose nuk i pranojnë ato. Nëse keni bërë analiza statistikore, duhet të jepni vlerën e proba¬bilitetit (p) dhe të tregoni se është shprehës (sinjig në nivelin që ju po testoni. Varësisht nga analizat e përdorura, gjithashtu mund të jetë e rëndësishme të jepni intervalet e besueshmërisë së rezultateve (Confidence Interval –

which it was first described and mentioned any modifications you have made. Give the reasons for using them, and evaluate their limitations. Finally,, describe how you analysed your data, including the statistical methods and software package used.

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data.

Use the third person passive voice when documenting methods which would focus the readers' attention on the work rather than the investigator.(e.g. Were taken, was performed, were presented itd.)

2. a) Statistics: Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as p values, which fail to convey important information about effect size. Give details about the randomization and describe the methods and success of observations while using blinded trials. Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

3. Results: This section should make your findings clear. Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all the data in the tables or illustrations in the text. Emphasize or summarize only the most important observations.

When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them.

Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Using graphs to represent your data as an alternative to tables will improve the reader's understanding. Do not duplicate data in graphs and tables. You need to be clear what type of graphs is suitable for your information. For example, to represent the correlation between two variables, a line graph is preferred to a pie chart or a bar chart.

As with all sections, clarity and conciseness is vital. Don't present the same data more than once. Restrict yourself to the data that helps to address your hypotheses. This is important whether the data supports or disproves them. If you have carried out a statistical analysis, you should give the probability (P) value and state it is significant at the level you are testing. Depending on the analysis used, it may also be important to give the confidence intervals of the results, or the statistical parameters such as the odds ratios. Provide a caption for each figure making the gen¬eral meaning clear without reference to the main text, but don't discuss the results. Let the readers decide for themselves what they think of the data. Your chance to say what you think comes next, in the discussion.

3. Tables: Each table should be inserted at the point of the text where they have to be placed logically, typed by the same rules

CI), ose parametrat statistikorë si proporcionet e rastit (odds ratio). Bëni përshkrimin tek secila figurë duke bërë të qartë domethënien e përgjithshme pa referencë në tekstin kryesorë, por mos diskutoni rezultatet në të. Lëreni lexuesin të vendosë vetë se çfarë men-don për të dhënat. Mundësia juaj për të thënë se çfarë mendoni, është në vazhdim, tek diskutimi.

3. Tabelat: Secila tabelë duhet të vendoset në vendin e tekstit ku duhet të vihet logjikisht, e plotësuar me të njëjtat rregulla sikur teksti i plotë. Mos i dërgoni tabelat si fotografi. Secila tabelë duhet të citohet në tekst. Tabelat duhet të jenë me numra ashtu që të jenë në koordinim me refer-encat e cituara në tekst. Shkruani një përshkrim të shkurtë të tabelës nën titullin. Çdo sqarim shtesë, legjendë ose sqarim i shkurtesave jostan¬darde, duhet të vendoset menjëherë poshtë tabelës.

4. Diskutimi: Ky paragraf është pjesa ku ju mund të interpretoni të dhë-nat tuaja dhe të diskutoni duke ballafaquar dhe krahasuar gjetjet tuaja me ato të hulumtuesve të mëparshëm. Rishikoni referencat e literaturës dhe shihni nëse mund të përfundoni se si të dhënat tuaja përkojnë me atë që keni gjetur.

Ju gjithashtu duhet të llogarisni rezultatet, duke u fokusuar në mekaniz¬mat në prapavij të vrojtimit. Diskutoni nëse rezultatet tuaja mbështesin hipotezat tuaja origjinale. Gjetjet negative janë aq të rëndësishme në zhvillimin e ideve të ardhshme sikur gjetjet pozitive.

E rëndësishme është se, nuk ka rezultate të këqija. Shkenca nuk të bëjë me të drejtën dhe të gabuarën, por merret me zgjerimin e njohjeve të reja.

Diskutoni si janë paraqitur gabimet në studimin tuaj dhe çfarë hapa keni ndërmarrë për të minimizuar ato, kështu duke treguar se ju çmoni ku¬fizimet e punës tuaj dhe fuqinë e përfundimeve tuaja. Duhet gjithashtu të merrni në konsideratë ndërlikimet e gjetjeve për hulumtimet në të ardhmen dhe për praktikën klinike. Lidhni përfundimet me qëllimet e studimit, por evitoni qëndrimet dhe përfundimet e pakualifikuara, që nuk mbështeten në mënyrë adekuate nga të dhënat. Shmangni prioritetet deklarative apo të aludoni në punën që nuk është krahasuar.

5. Referencimi: Referencat janë baza mbi të cilën është ndërtuar raporti juaj. Shqyrtimi i literaturës dhe leximi i referencave gjithmonë duhet të jetë pikë fillestare e projektit tuaj. Ky paragraf duhet të jetë i saktë dhe të përfshijë të gjitha burimet e informacionit që keni përdorur.

Në formatin " Vancouver" , referencat numërohen një nga një, sikur që shfaqen në tekst dhe identifikohen me numra në bibliografi..

Shënoni të gjithë autorët kur janë gjashtë e më pak; kur janë shtatë ose më tepër, shënoni tre të parët, pastaj shtoni "et.al." Pas emrave të autorëve shkruhet titulli i artikullit; emri i revistës i shkurtuar sipas mënyrës së Index Medicus; viti i botimit; numri i vëllimit; dhe numri i faqes së parë dhe të fundit.

Referencat e librave duhet të jepen sipas emrit të autorit, titulli i librit (mund të citohet edhe titulli i kapitullit para titullit), vendi i botimit, botuesi dhe viti.

as for the full text. Do not send tables as photographs. Each table should be cited in the text.Tables should be numbered so that they will be in sequence with references cited in the text. Provide a brief explanation of the table below the title. Any additional explanations, legends or explanations of non¬standard abbreviations, should be placed immediately below the table.

4. Discussion: This section is where you interpret your data and discuss how your findings compare with those of previous researchers. Go over the references of your literature review and see if you can determine how your data fits with what you have found.

You also need to account for the results, focusing on the mechanisms be¬hind the observation. Discuss whether or not your results support your original hypotheses. Negative findings are just as important to the de¬velopment of future ideas as the positive ones.

Importantly, there are not bad results. Science is not about right or wrong but about the continuing development of knowledge.

Discuss how errors may have been introduced into your study and what steps you took to minimise them, thus showing that you appreciate the limitations of your work and the strength of your conclusions. You should also consider the implications of the findings for future research and for clinical practice. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. Avoid claiming priority or alluding to work that has not been compared.

5. Referencing: The references are the foundation on which your report is built. Literature searches and reading of references should always be the starting point of your project. This section must be accurate and in¬clude all the sources of information you used.

In the Vancouver format, references are numbered consecutively as they appear in the text and are identified in the bibliography by numerals.

List all authors when there are six or fewer; when there are seven or more, list the first three, then add "et al." The authors' namer are fol-lowed by the title of the article; the title of the journal abbreviated ac-cording to the style of Index Medicus; the year of publication; the volume number; and the first and last page numbers.

References to books should give the names of any editors, place of publication, editor, and year.

In the text, reference numbers are given in superscript. Notice that issue number is omitted if there is continuous pagination through¬out a volume, there is space between volume number and page numbers, page numbers are in elided form (51-4 rather than 51-54) and the name of journal or book is in italics.The following is a sample reference:

Në tekst, numrat e referencave jepen me indeks të sipërm. Vëreni se çështja e numrave neglizhohet nëse ka numërtim të vazhdueshëm përg¬jatë gjithë vëllimit, ka hapësirë mes numrit të vëllimit dhe numrit të faqes, numrat e faqeve janë në këtë formë: 51-4 në vend të 51-54, dhe emri i revistës ose librit është në italic. Në vazhdim është një shembull i referencës:

Artikujt e revistave:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. *N Engl J Med* 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. *BMJ* 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. *Lancet* 1997;349: 1498-504.

Librat dhe tekste tjera:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. *National service framework for coronary heart disease*. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Kamberi A, Kondili A, Goda A, dhe bp; *Udhërrëfyes i shkurtër i Shoqatës Shqiptare të Kardiologjisë për parandalimin e Sëmundjes Aterosklerotike Kardiovaskulare në praktikën klinike*, Tiranë, 2006
7. Azemi M, Shala M, dhe bp. *Pediatria sociale dhe mbrojtja shëndetësore e fëmijëve dhe nënave*. Pediatria, Prishtinë 2010; 9-25

Shmangni përdorimin e abstrakteve si referenca; "të dhëna të papub-likuara" dhe "komunikime personale". Referencat e pranueshme, por ende të papublikuara lejohet të merren, vetëm nëse shënoni se janë "në shtyp".

6. Mirënjohjet: Ju mund të keni dëshirë të falënderoni njerëzit që ju kanë ndihmuar. Këto mund të rangohen prej atyre që ju kanë përkrahur me teknika eksperimentale deri tek ata që ju kanë këshilluar deri në bër¬jen e dorëshkrimit final.

7. Formati i fajllit të të dhënave për **ilustrimet** (**figurat**): JPG

Nëse përdoren fotografitë e pacientëve, qoftë subjekti, qoftë fotografitë e tyre nuk duhet të jenë të identifikuara, ato duhet të shoqërohen me lejen e shkruar nga ta për përdorimin e figurës. Format e lejuara janë në dispozicion nga redaksia.

Nëse fajllet e të dhënave janë shumë të mëdha për t'u dërguar me e-mail, rekomandohet dërgimi me CD në adresën tonë.

8. Legjendat për Ilustrimet (Figurat)

Legjenda e tabelës duhet të vendoset mbi tabelë. Referenca e një tabeleje, e cila është marrë nga ndonjë publikim tjetër, duhet të vendoset poshtë tabelës. (Është përgjegjësi e autorit të sigurojë lejen e ribotimit nga botuesit e atij botimi) Legjenda e figurës duhet të vendoset në fund të faqes. Referenca e figurës e marrë nga ndonjë tjetër publikim vendoset në fund të legjendës. (Leja e ribotimit duhet të sigurohet nga botuesi i këtij botimi).

Journal articles:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. *N Engl J Med* 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. *BMJ* 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. Lancet 1997;349: 1498-504.

Books and other monographs:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. *National service framework for coronary heart disease*. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Osler AG. *Complement: mechanisms and functions*. Englewood Cliffs: Prentice-Hall, 1976.

Avoid using as references abstracts; "unpublished data" and "personal communications". References to accepted but yet unpublished articles are allowed to be made, only if you note "in press".

6. Acknowledgements: You may wish to acknowledge people who have helped you. These can range from those who supported you with exper¬imental techniques to those who read or offered advice on your final manuscript.

7. Data file format for **illustrations** (**figures**): JPG

If photographs of patients are used, either the subjects should not be identifiable or their pictures must be accompanied by written permis-sion to use the figure. Permission forms are available from the Editor.

If data files are too big for transmission as an Email attachment submis¬sion of a CD to our address is recommended.

8. Legends for Illustrations (Figures)

The legend of a table has to be placed above the table. The reference of a table, which has been taken from another publication, must be placed below the table. (It is the author's responsibility to obtain the permission of reproduction from the publishers of the publication.) Figure legends are to be placed at the end of the paper. The reference of a figure taken from another publication stands at the end of the legend. (Permission of reproduction must be obtained from the publishers of this publication).