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УПРАВУВАЊЕ СО БИОМЕДИЦИНСКИ ОТПАД

BIOMEDICAL WASTE MANAGEMENT

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Апстракт

Медицински отпад е целиот оној отпад кој се создава во здравствените институции, како на пример болниците, клиниките, амбулантите, стационарите, ветеринарните амбуланти, како и местата за медицински испитувања и лабораториите.

Неорганизирано и слабо менаџирање на отпадните материјали потенцијално можат да го загрозат здравјето на здравствените работници, управувачите на отпадот, пациентите, како и околината преку инфекции, токсични ефекти и секако ризикот кој постои од загадување. Многу е важно целиот медицински отпад да биде поделен според видот, безбедно одвоен и со него соодветно да се постапува сè до неговото отстранување.

Клучни зборови: биомедицински, стоматолошки, медицински отпад, здравствен ризик, управување со отпад

Abstract

Medical waste is all waste material generated in health care facilities, such as hospitals, clinics, physician's offices, dental practices, blood banks, and veterinary hospitals/clinics, as well as medical research facilities and laboratories. Poor management of health care waste potentially exposes health care workers, waste handlers, patients and the community at large to infection, toxic effects and injuries, and risks polluting the environment. It is essential that all medical waste materials have to be segregated at the point of generation, appropriately treated and disposed of safely.

Keywords: biomedical, dental, medical waste, health-care risk, waste management

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Introduction

In the process of health care, waste is generated which usually includes sharps, human tissue or body parts and other materials referred to as "Hospital Solid Waste" and "Bio-medical Solid Waste" [1].

According to the law of waste management in many countries in Europe, USA and India [2-6] and in the Republic Macedonia regulated by Law of medical waste management (Official Gazette of Republic Macedonia №68/ 2004 and correction in № 71/2004) [7] medical and clinical waste is waste generated in medical and health institutions (dispensaries, hospitals, polyclinics and outpatient clinics, dental clinics, veterinary stations etc.), originated as a product of used items and materials during diagnosis, convalescence, treatment and prevention in humans and animals [8]. The major sources of healthcare waste are:

- hospitals and other health facilities,
- laboratories and research centers,
- mortuary and autopsy centers,
- animal research and testing laboratories,
- blood banks and collection services,
- nursing homes for the elderly.

Medical waste that is a result of the provision of health care can be divided into two groups-municipal and hazardous medical waste. The municipal medical waste includes: paper, carton, glass, food and other common debris arising in the administration, kitchen and laundries [1]. On the other hand, hazardous medical waste contains elements of chemical and biological threat, in solid, liquid or gaseous form. The properties of hazardous medical waste are virulence, ability for infection, toxicity, carcinogenicity, and so on. According to these properties hazardous medical waste differs from the municipal medical waste.

Definitions and type of medical waste

Medical (clinical) waste is defined as waste consisting of: **Needle, syringe with needle, surgical instrument** of other article that is discarded in the course of medical, dental or veterinary practice or research and has a sharp edge or point capable of inflicting a penetrating injury on a person who comes into contact with it, or

1. **Human tissue, bone, organ, body part or fetus, or**

2. **A vessel, bag or tube containing a liquid body substance**, or
3. **An animal carcass** discarded in the course of veterinary research or medical practice or research, or
4. **A specimen or culture** discarded in the course of medical, dental or veterinary practice or research and any material that has come into contact with such a specimen or culture, or
5. **Any other article or matter** that is discarded in the course of *medical, dental or veterinary practice or research* and that poses a significant risk to the health of a person who comes into contact with it [9].

Although there is no universally accepted definition for medical waste, the definitions offered by most regulatory agencies are similar. Most federal and state agencies differentiate between common medical waste and those wastes with the potential for causing infection and for which special precautions are prudent. Depending on the state, these wastes are referred to as: regulated medical waste, infectious waste, biomedical waste. Some state regulations use a general definition, while others list specific wastes and categories of waste that are considered infectious. The following six medical wastes are commonly regulated [10]:

- **Pathological waste.** Tissues, organs, body parts, and body fluids removed during surgery and autopsy.
- **Human blood and blood products.** Waste blood, serum, plasma and blood products.
- **Cultures and stocks of infectious agents** (microbiological waste). Specimens from medical and pathology laboratories. Includes culture dishes and devices used to transfer, inoculate, and mix. Also includes discarded live and attenuated vaccines.
- **Contaminated sharps.** Contaminated hypodermic needles, syringes, scalpel blades, Pasteur pipettes, and broken glass.
- **Isolation waste.** Generated by hospitalized patients isolated to protect others from communicable disease.
- **Contaminated animal carcasses, body parts and bedding.** From animals intentionally exposed to pathogens in research, biologicals production, or in vivo pharmaceuticals testing.

Definition of biomedical waste "Any solid, fluid or liquid waste, including its container and any intermediate product, which is generated during the diagnosis, treatment or immunization of human beings or animals, in research pertaining there to, or in the production or testing of biological and the animal waste from slaughter houses or any other like establishments" [11,12] Namely, the term clinical waste is associated with waste originating from medical, dental and veterinary sources and has been defined as "*waste that is contaminated with blood, saliva or any other bodily hazardous fluids and which may prove hazardous to any person coming into contact with it*".

The World Health Organization (WHO) has defined healthcare waste as "all waste produced by healthcare

establishment, research facilities and laboratories including the waste originating from "minor" or "scattered" sources such as that produced in the courses of health-care undertaken in the home (such as dialysis and insulin injections) (WHO1999 p.6) [13]. 85% of the waste produced by health-care providers is non-risk or "general" health-care waste, comparable to domestic waste. This type of waste usually comes from the administrative and housekeeping functions of health-care establishments and may also include waste generated during maintenance of health-care premises. The remaining 10-15% of health-care waste as shown in Figure 1 is regarded as hazardous and may create a variety of health risks (WHO, 1999) [13].

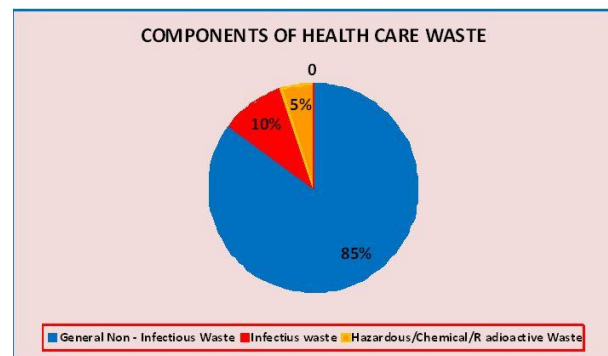


Fig. 1. Components of health care waste (WHO 1999) [13]

Waste and by-products cover a diverse range of materials, as the following list illustrates:

- **infectious waste:** waste contaminated with blood and other bodily fluids (e.g. from discarded diagnostic samples), cultures and stocks of infectious agents from laboratory work (e.g. waste from autopsies and infected animals from laboratories), or waste from patients in isolation wards and equipment (e.g. swabs, bandages and disposable medical devices);
- **pathological waste:** human tissues, organs or fluids, body parts and contaminated animal carcasses;
- **sharps:** syringes, needles, disposable scalpels and blades, etc.;
- **chemicals:** for example, solvents used for laboratory preparations, disinfectants, and heavy metals contained in medical devices (e.g. mercury in broken thermometers) and batteries;
- **pharmaceuticals:** expired, unused and contaminated drugs and vaccines;
- **genotoxic waste:** highly hazardous, mutagenic, teratogenic or carcinogenic, such as cytotoxic drugs used in cancer treatment and their metabolites;
- **radioactive waste:** such as products contaminated by radionuclides including radioactive diagnostic material or radiotherapeutics materials; and
- **non-hazardous or general waste:** waste that does not pose any particular biological, chemical, radioactive or physical hazard.

The following materials are not usually regarded as medical waste unless they fall into category of the medical waste definition: dressing and bandages; materials stained with or having had contact with body substances; containers no longer containing body substances; disposable nappies and incontinence pads; sanitary napkins [14]. Medical waste is a risk to those who produce, pack, store, transport, treat and perform disposition. The possibility of infection by some diseases and their spread in hospitals is possible due to negligence in handling of medical waste. The entire staff at the medical institutions should be trained/informed in medical waste management and disposition to be able to reduce the risk to minimum.

Dental practices produce large amounts of waste such as plastic, latex, cotton, glass and other materials, most of them can be contaminated with infected body fluids. Dental practices also produce tiny amount of other types of waste, such as silver amalgam, mercury and various chemical solvents [15-18]. The dental office generate only 3% of total medical waste estimated by US medical waste tracking system [19]. The quantity of waste generated is equally important. A lesser amount of biomedical waste means a lower burden on waste disposal work, a more effective waste disposal system and cost-saving [13].

Infectious waste

Potentially infectious wastes from patients care include: Dressings and swabs, contaminated with blood/body fluids; Laboratory waste including laboratory samples, cultures stocks of infectious agent, laboratory glassware; Instruments used in patient care: those range from diagnostic equipment such as endoscopes, ultrasound probes, syringes and needles, sharps and other instruments, tubings and bags; Potentially infected materials: Placenta, tumors, organs or limbs, which are removed during surgery; Potentially infected animals used in diagnostic or research studies. In all these wastes the major concern is to prevent potential accidental transmission of infection [20]. **Toxic wastes:** Potentially toxic wastes include: Radioactive waste: these may be solids, liquids and gases used for analytical procedures, body organ imaging and tumor localization and treatment; Chemical waste: these may be hazardous, toxic, corrosive, flammable, reactive or genotoxic; Pharmaceutical agents: these may enter hospital because there was surplus stock, spillage or contamination was detected or the expiry date was over [21].

Categories of medical waste

Pathological & Anatomical Waste: All human anatomical wastes and all wastes that are human tissues, organs, or body parts removed by trauma, during surgery, autopsy, birth, research studies, or another hospital procedure, and which are intended for disposal. Pathological waste differs from anatomical waste in that these are typically

samples of tissues that are examined in a laboratory setting to understand the nature of the disease or make a diagnosis. For the most part, pathological waste refers to very small tissue sections and body material derived from biopsies or surgical procedures that are then examined in the lab. Anatomical wastes are typically distinguished as recognizable human organs, tissue and body parts, and may require special treatment under some state regulations. Some states do not consider hair, teeth and nails to be pathological/anatomical waste [21-23].

Bulk human blood, blood products, bulk body fluids or other potentially infectious material (OPIM): This waste category typically includes bulk waste human blood, human blood components or products derived from blood including serum, plasma and other blood components, or bulk human body fluids as defined as other potentially infectious materials (OPIM), including the following human body fluids: semen, vaginal secretions, cerebrospinal fluid, synovial fluid, pleural fluid, pericardial fluid, peritoneal fluid, amniotic fluid, saliva in dental procedures, anybody fluid that is visually contaminated with blood, and all body fluids in situations where it is difficult or impossible to differentiate between body fluids. This category includes sample of these fluids taken in hematology labs, as well as drainage from surgery, and urine or feces when visibly contaminated by blood.

Microbiological Waste: Microbiological waste is made up of cultures and stocks of infectious agents, and associated microorganisms and biologicals. This waste stream is primarily generated by the healthcare organization's labs. Discarded cultures, culture dishes and devices used to transfer, inoculate and mix cultures, stocks, specimens, live and attenuated vaccines and associated items are considered microbiological waste, if they contain organisms likely to have been contaminated by organisms that may be pathogenic to healthy humans. Also typically included in this category are discarded etiologic agents and wastes from the production of biologicals and antibiotics likely to have been contaminated by organisms likely to be pathogenic to healthy humans, as well as waste that originates from clinical or research laboratory procedures involving communicable infectious agents [21-23].

Sharps: "Sharps" is a term applied to objects such as needles and scalpel blades-anything that can cut or puncture the skin. Their special hazard lies in the fact that, having been designed to pierce the skin, they are very efficient delivery mechanisms for putting infectious agents directly into the bloodstream. Wastes containing both infectious material and sharp objects create particular hazards for anyone handling them, or coming into contact with them.

Isolation Wastes (Wastes from Highly Communicable Diseases): This waste category includes biological waste and discarded materials contaminated with blood, excretion, exudates or secretion from humans or animals who

are isolated to protect others from highly communicable diseases (Lassa fever virus, Marburg virus, monkey pox virus, Ebola virus and others).

Animal Waste: Many facilities have affiliated animal research laboratories as part of their organizational footprint. This waste category includes animal carcasses, body parts, bedding and related wastes that may have been exposed to infectious agents during research, production of biologicals, or testing of pharmaceuticals.

As a **special heterogeneous mixture** of municipal, infectious, pathological, pharmaceutical, laboratory waste, disinfection agents and packaging, as well as radioactive and chemical waste, hazardous medical waste can be divided into *several subgroups* for easier and more accurate identification [24-26] and, therefore, is divided to:

- Infectious (laboratory cultures, fluids, materials and equipment that have been in contact with infected patients);
- Pathological (blood, other body fluids, body parts, fetuses);
- Sharp (objects of needles, scalpels, knives, broken glass);
- Pharmaceutical (drugs, residues of drugs);
- Genotoxic (cytostatic, genotoxic chemicals);
- Chemical (solvents, laboratory reagents, disinfectants);
- Heavy metal (batteries, sphygmomanometers, thermometers);
- Pressure vessels (gas cylinders, metal vessels) and
- Radioactive waste (scrap used in radiation therapy, urine and fluids of patients treated with radio-nuclides).

Management of medical waste

The Hospital Waste Management is part of hospital hygiene and maintenance activities and it involves range of activities, which are mainly engineering functions, such as collection, transport, treatment/processing and disposal waste. Initial segregation and storage activities are direct responsibility of nursing personal who are engaged in the hospital.

The actual management of medical waste [24,25] is an organized process that consists of five elements: *separation, identification, handling, treatment and disposal*.

Collection of Medical Waste

Medical waste must be collected and stored prior to treatment in a way that reduces the possibility of interaction with humans, animals, or the environment. Medical waste containers are generally red, contain the word "biohazard" and are imprinted with the universal three-sided biohazard symbol (Table 1, Figure 2-4). This standardization immediately identifies these containers

as medical waste. General storage guidelines include the following:

- Contaminated reusable sharps must be placed in containers that are puncture resistant, closeable, leak-proof on sides and bottoms, and labeled or color coded,
- Reusable sharps that are contaminated with blood or other potentially infectious materials must not be stored or processed in a manner that requires employees to reach by hand into the containers,
- Specimens of blood or other potentially infectious material are required to be placed in a container that is labeled and color coded and closed prior to being stored, transported or shipped,
- Regulated wastes (liquid or semi-liquid) must be placed in containers that are constructed to contain all contents and prevent leakage of fluids, labeled or color coded, and closed prior to removal,
- All bins, pails, cans, and similar receptacles intended for reuse are required to be inspected and decontaminated on a regularly scheduled basis,
- Labels must include the biohazard symbol, be fluorescent orange or orange-red or predominantly so, with lettering and symbols in contrasting color, and affixed as closely as possible to the container by adhesive or wire to prevent loss or removal.

The most visible form of medical waste collection is the sharps container. Sharps containers are found in every medical office, and often in public places, for medical personnel and the general public to safely dispose of hypodermic needles. These containers are designed so the user is never exposed to any of the sharps already in the container, eliminating the possibility of contact or puncture by any of the used needles. Sharps containers are generally made of thick plastic, and have a door that opens and the user can insert the sharp into the container. When the door is closed, the sharp is dropped down into the main chamber of the container. The container functions much like a standard post office mailbox, in that the user cannot reach the sharps inside the container via the door. Sharps containers are also used for other categories of sharps, including scalpels and lancets.

Community Hazardous Waste Collection

Many municipalities have occasional household hazardous waste collection days when authorities designate a place where residents bring waste from their homes. These are intended to be strictly for residential/household waste, not from commercial facilities. Different authorities have different rules, but usually these collection days explicitly prohibit infectious waste.

Table 1. Category of medical and biomedical waste and disposal [25]

	Consist of	Disposal
Human Anatomical Waste	Human tissue, organs, body parts	Incinerations / deep burial
Animal Waste	Animal tissue, animals used in research, waste from veterinary hospitals, colleges, and animal houses	Incinerations / deep burial
Microbiology&Biotechnology Waste	Wastes from laboratory cultures, stocks or specimens of microorganisms live or attenuated vaccines, toxins, dishes and devices used for transfer of cultures	Incinerations
Waste sharps	Needles, syringes, scalpels, blades, glasses, etc.	Autoclaving / shredding
Discarded Medicines and Cytotoxic Drugs	Outdated, contaminated and discarded medicines	Incinerations and secured landfills
Solid Waste	Items contaminated with blood and body fluids, including cotton, dressing, soiled plaster casts, beddings	Autoclaving, microwaving
Solid Waste III	Waste generated from disposable items like tubings, catheters, intravenous sets etc.	Autoclaving, microwaving and shredding
Liquid Waste	Laboratory and washing, cleaning, housekeeping in hospitals	Treatment and discharge into drains
Incineration Waste	Ash from incineration of any biomedical waste	Disposal in municipal landfill
Chemical Waste	Chemicals used in production of biologicals, chemicals used in chemical treatment and disinfections, as insecticides	Discharge into drains for liquids and secured landfill

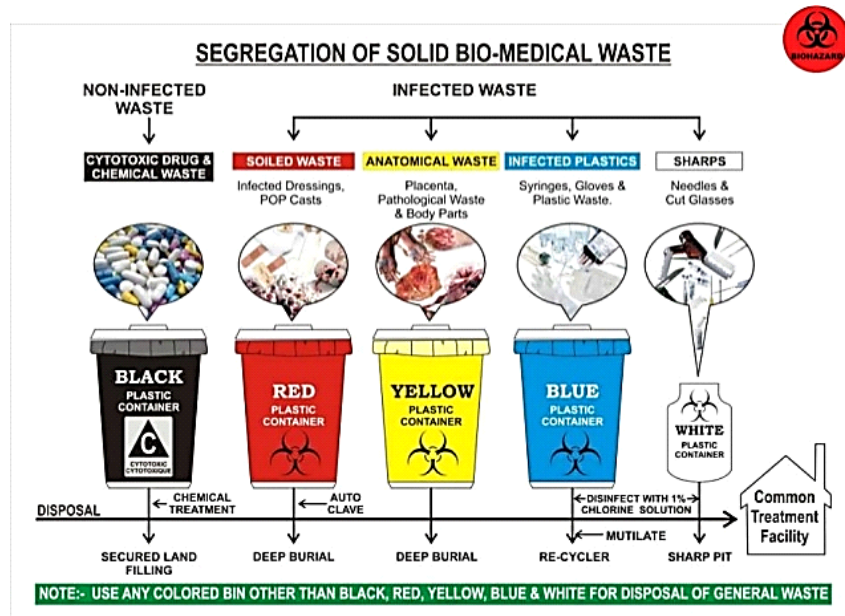


Fig. 2. Segregation of medical and biomedical waste [26]

SEGREGATION OF WASTE IN COLOR CODED BAGS			
BLACK CARBOY Needles without syringes, blades, sharps and metal articles	BLUE BAGS All types of glass bottles and broken glass articles outdated & discarded medicines	RED BAGS Plastic waste such as catheters, injections, syringes, tubings i.v.bottles	YELLOW BAGS Infectious waste, bandage, gauzes, cotton, or any other things in contact with body fluids, human body parts, placenta

Fig. 3. Segregation of waste in color coded bags [25]



Fig. 4. Medical Waste Containers [27]

Treatment of Medical Waste

The primary methods of treatment and disposal of medical waste are:

- Incineration
- Autoclaves
- Mechanical/Chemical Disinfection
- Microwave
- Irradiation

The treated waste (if sufficiently sterile) can generally be disposed with general waste in a sanitary landfill, or in some cases discharged into the sewer system. In the past, treatment of medical waste was primarily performed on-site at hospitals in dedicated medical waste facilities. Over time, the expense and regulation of these facilities have prompted organizations to hire contractors to collect, treat, and dispose medical waste, and the percentage of medical organizations that perform their own treatment and disposal is expected to drop [24,25,28]. To ensure that each treatment method provides the proper environment for the destruction of biologicals, test indicators for microbiological spores measure the treatment effectiveness. Microbiological spores are the most difficult of biologicals to destroy, so when the test package cannot be cultured after treatment, the waste is considered properly treated. In treatment methods where shredding or maceration is employed, the test package is inserted into the system after the shredding process to avoid physical destruction of the test package. The test package is then retrieved from the waste after treatment.

Incineration

According to the EPA, 90% of medical waste is incinerated. Incineration is the controlled burning of the medical waste in a dedicated medical waste incinerator. Among industry folks, these units are often referred to as hospital/medical/infectious waste incinerators (HMIWIs) [24,2,28-30].

Autoclaves

Autoclaves are closed chambers that apply both heat and pressure, and sometimes steam, over a period of time to sterilize medical equipment. Autoclaves have been used for nearly a century to sterilize medical

instruments for re-use. Autoclaves are used to destroy microorganisms that may be present in medical waste before disposal in a traditional landfill [25, 28-30].

Disposal

Mechanical/Chemical Disinfection

Chemical disinfection, primarily through the use of chlorine compounds, is another method to treat medical waste. The use of chlorine bleach for cleaning and disinfecting is well known and this method has been in use for many years. The mechanical/chemical disinfection process provides control and consistency to the disinfection process. The EPA identifies chemical disinfection as the most appropriate method to treat liquid medical waste. Chemical disinfection processes are often combined with a mechanical process, such as shredding or maceration, to ensure sufficient exposure of the chemicals to all portions of the waste [15].

Microwave

The use of microwaves to disinfect medical waste has only recently been introduced in the United States. Microwave treatment units can be either on-site installations or mobile treatment vehicles. In this type of disinfection process, the waste is first shredded. The shredded waste is then mixed with water and subjected to microwaves. The microwaves internally heat the waste, rather than applying heat externally, as in an autoclave [11].

Irradiation

Another method used to sterilize medical equipment or waste is irradiation, generally through exposure of the waste to a cobalt source. The gamma radiation generated by the cobalt inactivates microbes. Dedicated sites are required for this form of treatment, while mobile versions are available for other non-incineration methods [29]. The World Health Organization recommends as protective gear for anyone who comes into contact with medical waste to wear: helmet; protective face mask; goggles; special jumpsuits; industrial aprons; feet guards; boots etc. [29].

Conclusion and Recommendations

It is important to underline that the management of medical waste takes over the strict control and record the waste from the spot of occurrence and up to final storage. This process requires the preparation of strict procedures to be applied to the site of occurrence (e.g. in a hospital room, clinic, laboratory, etc.). In this way, the problem with the management of medical waste in health care could be reduced to the level of no risk or less risky waste.

In each health institution, actions should be organized and controlled with regards to the occurrence of the medical waste stream and reduce the amount of hazardous materials medical waste, as well as on-site waste collection.

It's important to clearly define the responsibility for proper waste management, to the process of its final processing. It is necessary to develop a comprehensive and planned management system that beside responsibility should provide funds for safe implementation of waste. This is a long process that despite organizational structure requires individual and professional commitment.

Bio-Medical Waste management program cannot successfully be implemented without the devotion, self-motivation, willingness, cooperation and participation of all sections of employees of any health care establishment.

Conflict of interest statement. None declared.

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УЛОГАТА НА СТАНДАРДИЗИРАНАТА ЕХОГРАФИЈА ВО ПРЕДОПЕРАТИВНА ПРИПРЕМА НА ПАЦИЕНТИ СО СЕНИЛНА КАТАРАКТА**THE ROLE OF STANDARDIZED ECHOGRAPHY IN PREOPERATIVE PREPARATIONS OF PATIENTS WITH SENILE CATARACT**

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Апстракт

Вовед. Стандардизирана ехографија е неинвазивна, едноставна, ефикасна и безболна дијагностичка метода, која овозможува визуализација и евалуација на задниот очен сегмент кај непровидните очни медиуми, како што е и заматувањето на леќата односно катарактата. Цел на трудот е да се укаже и потенцира значењето на стандардизираната ехографија во предоперативно припремање и евалуација на задниот очен сегмент кај пациенти со сенилна катаракта.

Методи. Во период од 6 месеци, од 05.05.2015 до 05.11.2015 година, на Универзитетската клиника за очни болести во Скопје, во кабинетот за ехографија се направени 718 ехографски прегледи кај пациенти со претходно дијагностицирана сенилна катаракта. Прегледите беа направени со користење на апарат од типот Sonomed E-Z Scan-AB 5500+.

Резултати. Од вкупен број ехографски испитувани пациенти со сенилна катаракта -718, кај 295 (24,30%) се дијагностицирани опацицитети во стаклестото тело (opacitates corpori vitrei), кај 128 (18,08%) -одлепување на стаклесто тело (posterior vitreous detachment), synchysis scintillans кај 8 (1,11%), крварење во стаклесто тело (haemophthalmus) кај 5 (0,70%) пациенти и кај 3 (0,42%) -одлепување на мрежница (ablatio retinae). Со уреден ехографски наод беа 302 (42,06%) пациенти.

Заклучок. Добиените резултати укажуваат на неопходност од предоперативно извршување на ехографски преглед кај пациенти со сенилна матурна и хиперматурна катаракта.

Клучни зборови: ехографија, катаракта, предоперативна подготовка

Abstract

Introduction. The standardized echography is a non-invasive, simple, efficient and painless diagnostic method, which allows visualization and evaluation of posterior eye segment through non-transparent media, such as blurring lens or cataract. The aim of the study was to emphasize the role and importance of standardized echography in preoperative preparation of patients and evaluation of posterior eye segment in patients with senile cataracts.

Methods. During a 6 month-period, from 05.05.2015 to 11.05.2015, a total of 718 ultrasound examinations were made in patients with previously diagnosed senile cataracts at the University Clinic for Eye Diseases in Skopje, in the Echography cabinet. Examinations were made by using the apparatus Sonomed E-Z Scan-AB 5500+.

Results. Out of the total number of 718 patients with senile cataracts examined by echography-in 295 (24.30%) opacities in the vitreous body were diagnosed, in 128 (18.08%)-posterior vitreous detachment, in 8 (1.11%) synchysis scintillans, in 5 (0.70%) hemophthalmus and in 3(0.42%) detachment of the retina. A total of 302 (42.06%) patients were with normal echographic findings.

Conclusion. The results obtained indicate the necessity of preoperatively echographic examination in patients with senile mature and hypermature cataracts.

Keywords: echography, cataracts, preoperative preparation

Вовед

Стандардизирана ехографија е ефикасна, неинвазивна, едноставна и безболна метода во дијагностика на очните и орбитални заболувања [1-4]. Очното јаболко и дел од орбитата без апексот претставуваат погодна анатомска целина за примена на ултразвук во дијагностички цели. Подобрување на резолуција од една страна и анализа на промени во различни длабочини од друга страна, овозможуваат прецизна дијагностика на задниот сегмент на окото и орбитата [4,5].

Ултразвучната енергија, која се употребува во офталмологијата во дијагностички цели, не ги оштетува очните ткива и прегледите можат да се повторуваат повеќе пати без никакви последици [2]. Основни индикации за ехографија се непровидни очни медиуми и неможност за визуелизација на задниот очен сегмент, а најголем број од пациенти кои доаѓаат во Кабинет за ехографија се пациенти со заматена леќа, односно со катаракта. Катарактата е една од водечките причини за унилатерален, билатерален морбидитет и редуцирана видна острина во светот.

Во денешно време со забрзаниот техничко-технолошки развој и примена на апаратура, неопходно е добро предоперативно припремање на пациентите. Стандардизираната ехографија е единствена неинвазивна метода во проценка на задниот сегмент кај случаи со заматени медиуми.

Цел на трудот е да се укаже и потенцира значење на стандардизираната ехографија во предоперативно припремање на пациенти и евалуација на задниот очен сегмент кај пациенти со сенилна катаракта.

Материјал и методи

Во ретроспективна студија, спроведена во периодот од 6 месеци, од 05.05.2015 до 05.11.2015 година, на Универзитетската клиника за очни болести во Скопје, во кабинетот за ехографија се направени вкупно 718 ехографски прегледи кај пациенти со претходно дијагностицирана сенилна катаракта. Прегледите беа направени со помош на апарат од типот Sonomed E-Z Scan-AB 5500 + (слика 1). Примарно беше користена Б скен техника, додека А скен имаше корелативна и потврдувачка улога. Close-lid техниката беше применета кај сите испитувани пациенти.



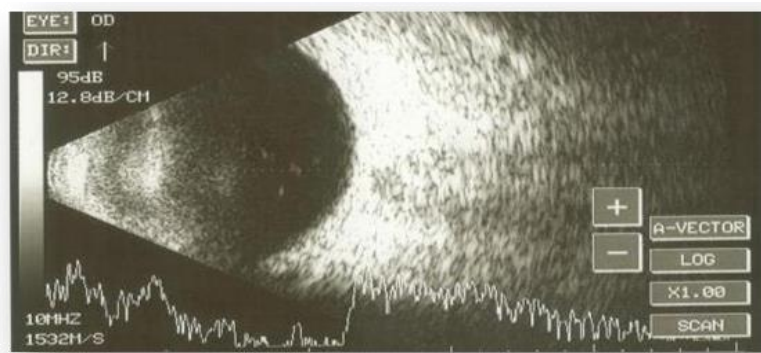
Сл. 1. Ехографски апарат-тип Sonomed E-Z Scan-AB 5500+

Резултати

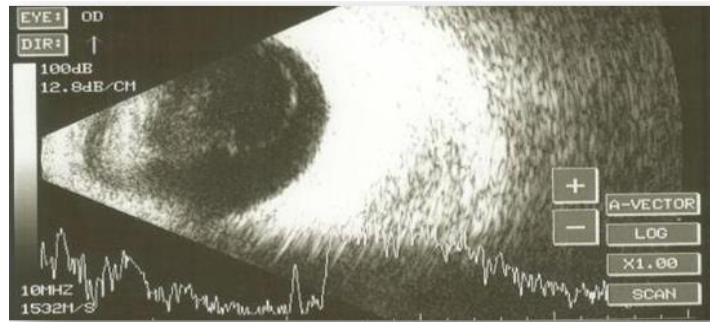
Од вкупен број ехографски испитувани пациенти со сенилна катаракта -718, кај 295 (24,30%) се дијагностицирани опацицитети во стаклестото тело (opacitates corpori vitrei, слика 2), кај 128 (18,08%) -одлепување на стаклесто тело (posterior vitreous detachment, слика 3), synchysis scintillans кај 8(1,11%), крвавење во стаклестото тело (haemophthalmus, слика 4) кај 5(0,70%) пациенти и кај 3(0,42%) - одлепување на мрежницата (ablatio retinae, сл.5). Со уреден ехографски наод беа 302(42,06%) пациенти. Некои од испитуваните пациенти имаа повеќе од еден ехографски наод. Во табела 1 се прикажани ехографските наоди од испитуваните пациенти.

Табела 1. Ехографски наоди од испитуваните пациенти со сенилна катаракта

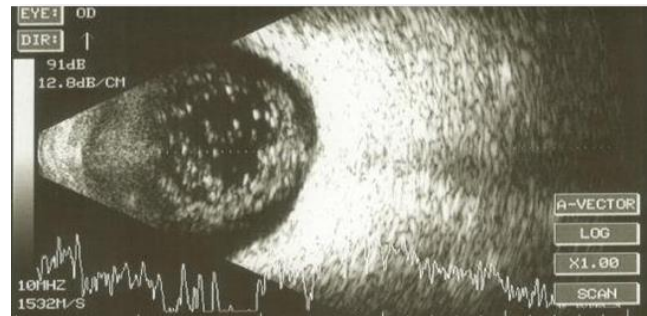
Ехографски наоди	Вкупно N=718 (100.0%)
Opacitates corpori vitrei	295 (24,3%)
Posterior vitreous detachment	128 (18,08%)
Synchysis scintillans	8 (1,11%)
Haemophthalmus	5 (0,70%)
Ablatio retinae	3 (0,42%)
Уреден наод	302 (42,06%)



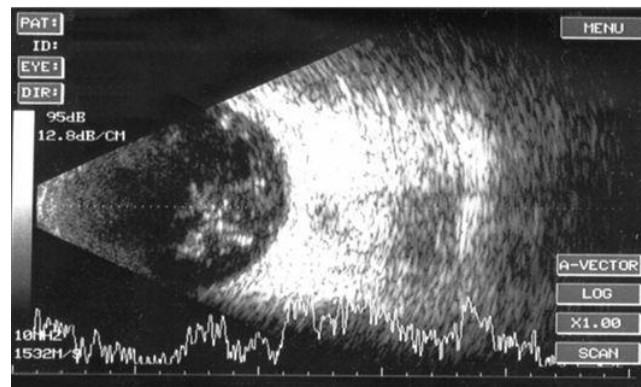
Сл. 2. АБ скен - opacitates corpori vitrei



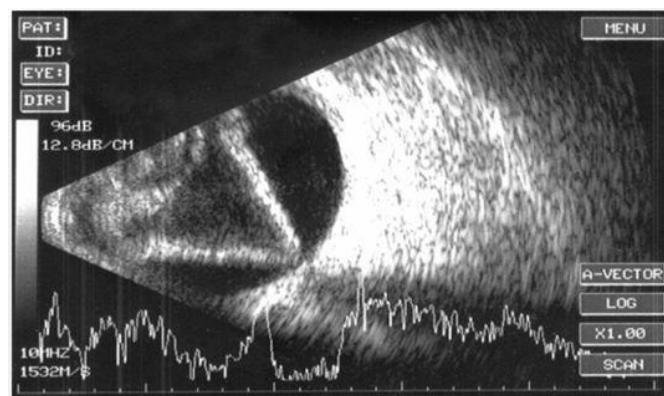
Сл. 3. АБ скен - posterior vitreous detachment



Сл. 4. АБ скен - synchysis scintillans



Сл. 5. АБ скен- haemophthalmus



Сл. 6 АБ скен - ablatio retina

Дискусија

Во повеќе студии е докажано дека стандардизираната ехографија е клучна метода во диференцијална дијагноза на различни патолошки про-

мени на задниот сегмент на окото [2,5-10].

Инволвирањето на задниот сегмент на окото е важен фактор во индицирање на лоша прогноза, конкретно, haemophthalmus и ablatio retina го зго-

лемуваат ризикот за намалена видна острина или евентуално слепило [11].

Опацитетите во стаклестото тело (opacitates corpori vitrei) со 24,3% беа најзастапениот ехографски наод кај испитуваните пациенти со сенилна катаракта (слика 2).

Одлепување на стаклестото тело (posterior vitreous detachment) беше застапено со 18,08% во нашата студија. На Б скенот се прикажува како тенка, подвижна континуирана мембрана, која нема инсерција на п.орџисус, а на А скенот како висок забец (слика 3).

Synchisis scintillans беа застапени со 1,11% (слика 4). Крварење во стаклестото тело (haemophthalmus) при ехографското испитување, кај нашите пациенти, беше со застапеност од 0,70% (слика 5). Со помош на ехографијата може да се следи обемот и распространетоста на крвната маса и да се евалуираат резултатите од терапијата, односно да се следи текот на нејзината ресорбција [11]. Доколку не се ресорбира крварењето во стаклестото тело треба да се изврши витректомија. Во нашата студија кај 0,42% од пациентите беше регистрирано одлепување на мрежницата (ablatio retinae), која ехографски се прикажува како високо ехогена подвижна мембрана со инсерција на ретината на п. орџисус и напред за ora serata. На А скен се гледа висок забец во corpus vitreum, кој ја достигнува висината на склерата и е пред заштите од склера и орбита (слика 6).

Компарирајќи ги резултатите со студиите на Bello [5], Brazitikos [6], Qureshi [10] и Salman [12], дојдовме до слични сознанија во однос на значењето на оваа дијагностика во предоперативно припремање на пациенти со катаракта.

Кај ниту еден пациент со сенилна катаракта во нашата студија, ехографски не е дијагностициран интраокуларен тумор. Меѓутоа, можноста за откривање на евентуално присутен, претходно не дијагностициран интраокуларен тумор е дополнителна причина за рутинска ехографска проверка на задниот очен сегмент пред планираната операција на катаракта.

Добиените ехографски наоди имаат важна улога во планирање на хируршка интервенција [13]. Ехографските резултати се и од голема важност во предоперативниот разговор со пациентите и нивно навремено информирање за прогноза и очекуван постоперативниот визуелен резултат.

Заклучок

Стандардизираната ехографијата има незаменлива улога во клиничка проценка на промените на задниот очен сегмент кај пациенти со катаракта. Ехографските наоди од нашите пациенти укажуваат на неопходност од рутински предоперативен ехографски преглед кај секој пациент со матурна и хиперматурна катаракта. Нашите резултати покажаа дека најзастапен ехографски наод се опацитетите во стаклесто тело со 24,3% и одлепување на стаклесто тело со 18,08%.

Конфликт на интереси. Не е деклариран

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АСОЦИЈАЦИЈА ПОМЕЃУ БАКТЕРИСКАТА ВАГИНОЗА И СКВАМОЗНИТЕ ИНТРАЕПИТЕЛНИ ЛЕЗИИ НА ГРЛОТО НА МАТКАТА**ASSOCIATION BETWEEN BACTERIAL VAGINOSIS AND SQUAMOUS INTRAEPITHELIAL LESIONS OF THE UTERINE CERVIX**

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Abstract

Introduction. Bacterial vaginosis is polymicrobial, primarily anaerobic infection, previously called non-specific vaginitis or vaginitis accompanied by *Gardnerella vaginalis*. It is a result of an imbalance between different types of bacteria in the vagina. The aim of the study was to determine the association between bacterial vaginosis and squamous intraepithelial lesions of the uterine cervix.

Methods. This cross-sectional study was conducted in a series of 338 sexually active women with cytologically diagnosed squamous intraepithelial lesion of the uterine cervix at the University Clinic of Gynecology and Obstetrics in Skopje in the period from October 2014 to October 2015. The age of the patients ranged from 20 to 59 years (35±10.49). All women underwent cervical biopsy with endocervical curettage for histopathological analysis and cervical biopsy for detection and HPV typing. Criteria for diagnosis of bacterial vaginosis was the presence of ≥20% clue cells of ePapnicolaou smear.

Results. Bacterial vaginosis was detected in 19.5% (66/338) of the examined women. The most affected was the young population under the age of 30 years. The results showed an association between bacterial vaginosis and squamous intraepithelial lesions of the uterine cervix (p=0.032). There was no association between bacterial vaginosis and the grade of lesion of the uterine cervix (p=0.118), nor with HPV infection (p=0.570). But, however an association was found between HPV infection and squamous intraepithelial lesions of the uterine cervix (p=0.001).

Conclusion. The most common risk factor for squamous intraepithelial lesions of the uterine cervix are persistent high-risk HPV infections. Bacterial vaginosis is the most common co-infection.

Keywords: bacterial vaginosis, intraepithelial lesions, clue cells, human papillomavirus

Апстракт

Вовед. Бактериската вагиноза е полимикробна, примарно анаеробна инфекција, претходно наречена неспецифичен вагинитис, или вагинитис придружен со *Gardnerella Vaginallis*. Последица е на нарушена рамнотежа меѓу различни типови бактерии во вагината. Целта на студијата е се одредување на поврзаноста меѓу бактериската вагиноза и сквамозните интраепителните лезии на грлото на матката.

Методи. Студија на пресек (cross-sectional study), спроведена врз серија од 338 сексуално активни жени со цитолошки наод на сквамозна интраепителна лезија на грлото на матката, на Универзитетската клиника за гинекологија и акушерство во Скопје, во периодот од октомври 2013 година, до октомври 2014 година, на возраст од 20 до 59 години (35±10,49). Кај сите пациентки е направена цервикална биопсија со ендоцервикална киретажа за хистопатолошка анализа и цервикална биопсија за детекција и за ХПВ типизација. Критериум за поставување дијагноза на бактериска вагиноза е присуството на ≥20% "патоказни" (clue) клетки на Папаниколау тестот.

Резултати. Бактериска вагиноза детектирана кај 19,5% (66/338) од испитаните жени. Најафектирана е младата популација на возраст под 30 години. Резултатите покажаа асоцијација меѓу бактериската вагиноза и сквамозните интраепителните лезии на грлото на матката (p=0,032). Не е најдена поврзаност на бактериската вагиноза со степенот на лезија на грлото на матката (p=0,118), ниту пак, со ХПВ инфекцијата (p=0,570). Детектирана е асоцијација меѓу ХПВ инфек-

цијата и сквамозните интраепителните лезии на грлото на матката ($p=0,001$).

Заклучок. Најчест ризик фактор за појава на сквамозните интраепителните лезии на грлото на матката се перзистентните високо-ризични ХПВ инфекции. Бактериската вагиноза е најчеста коинфекција.

Клучни зборови: бактериска вагиноза, интраепителни лезии, "патоказни" клетки, хуман папилома вирус

Introduction

Bacterial vaginosis is the most common vaginal syndrome in a woman's reproductive period. Cervical cytological abnormalities are found more in women with abnormal vaginal flora, which suggests a possible association between bacterial vaginosis and squamous intraepithelial lesions of the uterine cervix [1,2].

Bacterial vaginosis is polymicrobial, primarily anaerobic infection, previously called nonspecific vaginitis or vaginitis accompanied by *Gardnerella vaginalis*. It is a result of an imbalance between different types of bacteria in the vagina. Instead of the normal predominance of *Lactobacillus*, different types of microorganisms can be found in the vagina, such as: *Gardnerella vaginalis*, *Mycoplasma hominis*, *Ureoplasma urealyticum*, *Peptostreptococcus*, *Mobiluncus* species, *Prevotella* species and *Bacteroides* [3,4].

Risk factors that may be associated with bacterial vaginosis are: smoking, use of intrauterine device, frequent vaginal discharge, promiscuity and early first intercourse [5].

Bacterial vaginosis can be associated with some sexually transmitted infections, such as infection with *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, with the Human Immunodeficiency Virus and Human papilloma virus [6-8].

The diagnosis of bacterial vaginosis can be established by using Nugen's scoring system, Amsel's clinical criteria, modified Amsel's criteria, microbiological criteria or by the presence of clue cells of the Papanicolaou (PAP) smear [9,10].

The diagnosis of bacterial vaginosis only by the presence of clue cells in a wet sample or the presence of ≥ 20 clue cells of the PAP smear as inclusion criteria is an accurate method and a good predictor of bacterial vaginosis [11].

Clue cells are cells of the vaginal epithelium overlapping with *Gardnerella* and other microorganisms, which look like to be sprinkled with powdered sugar [12].

Previous studies that investigated the association between bacterial vaginosis and squamous intraepithelial lesions of the uterine cervix have provided conflicting results and different conclusions; from the

existence of a strong association [13] to the lack of association between bacterial vaginosis and squamous intraepithelial lesions of the cervix [14].

The aims of the study were: to determine the prevalence of bacterial vaginosis, to determine the most affected age group of patients, to determine the association between bacterial vaginosis and HPV infection, to determine the association between bacterial vaginosis and squamous intraepithelial lesions of the uterine cervix and the grade of the lesion and to determine the association between HPV infection and squamous intraepithelial lesions of the cervix.

Material and methods

This was a cross-sectional study conducted in a series of 338 sexually active women with cytologically diagnosed squamous intraepithelial lesion of the uterine cervix at the University Clinic of Gynecology and Obstetrics in Skopje in the period from October 2014 to October 2015. The age of the patients was between 20 and 59 (35 ± 10.49). All women underwent cervical biopsy with endocervical curettage for histopathological analysis and cervical biopsy for detection and HPV typing. Criteria for diagnosis of bacterial vaginosis was the presence of $\geq 20\%$ clue cells of the Papanicolaou smear.

From a total of 350 women with cytologically diagnosed squamous intraepithelial lesion of the uterine cervix, 12 were with histopathological finding of invasive squamous cell carcinoma of the uterine cervix.

Criteria of inclusion

The study included 338 sexually active women with squamous intraepithelial lesion of the uterine cervix of the PAP smear.

Criteria of exclusion

The study did not include: pregnant women, women with previous surgery of the uterine cervix (cervical conization, carbon dioxide laser vaporization), women receiving antibiotic therapy and women with histopathological diagnosis of invasive squamous cell carcinoma of the uterine cervix.

Methods of examination

All 350 women underwent cervical biopsy with endocervical curettage for histopathological analysis and cervical biopsy for detection and HPV typing.

All samples for cytology were taken using Thin Prep PAP smear cytology and were analyzed in the Laboratory of the University Clinic of Gynecology and Obstetrics in Skopje by a doctor-cytopathologist. Cytological results were classified according to the revised

Bethesda classification [15,16], such as: Atypical Squamous Cells of Undetermined Significance-ASC-US, Atypical Squamous Cells cannot exclude HSIL-ASC-H, Low-grade Squamous Intraepithelial Lesion-LSIL (productive HPV infection, Cervical Intraepithelial Neoplasia grade 1-CIN1), High-grade Squamous Intraepithelial Lesion-HSIL (CIN2, CIN3, CIS) and invasive squamous cell carcinoma.

Criterion for diagnosis of bacterial vaginosis was the finding of $\geq 20\%$ clue cells in the visual field of the PAP smear under an optical microscope at 1000 times magnification.

The first step in PAP testing was taking and collecting the cytological material. The material for cytological analysis was taken with a special "blue" cyto brush, which simultaneously collects material from exocervix and endocervix. It was collected in special plastic collectors for Thin Prep PAP smear (Hologic, USA), containing 20 ml PreservCyt solution. The name of the woman and outpatient's number were written on each collector.

The second step was preparation of a microscopic slide in three stages: making smear, smear fixing and coloring the smear.

The third step of the PAP test was examination of the slides under an optical microscope (Olympus BH-2, USA). The microscopic examination was done with 100 times magnification of the lens and 10-fold increase in the microscope eyepiece. Criterion for diagnosis of bacterial vaginosis was the finding of $\geq 20\%$ clue cells in the visual field of the slide of the PAP smear. Samples for histopathological analysis were taken to the University Clinic of Gynecology and Obstetrics in Skopje and were analyzed at the University Clinic of Radiotherapy and Oncology in Skopje, at the Department of Histopathology and Clinical Cytology by an experienced expert in pathohistology. According to morphology of the bioptic samples, the cervical findings were characterized as: normal finding (non-specific cervicitis), Low-Grade Squamous Intraepithelial Lesion-LGSIL (Flat condyloma, cervicitis chronic virosa, mild dysplasia), High-Grade Squamous Intraepithelial Lesion-HGSIL (moderate dysplasia, severe dysplasia, carcinoma in situ) and invasive squamous cell carcinoma.

The analysis of the samples from the cervical biopsy, detection and HPV typing were made at the University Clinic of Gynecology and Obstetrics in Skopje, in the Laboratory for HPV typing.

The first step in HPV testing was the isolation of DNA from the collected cells of the cervical biopsies.

The second step was detection of HPV DNA using multiplex polymerase chain reaction (PCR).

The third step was genotyping using the reverse hybridization. It is a method that is based on the hybridization of specific DNA probes that are immo-

bilized on nitrocellulose or nylon tapes.

Statistical Methods

Data were analyzed by a specific software for databases (Excel). Statistical analysis of the established statistical series was made with the statistical program SPSS, version 12.0.

The structure of numerical signs was analyzed by determining the measures of central tendency (arithmetical mean) and measures of dispersion (standard deviation).

Analysis of the relationship (the existence of association) between two sets of attribute variables was performed using the Chi-square test.

Statistical significance was defined as a p value < 0.05 .

Results

Of the 338 examined patients aged from 20 to 59 years (35 ± 10.49) 144 (42.6%) were aged 20-29 years, 92 (27.2%) 30-39 years, 60 (17.8%) 40-49 years and 42 (12.4%) were aged 50-59 years (Table 1).

Table 1. Distribution of patients according to age groups

Age group	Number	%
20-29	144	42.6
30-39	92	27.2
40-49	60	17.8
50-59	42	12.4
Total	338	100

Of the total of 338 patients, bacterial vaginosis was found in 66 (19.5%) patients.

The frequency of bacterial vaginosis according to age group in 66 patients is shown in Figure 1.

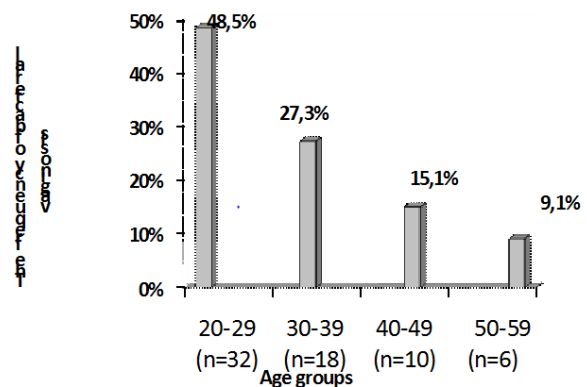


Fig. 1. Frequency of bacterial vaginosis according to age group in 66 patients

The association between bacterial vaginosis and HPV infection is shown in Table 2.

Table 2. Association between bacterial vaginosis and HPV infection

		Bacterial vaginosis			
		Present		Absent	
		n	(%)	n	(%)
HPV infection	Present	4	(18.8)	203	(81.2)
	n=250	7			
	Absent	1	(21.6)	69	(78.4)
	n=88	9			
Total		6	(19.5)	272	(80.5)
n=338		6			

Of the total of 338 patients, 47(13.9%) were found to have bacterial vaginosis and HPV infection at the same time. Of the 250 HPV DNA positive patients, bacterial vaginosis was present in 47(18.8%) patients, and absence of bacterial vaginosis was observed in 203 (81.2%) of the HPV DNA positive patients.

The data analysis showed no association between bacterial vaginosis and HPV infection (chi-square test=0.323, p=0.570, p>0.05).

Table 3. Prevalence of HPV DNA genotypes in 47 women with bacterial vaginosis

HPV DNA genotype	Type of infection	Bacterial vaginosis total (n=47)	
		n	%
16	single	17	(36.2)
	mixed	13	(6.4)
18	single	5	(10.7)
	mixed	1	(2.1)
31	single	12	(25.5)
	mixed	1	(2.1)
33	single	1	(2.1)
	mixed	0	(0)
45	single	1	(2.1)
	mixed	1	(2.1)
52	single	0	(0)
	mixed	1	(2.1)
6	single	2	(4.3)
	mixed	2	(4.3)

Distribution of bacterial vaginosis compared to histopathological diagnosis is shown in Table 4.

Table 4. Distribution of bacterial vaginosis compared to histopathological diagnosis

		Bacterial Vaginosis			
		Present		Absent	
		n	(%)	n	(%)
Histopathological diagnosis	Squamous intraepithelial lesion	58	(22.0)	206	(78.0)
	n= 264				
	Normal finding	8	(10.8)	66	(89.2)
	n= 74				
Total		66	(19.5)	272	(80.5)
n= 338					

Of the total of 338 patients, bacterial vaginosis was found in 66(19.5%) patients. Of these 58(22.0%) were with histopathological finding of squamous intraepithelial lesion of the uterine cervix, and 8 with normal histopathological finding.

Data analysis showed an association between bacterial

vaginosis and intraepithelial lesions of the uterine cervix (chi-square test=4.580, p=0.032, p<0.05).

Distribution of bacterial vaginosis in correlation with the grade of squamous intraepithelial lesion of the uterine cervix is shown in Table 5.

Of the total of 124 patients with histopathological fin-

Table 5. Distribution of bacterial vaginosis in correlation with the grade of squamous intraepithelial lesion of the cervix

		Bacterial Vaginosis			
		Present		Absent	
		n	(%)	n	(%)
Grade of squamous intraepithelial lesion	Low grade SIL	22	(17.7)	102	(82.3)
	n= 124				
	High grade SIL	36	(25.7)	104	(74.3)
	n= 140				
Total		58	(22.0)	206	(78.0)
n= 264					

SIL-squamous intraepithelial lesion

ding of low-grade squamous intraepithelial lesions of

the uterine cervix, bacterial vaginosis was found in

22(17.7%) patients, while of 140 patients with histopathological diagnosis of high-grade squamous intraepithelial lesion of the uterine cervix, bacterial vaginosis was found in 36 (25.7%) patients.

The data analysis showed no association between the presence of bacterial vaginosis and the grade of cervical lesion (chi-square test=2.438, $p=0.118$, $p>0.05$).

The distribution of the findings of HPV testing compared to histopathology findings is summarized in Table 6. After the HPV testing, from the total of 338 patients 250(74.0%) were HPV DNA positive, while 88(26.0%) were HPV DNA negative. In patients with squamous

Table 6. Distribution of findings of HPV testing compared to histopathological diagnosis

Histopathological diagnosis	n	HPV testing	
		HPV DNA positive	HPV DNA negative
		n (%)	n (%)
Squamous intraepithelial lesion n= 264	215	(81.4)	49 (18.6)
Normal finding n= 74	35	(47.3)	39 (52.7)
Total n= 338	250	(74.0)	88 (26.0)

intraepithelial lesion on the cervix, 215 (81.4%) were HPV DNA positive, while of the patients with pathologically normal findings 35(47.3%) were HPV DNA positive.

Data analysis showed an association between HPV infection and intraepithelial lesions of the cervix (chi-square test=34.987, $p=0.001$, $p<0.05$).

Discussion

Early detection and treatment of intraepithelial lesions of the cervix play a key role in the prevention of cervical cancer [17].

Bacterial vaginosis can be associated with several obstetric and gynecological complications, such as preterm birth, chorioamnionitis, endometritis after cesarean section, pelvic inflammatory disease, postoperative infections after hysterectomy and with abnormal cervical finding [13,18,19].

In our study the prevalence of bacterial vaginosis was 19.5%. In previous published studies where bacterial vaginosis was detected by the presence of clue cells, as in our study, the prevalence ranged from 15.0-24.18% [20-23].

A higher percentage of bacterial vaginosis (up to 41.67%) was found in studies where the diagnosis of bacterial vaginosis was made on the basis of clinical Amsels' criteria [24]. The highest percentage of bacterial vaginosis (up to 49.02%) was is detected by Nugent's score, as the "gold standard" for diagnosis of bacterial vaginosis [25,26]. These data support the idea of detecting vaginal bacteriosis by the Nugent's score as the "gold standard" that should be used in the future. In our study the highest rate of bacterial vaginosis of

48.5% (32/66) was found among the largest study group (young people under 30 years of age).

A high percentage of bacterial vaginosis among young people was also found in some previously published studies [27,28].

HPV infection plays a major role in changing the vaginal environment, helping the development of bacterial vaginosis [14]. On the other hand, women with bacterial vaginosis are more susceptible to getting and reactivation of HPV infection [29]. Many studies present conflicting results regarding the association between bacterial vaginosis and HPV infection [30-32]. In our study no association was found between bacterial vaginosis and HPV infection ($p=0.570$), which is similar to the results in some previously published studies [33-36].

The most common HPV DNA genotypes in women with bacterial vaginosis, in descending order, were HPV16 (42.6%), HPV31 (27.6%), HPV18 (12.8%), HPV6 (8.6%), HPV45 (4.2%), HPV33 (2.1%) and HPV52 (2.1%).

A number of previously published studies have presented a different relationship between bacterial vaginosis and intraepithelial lesions of the cervix. The found association between bacterial vaginosis and intraepithelial lesions of the cervix in our study ($p=0.032$) was also found in some previously published studies [24,28,37-39]. In the study of Antovska *et al.* bacterial vaginosis was more common in the subgroup of women with invasive squamous cell carcinoma of the uterine cervix (6.3%) than in the subgroup with low-grade squamous intraepithelial lesions of the uterine cervix (2.1%) [40].

Several hypotheses are explaining the connection between bacterial vaginosis and intraepithelial lesions of the cervix. One of them assumes that in women with bacterial vaginosis mucin degradation enzymes grow. These enzymes such as sialidase (neuraminidase) play a key role in degradation of the protective layer of the cervical epithelium, causing microabrasion or changes in epithelial cells leading to destruction of the mucosal barrier protection [41].

In our study an association between bacterial vaginosis and the grade of the cervical lesion was found, and it was identical to some previously published studies [35,38]. In the future, it is necessary to conduct a study where the diagnosis of bacterial vaginosis will be made by using Nugent's score system or Amsel's clinical criteria.

The most common risk factor for pre-cancerous lesions of the cervix is infection with human papillomavirus (HPV), particularly with high-risk HPV genotypes [42,43]. In our study the prevalence of HPV infection was 74.0%. Our results showed that there was an association between HPV infection and intraepithelial lesions of the cervix ($p=0.001$).

Conclusion

This study showed prevalence of bacterial vaginosis was (19.5%); the most affected were the young people under the age of 30 years; there was no statistically significant association between bacterial vaginosis and HPV infection; there was an association between bacterial vaginosis and squamous intraepithelial lesions of the cervix; there was no association between bacterial vaginosis and the grade of the lesion of the uterine cervix and there was an association between HPV infection and squamous intraepithelial lesions of the uterine cervix.

Conflict of interest statement. None declared.

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ВЛИЈАНИЕТО НА ФИЗИКАЛНИТЕ ТЕРАПИСКИ МОДАЛИТЕТИ НА БОЛКАТА КАЈ ПАЦИЕНТИТЕ СО ОСТЕОПОРОЗА: првични резултати во третманот со физикална терапија

INFLUENCE OF PHYSICAL THERAPY MODALITIES ON PAIN IN OSTEOPOROSIS PATIENTS: initial results of the treatment with physical therapy

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Abstract

Introduction. Osteoporosis causes chronic back pain leading to restriction of functional capacity and quality of life. The aim of this study was to examine the influence of physical therapy modalities on pain in patients with osteoporosis.

Methods. This is a prospective study of patients with osteoporosis, randomly chosen and followed for three months in the Institute of Physical Medicine and Rehabilitation (IPMR). Physical therapy consisted of physical modalities and therapeutic exercises. Physical therapy modalities included interferential currents and pulsed low-frequency electromagnetic field conducted each day with weekend breaks, 21 in total. Patients had therapeutic exercises 3 times a week during the entire follow-up period. Patients were assigned into two groups. The first group consisted of nine patients who underwent physical procedures and the second group consisted of nine patients who did not receive physical therapy modalities. Two check-ups were made on day 21 and at the end of the third month. Assessment of pain intensity was made by the use of a numeric pain rating scale.

Results. No significant difference between the groups was observed regarding mean age of patients ($p < 0.21$). The first check-up showed a significantly higher pain score in the second group of patients ($p = 0.0003$). There was no significant difference in pain intensity between both groups of patients in the three-month period of investigation ($p < 0.63$).

Conclusion. Physical therapy modalities influence on pain in patients with osteoporosis. Our investigation included a small number of patients and hence further studies are necessary.

Keywords: osteoporosis, physical procedures, pain

Апстракт

Вовед. Остеопорозата предизвикува хронична болка во грбот, која доведува до намалување на функционалната способност и квалитет на живот.

Цел. Да се испита влијанието на физикалната модалитети на болката кај пациентки со остеопороза.

Методи. Проспективно истражување на пациентки со остеопороза избрани по случаен избор, следени три месеци во Заводот за физикална медицина и рехабилитација (ЗФМР-Скопје). Физикалната терапија се состои од физикални модалитети и вежби. Од физикални модалитети се применуваат интерферентни струи и пулсно-нискофреквентно електромагнетно поле, секој ден со викенд пауза, вкупно 21 ден. Пациентките вежбаат три пати неделно за целиот период на следење.

Пациентките се поделени во две групи. Прва група со 9 пациентки, кои примаат физикална процедури и втора група од 9 пациентки, кои не примаат физикални модалитети. Направени се две контроли на 21 ден и на крајот од третиот месец. Проценката на јачината на болка е со нумеричка скала за болка.

Резултати. Нема сигнификантна разлика меѓу групите, во однос на просечна возраст, ($p < 0.21$). На првата контрола, резултатите од Mann-Whitney U Test, покажаа дека пациентките од втората групата имаат значително повисок резултат за болка ($p = 0.0003$). Нема статистички значајна разлика во јачината на болката меѓу двете групи на пациентки за период од три месеци на истражувањето ($p < 0.63$).

Заклучок. Физикалните модалитети влијаат на болката кај пациентките со остеопороза. Заради малиот примерок се неопходни натамошни истражувања.

Клучни зборови: остеопороза, физикални процедури, болка

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Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture (Consensus Development Conference, 1993) [1].

Osteoporosis is asymptomatic and thus it is named silent epidemics. The first clinical manifestation is low-energy fracture, most commonly at 7, 8, 9 thoracic and first lumbar vertebrae presenting as an acute pain that lasts for days and weeks and very often is transformed into a chronic pain [2].

In time spinal curvature is physiologically changed and more prominent thoracic kyphosis develops. Spinal deformity contributes to compression and secondary pressure on discs and surrounding ligaments. Consequently, chronic pain develops, which patients describe as back pain. It usually extends to thorax and abdomen, and sometimes patients present with pains in the hips, arms, ribs and knees.

For pain treatment non-steroid anti-inflammatory agents, opioids, anti-epileptic drugs and antidepressants are recommended. Having in mind the adverse events and side effects of these drugs, physical agents including electrotherapy play an important role in management of chronic pain [3].

It is recommended to treat osteoporosis with bisphosphonates, proper nutrition which means intake of 800-1000 ml calcium per day and 800 IU vitamin D per day as well as physical activity and exercises.

In our study of chronic pain treatment we applied two modalities of physical therapy: interferential current therapy and magnetic therapy.

Interferential current (IFC) therapy has physiological and therapeutic effect on tissues, which is analgesic, sympatholytic, and positive trophic. In addition, it enhances tissue metabolism, accelerates resorptive processes, and has anti-edematous and anti-inflammatory effect [4].

IFC are alternating medium-frequency amplitude modulated currents with sinusoidal form, by interference of two medium-frequency non-modulated currents with two independent electric circuits that differ by intensity, phase and frequency ranging from 1 to 100 Hz. Meta-analysis of Fuentes JP *et al.* [5] presented interferential currents as an efficient treatment in pain relief.

We recommend application of IFC with constant frequency of 100 Hz for analgesia [6].

Magnetic therapy is an indispensable segment of physical therapy; it is easily administered and to a large extent harmless to the human organism. We applied low-frequency pulsed electromagnetic fields (PEMF). It has influence on each cell in the body where it is applied.

Cell membrane permeability is changed; it affects the process of diffusion and active transport, enhances tissue oxygenation and metabolism; it activates osteoblasts, chondroblasts and fibroblasts [7].

PEMF is efficient in reducing chronic pain, which is a result of deterioration of connective tissue (cartilage, tendons, ligaments and bones). It can be applied as an alternative to the non-steroid inflammatory drugs in management of chronic pain. Relief from chronic pain due to osteoarthritis has been reported with treatment by EMFs. [8].

The aim of this study was to examine the effectiveness of physical therapy modalities (interferential currents and PEMF) in management of pain in osteoporosis patients.

Material and methods

The study included 18 patients with osteoporosis diagnosed at the Institute of Physical Medicine and Rehabilitation in Skopje, R. Macedonia, according to the criteria of the World Health Organization, a T-score of ≤ -2.5 being indicative of osteoporosis. Patients with diagnosed osteoporosis met the inclusion criterion for the study. Exclusion criteria were as follows: febrility, lumbar sciatica, pacemaker, unstable cardiopulmonary condition, arrhythmia, malignant disease, neurological diseases. Patients were assigned to two groups: the first group of 9 patients received physical modalities (IFC, MT) on thoracic-lumbar spinal region and the second group of 9 patients did not receive physical modalities on thoracic-lumbar spinal region.

All patients made therapeutic exercises and took medications for osteoporosis, which consisted of bisphosphonates, calcium 1000 mg per day and vitamin D 800 IU per day. Patients from both groups did not take analgesic pharmacologic agents.

Patients underwent physical modalities once a day for 21 days in total with weekend breaks. Therapeutic exercises started at the Institute of Physical Medicine and Rehabilitation and patients practiced them twice a week during the period of investigation.

The follow-up period was 3 months, when two check-ups were made; the first one on day 21 and the second control visit at 3 months.

All patients were informed on the type and modalities of therapy and were given answers to all questions related to the examination. All patients were treated in compliance with the Declaration of Helsinki.

Back pain intensity in all patients was determined by the use of a numeric pain rating scale consisting of 11 items described in Figure 1. This scale has been recognized in clinical metric pain relevance [9].

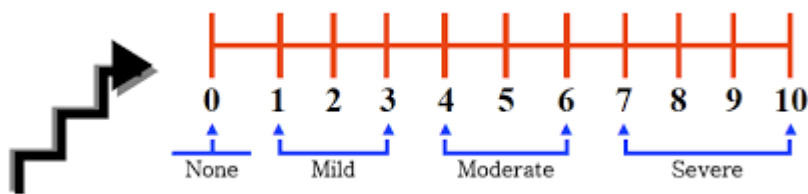


Fig. 1. Numeric pain rating scale
 Score 0-patients have no pain; Rating 1,2,3-patients have mild pain, score 1;
 Rating 4,5,6-patients have moderate pain, score 2; Rating 7,8,9-patients have severe pain, score 3.

Pain rating scale was made at the beginning, on day 21 and at the end of the examination.

Physical modalities

Interferential currents (IFC) are produced by the machine Inteldin, serial number 1177, Electronic Design. IF current is applied, constant 100 Hz, for 15 minutes. The current is applied at the thoracic-lumbar level using four electrodes. They are isolated with damp sponge, well squeezed, and placed on patient’s skin, fixed with bags. The skin has to be intact, healthy. Patients feel the therapy as a tingling sensation at the contact area and they do not feel any discomfort.

Magnetic therapy is conducted with low frequency pulsed electromagnetic field produced by the apparatus Magomil 2 of Electronic Design, with 8 MT intensity and 25 Hz frequency in the thoracic-lumbar region in duration of 30 minutes.

Kinesitherapy is consisted of exercises, which are isometric and isotonic for strengthening and extending the paravertebral muscles, muscles of the upper and lower extremities, pectoral muscles, abdominal muscles and respiration exercises.

Statistical analysis of data was done with standard statistical methods, which were used to calculate the percentage of arithmetic mean with standard deviation.

The following statistical tests were used: t-test, Mann-Whitney U Test and Friedman ANOVA. Comparison of pain intensity was made in each group and between the two groups at the beginning of the investigation, on day 21 and at the end of the third month. Values of $p < 0.05$ were considered to be statistically significant.

Results

The study included 18 patients divided into two groups: group 1 who received physical therapy modalities and group 2 who did not undergo physical procedures. Patients of both groups practiced therapeutic exercises.

Table 1 presents patients from group 1 and group 2 according to age, menopause, body mass index, total T-score of lumbar spine and total T-score of femur. Results obtained showed insignificant difference regarding age ($p=0.14$), menopause ($p=0.14$), T-score lumbar spine

($p=1$) and T-score of femur (0.51) between group 1 and group 2.

Table 1. Patients from group 1 and group 2 according to age, menopause, body mass index, total T-score of lumbar spine and total T-score of femur

	Mean± Std. dev.		t-value	P
	Group 1	Group 2		
age	61.67±9.27	66.56±2.50	-1.53	0.14
menopause	14.33±6.73	18.55±4.61	-1.55	0.14
T-score lumbar	-2.92±0.42	-2.92±0.40	-0.00	1.00
T-score femur	-1.89±0.40	-1.76±0.44	-0.67	0.51

There was no significant difference in the pain intensity between the groups at the beginning of the investigation ($p=0.93$).

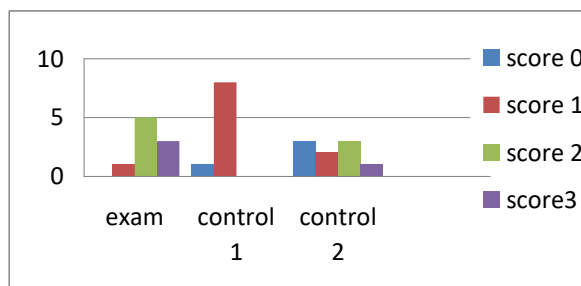


Fig. 1. Patients from group 1 who received physical therapy modalities

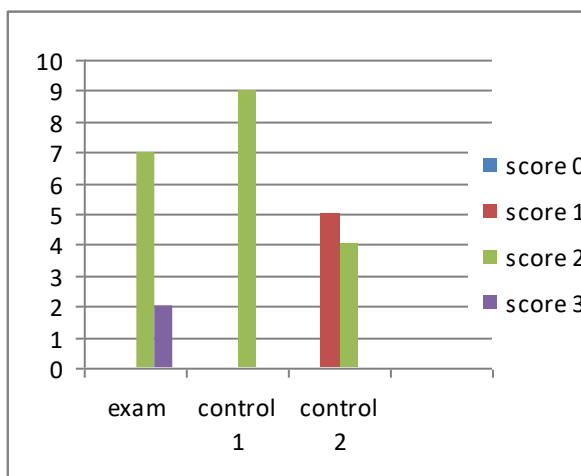


Fig. 2. Patients of group 2 who did not receive physical therapy modalities

Patients from group 1 are given in Figure 1 and they are presented according to pain intensity expressed in scores (0, 1, 2, and 3) and the number of patients at their first examination as well as at first and second control visits. Statistical analysis showed that patients of group 1 had a significant difference in the pain intensity at first and at second control ($p=0.0024$).

Figure 2 shows patients from group 2 presented according to pain intensity expressed in scores (0, 1, 2, and 3) and their number of check-ups, first and second control visits. Statistical analysis showed that patients of group 2 had also a significant difference in the pain intensity at first and at second control ($p=0.0038$).

The results obtained at the first check-up, when comparison of the pain score between both groups of patients was made, are presented in Figure 3. Patients of group 2 were shown to have a significantly higher pain score ($p=0.0003$).

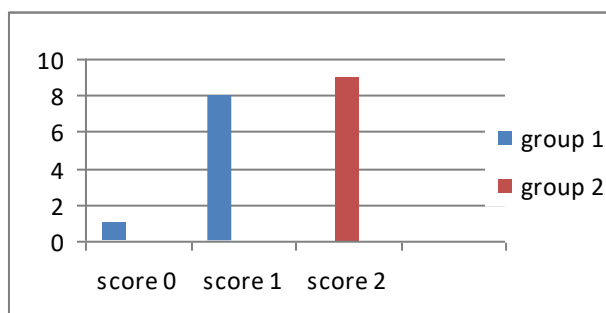


Fig. 3. Pain intensity in patients of group 1 and group 2 at first control visit

The results obtained at the second check-up, when comparison of the pain score between both groups of patients was made, are presented in Figure 4. As it is illustrated no significant difference in the pain score between the groups was observed ($p=0.63$).

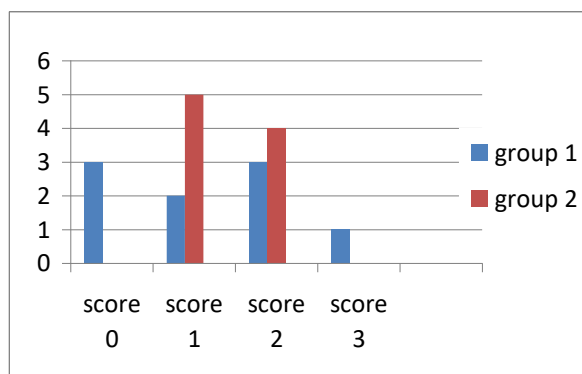


Fig. 4. Pain intensity in patients of group 1 and group 2 at second control visit

Discussion

We live in a society where the percentage of elderly population is increasing and hence the focus of interest is

on osteoporosis. Since it is a silent disease, its first clinical manifestation is low-energy fracture that is presented with back pains. Patients suffering from long-term and persistent pain take analgesic agents for a considerable period. Long-term usage of analgesic agents is harmful for the health due to their adverse effects. On the other hand, physical modalities such as interferential currents and magnetic therapy are safe for the patient.

In our study we examined the combined analgesic effectiveness of interferential current therapy and analgesic effectiveness of magnetic therapy along with their pooled effect on pain intensity. Osteogenic stimulatory effect of magnetic therapy was not analyzed due to the short follow-up period.

The results obtained showed that in both groups of patients a significant pain relief was observed in the first group who received physical therapy modalities ($p=0.0024$), and in the second group of patients who did not receive physical therapy modalities ($p=0.0038$). However, on the first check-up, when the results of both groups were compared, an improvement was noticed in the first group of patients who received interferential currents and magnetic therapy, that is, pain intensity reduction and an increased number of patients with smaller pain score was observed. On the other hand, pain score was significantly higher in the second group of patients ($p=0.0003$). At the first control an increased pain score in the second group of patients was found as they did not receive physical therapy modalities. These results are in agreement with those presented in the prospective control study of Feber *et al.* where the effect of combined physical modalities on pain had been investigated [10]. It was shown that a combination of several physical therapy procedures significantly reduced the pain.

The results from the second control, which was at the end of the third month of patients' follow-up, showed no statistically significant difference between the groups with regard to pain intensity ($p=0.63$). The results of the second control encourage us to conduct further studies. On one hand, they might be a result of regular practicing of exercises for osteoporosis because patients from both groups continued with their exercises three times a week following the first control visit. On the other hand, this is most probably a result of a small number of examined patients included in this study. However, this is a part of an ongoing research and a larger number of patients is planned to be included.

Conclusion

Interferential currents and pulsed low-frequency electromagnetic field is one of the possible combinations of physical therapy modalities that influence on pain relief in osteoporosis. Our results are initial and modest, but they give us insight in the effect of these physical therapy modalities. Due to the small number of

comprised patients in this study, the efficacy of these physical therapy modalities should be further examined.

Conflict of interest statement. None declared.

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Ц-РЕАКТИВЕН ПРОТЕИН-МАРКЕР НА ИНФЛАМАЦИЈА КАЈ ПАЦИЕНТИ СО ПНЕВМОНИЈА**C-REACTIVE PROTEIN –BIOLOGICAL MARKER OF INFLAMMATION IN PATIENTS WITH PNEUMONIA**

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Abstract

Introduction. The term biomarkers or biological markers generally refers to proteins measured in the circulation (blood), whose concentration indicates some normal or pathological state or condition. The biomarker is objectively measured and evaluated as an indicator of normal biological processes or pharmacological responses to therapeutic interventions. One of these biological markers is C-reactive protein (CRP).

Aim. To evaluate the efficiency of using adequate and appropriate biomarkers for diagnosis, treatment and monitoring of pneumonia in children.

Methods. This study included 30 patients with diagnosed pneumonia, who were admitted at our Institute. Blood samples were taken prior to initiation of treatment in patients with pneumonia and 7 and 14 days after the treatment. The control group included physically active and healthy individuals without family history of disease, aged from 1 to 14 years. All the results of the biochemical analyses were within the reference values, and none of the control individuals received therapy. In our country, for serum C-reactive protein, as well as for other parameters that determine the diagnosis of the patient, we use a common method for determining normal values, by choosing a huge representative sample from the screening population, consisting of healthy individuals without any disease, especially with no sign of this disease (the children who should be checked up). Further, normal values obtained in this way are taken as reference values.

Results. The average serum CRP protein levels prior to antibiotic therapy were the following: (1-2) $\bar{x} \pm sd = 34.94 \pm 20.44$ mg/L, (3-6) $\bar{x} \pm sd = 68.20 \pm 10.87$ mg/L, (7-11) $\bar{x} \pm sd = 65.59 \pm 12.01$ mg/L, whereas in patients with pneumonia after 7-day antibiotic treatment the values were the following: $\bar{x} \pm sd = 24.64 \pm 11.57$ mg/L / $\bar{x} \pm sd = 40.10 \pm 6.83$ mg/L / $\bar{x} \pm sd = 32.09 \pm 6.68$ mg/L ($P < 0.05$),

and after 14-day-therapy $\bar{x} \pm sd = 6.80 \pm 1.14$ mg/L / $\bar{x} \pm sd = 7.20 \pm 0.82$ mg/L / $\bar{x} \pm sd = 8.10 \pm 0.89$ mg/L ($P < 0.05$). Also, CRP in serum correlated with the severity of the clinical condition ($P < 0.05$).

Discussion and conclusion. This study is useful for showing the importance of C-reactive protein in serum for early diagnosis and follow-up of the pneumonia. CRP is very important as a biomarker, both from clinical and scientific aspect. It can be used for early rapid diagnosis, monitoring of pneumonia and can successfully be used in a large number of diagnosis. It opens new opportunities for further research in this field.

Keywords: biomarkers, CRP, children, pneumonia

Апстракт

Вовед. Со поимот биомаркери, во медицината се означуваат, најчесто, протеини измерени во циркулацијата (крв), чија концентрација укажува на нормален или на патолошки одговор на организмот, како и на фармаколошкиот одговор кон примената терапија. Еден од нив е и C-реактивниот протеин во серум (CRP).

Цел. Да се види дали Ц-реактивниот протеин како маркер е важен и корисен за брза дијагноза, терапија и следење на пневмонијата кај децата.

Методи. Во рамките на овој труд беа вклучени 30 пациенти со дијагностицирана пневмонија, хоспитализирани во нашиот Институт. Крв за анализа беше земена непосредно пред почнување со терапијата и по 7 и 14 дена по третманот кај пациентите со пневмонија. Во контролната група беа опфатени испитаници на возраст од 1 до 14 години, физички активни, здрави и без фамилијарна историја за одредена болест. Сите биохемиски анализи беа во границите на референтни вредности, ниту еден од испитаниците од контролната група не примаше терапија. Кај нас, за Ц-реактивниот протеин во серум, како и за другите параметри кои ја детерминираат дадената дијагноза кај еден пациент, се применува вооби-

чаената метода за одредување на нормалните вредности преку одбирање доволно голем репрезентативен примерок од испитуваната популација, составен од наизглед здрави испитаници и без клинички знаци на некакво заболување, особено без знаци за постоење на оваа болест (деца дојдени на контрола), така што добиените нормални вредности ги земаме како референтни вредности.

Резултати. Просечната вредност на SRP во серумот пред антибиотската терапија изнесуваше (1-2) $\bar{x} \pm \text{sd} = 34,94 \pm 20,44$ mg/L, (3-6) $\bar{x} \pm \text{sd} = 68,20 \pm 10,87$ mg/L, (7-11) $\bar{x} \pm \text{sd} = 65,59 \pm 12,01$ mg/L, додека кај возрастните групи со пневмонија, по 7 дена од антибиотски третман, изнесуваа $\bar{x} \pm \text{sd} = 24,64 \pm 11,57$ mg/L / $\bar{x} \pm \text{sd} = 40,10 \pm 6,83$ mg/L / $\bar{x} \pm \text{sd} = 32,09 \pm 6,68$ mg/L ($P < 0.05$), и по 14 дена $\bar{x} \pm \text{sd} = 6,80 \pm 1,14$ mg/L / $\bar{x} \pm \text{sd} = 7,20 \pm 0,82$ mg/L / $\bar{x} \pm \text{sd} = 8,10 \pm 0,89$ mg/L ($P < 0.05$).

Исто така, CRP во серум корелира со тежина на клиничката слика ($P < 0.05$).

Дискусија и заклучок. Од овој труд се гледа дека C-реактивниот протеин во серум е многу важен како биомаркер, и од клинички и од научен интерес, за навремено, брзо дијагностицирање и следење на пневмонијата, може успешно да се искористи за поголем број дијагнози, што отвора широки можности за натамошни истражувања на ова поле.

Клучни зборови: биомаркери, CRP, деца, пневмонија

Introduction

The term biomarkers or biological markers generally refers to proteins measured in the circulation (blood), whose concentration indicates some normal or pathological state or condition. The biomarker is objectively measured and evaluated as an indicator of normal biological processes or pharmacological responses to therapeutic interventions.

One of these biological markers is C-reactive protein (CRP), which is a protein in the human blood that belongs to the pentraxin family [1].

C-reactive protein or acute-phase protein belongs to a group of complex mucoproteins, e.g. complex proteins which are composed of more than 15% of carbohydrate. In addition, CRP in healthy individuals is found in low concentrations.

CRP is produced in the liver and by the mast cells (adipocytes) [2]. CRP is a glycoprotein, known as C-reactive protein, an acute-phase protein found in the blood which increases rapidly in response to inflammation; the CRP levels can increase up to 100 times for

24 hours during acute inflammation. Therefore, in the last few years CRP is frequently used for diagnosis instead of erythrocyte sedimentation, which was used for more than 50 years [3].

CRP is a protein with many physiological roles within the human immune system, such as binding phosphocholine expressed on the surface of dead or degraded cells (damaged by infection, disease or trauma), binding of nuclear antigens and certain pathogenic organisms, which bound in this way, activates the composition of a complement (which participates in the cell destruction) or activates macrophages or bound to a cell serves as opsonin [4]. In clinical practice, CRP is an essential marker for many pathological diseases, such as: malignant diseases, lymphomas, systemic lupus erythematosus, rheumatoid arthritis, vasculitis, pneumonia, heart attack, fungal infection, intestinal inflammation, rheumatic fever, tuberculosis, etc. [5,6].

C-reactive protein is known to be the most commonly analyzed protein of plasma in laboratory diagnostics, which serves as a marker of inflammation. CRP is considered to be an early indicator of infection or inflammation and a marker for disease activity.

CRP is a biomarker used for detecting the inflammation in the human body, but a CRP test cannot show where the inflammation is located.

CRP is essential in distinguishing viral and bacterial infection. In viral infections that are followed by rapid sedimentation and increased leukocytes, CRP levels are normally low in the blood [7,8].

CRP levels are quite increased in invasive bacterial infection.

Besides detection of acute inflammation, measurement of CRP concentration is useful for assessment of the progression of the disease or assessment of the effectiveness of therapy. For example, with successful antibiotic therapy the level of CRP concentration in the serum will fall faster than erythrocyte sedimentation rate (SE), and by monitoring its concentration can prevent unnecessary use of less effective or ineffective antibiotics, hence it gives time to replace ineffective antibiotics with other, more efficient and more effective ones [9]. CRP concentrations drop more rapidly in response to effective antibiotic treatment than erythrocyte concentrations (SE). In contrast, inadequate treatment is reflected in persistently high CRP levels. Monitoring of CRP concentrations can alert to complications of inadequate therapy and is a substantial aid in helping the healthcare practitioners make the right diagnosis and reach the correct treatment decision [9]. The levels of CRP are of crucial importance in diagnostic tests and monitoring of the treatment of infections, especially in premature babies and newborns.

CRP-reactive protein is used to discover whether there is an infection after surgery. CRP normally rises within 2 to 6 days after surgery and then it decreases by the third day after surgery. If CRP stays elevated for 3 days after

surgery, an infection may be present, as a complication of the surgery.

CRP can help in distinguishing bacterial and viral infections, in monitoring the progression of the disease, in evaluating the benefits of the treatment, but it can also be used as a risk factor.

Normal concentrations in healthy human serum are 10 mg/L. High levels of 10-40mg/L are found in pregnant women, mild infections and viral infections, smokers, etc. CRP levels of 40-200mg/L show acute infection, bacterial infection. CRP levels higher than 200mg/L are found in severe bacterial infection and burns [10].

Pneumonia is an inflammatory condition of the lungs and it is one of the most common lung diseases. Pneumonia is due to infection caused primarily by bacteria and viruses and less commonly by fungi and parasites [11]. Pneumonias of bacterial origin, which will be the subject of our investigation may be caused by gram positive and gram negative bacteria. In practice, despite microbiological examination that is used in detecting the etiologic cause, frequently biochemical and immunological methods for differentiation of pneumonia are used. Over the last decade there has been a significant progress in biochemical investigation, inflammation and sepsis. Examinations of the changes in proteins are of the greatest interest in clinical practice [12-14]. There are many acute phase proteins in medicine, but for the determination of acute phase proteins with rapid kinetics, with a short half-life and a wide range of variation in the acute period of the disease, we will broadly investigate C- reactive protein (CRP). This means that as a marker, it has a very large and important role in medical research and its application allows the perception of the mechanism and course of the disease [15,16].

Aim

Determination of the CRP concentrations in serum or whole blood in children suffering of pneumonia, with precise and sensitive immunofluorescence method for determining the concentration of C-reactive protein (CRP) in serum or whole blood (ELFA).

Materials and methods

Of all respondents involved in this study, blood sample was taken on an empty stomach early in the morning without giving anticoagulation agents. In the control

group were included subjects aged from 1 to 14 years, physical active, healthy individuals that had no family history for the particular disease. All biochemical analyses were within the reference values and these subjects did not receive any therapy. In our country, for serum C-reactive protein, as well as for other parameters that determine the diagnosis of a patient, we use a common method for determining normal values, by choosing a huge representative sample from the screening population, consisting of healthy individuals without any disease, especially with no sign of this disease (the children who should be checked up). Further, normal values obtained in this way are taken as reference values. The study group included 30 patients diagnosed with pneumonia.

Blood sample was taken immediately before the commencement of treatment and one month later in patients with pneumonia. In this analysis the quantitative method for determination of CRP in serum or whole blood was used, which is based on laser-epifluorescence immune response (ELFA). The reference values of CRP in serum or whole blood is less than 10 mg / L.

Statistical analysis of data was done by using all variants of Student's t-test. Calculations were performed using the computer program EXCEL.

Values of p less than 0.05 were considered to be statistically significant.

Results

This study included 30 patients with pneumonia who were treated at the Institute of Lung Diseases in Children, Skopje. All participants were followed by doctors who work in the departments of pneumonia. Necessary diagnostic procedures for detection of specified disease and initiation of antibiotic therapy were made.

Table 1. Distribution according to age of patients with pneumonia

Age (years)	1-2	3-6	7-11	total
Number of patients	4	10	16	30

Table 1 presents the groups aged 1-11 years, patients with pneumonia, with mean age $\bar{x}=6.43$ while the age of control individuals was in the range from 1 to 14 years, mean age $\bar{x}=7,7$ years.

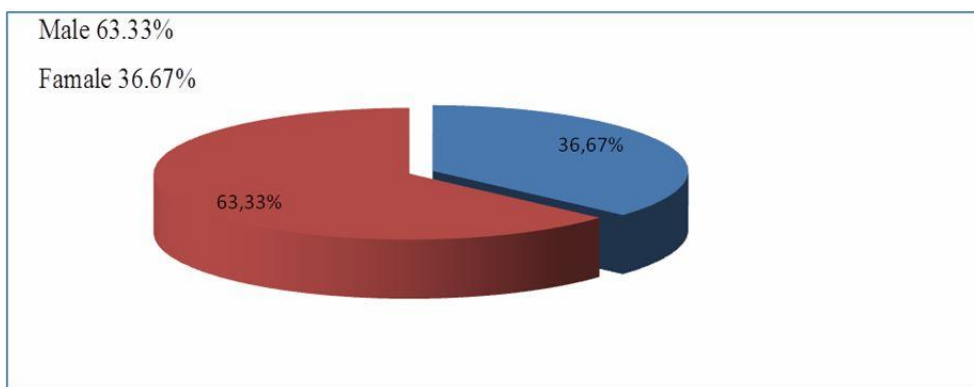


Fig. 1. Distribution according to sex in patients with pneumonia

Table 2. Serum CRP levels in patients with pneumonia

Number	Group	Age (years)	CRP mg/L
1	Controlled group	1-14	4.97±0.38
2	Group of patients with pneumonia before the treatment	1-2	34.94±20.44
		3-6	68.20±10.87
		7-11	65.59±12.01
3	Group of patients with pneumonia after 7 days of the treatment	1-2	24.64±11.57
		3-6	40.10±6.83
		7-11	32.09±6.68
4	Group of patients with pneumonia after 14 days of the treatment	1-2	6.80±1.14
		3-6	7.20±0.82
		7-11	8.10±0.89

*Mean ± standard deviation

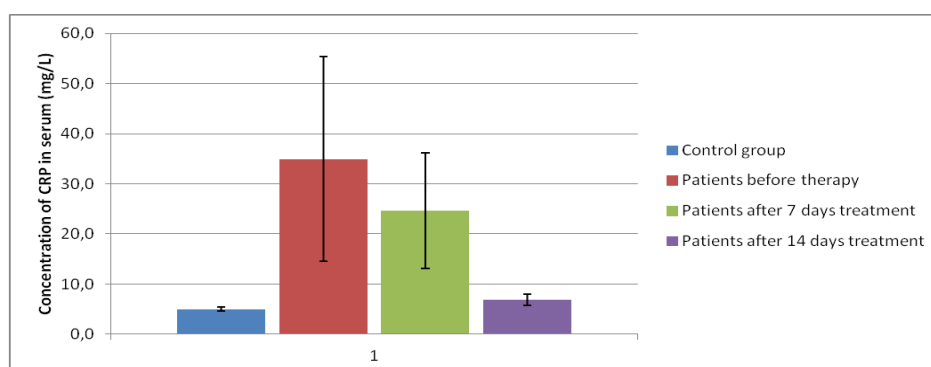


Fig. 2. Serum CRP levels in patient with pneumonia

Figure 1 presents the predominating male gender 19 (63.33) among patients with pneumonia versus female gender 11(36.67).

Table 2 and Figure 2 show the concentration of C-reactive protein in serum in children with pneumonia one month after the application of antibiotics, where the average value of CRP in serum in patients before antibiotic treatment was $\pm sd=62.37 \pm 7.86$ mg/L, while in the group after antibiotic treatment it was $\pm sd=10.29 \pm 0.71$ mg / L.

There was an evident difference in the first group of children with pneumonia before treatment compared to the second group after treatment ($p < 0.05$), which indicates the severity of the disease and the concentration of C-reactive protein in serum at the beginning. Furthermore, there was an evident upward trend of the ave-

rage values of C-reactive protein in serum as the disease progressed; the measured average concentrations were significantly higher in the control group ($p < 0.05$). In children with pneumonia after antibiotic treatment, the average concentration of C-reactive protein in the serum did not differ significantly compared to the control group ($p > 0.05$).

Table 3. The number of positive culture in patients with pneumonia

Positive culture	The number of enrolled patients
Moraxella catarralis	4
Haemophilus influenzae	6
Streptococcus pneumoniae	8
Escherichia coli	6
Others	6

Table 3 shows the number of tested patients and isolated bacteria. In the group of children with pneumonia before treatment there were 24 isolated bacteria, while the

number of the rest was either small or there were no isolated bacteria and were placed in the group of other bacteria.

Table 4. Distribution according to the severity of the clinical picture

	Number	Rate (%)	CRP (mg/L) x±sd
Severe clinical diagnosis	17	56,6	91,55 ± 8,45
Moderate severe clinical diagnosis	13	43,3	24,23 ± 2,57

Severe clinical diagnosis-WBC>16x10⁹, GR>70%, X-ray (massive findings), hypoxia

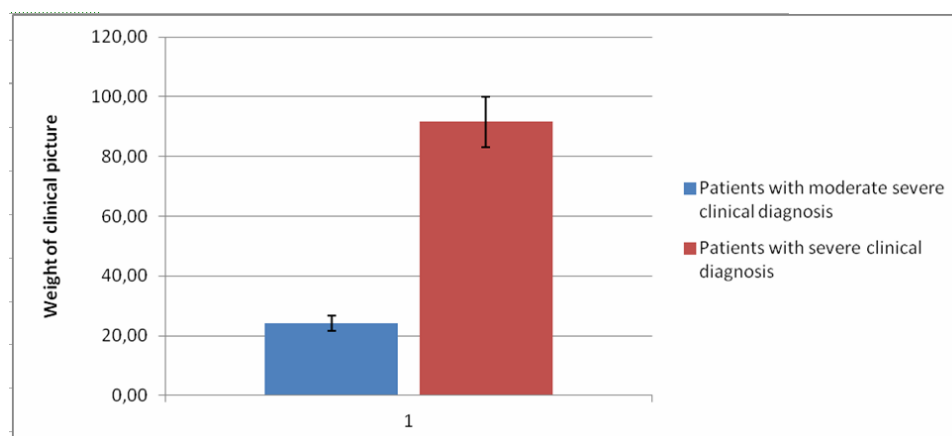


Fig. 3. Distribution according to the severity of the clinical picture

Table 4 and Figure 3 show the distribution of patients according to the severity of the clinical condition and the correlation of CRP with the severity of the clinical condition of the patients ($p < 0.05$).

Discussion

Increased respiratory infection in infants and young children affects on physical depending on the environment where they live. Unfavorable conditions of the external environment (air pollution, unventilated apartments, smoking) has a detrimental (harmful) effect more on the young than on the older children because the terminal parts of the lungs are less distant from the external environment thus easily enter microbial and no-microbial agents.

Despite exposure to large amounts of these harmful organisms, there are certain conditions which may lead to pneumonia in an individual. Certainly, the lack of normal anatomical structure may increase the risk of developing pneumonia.

Viruses may interfere with ciliary function, letting themselves or other harmful microorganisms (such as bacteria) to penetrate into the lower respiratory tract. Various chronic conditions predispose to infection with pneumonia. These include asthma, cystic fibrosis and neuromuscular diseases that can hinder closing the epiglottis. Esophageal disorders can cause spillage of substances from the stomach back into the esophagus. In childhood, one third of pneumonias are from viral etiology, one

third belongs to unknown etiology, and the rest are probably caused by bacteria [17].

In practice the cause of pneumonia is based on epidemiological, clinical, radiological and hematological tests as well as on the basis of pneumonic lesion response to antibiotics and other treatment. In other words, in practice non-specific, indirect methods of etiological differentiation of pneumonia are often used, not a microbiological examination which is the only authoritative method in detecting the etiologic cause. It is known that pneumonia in infants is more critical than in older children. The severity of pneumonia depends on the etiologic cause, the nature of the lesion, and the degree of intoxication and impairment of lung function which is important for prognosis and therapy.

Pneumonia is divided according to etiological and anatomical criteria [18]. This division is used in everyday work. It is often difficult to diagnose pneumonia, because most often the diagnosis is based on the etiological causes. There are few institutions, including our, where one can identify bacterial etiologic factor for pneumonia in children. In the first stage in children with pneumonia of bacterial origin, which takes several hours, interalveolar capillaries expand and the alveoli begin to fill up with serous exudate, rare polymorphonuclear leukocytes and a huge amount of mucus, which has been confirmed by our results.

Also, the values of C-reactive protein as a biomarker in serum in patients with bacterial pneumonia, and the procalcitonin in the serum are confirmed in the studies

of many scientists [19], which state that later in the second phase the alveoli are filled with a number of neutrophils and fibrin; while in the last stage of the disease remains a heavy exudate, the number of macrophages and neutrophils increases and occurs necrosis. This is followed by an increase in sedimentation of the erythrocytes and leucocytes.

Cellular immunity is an important mechanism in defense agents of these intracellular pathogens [20], proving our values of neutrophils in blood. With the advent of penicillin and other antibiotics, modern surgical techniques and intensive care in the 20th century, the rate of death from pneumonia sharply declines. Highly evident is the need for vaccination of newborns, which has been confirmed by our research [21].

Vaccination of infants against *Haemophilus influenzae* type B began in 1988 and led to a dramatic decline in cases shortly thereafter. Vaccination against *Streptococcus pneumoniae* in adults began in 1977, and in children in 2000 and resulted in a similar outcome.

Concentrations of C-reactive protein in serum of patients with proven bacterial pneumonia after applying antibiotic therapy were highly reduced, and were confirmed in investigations of many scientists.

Reduction in use of antibiotics is an essential object in modern medicine, which will result in reduced costs. Avoiding the side effects of treatment will lead to reduction of bacterial resistance. Very often, after taking a detailed history, physical examination, laboratory tests and x-ray of the lungs, clinicians cannot set reliable diagnosis because of overlapping symptoms and signs in bacterial and viral infections. In order to eliminate the uncontrolled use of antibiotics, there is a need for fast and reliable differentiation of bacterial infection from a viral infection of the respiratory tract. In pneumonia which is defined as inflammation of the pulmonary parenchyma, often caused by bacterial cause, there is elevated CRP [23].

Conclusion

The value of the serum C-reactive protein correlates with the severity of clinical form and the evolutionary progress of the disease. Hence, the conclusion that C-reactive protein is an important biomarker of pneumonia as a diagnosis, as well as other diseases. On the other hand, this newly introduced method can be successfully used for multiple diagnoses, which opens up broad opportunities for further research in this field.

Conflict of interest statement. None declared.

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CURRENT STATUS IN MANAGEMENT OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) IN REPUBLIC OF MACEDONIA**СЕГАШНА СОСТОЈБА ВО ТРЕТМАНОТ НА БОЛНИТЕ СО ХРОНИЧНА ЛИМФАТИЧНА ЛЕУКЕМИЈА (ХЛЛ) ВО РЕПУБЛИКА МАКЕДОНИЈА**

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Abstract

Chronic lymphocytic leukemia (CLL) is the most commonly diagnosed type of leukemia in Western Europe and North America, and represents about 30% of all leukemias in adults. CLL is a disease of elderly, who often have multiple comorbidities. These factors affect further treatment decisions, despite the great progress in the therapy of CLL in the last two decades.

The aim of this study was to evaluate the current status in the management of patients with CLL in the Republic of Macedonia and to compare it with CLL patients in other western countries.

We analyzed 102 patients with CLL referred to our Institution for control and/or treatment in the period from January 2015 to October 2015. Median age of our group of patients at the time of diagnosis was 62.7 years with almost 40% of patients older than 64 years. Male to female ratio was 1.3:1 and 54% of patients were diagnosed in stage "0" according to Rai staging system. Watch and wait was the most common treatment approach (58.8%) at the time of diagnosis, but at the moment of analysis only 33% of patients were still without treatment. The most common treatment in this group of CLL patients was FCR protocol with 39.5% of patients treated with an average of 5 cycles of this immunochemotherapeutic regimen. The average time of progression free survival (PFS) in all treated patients was 32.8 months with range between 2-72 months.

In summary, clinical characteristics of CLL patient in our clinical settings and the most common therapeutic approach at our Institution do not differ significantly from the characteristics of the average CLL patient in other studies.

Key words: chronic lymphocytic leukemia, treatment, FCR

Апстракт

Хроничната лимфатична леукемија (ХЛЛ) е најчест тип на леукемија во Западна Европа и Северна Америка и претставува 30% од леукемиите кај возрасните. ХЛЛ е болест на повозрасната популација, која често има мултипли коморбидитети. Овој фактор во голема мера влијае на терапискиот избор и покрај големиот напредок во третманот на ова заболување во последните две децении.

Цел на овој труд е евалуација на сегашната состојба во третманот на пациентите со ХЛЛ во Република Македонија и споредба со третманот на ова заболување во другите западни земји.

Анализираме 102 пациенти со ХЛЛ кои се јавиле за контрола и/или терапија, на нашата Клиника во период од јануари 2015 до октомври 2015 година. Медиана на возраста во нашата група на болни во моментот на поставување на дијагнозата беше 62,7 години и речиси 40% од пациентите беа постари од 64 години. Соодносот мажи спрема жени беше 1,3:1 и речиси 54% од болните беа дијагностицирани во "0" стадиум според Rai стејдинг системот. Опсервацијата на болните беше најчестиот тип на тераписки пристап (58.8%) во моментот на поставување на дијагнозата, додека во моментот на анализа на пациентите од ова група само 33% беа сè уште без третман. Најчест тип на третман во нашата испитувана група беше FCR протоколот и 39,9% од болните беа третирани со просечно 5 циклуса на овој имунохемотераписки протокол. Просечно траење на периодот без прогресија на болест кај лекуваните пациенти изнесуваше 32,8 месеци (2-72 месеци).

Клиничките карактеристики и терапискиот пристап на најголем број пациенти со ХЛЛ во нашата институција не се разликуваат сигнификантно во споредба со карактеристиките и третманот на болните со ХЛЛ во другите студии.

Клучни зборови: хронична лимфатична леукемија, третман, FCR.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in Western Europe and North America, with an incidence of 4.1/100,000 inhabitants [1-3]. CLL affects mainly older and male patients; the median age at diagnosis is 67-72 years [3] and almost 70% of patients are older than 65 years. Because the incidence rises with age, it is projected that the CLL prevalence will increase in the forthcoming years due to the constant aging of the population [1,2].

The diagnosis of CLL is established when the blood count shows a lymphocytosis with $>5.000/\mu\text{l}$ clonal B-lymphocytes, a peripheral blood smear with small, morphologically mature lymphocytes with immunophenotype characterized by the coexpression of CD5 and B-cell surface antigens CD19, CD20, CD 23 and clonal expression of either kappa or lambda immunoglobulin light chains [4]. These clonal mature B cells can accumulate in the peripheral blood and bone marrow, as well as the lymph nodes, liver and spleen. Nowadays, mandatory diagnostic tests for CLL are complete blood count with peripheral blood smear and immunophenotyping of the lymphocytes with flow cytometry. Diagnostic tests like bone marrow biopsy, lymph node biopsy and cytogenetic evaluation are not necessary for diagnosis, but are recommended to differentiate autoimmune cytopenia from cytopenia resulting from bone marrow infiltration, in case of Richter transformation or to define some genetic risk factors.

The clinical course of CLL is very heterogeneous. Some patients do not need treatment for many years, while others have rapidly progressive disease requiring immediate treatment. The clinical staging system by Binet [5]

guish which patients should be treated or managed with a watch and wait approach (Table 1). Both staging systems require clinical examination of the lymph node, spleen, liver enlargement and blood count. Treatment should be initiated in patients with advanced CLL (Binet stage C or Rai stages III/IV), which are defined by a thrombocytopenia and/or anemia, related to bone marrow infiltration. Treatment is also indicated in case of constitutional symptoms, such as weight loss, night sweats, fever, rapid lymphocyte doubling time and/or symptomatic enlargement of lymph nodes or spleen [4]. Both staging systems lack the accuracy to predict CLL outcome on an individual basis. Therefore, many molecular and biological factors were proposed for prediction of disease progression and survival [7] and continuous attempts are made to define the most relevant prognostic factors [8]. These factors include the mutational status of immunoglobulin heavy chain [9], the expression of ZAP-70 protein in CLL cells [10], the expression of CD 38 antigen [11], but the most important practical significance have the cytogenetic abnormalities, especially 17p deletions and TP53 gene mutations [12,13]. The presence of a deletion of the short arm of the chromosome 17p or TP53 mutations are associated with a poor prognosis and resistance to most chemotherapeutic agents. Treatment decisions in CLL patients depend not only on these prognostic factors, but even more on the patient's physical fitness, comorbidities and concomitant medical treatment. According to these patient's characteristics, we can divide CLL patients in three groups "go go"; "slow go" and "no go". The first group consists of physically fit patients without or with mild comorbidities and they should be treated with the standard treatment that includes FCR protocol. The second group "slow go" includes patients with relevant comorbidities that impact the life expectancy and should be treated with reduced-intensity protocols. The third group are "no go" patients with markedly reduced life expectancy due to multiple and severe comorbidities, who should be treated with the best supportive treatment. The standard first-line treatment for younger or older but fit CLL patients (the so-called "go go") nowadays is immunochemotherapy with purine analogues (fludarabine or cladribine), cyclophosphamide and anti-CD20 monoclonal antibodies-rituximab (FCR regimen). It is recommended to give 6 cycles of FCR, as it increases the probability of eradication of minimal residual disease (MDR) and improves the progression-free survival (PFS) and overall survival (OS) [13-15]. Treatment of patients with relevant comorbidities (the so-called "slow go") includes therapy with chlorambucil or bendamustine and anti-CD20 monoclonal antibodies-rituximab [16]. The combination of chlorambucil or bendamustine and ofatumumab or obinutuzumab, another anti-CD20 monoclonal antibodies which might have a higher complement-dependent cytotoxicity (CDC) than rituximab, offers safe and effective treatment of this

Table 1. Staging systems in CLL

BINET Stage	Features
A	<3 Lymphoid areas*
B	>3 Lymphoid areas
C	Hemoglobin <100 g/L or platelet count <100x10 ⁹ /L
RAI Stage	
0	Lymphocytosis only
I	Lymphadenopathy
II	Hepatomegaly or splenomegaly with lymphocytosis
III	Anemia (Hemoglobin <110 g/L)
IV	Platelet count <100x10 ⁹ /L

*The five lymphoid areas comprise: uni or bilateral cervical, axillary and inguinal lymphoid, hepatomegaly and splenomegaly

and Rai [6] were introduced decades ago and are still widely used as simple and inexpensive tools to distin-

group of patients [17,18]. Treatment of refractory and relapsed fit patients nowadays includes novel agents like ibrutinib (Bcr-1 tyrosine kinase-BTK inhibitor) and idelalisib (phosphatidylinositol-3-kinase inhibitor) or allogeneic stem cell transplantation for young patients refractory to first-line therapy [19-21].

The aim of this study was to evaluate the current status in the management of patients with CLL in the Republic of Macedonia and to compare it with CLL patients in other western countries.

Materials and methods

We analyzed 102 patients with CLL referred to our Institution for control and/or treatment in the period from January 2015 to October 2015. All patients were diagnosed at the University Clinic for Hematology in Skopje, R. Macedonia in the period between 1997-2015 with standard diagnostic procedures according to the recommendation of IWCLL (International Workshop on Chronic Lymphocytic Leukemia) [4].

Data collected from medical records were: age at diagnosis, gender, clinical stage by Rai, symptoms, type of treatment, period without progression of disease with or without treatment. The data were analyzed using stan-

dard statistical tests in Microsoft Office Excel 2003 and SSPP 7.

Results

Median age of our group of patients at the time of diagnosis was 62.7 years with 39/102 (38%) patients older than 64 years. Age distribution of patients with CLL at the time of diagnosis is presented in Figure 1. Only 3 patients were younger than 45 years, 15 patients were between 45-54 years old, 45 patients were between 55-64 years old, 29 patients were between 65-74 years old and 10 patients were older than 75 years. Average life expectancies in the Republic of Macedonia are 76 years; 73 for men and 78 years for women. Median age of patients with CLL in our group was 62.7 years at the time of diagnosis. Male to female ratio in our group of patients was 1.3:1 and 58/102 (56.9%) patients were male. Distribution of the patients according to Rai staging system is presented in Figure 2 and 55/102 (54%) patients were in the early stage of disease (Rai grade "0"), 21 patients were in grade "1", 5 patients were grade "2", 16 patients grade "3" and 5 patients grade "4" (Figure 2). In our group of patients 81% had at least one comorbidity and the most common were cardiovascular diseases.

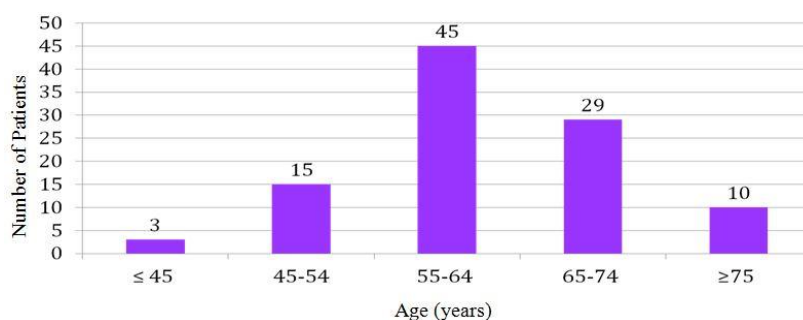


Fig. 1. Age distribution of CLL patients at the time of diagnosis

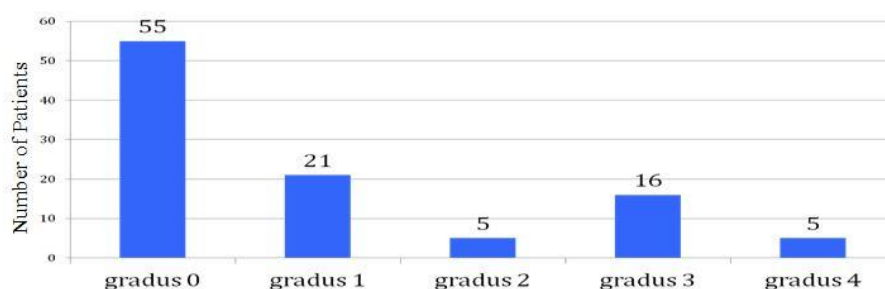


Fig. 2. Distribution of CLL patients according to Rai staging system at the time of diagnosis

Watch and wait was the most common treatment approach at the time of diagnosis with 58.8% of patients (59/102) who did not require therapy at the time of diagnosis. At the moment of analysis only 33% of patients were still without treatment. Average time of observation without treatment in our group of patients was 3.6 years, with range between 0-18 years. Overall time from diagnosis was 7.3 years, with range between 0-18 years.

The most common treatment modality in our group of CLL patients was FCR protocol with 39.5% of patients treated with average of 5 cycles of this immunochemotherapeutic regimen. The second most common treatment option was monotherapy with chlorambucil and the third was R-CVP immunochemotherapeutic regimen (Figure 3). Average time of progression free survival (PFS) in all treated patients was 32.8 months with

range between 2-72 months. Average time of PFS in patients treated with FCR was 35.1 months (range: 12-72+ months), compared to 18.6 months (range: 2-30)

in patients treated with R-CVP protocol (Table 2). These results confirmed the superiority of FCR as a therapeutic regimen versus R-CVP.

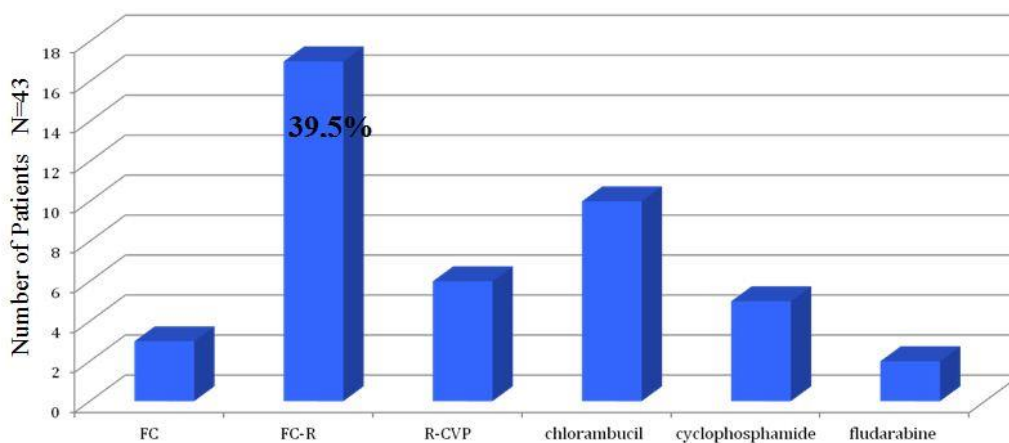


Fig. 3. Distribution of CLL patients according to treatment options
 FC = fludarabine+cyclophosphamide, FCR = fludarabine+cyclophosphamide+rituximab, R-CVP = rituximab+cyclophosphamide+vincristine+prednisolone

Table 2. Progression free survival in different treatments in CLL patients

Treatment	No patients	Mean Age	Mean No of cycles	PFS months	Range months
FCR	17(39.5%)	62.4	4.3	35.1	12-72+
R-CVP	6(14%)	65.6	6.1	18.6	2-30

Discussion

Population studies show that the median age at diagnosis of CLL patients is 71 years in USA and 70 years in Europe, while in clinics the median age at diagnosis is much younger (64 years at the Mayo Clinic; 58 years at MD Anderson Cancer Center) [22,23]. In our study, the median age at diagnosis of the referred patients was also younger (62.7 years) than the reported one. The median age of CLL clinic patients is relatively close to the population median age, but there are still a substantial number of elderly patients in the nonreferred group. This suggests that younger patients are more often being referred to the clinic for therapy, while elderly patients may not be referred as they are considered not fit enough for treatment.

Distribution of the patients according to Rai staging system in our study was similar to that reported in the literature [4-6], as well as the sex distribution [3]. Male sex is prevailing in CLL patients and early stages of disease are more common at the time of diagnosis. Comorbidities are very common in CLL patients due to the advanced age of these patients. A typical CLL patient is older than 65 years; she/he has three different comorbidities (most commonly cardiovascular disease, arthritis and psychiatric disease) and 44% of patients older than 65 years have some degree of renal insufficiency [24]. In our group of patients 81% had at least

one comorbidity and the most common were cardiovascular diseases.

Observation was most common treatment approach at the time of diagnosis with 58.8% of patients not requiring therapy in the beginning, but later during the course of disease only 33% of patients were still without treatment. The average time of observation without treatment was 3.6 years, with range 0-18 years. Similar to other studies, the most common treatment was FCR protocol, with almost 40% of patients treated with this immunochemotherapeutic regimen. The average time of PFS in patients treated with FCR was 35.1 months (range: 12-72+ months). Almost 60% of patients requiring treatment in our study were treated with less aggressive therapeutic regimens due to the advanced age and/or comorbidities.

In summary, in this study we presented the most common clinical characteristics of an CLL patient in our clinical settings and the most common therapeutic approach at our Institution that do not differ significantly from the characteristics of CLL patient in other studies.

Conflict of interest statement. None declared.

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КОЛОР ДУПЛЕКС СОНОГРАФСКИ НАОД НА КАРОТИДНИТЕ АРТЕРИИ И АСОЦИРАНИ ФАКТОРИ НА РИЗИК КАЈ ПАЦИЕНТИ СО ТРАНЗИТОРНА ИСХЕМИЧНА АТАКА**COLOR DUPLEX SONOGRAPHY FINDINGS OF THE CAROTID ARTERIES AND ASSOCIATED RISK FACTORS IN PATIENTS WITH TRANSIENT ISCHEMIC ATTACK**

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Апстракт

Вовед. Транзиторна исхемична атака (ТИА) претставува акутна епизода на временна невролошка дисфункција која типично трае помалку од еден час. Атеросклеротичните плаки на каротидните артерии можат да предизвикаат ТИА преку стеснување на луменот или преку механизам на тромбоемболија. Целта на овој труд е да се анализираат промените на каротидните артерии кај пациенти со ТИА и со асоцираните фактори на ризик.

Методи. Направена е ретроспективна анализа на 62 пациенти со ТИА. Кај сите е направено колор дуплекс сонографско испитување на каротидните артерии и се анализирани ризик факторите.

Резултати. Анализирани се 15 (24%) жени и 47 (76%) мажи со ТИА, на возраст од 45 до 79 години. Хипертензијата е најзастапен ризик фактор-присутна кај 57 пациенти (91,9%). Најчести промени на екстракранијалните сегменти на каротидните артерии се атероматозни плаки (застапени кај 25,8%) и стеноза од низок степен (40-59%) визуелизирана кај 24,1% од испитаниците. Доминираат мултипли плаки, претежно локализирани во предел на бифуркација и почетниот сегмент на внатрешната каротидна артерија (67,7%), со нерамна површина (кај 58,1%), хетерогена структура (70,9%) и претежно хипоехогени (46,8%).

Заклучок. Овие податоци покажуваат сигнификантна поврзаност меѓу ултразвучните карактеристики на каротидните плаки и појавата на ТИА. Поради тоа, кај сите пациенти со ТИА треба да биде направена колор дуплекс сонографска егзаминација на каротидните артерии и да се евалуираат факторите на ризик, со цел да се преземат соодветни терапевтски мерки, како и превенција на појавата на дефинитивен мозочен удар.

луираат факторите на ризик, со цел да се преземат соодветни терапевтски мерки, како и превенција на појавата на дефинитивен мозочен удар.

Клучни зборови: транзиторна исхемична атака, каротидни артерии, колор дуплекс сонографија, фактори на ризик

Abstract

Introduction. A transient ischemic attack (TIA) is an acute episode of temporary neurologic dysfunction that typically lasts less than an hour. Atherosclerotic plaques in the carotid arteries may cause TIA by lumen stenosis or plaque-related thromboembolism. The aim of this paper was to analyze the changes of the carotid arteries in patients with TIA and associated risk factors.

Methods. A retrospective analysis of 62 TIA patients was performed. Color duplex sonography of the carotid arteries and risk factor assessment was carried out in all patients.

Results. We analyzed 15(24%) females and 47(76%) males with TIA, aged 45-79 years. The most frequent risk factor was hypertension, present in 57 patients (91.9%). The most common findings of the extracranial segments of the carotid arteries were atheromatous plaques present in 25.8% and low-grade stenosis (40-59%) visualized in 24.1% of patients. Multiple plaques predominated, mostly localized in the region of bifurcation and the beginning of the internal carotid artery (67.7%), with irregular surface (in 58.1%), heterogenous structure (70.9%) and mostly hypoechogenic (46.8%).

Conclusion. These data have demonstrated a significant relationship between carotid artery ultrasound plaque characteristics and TIA occurrence. That is why color duplex sonography of the carotid arteries should be carried out in all TIA patients and risk factors should

be evaluated, in order to take appropriate therapeutic measures for prevention of definitive stroke.

Keywords: transient ischemic attack, carotid arteries, color duplex sonography, risk factors

Вовед

Транзитрна исхемична атака (ТИА) е акутна епизода на привремена невролошка дисфункција, која вообичаено трае помалку од 1 час и се јавува како резултат на фокална исхемија на мозокот, рбетниот мозок или ретината и не е асоцирана со акутен инфаркт на ткивото [1]. Кај лицата кои доживеале ТИА, инциденцата на последичен мозочен удар е висока и изнесува 11% во текот на следните 7 дена, а 24-29% во текот на следните 5 години [2]. Атеросклерозата на каротидните артерии, најчесто лоцирана во предел на бифуркација и почетниот сегмент на внатрешната каротидна артерија, е асоцирана со ТИА и мозочен удар поради стеноза на луменот и/или руптура на плакот, со или без суперпонирана тромбоза. Колор дуплекс сонографската егзаминација овозможува визуелизација на сидот на крвниот сад, мерење на дебелината на слојот интима-медија (ИМТ), анализа на плаките (големина, структура, локализација) и мерење на процентот на стеноза [3]. Целта на оваа ретроспективна студија е да се анализираат наодите на каротидните артерии со помош на колор дуплекс сонографија, како и асоцираните традиционални фактори на ризик (хипертензија, заболувања на срцето, дијабетес, пушење, хиперлипидемија).

Материјал и методи

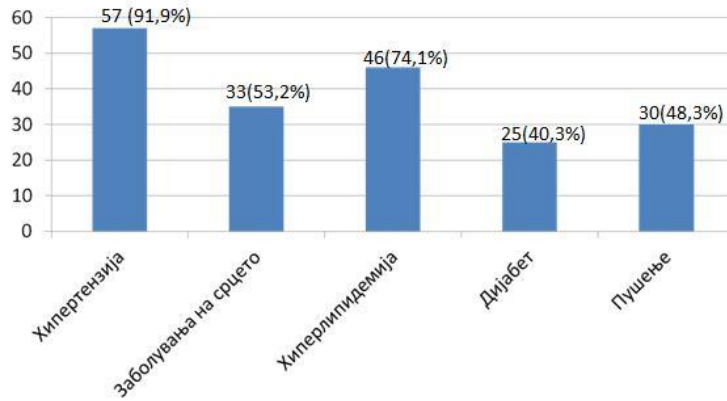
Направивме ретроспективна анализа на 62 пациенти со ТИА кои беа амбулантски иследувани на Универзитетската клиника за неврологија. Екстракранијалните сегменти на каротидните артерии беа визуелизирани со помош на ултразвучен апарат за колор дуплекс сонографија Hitachi-Alosa, со ултразвучна сонда од 7,5 MHz. Испитувањето е извршено по протокол, на лонгитудинален и трансферзален пресек, со посебен осврт на пределот на бифуркација и почетниот

сегмент на внатрешната каротидна артерија [4]. Со B-mode беше мерена дебелината на ИМТ, а кај присутните плаки е направена морфолошка анализа, со одредување локализација, ехогеност, структурни и површински карактеристики и процент на стеноза, согласно Концензусот за одредување на морфологијата на плаките [5]. За зголемена ИМТ е земена вредноста над 0,9 mm [6]; присуството на плаки е нотирано при стеснување на луменот од 1 до 39%, за низок степен на стеноза се смета стеснување на луменот од 40 до 59%, стеноза од умерен степен е сметана од 60 до 79%, стеноза од висок степен од 80 до 97%, субоклузија од 98 до 99% и оклузија-100% опструкција на луменот [7].

Спектралната анализа овозможи процена на хемодинамскиот ефект на патолошките промени [8], а во случаите на хипоехогени лезии овозможи подобра визуелизација и претставува важна дијагностичка потпора. Клиничката информација е добиена преку анамнеза и невролошки преглед на секој пациент, вклучително возраст, пол, историја за хипертензија, заболувања на срцето, дијабетес, пушење, хиперлипидемија. Статистичката обработка е извршена со програмот Statistica for Windows 12. Споредбата на две атрибутивни варијабли е направена со тестот Х-квадрат. За статистички значајна разлика е земена вредноста $p < 0,05$.

Резултати

Анализирани 15 (24%) жени и 47 (76%) мажи со ТИА, на возраст од 45 до 79 години (средна возраст 65,7 години). Најзастапен фактор на ризик-хипертензијата, присутна кај 57 пациенти (91,9%), а потоа следува хиперлипидемијата, застапена со 74,1% (слика 1). Најчести промени на екстракранијалните сегменти на каротидните артерии, визуелизирани со колор дуплекс сонографија-атероматозни плаки застапени кај 25,8% од пациентите (слика 2) и стеноза на луменот од низок степен (40-59%) визуелизирана кај 24,1% од испитаниците. Зголемена ИМТ регистрирана кај 17,7%, низок степен на стеноза беше регистриран кај 24,1%, умерен степен кај 14,5%, висок степен на стеноза кај 11,2% (слика 3), субоклузија кај 4,8% и оклузија (слика 4) кај 1,6% од испитаниците.



Сл 1. Застапеност на факторите на ризик кај пациенти со ТИА

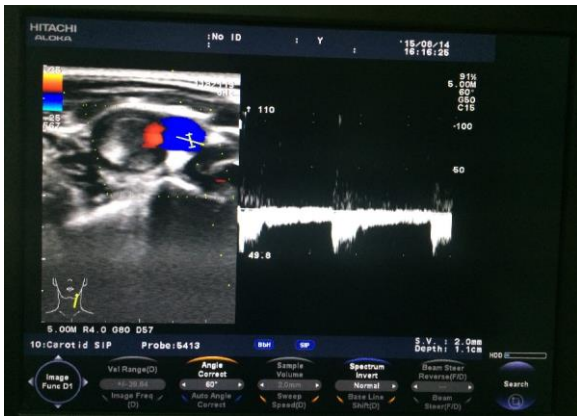


Сл. 2. Плаки во предел на бифуркација на каротидната артерија

лизирани во почетниот сегмент на внатрешната каротидна артерија се присутни кај 9(14,5%) од



Сл. 3. Оклузија на внатрешната каротидна артерија



Сл. 3. Високо-степенена стеноза на внатрешната каротидна артерија

испитаниците. За X -квadrat=10.0 и $p<0.05$, доминацијата на испитаниците со двојна локализација е значајна. Мазната површина на плаките е застапена кај 15 испитаници (24,2%), додека нерамна површина е визуелизирана кај 36 испитаници (58,1%), оваа разлика е значајна за $p<0,05$. Хетерогена структура на плакот е застапена кај 44 испитаници (70,9%), значајно повеќе во однос на испитаниците со хомогена структура која беше визуелизирана кај 7 испитаници (11,2%), $p<0.05$. Во однос на ехогеноста на плаките, кај 29 испитаници (46,8%) беа регистрирани хипоехогени плаки, додека кај 22(35,5%) беа визуелизирани хиперехогени плаки, разликата е незначајна ($p>0.05$).

Морфолошката анализа на атероматозните плаки покажа дека доминираат мултипни плаки, застапени кај 43(69,4%) испитаници, во однос на единечните, застапени кај 8(12,9%), а разликата е сигнификантна за X -квadrat=4.0 и $p<0.05$. Во однос на локализација на плаките, доминираат испитаници каде плаките се во предел на бифуркација и почетниот сегмент на внатрешната каротидна артерија (42-67,7%), додека плаки кои се лока-

Дискусија

Во нашиот труд најзастапен фактор на ризик е хипертензијата, која беше присутна кај 57 пациенти (91,9%), а потоа следува хиперлипидемијата која беше застапена со 74,1%. Овие податоци корелираат со податоците од литературата каде е наведено дека хипертензијата и покаченото ниво на холестерол се најчестите фактори на ризик за ТИА [9,10]. Во однос на локализација

на плаките, сигнификантно доминираат испитаници каде плаките се лоцирани во предел на бифуркација и почетниот сегмент на внатрешната каротидна артерија (67,7%). Овие податоци се во согласност со податоците од литературата [11], каде е наведено дека предилекционо место за развој на каротидните атероматозни промени се бифуркацијата и почетниот сегмент на внатрешната каротидна артерија. Лезиите кои даваат клинички манифестации се наоѓаат 2-3 cm дистално и 1 cm проксимално од местото на разделување на крвотокот.

Локацијата во најголем број на случаи е константна и е независна од полот, возраста и расата. Во однос на структурата на плаките, доминираат испитаници кои имаат хипоехогени плаки (46,8%), со нерамна површина (58,1%) и хетерогена структура (70,9%). Резултатите од досегашните студии [12,13] покажуваат дека одредени плакови карактеристики (нерамна површина, хипоехогеност и хетероген состав) се асоцирани со зголемена инциденца на ТИА.

Заклучок

Овие податоци покажуваат сигнификантна поврзаност меѓу ултразвучните карактеристики на каротидните плаки и појавата на ТИА. Поради тоа кај сите пациенти со ТИА треба да се направи колор дуплекс сонографска егзаминација на каротидните артерии и да се евалуираат факторите на ризик, со цел да се превземат соодветни терапевтски мерки и да се превенира појавата на дефинитивен мозочен удар. Овие наоди ги охрабруваат понатамошните проспективни студии кај асимптоматските пациенти за да се одредат ехографските карактеристики на каротидните плаки како предиктори на последователна ТИА или мозочен удар.

Конфликт на интереси. Не е деклариран.

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ПОЈАВА НА СРЦЕВО ОШТЕТУВАЊЕ КАЈ ТРУДНИЦИ СО ПРЕЕКЛАМПСИЈА: ПРИКАЗ НА СЛУЧАЈ**HEART DAMAGE IN PREGNANCIES COMPLICATED WITH PREECLAMPSIA: CASE REPORT**

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Abstract

Introduction. Heart function in pregnancy is a subject of many debates and studies. A large number of epidemiologic studies have found association between preeclampsia and cardiovascular morbidity/mortality. About 5-8% of deliveries are complicated with preeclampsia. Until recently, heart damage associated with preeclampsia has not been studied. A number of heart difficulties only appear long after the reproduction period has ended. Preeclampsia increases the risk for B stage (asymptomatic) of heart failure.

Case report. A 37-year-old pregnant patient, G2P1 27 weeks of gestation, paid her first visit to the Gynecology Outpatient Clinic. She complained on heavy breathing, difficulty with movement and hypertension. She was referred for further evaluation to the Cardiology Outpatient Clinic with a suspicion of gestational hypertension and heart abnormalities.

The pregnancy was evaluated several times at the Outpatient Clinics of Gynecology and Cardiology with the diagnosis of gestational hypertension. Echocardiography showed abnormal heart remodeling. In the 36 g.w laboratory findings showed urine dip stick ++, TA160/110. The diagnosis was changed to preeclampsia. The patient was delivered with a re-caesarean section because of previous S.C and preeclampsia. Postpartum echocardiography confirmed left chamber hypertrophy with persistent hypertension.

Results. Clinical cardiovascular complications in preeclampsia continue long after the pregnancy has ended. Studies show that pregnancies with both early and late preeclampsia have an increased risk for asymptomatic left chamber dysfunction/hypertrophy and essential hypertension in the next 2 years after delivery. If the damages are caught early prevention can be started sooner rather than later before patients become symptomatic (C stage of heart failure).

Keywords: preeclampsia, heart damage, echocardiography, pregnancy

Апстракт

Вовед. Срцевата функција во бременоста е предмет на мноштво дискусии и истражувања. Голем број епидемиолошки студии наоѓаат силна асоцијација помеѓу прееклампсија со последователен кардиоваскуларен морбидитет/морталитет. Се смета дека околу 5-8% од сите бремености се комплицирани со прееклампсија. Срцевите оштетувањата поврзани со прееклампсија до скоро не беа предмет на интерес. Најголем дел од срцевите промени поврзани со овие заболувања стануваат манифестни во подоцнежна возраст, односно кога веќе е завршен репродукцискиот период кај жената. Имено, прееклампсијата неколкукратно го зголемува ризикот за Б стадиумот (асимптоматски) на срцево оштетување.

Приказ на случај. 37-годишна трудница, G2P1 во 27 г.н. со присутна хипертензија, тешко дишење и замор при движење. Поставено сомнение за гестациска хипертензија со срцева слабост, препратена на Клиниката за кардиологија за доевалуација.

Трудницата е иследувана во неколку наврати на Клиниката за гинекологија и Клиниката за кардиологија под работна дијагноза гестациска хипертензија.

Наодите од контролите на клиниките во прилог на абнормално срцево ремоделирање. Во 36 г.н. недела лабораториски наод во прилог на прееклампсија (TA 160/110 квалитативно (++) протеини. Пациентката породена со повторен царски рез заради претходен царски рез и прееклампсија. Постпартално на две контроли потврдена почетна левокоморна хипертрофија и перзистентна хипертензија.

Резултати. Кардиоваскуларните импликации поврзани со прееклампсија не престануваат со завршување на бременоста. Студиите докажуваат дека кај бремените жени со рана прееклампсија и во помала мера доцна прееклампсија постои значаен ризик за асимптоматска левокоморна дисфункција/хипертрофија и

есенцијална хипертензија во период од 2 години по породувањето. Доколку навреме се откријат постојните срцеви оштетувања би можела да се спроведе рана превенција, односно да се започне соодветен третман пред пациентките да станат симптоматски (Ц стадиум на срцево оштеување).

Клучни зборови: преeklampсија, Б стадиум на срцево оштетување, превенција, бременост

Introduction

Preeclampsia presents as a medical condition in pregnancy that is manifested with increased blood pressure and protein urine. It occurs in 5-8% of pregnancies [1]. Most of the hemodynamic changes that happen with pregnancy are reversible and subside after delivery. Preeclampsia and the hemodynamic changes that occur can lead to preterm delivery and fetuses with IUGR [2,3]. Women with a history of pregnancy aggravated with preeclampsia are with an increased risk of developing cardiovascular disease in latter life [4].

Preeclampsia is a pregnancy-related disorder that involves increased blood pressure $>140/90$ mmHg and increased amount of urine protein >0.3 gr/l [5]. Preeclampsia usually develops in the last third of pregnancy. With advancing pregnancy preeclampsia gets more difficult [6]. In more severe cases of the disorder it's possible to see decreased number of platelets, erythrocytes breakdown, liver and kidney failure, swellings, pulmonary edema and even death [7]. A severe form of preeclampsia can lead to an eclamptic seizure.

Additional risk factors for preeclampsia include: obesity, previous hypertension, family history of preeclampsia, previous preeclampsia, age <20 and age >45 years and diabetes. It is more common in the first pregnancy and in twin pregnancies. Most of the studies investigate the main hemodynamic parameters (blood pressure, heart volume, heart frequency ...) while other studies go into bigger detail and investigate biochemical markers (endothelial dysfunction, dislipidemia, oxidative stress and glucose levels). All studies have similar hypothesis that in pregnancies with a history of preeclampsia the risk of heart damage is several fold higher compared to normal pregnancies.

Case report

A 37-year-old pregnant patient, G2P1 paid her first visit to the Gynecology Outpatient Clinic in her 29 weeks of gestation. She complained on heavy breathing, fatigue, hypertension in the past two weeks and headaches. She was sent to several primary physicians before appearing in our Outpatient Clinic. Fetal ultrasound showed an eutrophic baby with EFW 1730 gr with normal cerebroplacental index. The examination showed: TA-160/90, BMI-

34, complete blood work and urine sample were normal. She was given antihypertensive medication (Methyropa 4x250 mg). This was her second pregnancy, and she revealed that in her previous pregnancy she suffered from hypertension discovered in the 37 g.w and treated. She delivered her first baby in the 41 g.w with a caesarean section. Family history revealed that her mother had hypertension when she was pregnant with ecamptic seizures. A check up was scheduled in two weeks.

Management and outcome

A hypothesis was made that this was a gestational hypertension with heart involvement. On the second visit in the 31 g.w. laboratory findings were normal and hypertension was under control but fatigue and heavy breathing were still present. She was referred to the Cardiology Outpatient Clinic where EKG and echocardiography were done. Echocardiography showed a first sign of left ventricular hypertrophy with LV diastolic dysfunction (abnormal relaxation). Follow-up was scheduled after delivery. In the 36 g.w. at a routine check-up in the Obstetrics Outpatient Clinic laboratory findings showed urine dipstick ++, TA 160/100. The patient was hospitalized in the Department for pathologic and high-risk pregnancies, complete blood work was done. A second antihypertensive drug was administered (nifedipine) and 24h urine was collected. The urine sample showed 2.4 gr/l of protein. The previous diagnosis of gestational hypertension was changed with preeclampsia. Two days after admission resection caesarean was done which resulted in delivery of a healthy girl (3000/49 AS 8/9).

Two weeks after delivery echocardiography was done, which revealed left ventricular hypertrophy with LV diastolic dysfunction (IVS >12 mm). Hypertension was still present and the patient was switched to different antihypertensive drugs. Advice was given for a follow-up at 6 months with third echocardiography. The results confirmed the left ventricular hypertrophy with LV diastolic dysfunction (IVS >12 mm), and hypertension was persistent. She was then scheduled for routine follow-up every 6 months in the Cardiology Outpatient Clinic.

In the future every patient with preeclampsia should be monitored carefully. There is no clear consensus on how often check-ups should be done. We believe that it is probably best to schedule new echocardiography every 6 months up to a year depending on the changes seen on the ultrasound. If hypertension is still an issue a new antihypertensive drug should be administered.

Discussion

Pregnancies with preeclampsia have an increased risk to acquire heart damage (usually B stage) and chronic hypertension after delivery associated with increased cardiovascular morbidity and mortality [8]. Preeclampsia involves left heart chamber remodeling in both systolic

and diastolic phases with reduced heart contractility [9]. There is an increasing number of evidence that pregnant women with preeclampsia compared to those with a normal pregnancy have persistent abnormal chamber geometry as well as reduced diastolic function. In the case we described additional risk factors were obesity and family history of preeclampsia (preeclampsia is known to appear in siblings up to 40% and in close relatives up to 20%).

In the literature there are small observational prospective studies. Pregnant women are first completely managed obstetrically, which includes fetal biometry, Doppler analysis (cerebral-placental index) and complete blood work to confirm preeclampsia. Of interest are: age of the women, number of previous pregnancies, previous cardiovascular diseases, and previous pregnancy complicated with preeclampsia or hypertension, pregnancy outcome. In a number of studies subjects were followed with echocardiography up to 2 years postpartum.

The following parameters were investigated:

- BMI (body mass index)
- Systolic and diastolic blood pressure
- Heart frequency
- Echocardiography of the heart structure and function
 - o Left ventricular geometric pattern
 - o Dimension and volume of the left chamber
 - o Left systolic function (ejection fraction and fraction shortening)
 - o Diastolic function parameters with pulse Doppler: peak flow velocity in early diastole (E wave velocity) and during atrial contraction (A wave velocity), E/A ratio, E and A wave time-velocity integrals: deceleration time of the E-wave (DtE) and duration of the A wave (A wave duration), isovolumetric relaxation time of the left ventricle (IVTR)
- Total peripheral vascular resistance
- Renal function

Echocardiography is the best method to see hemodynamic changes that involve the heart in pregnancy. The results presented in most studies conclude that pregnancies with preeclampsia compared to normal pregnancies up to 6 months postpartum have increased asymptomatic left chamber abnormalities (B stage of heart failure) and increased cardiovascular risk. If the abnormalities are not resolved 6 months after delivery, then it is a sign that the changes will remain permanently. Postpartum increased risk of left chamber dysfunction is especially higher in early preeclampsia (< 34 g.w.). The earlier the disorder develops the bigger the heart damage is. In the study by Melchiorre K. and Thilaganathan B. in majority of the evaluated cases after delivery normalization of the heart function was found, which was not the case in patients with early preeclampsia. In about 20% of cases with preterm preeclampsia there was a systolic and/or diastolic dysfunction of the right chamber, 6% in the

term preeclampsia and none in the control group. The function of the right chamber is closely linked with that on the left chamber. Reduced myocardial relaxation and high amplitude of post-systolic shortening can be seen in both preterm and term preeclampsia groups. The seemingly normal heart function evaluated on the basis of symptoms and physical findings can be further evaluated with more subtle methods such as echocardiography and show subclinical chamber dysfunction. The study by Bijmens BH showed that myocardial damage contributes to systolic and/or diastolic dysfunction [10]. The most important thing about these studies is that they help in determining cardiovascular outcome. Both term and preterm preeclampsia are strongly associated with persistent left chamber dysfunction/hypertrophy up to 6 months postpartum and there is an increased risk of hypertension in the next two years [11]. Recent studies have shown that in previous preeclampsia patients that have a new pregnancy preeclampsia can be expected if diastolic dysfunction and left ventricular hypertrophy are still present [12]. Lower stroke volume and cardiac output are also warning signs of a new preeclampsia pregnancy. Echocardiography may be considered as a cost-effective method in patient follow-up, especially in pregnancies after preeclampsia. This is especially so because most of the changes that occur in normal pregnancy subside after delivery, which is not the case with preeclampsia pregnancies. Asymptomatic left chamber dysfunction is also known as B stage heart failure. The progression of B stage heart failure to stage C (symptomatic) of heart failure is associated with 5 time greater risk for sudden heart death [13]. All of this can be prevented if the heart damage is recognized on time and treatment is started [14,15].

Conclusion

In terms of clinical perspective cardiovascular implications with preeclampsia do not end with pregnancy. Numerous studies conclude that pregnant women with early and with late preeclampsia have a substantial risk for asymptomatic left chamber dysfunction/hypertrophy and risk of essential hypertension in a period of 2 years. Studies also indicate that if the changes are seen early, there is a possibility of early prevention. Treatment can be started before patients become symptomatic (C stage of heart failure). A new algorithm can be put in place for preeclampsia treatment and follow-up. We suggest initial follow-up every six months (with echocardiography and a physical exam). More should be done to discover high risk groups, offer them echocardiography screening, which will consequently decrease cardiovascular morbidity and mortality. Better cooperation is needed between obstetricians and cardiologists in early signs recognition and treatment.

Conflict of interest statement. None declared.

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ЛЕИОМИОМ НА ИЛЕУМ - ПРИКАЗ НА СЛУЧАЈ И ПРЕГЛЕД НА ЛИТЕРАТУРА

LEIOMYOMA OF THE ILEUM: A CASE REPORT AND LITERATURE REVIEW

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Апстракт

Вовед. Леиомиомите се ретко локализираны на илеумот. Тие случајно се откриваат или поради компликации од нивното присуство.

Приказ на случај. Кај пациент на 65 годишна возраст, на КТ ангиограм, индициран поради болка, оток и студенило во долните екстремитети е откриена доброваскуларизирана туморозна формација на тенкото црево. Анамнестичките податоци и лабораториските резултати се негативните за постоење карциноид. Направена е експлоративна лапаротомија со парцијална ресекција на илеумот, со No-Touch техника и термино-терминална анастомоза.

Резултати. Уреден оперативен и остоперативен тек. Хистопатолошкиот наод потврди leiomyoma intestini tenui.

Заклучок. Леиомиомите на тенкото црево се ретки и со нетипична клиничка презентација. Основна хируршката терапија е индицирана и кај случајно откриени промени. Дефинитивна дијагноза се потврдува со хистопатолошка анализа од која зависи натамошната терапија.

Клучни зборови: леиомиом на илеум, КТ ангиограм, доброваскуларизирана туморска формација

Abstract

Introduction. Leiomyomas are infrequently localized on the ileum. They are diagnosed accidentally or due to complications from their existence.

Case report. We present a case of a 65-year-old patient, with CT angiogram performed due to a pain, swelling and coldness in the lower extremities, which pointed to a well-vascularized tumorous formation on the small intestines. Anamnestic and laboratory findings were negative for the existence of carcinoid. Exploratory lapa-

rotomy with partial resection of the ileum was performed, using "no touch" technique and a termino-terminal anastomosis was done.

Results. The operative and postoperative period were uneventful. The histopathological finding confirmed leiomyoma of the small bowel.

Conclusions. Leiomyomas of the small intestines are rare and their clinical presentation is atypical. The surgical therapy is primary and often indicated to accidentally discovered lesions. Definitive diagnosis is confirmed with histopathological analysis from which the further therapy depends.

Key words: leiomyoma, ileum, CT angiogram, well vascularized tumorous formation

Вовед

Леиомиомите се бенигни тумори со потекло од мазните мускули и можат да се јават во секој орган во којшто постои мазна мускулатура. Од цел гастроинтестинален тракт, најчесто се јавуваат на желудникот (40%), а потоа на јејунумот (20%), илеумот и ректумот (14,3% секој), дуоденумот (8,57%) и езофагусот (2,86%) [1]. Макроскопски тие се сиво-беличести лезии кои можат да имаат интралуминален, интрамурален или екстралуминален раст. Микроскопски содржат добро диференцирани мазно-мускулни клетки без митози, што ги диференцира од нивниот малиген двојник-леиомиосаркомот [1].

Дијагнозата на леиомиомите на тенкото црево, најчесто, е одложена поради нетипичната клиничка слика, или пак, се откриваат случајно. Нивна највообичана клиничка презентација е крвавење или интестинална опструкција [2]. Но, и покрај бројните дијагностички методи во денешно време, како нативна РТГ на абдоменот, бариумско иследување на ГИТ (цревна пасажа и ентероклиза), КТ, МР ангиографија, горнодигестивна ендоскопија, ентероскопија итн, тие претставуваат дијагностички предизвик. Постојат мислења дека МН-ентеролиза претставува нај-

добар радиолошки модалитет за испитување на тенкото црево и дека треба да се препорача како иницијална метода на испитување кај пациентите каде што постои сомневање за тумори на тенкото црево [3,4].

Со усовршување на дијагностичките техники и опрема, дијагностичката стапка е зголемена до 64% [5], што остава голем процент од пациентите без предоперативна дијагноза.

Нашиот случај претставува случаен наод на леиомиом на илеумот, без симптоми и знаци со потекло од гастроинтестиналниот тракт, откриен

при правење КТ ангиограм на абдоминална аорта и нејзините гранки.

Приказ на случај

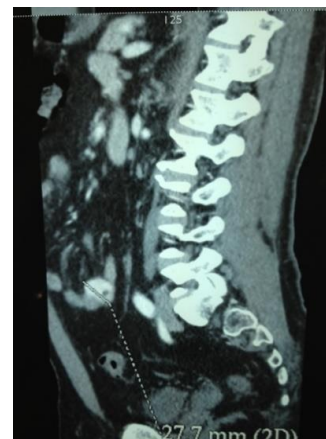
Пациентот З.П, на 65-годишна возраст, е примен на Универзитетската клиника за дигестивна хирургија-Скопје за елективен оперативен третман, поради наод на КТ ангиограм и КТ на абдомен со интравенски контраст, на добро васкуларизирана туморска формација на тенкото цре-



Сл. 1. КТ ангиограм на абдоминална аорта и нејзините гранки

во. Станува збор за случаен наод, односно пациентот се јавил на лекар поради болка, оток и студенило во левата нога. При правење КТ ан-

гиографија на абдоминална аорта и нејзините гранки (во друга здравствена установа) е добиен горенаведениот наод (слика 1).



Сл. 2. КТ на абдомен со интравенски контраст (со наод на добро васкуларизирана туморска формација на тенкото црево)

Во анамнезата за минати заболувања пациентот дава анамнестички податок за тромбоза на вените на десната потколеница и висок крвен притисок. При преглед, мек и безболан на палпација абдомен, без органомегалија. Со нормални лабо-

раториски вредности на серумската 5-хидроксииндол оцетна киселина (5-HIAA), со чија помош заедно со негативните анамнестички податоци за вцрвување (flushing), дијареа, хипотензија и тахикардија ја исклучивме можноста за пос-

тоење карциноиден тумор на тенкото црево. На компјутерска томографија на абдоменот (слика 2) немаше наод на далечни метастатски лезии во хепарот и другите интраабдоминални органи. По потребната предоперативна подготовка се направи експлоративна лапаротомија низ инфраумбиликална медијана лапаротомија. При експлорација на абдоминалната шуплина се најде сивобеличеста туморска формација на тенкото црево со цврста конзистенција и топчеста форма, јасно ограничена од околните органи и дијаметар од околу 2 см. Се направи лимитирана ресекција на туморот и се обнови континуитетот на цревата со термино-терминална анастомоза. Поради можноста да се работи за ГИСТ на тенкото црево, користена е No-Touch техника, со уреден оперативен и постоперативен тек. Хистопатолошката дијагноза на препаратот е леиомиом на тенко црево, со некротична и улцерирани лигавица, негативен на имунохистохемиски боења за CD34, CD117-(c-kit)-дијагностичките критериуми за ГИСТ [6].

Дискусија

Туморите на тенкото црево претставуваат само еден процент од гастроинтестиналните тумори, иако тенкото црево е претставник на 90% од површината на гастроинтестиналниот тракт [1]. Најчести бенигни неоплазми на тенкото црево се аденомите, но леиомиомите, како најчести бенигни лезии, кои даваат симптоми [1]. Клиничката презентација на леиомиомите е нетипична, поради

што и дијагнозата е одложена. Најчестите клинички знаци и симптоми се поврзани со присуство на абдоминална маса, крвавење и интестинална опструкција. Опструкцијата се јавува поради интралуминален туморски раст или интусусцепција. Најчесто е интермитентна или парцијална и може да биде поврзана со дијареа. Болка и крвавење се јавуваат поради туморска некроза. Крвавењето може да биде екстралуминално во перитонеалната шуплина или интралуминално, доведувајќи до хематемези, мелени или анемија.

Тоа што туморите на тенкото црево претставуваат дијагностички предизвик, и покрај бројните дијагностички методи во денешно време (табела 1.), се должи како на недостигот од специфични симптоми, така и на тешкотии кои се јавуваат при радиолошка евалуација на тенкото црево. Но, исто така, и реткоста на оваа болест, која не дозволува стекнување доволна експертиза. На пример, Куригин *и сор.* во еден голем преглед на 5.190 случаи со гастроинтестинални крвавења, забележале само 14 случаи со потекло од тумор на тенкото црево [7]. Клиневимол *и сор.* направиле преглед на 1.489 пациенти со гастроинтестинално крвавење и нашле само еден леиомиом во 10 случаи каде што крвавењето потекнувало од тенкото црево [8]. Додека пак, во еден радиолошки преглед, на Диксон *и сор.* за 1.465 иследувања на тенкото црево со

Табела 1. Споредба на дијагностички методи користени при евалуација на тенкоцревни неоплазми

Метода	Предности	Недостатоци
Нативна РТГ	визуелизира цревни опструкции	неспецифична
Цревна пасажа	визуелизира масивна лезија, мукозен дефект или интусусцепција	нема визуелизација надвор од луменот, некорисна за „стејџинг“
Енетроклиза	посензитивна од конвенционална цревна пасажа	потребна е дуоденална сонда и дополнителни технички вештини
КТ	дозволува „стејџинг“, може да помогне во дијагнозата на типот на туморот	недостига визуелизација на луменот или мукозната површина
МР	МР може да обезбеди исклучителни анатомски и функционални информации во реално време во евалуација на тенкоцревни тумори, без јонизирачко зрачење	подолго време на испитување
МР-ентероклиза		
МР-енетерографија		
Горнодигестивна ендоскопија	директна визуелизација на мукозната површина на дуоденумот, дозволува биопсија или полипектомија	инвазивна; ограничена на дуоденумот и може да се превидат субмукозни лезии доколку не се комбинира со ендоскопски ултразвук
Ентероскопија	ја проширува визуелизацијата во проксималниот јејунум, дозволува биопсија	инвазивна; може да се превидат субмукозни лезии, доколку не се комбинира со УЗ
Проширена тенко-цревна ендоскопија	дозволува визуелизација на 70% од тенкото црево, посензитивна од енетроклизата	неможност да се направи биопсија, може да трае до 8 часа

ентероклиза и потоа направена споредба со натамошниот исход, дава податок дека во 67,5% од

случаите каде што постоел абнормален наод на тенкото црево била поставена специфичната дијагноза [9,10], што во голем процент ја препушта одлуката за третманот да се заснова на клиничкиот наод.

Хируршки е третманот на тенкоцревните неоплазми. Хируршката ексцизија е индицирана поради опструкција или крвавење, потенцијален ризик од компликации, и поради неможност за дефинитивно потврдување на бенигноста на болеста без комплетна микроскопска евалуација. Хируршкиот третман на неоплазмите на тенкото црево може да биде лимитирана или радикална ресекција, во зависност од уверливоста на предоперативната дијагноза, туморската локализација и величина, и клиничката презентација. Третманот на леиомиомите со димензии под 5 см е лимитирана ресекција со чисти маргини. Лезиите поголеми од 5 см треба да се третираат со радикална ресекција поради повисокиот ризик за малигнитет. Лимфна дисекција не се изведува рутински зашто леиомиосаркомите не метастазираат преку лимфните јазли.

Заклучок

Леиомиомите на тенкото црево се ретки, со нетипична клиничка презентација, поради што дијагнозата е одложена. Хируршката ексцизија, најчесто, е индицирана поради опструкција или крвавење, но и поради потенцијален ризик од компликации, и неможност за поставување дефинитивна дијагноза за бенигноста или малигността на болеста без хистопатолошко испитување.

Конфликт на интереси. Не е деклариран.

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ПАРЦИЈАЛНА ХЕРНИЈАЦИЈА НА ЦРНИОТ ДРОБ НИЗ ИНЦИЗИОНАЛЕН ДЕФЕКТ НА ПРЕДНИОТ АБДОМИНАЛЕН СИД**PARTIAL LIVER HERNIATION THROUGH THE INCISIONAL DEFECT ON ANTERIOR ABDOMINAL WALL**

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Апстракт

Вовед. Херниите на предниот абдоминален сид се многу чести, но исклучително ретка е хернијацијата на црниот дроб. Хернијацијата на црниот дроб низ предниот абдоминален сид најчесто е инцизионална. Инцизионална хернијација на црниот дроб обично се јавува 2 до 3 години по претходна операција на абдоменот, која како последица доведува до фокална слабост на абдоминалниот сид.

Приказ на случај. Прикажуваме исклучително редок случај на инцизионална хернија на дел од левиот и помал дел од десниот лобус на хепарот кај жена на возраст од 64 години, како последица на претходно извршен оперативан зафат за отстранување на калкулозно жолчно кесе. Поради тоа, се јавува фокална слабост на предниот абдоминален сид низ кој се хернира дел од левиот и помал дел од десниот лобус на хепарот. Направена е КТ преглед на абдоменот, нативна серија. По завршување на снимањето е направена анализа на добиените КТ сkenови, како и на направените реконструкции во коронална и сагитална рамнина. Во предно горниот дел од абдоменот се гледа хернијација на дел од левиот и на помал дел од десниот лобус на црниот дроб низ фокална слабост на предниот абдоминален сид.

Дискусија. Инцизионалните хернии се одложени компликации на абдоминалната хирургија. Тие може да се јават насекаде на абдоминалниот сид и почесто се среќаваат при вертикални одошто при попречни резови. Вообичаено, инцизионалните хернии се манифестираат во текот на првите месеци по операцијата, но може да се јават и подоцна. Хернијација на црниот дроб преку предниот абдоминален сид е исклучително ретка сос-

тојба и обично е поврзана со претходни операции на горниот дел од абдоменот. Поради својата реткост тоа претставува дијагностички и терапевтски предизвик.

Заклучок. Може да заклучиме дека постои поврзаност на хернијацијата на црниот дроб во горниот дел од абдоменот со претходно извршени оперативни интервенции на абдоменот. КТ е метода на избор за дијагностика на хернијација на црниот дроб низ предниот абдоминален сид.

Клучни зборови: инцизионална хернија, дефект на преден абдоминален сид, хернија на црн дроб, КТ

Abstract

Introduction. Ventral hernias are quite common, but liver herniation is an extremely rare case. This type of abdominal protrusion of part of the liver usually occurs through incisional weak spots on the abdominal wall. Incisional herniation of the liver usually occurs 2 to 3 years after an abdominal operation consequently leading to focal weakness of the abdominal wall.

Case report. We present an extremely rare case of incisional herniation of part of the left and smaller part of the right liver lobe in a woman aged 64 years, as a consequence of a previous open cholecystectomy, creating a focal abdominal wall weakness. Abdominal CT scan was performed. Analysis of the CT scans, as well as of the reconstruction made in the coronal and sagittal plane was performed. Herniation of the left and the smaller part of the right liver lobe through an incisive focal weakness of the right upper quadrant of the abdominal wall was detected.

Discussion. Incisional hernias are delayed complications of abdominal surgery. They can occur anywhere on the abdominal wall and are more frequently encountered in a vertical than in a transverse incision. Typically, incisional hernias occur during the first months following surgery, but later occurrence has been reported as well.

Herniation of the liver through the anterior abdominal wall is an extremely rare condition and usually related to previous surgery on the upper abdomen. Due to its rarity it is both a diagnostic and therapeutic challenge.

Conclusion. We can conclude that there is a connection between liver herniation through the upper abdominal wall and a previously performed open abdominal surgery. CT is the method of choice for diagnosis of liver herniation through the anterior abdominal wall.

Key words: incisional hernia, weakness of the anterior abdominal wall, liver hernia, CT

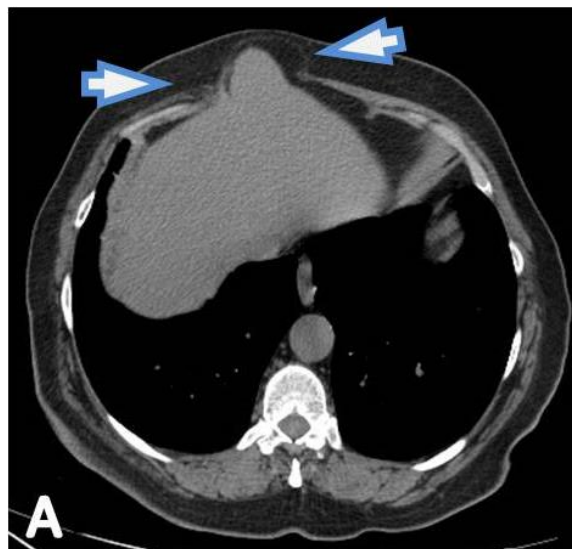
Вовед

Херниите на предниот абдоминален ѕид се доста чести, но исклучително ретки се хернијациите на црниот дроб. Повеќето случаи се поврзани со вродени дијафрагмални хернии на црниот дроб или пак се последица на траума на градниот кош поврзана со лезија на дијафрагмата и нарушување на нејзиниот континуитетот, по што доаѓа до хернијација на црниот дроб во торакалната шуплина [1]. Хернијациите на црниот дроб низ предниот абдоминален ѕид најчесто се инцизионални [2,3]. Инцизионална хернијација на црниот дроб обично се јавува 2 до 3 години по претходна операција на абдоменот која како последица доведува до фокална слабост на абдоминалниот ѕид [4,5]. Како ризик-фактори може да се наведат: прекумерната телесна тежина, постоперативни инфекции, напредната возраст и хронични белодробни заболувања [2-4,6]. Клиничката слика не е алармантна, бидејќи вообичаено постоперативниот дефект на предниот абдоминален ѕид е широк и не доведува до странгулирање на хернираниот дел од црниот дроб [7]. Најчести симптоми се: болки во стомакот, гадење и повраќање, а на физички преглед се детектира епигастрична хернија [8]. Дијагностички методи кои се користат за детекција на херниите на предниот абдоминален ѕид се ултразвук (УЗ) и компјутеризирана томографија (КТ). КТ поради својата супериорност во прикажувањето на анатомските детали и придружните компликации, како и поради можноста за реконструкција во повеќе рамнини (МПР), е дијагностичка метода на избор.

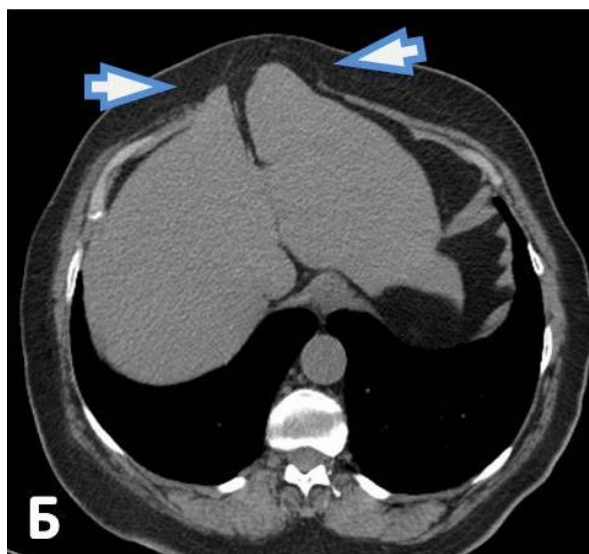
Приказ на случај

Случајот што го прикажуваме може да се смета за исклучително редок, бидејќи во светската литература се прикажани многу мал број на случаи, а во Република Македонија првпат е дијагностициран во нашата клиника. Станува збор за

инцизионална хернија на дел од левиот и помал дел од десниот лобус на хепарот низ фокална слабост на предниот абдоминален ѕид, која настанала како последица на претходно извршен оперативан зафат за отстранување на калкулозно жолчно кесе.



Сл. 1а.

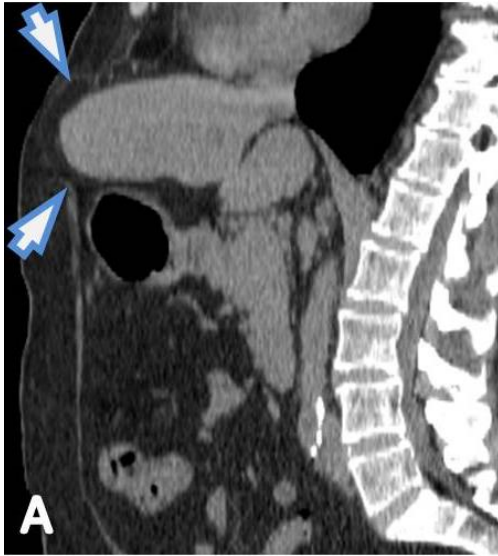


Сл. 1б.

Сл. 1а и 1б. Аксијални КТ пресеци на абдомен во висина на црниот дроб: На аксијалните КТ скенови јасно се гледа хернијација на дел од левиот лобус на црниот дроб (сегмент 2) и мал дел од десниот лобус (сегмент 4Б) низ дефект на предниот абдоминален ѕид (стрелки). Инцизионална хернија кај 64-годишна жена, која е оперирана од калкулозно жолчно кесе пред 6 години

Пациентката е на возраст од 64 години, која поради болки во абдоменот се јавила на лекар. Пациентката не наведува други симптоми освен абдоминалната болка, а извршените лабораториски испитувања се во нормални граници. По извршениот клинички преглед, таа е упатена на

натамошни радиолошки иследувања, односно за КТ на абдомен. Прегледот е извршен на MDCT скенер GE Bright Speed со 16 реда на детектори. По завршување на снимањето на абдоменот е направена анализа на добиените КТ сkenови, како и на направените реконструкции во коронална и сагитална рамнина. Во предногорниот дел од абдоменот се гледа хернијација на дел од левиот (сегмент 2) и на помал дел од десниот лобус на црниот дроб (сегмент 4Б) низ фокална слабост на предниот абдоминален ѕид (слика 1).



Сл. 2а.

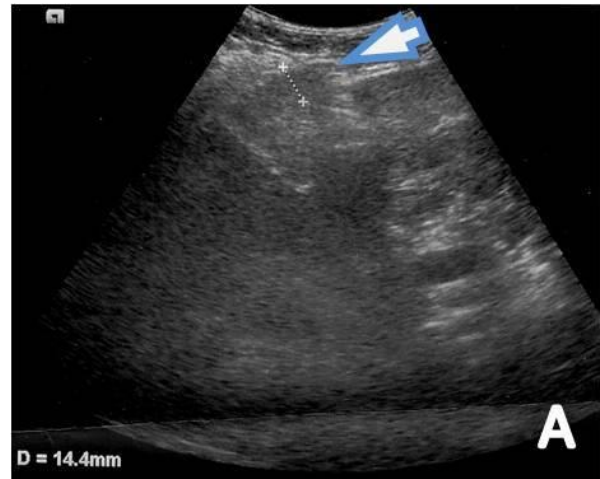


Сл. 2б.

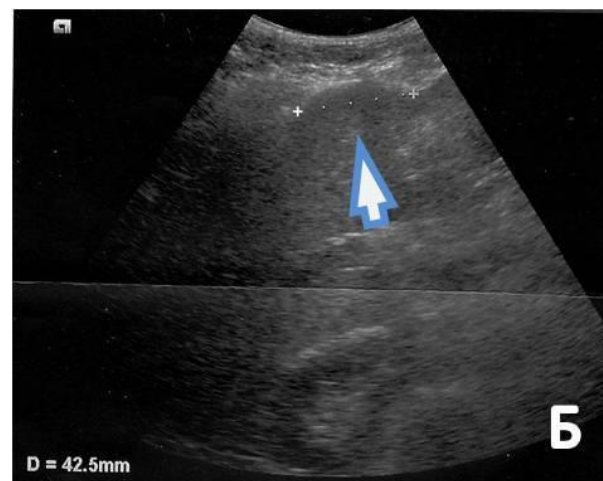
Сл. 2а и 2б. Сагитална и Коронална реконструкција на КТ на абдомен: а) На направената КТ реконструкција во сагитална рамнина се гледа инцизионална епигастрична хернија која содржи дел од левиот лобус на црниот дроб (стрелки). б) На направената КТ реконструкција во коронална рамнина јасно се гледа овален дефект на предниот абдоминален ѕид со хернијација на дел од левиот лобус на црниот дроб (стрелки)

Слабоста на предниот абдоминален ѕид е со широчина од 40 mm и височина од 32 mm. Низ отворот се хернира дел од левиот и помал дел од десниот лобус на црниот дроб, а хернираниот дел е со димензии од 34 mm x 30 mm (слика 2).

Кај пациентката пред 6 години оперативно е отстрането жолчното кесе поради калкулоза. Во изминатиот период пациентката не се штедела од работа и од кревање товар, што секако има придонес во настанувањето на хернијата. Како последица на оперативната интервенција се јавува фокалната слабост на предниот абдоминален ѕид низ кој се хернира дел од левиот и помал дел од десниот лобус на црниот дроб. По извршениот КТ преглед кај пациентката е направен и УЗ преглед на абдоменот. При изведување на УЗ прегледот, се забележува благо испакнување во горниот дел на предниот абдоминален ѕид. Кога



Сл. 3а.



Сл. 3б.

Сл. 3а и 3б. УЗ преглед на хепар: Се гледа хернијација на дел од левиот лобус на црниот дроб низ инцизионалниот дефект на предниот абдоминален ѕид (стрелка). Инцизионална хернија кај 64-годишна жена, која е оперирана од калкулозно жолчно кесе пред 6 години

конвексната ултразвучна сонда ја положивме на испакнувањето на предниот абдоминален сид се доби јасна визуелизација на ткиво на црн дроб кое проминира низ фокалната слабост на предниот абдоминален сид на местото на оперативниот рез. Станува збор за парцијална хернијација на дел од левиот лобус на хепарот, сегмент 2 (слика 3). Поради слабо изразената симптоматологија и отсуство на структурни промени на хернираниот дел од црниот дроб низ предниот абдоминален сид одлучено е пациентката да се третира конзервативно. Препорачани се редовни контроли со УЗ преглед на предниот абдоминален сид, а доколку постои сомнение за инкарцерација на хернираниот дел од црниот дроб да се направи и контролен КТ на горниот дел од абдоменот.

Дискусија

Инцизионалните хернии се одложени компликации на абдоминалната хирургија. Тие може да се јават насекаде на абдоминалниот сид и почесто се среќаваат при вертикални, одошто при попречни резови. Вообичаено, инцизионалните хернии се манифестираат во текот на првите месеци по операцијата, но може да се јават и подоцна. Преваленцата на инцизионалните хернии се движи од 0,5% до 13% за повеќето абдоминални операции [6]. Хернијацијата на црниот дроб преку предниот абдоминален сид е ретка состојба, вообичаено станува збор за инцизионални хернии на црниот дроб, кои се јавуваат како последица на претходен оперативен зафат на абдоменот кој доведува до фокална слабост на предниот абдоминален сид [4,8,9]. Низ таа слабост на предниот абдоминален сид се хернира дел од црниот дроб. Инцизионалните хернии се почести кај оние пациенти кои имале операција на аневрзма на аортата. Исто така, почести се и кај пациенти кои имаат болести на сврзното ткиво. Други ризици за појава на инцизионална хернија вклучуваат: пациенти постари од 65 години, од машки пол, со прекумерна телесна тежина и хронични белодробни заболувања [2-4,6].

Овие хернии се многу ретки така што се сметаат за исклучително редок феномен. Кај возрасната популација постојат не повеќе од 6 пријавени пациенти со стекната хернијација на црниот дроб преку дефект на предниот абдоминален сид [4,10,11,13-15]. Поради својата исклучителна реткост, тоа претставува дијагностички и терапевтски предизвик. Најчесто овие хернијации на црниот дроб не се придружени со изразена симптоматологија. Во литературата сретнавме три случаи со инкарцерација на хернираниот лобус на црниот дроб [7,9,15].

Исто така, многу ретко се среќава хернијација на црниот дроб во торакалната шуплина низ слабост или дефект на дијафрагмата, вообичаено се конгенителни или како последица на траума на градниот кош и лезија на дијафрагмата [16,17,1]. Shanbhogue и Fasih презентирале случај на 48-годишна жена со тринеделна историја на непријатност и оток во епигастриумот. Две години претходно, пациентката имала хируршка интервенција при што е направен коронарен артериски бајпас, кој дополнително е комплициран од постхируршка стернална дехисценција. КТ скенот покажа хернијација на левиот лобус на црниот дроб преку дефект на предниот абдоминален сид во средната линија.

Salemis *u cor.* презентирале случај на десна лумбална инцизионална хернија со хернијација на десниот лобус на црниот дроб. Losanoff *u cor.* презентирале случај на рекурентна интеркостална хернијација на црниот дроб. Adeonigbagbe *u cor.* презентирале случај на хернијација на црниот дроб преку слабост на *m. rectus abdominis* кој се манифестирал со постојани болки во абдоменот. Обично, хернијацијата на црниот дроб преку предниот абдоминален сид не е акутна состојба [6,8].

Сите извештаи за случаи на хернијација на црниот дроб покажуваат историја на претходни хируршки интервенции во горниот дел од абдоменот, како што е и во нашиот случај [4,10,11,13-15] И во нашиот случај, како и во другите случаи опишани во литературата, хернијација на црниот дроб е настаната по претходен оперативен третман во горниот дел од абдоменот.

Во литературата среќаваме само 6 случаи со потврдена хернијација на црниот дроб преку слабост на предниот абдоминален сид [4,10,11,13-15]. Според нашите сознанија, овој случај претставува седми случај на инцизионална хернија на црниот дроб низ преден абдоминален сид.

Третманот на овие хернии зависи од клиниката состојба на пациентот. Кај асимптоматските пациенти конзервативен третман е метода на избор. Хируршката терапија може да биде опција кај пациенти со изразена симптоматологија, а таа се изведува за да се затвори дефектот на абдоминалниот сид [2-4,8,11,13].

Заклучок

Може да заклучиме дека постои одредена поврзаност на хернијацијата на црниот дроб во горниот дел од абдоменот со претходно извршени оперативни интервенции на абдоменот. КТ е метода на избор за дијагностика на хернијацијата на црниот дроб низ предниот абдоминален

сид, но истото тоа може да се стори и со УЗ до- колку го изведува искусен радиолог. КТ овозмо- жува да се процени степенот и карактеристиките на хернијата, односно сосотојбата на одржливост на паренхимот во хернираниот дел од црниот дроб. КТ поради својата супериорност во прика- жувањето на анатомските детали и придружни- те компликации, како и поради можноста за ре- конструкција во повеќе рамнини, е дијагностичка метода на избор во дијагностиката на хернијаци- јата на црниот дроб низ предниот абдоминален сид.

Конфликт на интереси. Не е деклариран.

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УПАТСТВО ЗА ПРИЈАВА НА ТРУД ОД СОРАБОТНИЦИТЕ НА ММП

"Македонски медицински преглед" (ММП) е стручно списание на Македонското лекарско друштво, првенствено наменето на лекарите од општа практика, специјалистите од одделните медицински дисциплини и истражувачите во областа на базичните медицински и други сродни науки.

Списанието ги има следниве рубрики и категории на трудови:

1. **Изворни трудови**
2. **Соопштувања за клинички и лабораториски искуства**
3. **Прикази на случаи**
4. **Од практика за практика**
5. **Едукативни статии**
6. **Вариансе** (писма од редакцијата, општествена хроника, прикази на книги, извештаи од конгреси, симпозиуми и други стручни собири, рубриката „Во сеќавање,, и др).

Изворните трудови имаат белези на научни трудови, додека трудовите категоризирани во рубриците 2-5 имаат белези на стручни трудови.

Во ММП се објавуваат трудови на членовите на МЛД или на членови на други стручни здруженија. Авторите се одговорни за почитувањето на етичките начела при медицинските истражувања, а изнесените ставови, изведени од анализата на сопствените резултати, не се нужно и ставови на Редакцијата на ММП.

Редакцијата ги испраќа ракописите на стручна рецензија; рецензентот (ите) и Редакцијата ја определуваат дефинитивната категоризација на ракописот кој е прифатен за печатење. Редакцијата го задржува правото ракописите да ги печати според рецензираниот приоритет. Упатството за соработниците на ММП е во согласност со Ванкуверските правила за изедначени барања за ракописите кои се праќаат до биомедицинските списанија.

1. ТЕКСТ НА РАКОПИСОТ

Сите ракописи се испраќаат во електронска форма на електронската адреса (е-маил) на МЛД-ММП, со двоен проред и најмногу 28 редови на страница. Трудот се поднесува на англиски јазик латиничен фонт Times New Roman големина 12 и апстракт на македонски јазик. Лево, горе и долу треба да се остави слободна маргина од најмалку 3 см, а десно од 2,5 см.. Редниот број на страниците се пишува во десниот горен агол.

Ракописот на трудот треба да е придружен со писмо на првиот автор, со изјава дека истиот текст не е веќе објавен или поднесен/прифатен за печатење во друго списание или стручна публикација и со потврда дека ракописот е прегледан и одобрен од сите коавтори, односно со придружна декларација за евентуален конфликт на интереси со некој од авторите.

Насловната страна треба да има: наслов на македонски и англиски, имиња и презимиња на авторите, како и институциите на кои им припаѓаат, имињата на авторите и насловот на установата се поврзуваат со арапски бројки; автор за кореспонденција со сите детали (тел. е-маил); категорија на трудот; краток наслов (до 65 карактери заедно со празниот простор); како и информација за придонесот за трудот на секој коавтор (идеја, дизајн, собирање на податоци, статистичка обработка, пишување на трудот).

Насловот треба концизно да ја изрази содржината на трудот. Се препорачува да се избегнува употреба на кратенки во насловот.

Изворните трудови и соопштувањата го имаат следниов формален редослед: насловна страна, извадок на македонски јазик (вовед, методи, резултати, заклучок) со клучни зборови, извадок на македонски јазик со клучни зборови, вовед, материјал и методи, резултати, дискусија и заклучоци, литература и прилози (табели, графици и слики) и легенди за прилозите во еден фајл.

Приказите на случаи треба да содржат вовед, детален приказ на случајот, дискусија со заклучок и литература со прилози.

Извадокот на македонски јазик треба да содржи најмногу 250 зборови и да биде структуриран со сите битни чинители изнесени во трудот: вовед со целта на трудот, методот, резултати (со нумерички податоци) и заклучоци. Заедно со извадокот, треба да се достават и до 5 клучни, индексни зборови.

Извадокот на англиски јазик мора да е со содржина идентична со содржината на извадокот на македонски јазик. Клучните зборови треба да се во согласност со MeSH (Medical Subject Headings) листата на Index Medicus.

Воведот треба да претставува краток и јасен приказ на испитуваниот проблем и целите на истражувањето, со наведување на етичкиот комитет односно институцијата која го одобрила испитувањето (клиничка студија која се работи според принципите на Хелсиншката декларација за пациентите и нивните права).

Методите треба да бидат точно назначени, за да се овозможи повторување на прикажаното истражување. Особено е важно да се прецизираат критериумите за селекција на опсервираните случаи, воведените модификации на веќе познатите методи, како и идентификација на употребените лекови според генеричното име, дозите и начинот на администрација.

Резултатите треба да се прикажат јасно, по логичен редослед. Резултатите се изнесуваат во стандардните СИ единици. Во текстот треба да се назначи оптималното место каде ќе се вметнат табелите и илустрациите, за да се избегне непотребното повторување на изнесените податоци. Значајноста на резултатите треба да се обработи статистички, со детален опис на употребените статистички методи на крајот на делот *методи*.

Дискусијата треба да ги истакне импликациите од добиените резултати, споредени со постојните сознанија за испитуваниот проблем.

Заклучоците треба да не бидат подолги од 150 зборови.

2. ПРИЛОЗИ

Како прилог-документација на трудовите предложени за печатење, може да се достават до 5 прилога (табели, фигури,/слики - илустрации).

Табелите се доставуваат на крајот на трудот во истиот фајл. Секоја табела треба да има свој наслов и реден број кој ја поврзува со текстот. Хоризонтални и вертикални линии на табелата не се дозволени; ознаките на колоните во табелата се пишуваат скратено или со симбол, а нивното објаснување се пишува на дното на табелата, во вид на легенда.

Илустрациите се доставуваат со реден број како слика во црно-бела техника, а секоја слика треба да е придружена со легенда (опис).

Микрофотографиите може да содржат посебни ознаки во вид на стрелки или симболи. Покрај описот на сликата, мора да се наведе и зголемувањето и видот на боењето на препаратот (ако тоа веќе не е направено во секцијата *материјал и методи*).

Сите ознаки на фотографиите мора да бидат доволно големи, за да може јасно да се распознаат и по смалувањето во печатницата, при нивното вклучување во печатената страница на списанието.

3. ЛИТЕРАТУРА

Цитираната литература се пишува на крајот на трудот по заклучоците, со редни броеви според редоследот на појавувањето на цитатот на текстот на трудот ставени во средни загради и без простор меѓу нив (ако се последователни треба да се поврзани со црточка, на пр. [3-6]).

Литературата се цитира на следниов начин (кратенките за насловите на списанијата треба да се според листата прифатени во Index Medicus):

а) сџајија во сџисание (се наведуваат сите автори, ако ги има до 4 или помалку; ако ги има повеќе од 4 се наведуваат првите 3 автори и се додава: *и сор.*) Neglia JP Meadows AT, Robison LL *et al.* Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 325:1330-6.

б) заеднички авџор

GIVIO (Interdisciplinary group for cancer care evaluation). Reducing diagnostic delay in breast cancer. Possible therapeutic implications. *Cancer* 1986; 58: 1756-61.

в) без авџор - анонимно. Breast screening: new evidence. (*Editorial Lancet* 1984; i :1217-8).

г) џоѓлавје во книѓа или моноѓрафија

Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. Vo: Sodeman WA Jr, Sodeman WA, Ed. Pathogenic physiology: mechanisms of disease. Philadelphia; W B Saunders, 1974: 457-72.

Првите отпечатоци на трудовите им се праќаат на авторите за корекција: авторите се должни коригираниот отпечаток да и го вратат на Редакцијата на ММП во рок од 2 дена.

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Известување за членовите на МЛД

Сите што сакаат и натаму да го добиваат списанието треба да ја имаат уплатено членарината за 2014 година во висина од 600 денари и за тоа да ја информираат стручната служба на Македонско лекарско друштво, писмено или преку телефон.

Детални информации можете да добиете на телефонот на Друштвото 02 3 162 557.

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Во склад со правилникот на УКИМ рецензентите што навремено и одговорно ќе ја одработат рецензијата ќе добијат 0.4 бода кои се собираат за унапредување во академските звања. Бодовите можат да се добијат и ретроградно преку побарување во МЛД – 3162 557.