Izdavačka delatnost Društva lekara Vojvodine Srpskog lekarskog društva, Novi Sad, Vase Stajića 9
Glavni i odgovorni urednik: prof. dr GORDANA DEVEČERSKI

MEDICINSKI PREGLED

ČASOPIS DRUŠTVA LEKARA VOJVODINE SRPSKOG LEKARSKOG DRUŠTVA
PRVI BROJ JE ŠTAMPAN 1948. GODINE.

MEDICINSKI PREGLED izlazi dvomesečno (šest dvobroja godišnje), u tiražu od 1000 primeraka. Akontacija pretplate za pojedince sa teritorije Srbije za 2014. godinu iznosi 3.000,00 dinara (sa uračunatim PDV-om), a 4.000,00 dinara za pojedince van teritorije Srbije, a za ustanove 8.000,00 dinara (uz dodavanje PDV-a). Uplate se vrše na račun broj 340-1861-70 ili 115-13858-06, s naznakom „Dodatna članarina za Medicinski pregled".

**Rukopisi se dostavljaju sekretaru Redakcijskog odbora časopisa »Medicinski pregled« na adresu:
Društvo lekara Vojvodine Srpskog lekarskog društva, 21000 Novi Sad, Vase Stajića 9,
Tel. 021/528-767; Tel/Fax. 021/521-096;
E-mail: dlv@neobee.net; Web: www.dlv.org.rs**

Štamparija: Uprava za zajedničke poslove pokrajinskih organa - Odsek za poslove štamparije

Publishing Sector of the Society of Physicians of Vojvodina of the Medical Society of Serbia, Novi Sad, Vase Stajica 9,
Editor-in-Chief Prof GORDANA DEVECERSKI, MD, PhD

MEDICAL REVIEW

JOURNAL OF THE SOCIETY OF PHYSICIANS OF VOJVODINA OF THE MEDICAL SOCIETY OF SERBIA

THE FIRST ISSUE WAS PUBLISHED IN 1948

UDK and descriptor prepared by: the Library of the Faculty of Medicine, Novi Sad

MEDICAL REVIEW is published two-monthly (six double issues per a year) in the circulation of 1000 copies. Advance payment for individuals from the territory of Serbia for the year 2014 is 3,000.00 dinars (the VAT being calculated in) and 4,000.00 dinars for the individuals outside the territory of Serbia, and 8,000.00 dinars (+ the VAT) for the institutions. The payments are to be made to the account number 340-1861-70 or 115-13858-06, with the remark "Additional membership fee for the Medical Review".

The manuscripts are to be submitted to the secretary of the Editorial Board of the journal "Medical Review" to the following address: Društvo lekara Vojvodine Srpskog lekarskog društva, 21000 Novi Sad, Vase Stajića 9, Tel. 021/528-767; Tel/Fax. 021/521-096; E-mail: dlv@neobee.net; Web: www.dlv.org.rs

Printed by: Department for Joint Affairs of Provincial Authorities - Sector for Printing

M E D I C I N S K I P R E G L E D
ČASOPIS DRUŠTVA LEKARA VOJVODINE SRPSKOG LEKARSKOG DRUŠTVA
Novi Sad Vase Stajića 9 Srbija

Med Pregl 2014; LXVII (1-2): 1-66. Novi Sad: januar-februar.

SADRŽAJ

M E D I C A L R E V I E W
JOURNAL OF THE SOCIETY OF PHYSICIANS OF VOJVODINA OF THE MEDICAL SOCIETY OF SERBIA
Novi Sad *Vase Stajića 9* *Serbia*

Med Pregl 2014; LXVII (1-2): 1-66. Novi Sad: January-February.

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VEGETARIAN DIET IN INFANTS

VEGETARIJANSKA ISHRANA ODOJČADI

Olgica MILANKOV

Introduction

Vegetarianism is a specific diet that involves eating food of plant origin, sometimes milk and dairy products, eggs or fish, but abstaining from food containing meat and meat products. The word ”vegetarianism” is of Latin origin and is composed of two words: *vegetus* meaning alive and *vegetatio* which means the plants and vegetation [1, 2].

Depending on the extent to which the food of animal origin is excluded from the diet as well as on the ways, plans and tactics for including vegetarian food in the diet there are several types of vegetarian diet:

– lacto-vegetarianism - allows the use of milk and dairy products;

– lacto-ovo-vegetarianism - allows the use of milk and eggs, and all the products made of them;

– pesco-vegetarianism - allows the use of the fish meat;

– strict vegetarianism or veganism - does not allow the use of any animal product. It is not allowed to use milk and eggs, as well as wool, silk, leather, i.e. food and non-food items derived from by-products of animal origin (most products for personal hygiene). Often vegans do not use honey and some sweeteners, refined white sugar and maple syrup, because some animal products are used for their production. Dietary habits of most vegans are motivated by ethical reasons and awareness of the purposes to which animal products are used and how they can be substituted [1–3].

Besides consuming these types of diet, there are people, the so called raw vegans, who eat only raw food because they think that since cooking destroys large amounts of vitamins and phytonutrients, thermal processing makes harmful and carcinogenic substances. Macrobiotic practitioners use organic food without pesticides and chemical fertilizers based on whole grain cereals and legumes. They avoid white refined sugar, refined oil and wheat flour. Therefore, in their diet they use substitutes for oil in the form of olive oil, brown sugar instead of white sugar and wholemeal flour instead of white wheat flour. There are also people whose diet is based on fruits and seeds - fruitarians. There is a special type of these people known as radical fruitarians who eat exclusively fruit that has fallen to the ground [1–4].

The aim of this paper is to neither persuade nor discourage someone from consuming vegetarian foods, which can certainly be healthy and ethically justified, but to offer the truth and some medical facts that could help people make their own decisions.

Reasons for Choosing this Diet

Some people have decided to become vegetarians in order to reduce food intake and thus lose body weight; some people have opted for this diet for health reasons and others for religious and philosophical reasons [1].

Vegetarian diet is common in some parts of the world; however, it does not fit into the lifestyle of most people in our region. It takes some time and practice to get adapted to this type of diet.

Vegetarianism has been known for thousands of years in India, where it used to be a part of spiritual practice known as ahimsa (non-violence). The interest in this diet dates back to ancient time, starting from Socrates, Spinoza, Plato, Plutarch, Diogenes, Seneca, Cicero, etc, who advocated vegetarianism. It was further cherished by Leonardo da Vinci, Newton, Voltaire, Goethe, Nietzsche, Einstein, Tolstoy, Tesla, Gandhi, Bob Dylan, John Lennon, Linda McCartney and many others to the modern times [5].

It is known that in the USA today there are 3% of the population who claim to be vegetarians, of

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whom 2.5% are adults and about 2% are children, total number being about 5 million people. Many associations of vegetarians have been established throughout the world since 1977. These associations celebrate October 1st as their day and by doing so they want to demonstrate the value and benefits of this lifestyle and diet [3,5].

It has already been pointed out that there are many reasons for choosing vegetarian diet and lifestyle.

– *Ethical* - Vegetarian principles are based on the fact that the human needs should not be satisfied at the expense of other living beings by inflicting pain and taking a life. Life should be respected in all its forms. Vegetarians also think that keeping animals in confined space is neither humane nor ethical.

– *Religious and spiritual* – The Hinduists, Buddhists, Hare Krishna and many other Christian religious communities as well as Jews and members of the Islamic faith prohibit taking a life as a fundamental postulate of vegetarianism. However, Buddhists are not against the use of animal meat, they are against killing animals because they believe in reincarnation. As a result they are allowed to eat meat from animals that died naturally. By observing fasting on some days, Orthodox Christians are occasional vegetarians. Vegetarians believe that spiritual progress of man is achieved by stopping eating meat, "... meat is a mental state of aggression, plant-based diet is a mental state of peace"...

– *Environmental* - Vegetarians agree that meat production is a waste of money, because large amounts of natural resources used for breeding animals, in their opinion, may be used for other, more useful purposes and feed more people. For instance, about 9.5 kg of protein is necessary for physiological needs of animals, the inedible parts of the body, the bones, so that the quantity of meat that can be used for human diet is only about 0.5 kg of animal protein. In this way people can regain only 5% of protein invested in animal nutrition. In addition, plant foods provide 10-20 times more protein than meat if calculated by an acre. If protein-rich plants, such as peas and beans, are cultivated on an acre, that same acre can yield 130-230 kg of protein. If these plants are used for feeding animals, 18-25 kg of animal protein can be obtained. A certain amount of water which animals use for drinking should be added to this calculation definitely and that amount of water would be ten times larger than the one used for growing wheat. An area for grazing animals is another important reason why vegetarianism is more cost effective diet. It has been calculated that nearly half of the tropical forests in Central America have been destroyed in the last 25 years in order to produce sufficient quantities of beef to be consumed. The damage is enormous because the destruction of these forests has been slowly but surely destroying the "lungs of the planet".

– *Economic* - Meat production is economically less profitable, which is the reason for higher market prices of meat in comparison to vegetable. As a result, people from the "third world" eat mainly vegetarian food because this diet is cheaper than eating meat. By breeding animals we waste food that could be used as a meal for hungry people, destroy fertile land, burn forests, pollute water and air, so many people believe that our planet could be saved by giving up meat. Industry of meat, milk and eggs destroys the earth at great speed [1-3].

– *Health* - This diet reduces the following: obesity, the risk of heart and blood vessel diseases, hypertension, immunity disorders, digestive disorders and other stomach problems as well as the incidence of malignancy and it affects the manifestation of diabetes. In the opinion of vegetarians this diet has numerous benefits, which have their own importance in the prevention and treatment of modern diseases [1–3, 6–8].

Are people herbivores, carnivores or omnivores?

This question can be answered if the structure of the digestive tract of man and other animals are compared and observed patiently and accurately. The process of digestion begins in the mouth. In the mouth the food is chopped up, mixed with saliva, shaped into a bite and swallowed. The shape of the teeth and the jaw movements affect chopping food into smaller parts. The jaw can move into three directions: up and down, side to side, backwards and forwards and these movements provide adequate chewing of the food. Should the jaw move in only one direction chewing would be impossible. Our teeth (incisors, canines, premolars and molars), have their characteristic structure and function. The incisors are sharp and they split food into small pieces, the canines are pointed and they separate the softer parts of the food from the bones. The molars and premolars with their wide and flat surface grind and crush food. The above technique of forming a bite is more similar to feeding of herbivores [9,10].

Unlike herbivores, carnivores have small, sharp incisors which are used for catching the victim, and long and sharp canines which are used for killing the victim. The molars are sharp and by closing the jaw and making movements in only one direction, up and down, they separate the meat from the bones and such pieces of meat are swallowed without being mixed with saliva. Saliva of herbivores and human saliva have a high pH value, which results in better digestion of carbohydrates in the oral cavity. Saliva of carnivores provides an acidic environment which is more suitable for digesting protein and it is not capable of converting starch into sugar [9–11].

The food goes from the mouth through the oesophagus and arrives into the stomach. The main ingredient of gastric juice, apart from hydrochloric acid, is mucus that covers the stomach inside and protects it from acid-induced damage together with the stomach enzymes. The main difference in the composition of gastric juice between carnivores and herbivores is the strength of hydrochloric acid that is ten times stronger in carnivores in order to neutralize toxins made by decaying of meat and to enhance the bone decomposition.

The food goes downwards into the small intestine and the remaining food goes down into the colon. The intestines in humans are longer than in carnivores; the small intestine is about 7 meters long and the colon is up to 2 meters long. An intestine of that length can hold food up to three days without fear of producing toxins that could damage the intestine. The intestines in carnivores are much shorter so that the decayed flesh can stay in as little time as possible, thus avoiding undesirable consequences such as bowel cancer induced by the resulting toxins. Human intestines, however, are not so long as in herbivores (although the structure of the digestive tract of man rather resembles the structure of a plant-eating being); therefore the man can afford only an occasional meat meal. Should a herbivore consumed meat, it would soon die of poisoning [9].

By their anatomical structure and physiological function of their digestive system humans are mostly vegetarians and although eating meat is not a problem for people, it should not be their main food. All of this means that people belong to the ”omnivores”, which certainly does not imply that they have to eat meat, but it also means that people are able to digest meat. The decision not to consume meat is purely ethical and has nothing to do with health.

Humans process food in numerous ways (cooking, frying, roasting and technical transforming) in order to make it delicious and useful and at the same time to spare their own time by avoiding sitting for hours chewing leaves like gorillas (or a plate of beans, potatoes, cereals if you are a vegan); thus they solve the problem of the energy needs of their body and in order to satisfy their needs in vitamins and minerals they add delicious fruit and herbs to all that food [10–13].

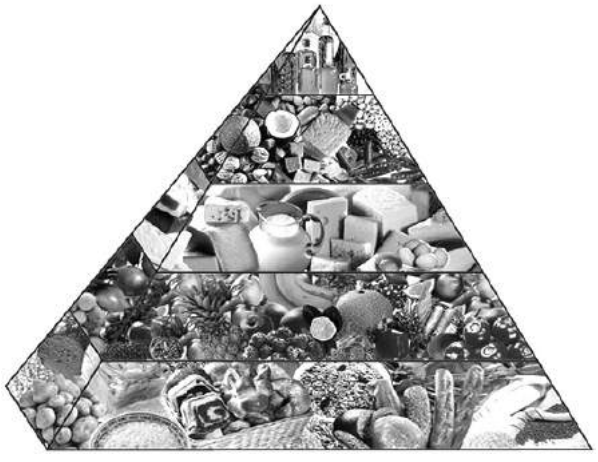

Figure 1. Vegetarian food pyramid
Slika 1. *Piramida vegetarijanske hrane*

Advantages of Vegetarian Diet

Nutritionists claim that there are a number of advantages of this type of diet. Numerous studies have shown that people who consume this type of diet have experienced a drastic decrease in the concentration of blood lipids (cholesterol), which is the cause of many health problems such as high blood pressure, other cardiovascular diseases, overweight and type 2 diabetes [1–3,7,8,14,15].

Recent studies have shown that this diet reduces the concentration of free radicals harmful to the body [16]. It has been observed that the incidence of colon cancer, breast cancer and prostate cancer is lower in this population [1-3]. In accordance with the principles of vegetarian diet, the World Health Organization has made the pyramid of healthy vegetarian diet which is based on whole grains and legumes **(Figure 1).** Fruit and vegetables come immediately afterwards in this pyramid. According to the World Health Organization, well-planned meals should be made of these four ingredients individually or in various combinations. If the pyramid is analyzed carefully, it can be noted that vegetable oils, dairy products, eggs and sugar can be used by choice. As these foods do not form the basis of a healthy diet they should be used in limited quantities [17].

Possible Problems with Vegetarian Diet

Vegetarian diet is usually accused of not providing enough calcium, iron, vitamin B 12, and protein, and therefore it is possible to develop certain deficiencies such as some types of anaemia (sideropenic, pernicious), rickets, and even some types of malnutrition. The reasons are justified since this specific diet does not recommend the consumption of milk and meat, and these very foods represent the main source of necessary nutrients [18–22].

Proteins are a vital part of all living tissues, muscles, blood, body fluids, bones and teeth. The basic elements of proteins are amino acids which in different combinations form protein molecules. Out of 22 known amino acids, thirteen are produced by the body. The remaining nine amino acids, known as essential amino acids, must be taken in with food. To obtain sufficient amounts of proteins, a diet must be varied and balanced. Even the temporary absence of one of the essential amino acids can affect protein synthesis. In fact, if any of the essential amino acids is present in quantities less than re-

quired or even missing, it will proportionally reduce the effectiveness of the other ones [1,2].

Animal proteins (meat, cheese, eggs, fish) contain all the essential amino acids in optimal proportions for the human body and with proper balanced diet present ”full or complete proteins” [1-3].

Protein intake in vegetarians is slightly lower than in people who eat traditional meals with meat. However, despite a lower intake vegetarians can satisfy certain daily needs. The question is whether it is justified to be concerned about the appropriate content of essential amino acids in plant proteins, which cannot be synthesized in the human body. Milk, dairy products and eggs provide these amino acids in lacto vegetarians and ovo vegetarians. The lack of essential amino acids, in the strict forms of vegetarian diet, can be compensated only partly by taking hazelnuts, almonds and pistachios. The problem arises in families with a positive atopic history, and when this food is consumed at the age of infants and small children because of the risk of a foreign body aspiration! However, when combined with small quantities of animal protein they become complete proteins [1-4].

Vitamin B12 (cyanocobalamin) is present exclusively in animal products. Daily needs are very small, about 2-3 μg. It takes a lot of time to recognize the deficit of this vitamin and to diagnose pernicious anaemia which manifests after a long time and causes severe, irreversible damage to the nerves. The human body needs a very low dose of vitamin B12, but the question is whether people who do not eat animal products can provide the required amount of this vitamin.

The necessary amount of vitamin B12 is provided by consuming the food of animal origin (cheese, eggs, meat, milk, etc). In fact, the food of animal origin is the only food where it is possible to find natural and sufficient amounts of vitamin B12. How do vegetarians solve this problem? Vegetarians find the solution by substituting this vitamin in the form of supplementary dietary products that contain vitamin B12, i.e. they consume soy milk, rice and cereals that are enriched with vitamin B12 and beverages based on yeast. Since the literature raises some doubts about the quantity of vitamin B12 intake in a vegetarian diet, nutritionists suggest that vegetarians should stick to the conservative ideas and provide substitute intake of B12 vitamin [1,2,23].

The body produces sufficient quantity of vitamin D when the skin is exposed to the sunlight, which is a natural source of vitamin D. It is recommended to expose children’s hands and face to the sunlight twice or three times a week for 20 minutes in order to provide a sufficient amount of vitamin D. Vitamin D can be found only in certain foodstuffs, and the only food that naturally contains vitamin D are liver and egg yolk. Vitamin D deficiency can lead to a bone deformity-rickets, a disease accompanied by many other symptoms. Therefore, in some countries, dairy products are enriched with vitamin D, as well as some food for vegetarians (soy and rice milk, other milk substitutes). For vegans, who are strict vegetarians, dieticians recommend daily intake of dietary supplements [24,25].

Rich sources of vitamin B6 (riboflavin) are milk, dairy products, eggs, and meat. Therefore, children who are ovo vegetarians and lacto vegetarians are not at risk of having hypovitaminosis B6. This vitamin is essential for the normal functioning of the enzymes responsible for the production of energy in macronutrients. To avoid this deficiency individuals on a vegetarian diet should periodically take brewer’s yeast and a lot of grain cereals enriched with this vitamin and dark green vegetables [1,2].

There is a lot of calcium in milk and dairy products which provide ¾ of the daily needs of the body. The importance of calcium is well known – it gives strength to the bones and teeth, it participates in the process of coagulation and functioning of the muscles, heart, and nerves, and in a variety of other biochemical processes. Sources of calcium are sesame seeds, almonds, hazelnuts, spinach, etc; however, calcium from fruits, vegetables, soy and nuts provides only 1/10 of the daily needs of the body. Foods with a lot of fibres (spinach, chard and broccoli) often contain a lot of oxalic acid which creates oxalate kidney stones with calcium.

The role of iron in the body is to transfer oxygen in the red blood cells. Iron in the body is in the form of haem, 40% of which comes from the food of animal origin and it is absorbed in the small intestine. Non-haem iron is mainly derived from the food of plant origin and it is difficult to be absorbed. Compared to haem iron, only 1/5 of non-haem iron is absorbed. Considering the fact that milk is the main food for infants, and that rapid growth at this age requires a lot of iron, the risks for developing anaemia are great because neither human nor cow’s milk has the sufficient amount of iron.

Zinc is also a ”problematic” nutrient for vegetarians. Scientists have not yet defined the amount of the recommended daily intake of zinc. Rich sources of zinc for vegetarians are: bran, kale, legumes, wheat germ, cooked millet, yogurt [1–3].

Conclusion

The human digestive tract has been adjusted to digest meat, but it has not adapted to its exclusive domination. The human body can live quite well without meat as long as the needs for the essential elements (vitamins, minerals, essential proteins, essential fats that the body can not produce) are provided. A well-planned vegetarian diet is appropriate for all stages of the human life cycle, including pregnancy, lactation and breastfeeding period [2,3]. From the historical point of view, it is tradi-

tion that should be respected, not fashion. We eat the food that our mothers eat and our children eat the same food as we do [4].

An adult who was adequately fed during intrauterine period and infancy can make an independent decision as an adolescent whether to become a vegetarian or not. This is a matter of individual choice!

Vegan diet, which excludes food of animal origin, is not recommended for children under the age of three, as well as in puberty i.e. during periods of rapid growth [18,20,21,26].

If a child is lacto or ovo vegetarian there is no risk of any deficiencies.

If the diet is balanced, varied and well planned, and the child consumes enough vitamins and minerals, and if foodstuffs are well combined, certain types of vegetarianism can be acceptable.

Vegetarian food is less concentrated and does not provide the required energy intake; since it is poor in fat, it is necessary to eat large meals. This is a problem for the infants because the amount of the raw food they need to take in exceeds their intestinal capacity [27,28].

Milk of women who are vegetarians is nutritionally adequate so the growth and development of the baby are adequate too [27]. Breastfeeding is imperative in diet of infants up to six months. Human milk provides normal growth and development, decreases infant morbidity and mortality, reduces the incidence of respiratory and gastrointestinal diseases, as well as the possibility of sensitization of infants to unfamiliar proteins (e.g. cow's milk protein) [29,30]. If the mother does not have enough milk, soy formulas are introduced in the infant's diet by the end of the first year of life. These formulas are often rich in iron and have the sufficient amount of vitamin D. The disadvantage of these formulas is that they do not contain the proper amount of proteins, carbohydrates and fats. After the age of one year, when the child begins to eat other foodstuffs besides milk, protein needs are becoming greater in comparison with the children who consume animal proteins. This means that instead of 15 g/kg of body weight proteins a child should have 19 g/kg of body weight proteins. The solution is to give a child a cup of soy protein preparations with 6 g of proteins or one cup of tofu (soy cheese) with 5 g of proteins. Introduction of other food starts between 4 and 6 months of age, when it is essential to provide a greater amount of energy and other nutriments for normal growth and development. Fortified cereals should be introduced first, then fruits and vegetables and finally protein food. Sufficient amounts of calcium and protein can be provided by carefully planned vegetarian diet, by consuming green leafy vegetables, whole grains and legumes. Sufficient amount of fat must be provided by the diet to produce energy and for the proper development of the brain and retina [26,27].

Vegetarian food is mostly based on carbohydrates and some protein (bread, potatoes, rice and fruit). Well-planned diet reduces the risk and danger of not consuming enough proteins. One of the problems is also a reduced intake of calcium and iron, and an increased intake of fibres (with low amount of calories and proteins). Except ovo vegetarian diet, other types of vegetarianism do not provide sufficient amounts of iron. In addition to that there is a great intake of foodstuffs that interfere with iron absorption, such as spinach, phytin in grains and tannin in tea. These are the reasons why a child should get certain iron supplements to prevent this microelement deficiency and hence the appearance of anaemia. If there is a slightest doubt in the correctness and regularity of the implementation of vegetarian diet it is necessary to think of some "additional remedies" that can give a sense of security and an adequate substitute of certain nutrients. If we decide to use additional multivitamin and multimineral preparations, the best choice are those which contain just a specific vitamin or mineral. It is not recommended to use these preparations every day, but several times a week [1–3].

Vegetarian diet should not be rejected, one just has to know and identify the differences between different types of vegetarianism and conventional-traditional diet.

Vegetarian diet is marked by compassion of people for animals. Vegetarians believe that there is plenty of food on our planet and that animals as food are not necessary for survival and therefore there is no justification for the excessive breeding of animals in order to kill them after a while and all of that just for the food to be eaten.

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Rad je primljen 19. IX 2013.
Prihvaćen za štampu 19. IX 2013.
BIBLID.0025-8105:(2014):LXVII:1-2:5-10.

ORIGINAL STUDIES
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Original study
Originalni naučni rad
UDK 616.728.3-089.168:616-022]-085
DOI: 10.2298/MPNS1402011R

INFECTIONS AFTER RECONSTRUCTIONS OF ANTERIOR CRUCIATE LIGAMENT

INFEKCIJE POSLE REKONSTRUKCIJA PREDNJEG UKRŠTENOG LIGAMENTA

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Summary

Introduction. Infections after anterior cruciate ligament reconstructions are rare, but, on the other hand, they are difficult to be treated. The aim of this study was to analyze causes of infections, risk factors, diagnostics, and possibilities of their prevention. **Material and Methods**. Seventeen deep infections (1.2%) were found in 1425 patients who had undergone anterior cruciate ligament reconstructions. Fifteen patients were males and two were females. Out of 475 professional athletes nine (1.9%) had this postoperative complication. Eleven patients with septic arthritis were allergic to penicillin. Three of them had immunosuppressive diseases. **Results**. Staphylococcus aureus was isolated in eleven cases (65%), other Staphylococcus and Streptococcus groups were found in four and three patients, respectively; while one patient had infection although the punctate was negative. Out of 965 patients with the patellar tendon grafts, ten (1.03%) had this complication, while the incidence was 1.52% (7/460) in those with the hamstring grafts. Fifteen infections were acute with obvious symptoms within 14 days after surgery. Severe pain, limited range of motion, swelling of the knee joint and fever were the most common symptoms, while rubor and pus developed rarely. The infection was three times more frequent in the patients who had undergone surgery lasting more than 1.5 hour. **Discussion and Conclusion**. The following population groups are at risk of developing septic arthritis after anterior cruciate ligament reconstructions: professional athletes, those who are allergic to penicillin, and those with immunosuppressive diseases. Staphyllococus aureus is the most common cause of infection. The patients with the hamstring autografts have a higher risk than those with the patellar tendon grafts. Preventive measures that should be performed include aseptic conditions in operative rooms, irrigation of the graft before its placement into the bone tunnels, experience of surgeon and proper antibiotics.

Key words: Anterior Cruciate Ligament; Anterior Cruciate Ligament Reconstruction; Infection; Postoperative Complications; Risk Factors; Staphylococcus aureus

Sažetak

Uvod. Infekcije nakon rekonstrukcija prednjeg ukrštenog ligamenta predstavljaju retke, ali za lečenje teške postoperativne komplikacije, te je cilj studije analiza uzroka infekcija, definisanje faktora rizika, prikaz dijagnostike i mogućnosti prevencije navedenih komplikacija. **Materijal i metode.** Na uzorku od 1 425 pacijenata, kod kojih je izvršena artroskopska rekonstrukcija prednjeg ukrštenog ligamenta, zabeležili smo 17 infekcija kolenog zgloba (1,2%). Petnaest pacijenata je bilo muškog pola, a dva ženskog. Od 475 operisanih aktivnih sportista, kod njih devet (1,9%) nastala je postoperativna infekcija kolenog zgloba. Čak 11 pacijenata je bilo alergično na penicilin. Tri pacijenta imali su imunokompromitujuća stanja. **Rezultati.** U 11 slučajeva izolovana je bakterija *Staphyllococus aureus* (65%), u četiri slučaja ostale podgrupe stafilokoka, u tri streptokok, a jedan pacijent je imao duboku infekciju i pored negativnog biograma. Od 965 pacijenata gde je izbor kalema bio kost–čašična veza–kost, njih 10 (1,03%) imalo je infekciju, dok je u grupi sa 460 operisanih kost–tetive polužilastog i vitkog mišića–kost kalemom zabeleženo 7 infekcija (1,52%). Petnaest infekcija su bile akutne, sa jasnim kliničkim znacima prvih 14 postoperativnih dana, u smislu: izrazitog bola u kolenom zglobu, ograničenja pokreta, otoka i povišene telesne temperature, a ređe su se javljali crvenilo kože i gnojni sekret. Pacijenti kod kojih je operacija trajala duže od 1,5 sata imali su tri puta češće infekcije od ostalih. **Diskusija i zaključak.** Rizičnu grupu pacijenata za infekciju, nakon rekonstrukcije prednjeg ukrštenog ligamentu, predstavljaju: aktivni sportisti, alergični na penicilin, sa imunokompromitujućim oboljenjima. *Staphyllococus aureus* je najčešći uzročnik. Zabeležili smo češće infekcije kod pacijenata kojima su izbor kalema bile tetive polužilastog i vitkog mišića. Prevencija infekcija sastojala bi se od: dezinfekcije operativnog polja pre ulaska u operacionu salu, mera antisepse u sali, mehaničkog ispiranja kalema pre postavljanja u koštane tunele, iskustva hirurga i antibiotske terapije.

Ključne reči: Prednji ukršteni ligament; Rekonstrukcija prednjeg ukrštenog ligamenta; Infekcija; Postoperativne komplikacije; Faktori rizika; Stafilokokus aureus

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Abbreviations

ACL – anterior cruciate ligament
BTB – bone-patellar tendon-bone
BHB – bone-hamstring tendons-bone
CRP – C-reactive protein
MRSA – Methicillin Resistent Staphylococcus aureus

Introduction

Anterior cruciate ligament (ACL) injuries most frequently happen during sports activities by non-contact rotatory movement of the knee joint [1, 2]. The reconstruction of ACL is a very popular surgery in the world. Only in the United States of America, this procedure is performed more than 200 000 times per year [3], while in Vojvodina we perform around 300 reconstructions annually [4].

The percentage of these successfully performed surgeries is very high, between 80-90% [3-6]; however, the number of postoperative complications is getting higher with the increasing number of reconstructions. Septic arthritis of the knee is a rare complication after arthroscopic ACL reconstruction. It happens after less than 2% of all surgeries [3, 6].

The risk factors depend on [7]:

– the patient (immunity, diseases, allergy to antibiotics, former surgeries);

– the surgeon (choice of antibiotics, operative technique, graft manipulation, experience of early detection and choice of treatment);

– general preventive measures and treating of intrahospital (nosocomial) infections (aseptic conditions in hospitals, operating rooms, sterile surgical instruments, gloves etc.)

These infections can compromise the result of surgery and endanger the patient's health [8-11]. The importance of early diagnostics is even greater because improper diagnostics and treatment can lead to graft failure, instability, and limited range of motion of knee joint, as well as the life-threatening condition of patient [6].

The aim of this study was to determine the incidence of septic arthritis after ACL reconstructions and to analyze the symptoms, causes, and risk factors in our material.

Material and Methods

A multicentre, retrospective study, performed at the Clinical Centre of Vojvodina in Novi Sad and General Hospital of Subotica, dealt with infections after ACL reconstructions in the sample of 1425 patients. Out of 17 patients who developed infection after surgery, 15 were males (88%) and two were females (12%), their average age being 24.5 years (18-39). The infection was detected in both the left and the right knee, i.e. in nine and eight cases, respectively.

Bone-patellar tendon-bone (BTB) graft was applied in 965 patients and the choice for reconstruction in other 460 patients was bone-hamstring tendons-bone (BHB) graft.

All of the patients were treated with prophylactic antibiotics preoperatively and three days after surgery [12] (Cephalosporines of the first generation and Gentamicin).

The total sample and the sub-groups of the patients were analyzed for the causes of infection, time that lapsed from surgery to the development of clinical and laboratory sings as well as the predisposing risk factors (associated with the patient, surgical technique and preventive measures).

The results were analyzed and compared among the groups, and they are graphically presented in the further text.

Results

Septic arthritis of the knee joint developed in 17 out of 1425 patients included in the study sample (1.2%). Out of 475 professional athletes, nine (1.9%) had this postoperative complication. Eleven patients (64.7%) were allergic to penicillin. Although the majority of patients were young people, three of them had immunosuppressive diseases (infective mononucleosis, sarcoidosis and respiratory infection, each).

Ten out of 965 patients with patellar tendon grafts had this complication (1.03%), while the incidence was 1.52% (7/460) in those with hamstring grafts.

The surgeries performed by more experienced surgeons lasted on average 64 minutes. The incidence of infection was 1.1% in that group. When ACL reconstruction lasted more than 90 minutes, the incidence of infection was 3.3%.

Infections became clinically evident from three to twenty days after the surgery (the average being 7.5 days); they were acute in 15 cases within the first 14 postoperative days and sub-acute in two patients in 2-4 postoperative weeks. The most common symptoms were severe pain, limited range of motion, swelling of the knee joint, and fever (37.3-39.8 Celsius degrees), while rubor and pus from the wound occurred rarely. **(Graph 1)**

Laboratory screening test were performed after the symptoms had occurred. Erythrocyte sedimentation was high and ranged from 50-113 (average 87.33). C-reactive protein (CRP) ranged from 126-210 (the average being 155). The treatment of infection was discontinued when CRP was reduced to normal values (under 5).

Staphylococcus aureus was isolated in eleven cases (65%), other Staphylococcus groups and Streptococcus were found in four (epidermidis and lungdunensis) and three patients, respectively, one patient had adenovirus infection, whereas one patient had infection although the punctate was negative.

Discussion

Anterior cruciate ligament reconstruction is a surgery with very rare complications [1]. Over the last 40 years, arthroscopic procedures have considerably reduced bleeding, scar size, operative

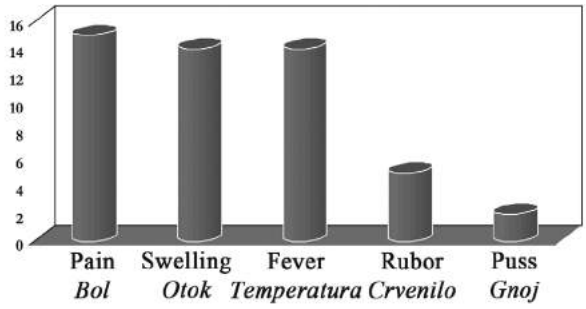
time and provided faster rehabilitation, and return to everyday activities [1].

Infection following an ACL reconstruction is a rare postoperative complication owing to prophylactic administration of antibiotics and intra-operative drainage of the joint with a lot of fluid as well as young age of the patients and because arthroscopy is a minimally invasive technique. The prevalence of septic arthritis after ACL reconstructions is less than 2.0% [6, 13-16]. The incidence in our study sample was 1.2%, which was higher than the one reported by Indelli et al [13] (0.14%), but lower than in the sample of Ejerhed and Eriksson, which was 1.9% [15, 16]. The factors influencing infection are sterilization of the equipment, antibiotics, duration of surgery and immunological system of patients [7, 13, 14].

Initially, bacteria can be conveyed into the joint or the periarticular tissue via arthroscopy medium or instruments [7] and when they are deposited in the synovial membrane, they can cause an acute inflammatory response [17]. As the synovial membrane does not exhibit a limiting barrier, bacteria infiltrate the synovial fluid easily and cause purulent infection [17]. Therefore, the main problem is the imminent danger of infection dispersion throughout the complete joint, protracted synovitis as well as irreversible cartilage damage. An organism that is not immunocompetent, as it was the case in our three patients, is not capable of eliminating pathogens via phagocytosis by synovial cells [17]. Therefore, the influence of surgeons is limited to the choice of patients to be operated on. Fatal outcomes of ACL reconstructions are extremely rare and they are reported mostly after infections caused by Clostridium bacteria [18, 19], which was not the case in our study sample. If neglected, unsuccessfully treated, or not treated at all, infections can even endanger the patient's life or cause severe damage to the affected joint in the form of cartilage damage, arthrofibrosis and graft failure [20].

According to a recently published study [21], professional athletes may be a part of a specific group of patients at higher risk of developing infection after ACL reconstruction. The prevalence of septic arthritis was 0.37% in the nonprofessional group and 5.7% in the professional athlete population (88 out of the total number of operated patients, which was 1957). Our results have also shown that active sportsmen are at risk of developing an infection for unknown reason, with the incidence of 1.9%. Sex and the side of the knee do not affect the infection [6, 13-16], as shown in our sample. The fact that men dominate in our study sample only shows that males are more prone to ACL injuries so they are operated three to eight times more frequently than females [2, 4, 22].

Infections can be acute (within two weeks after surgery), sub-acute (from two weeks to two months) and chronic (after two months). All of our infections were evident within three weeks postoperatively,



Graph 1. Symptoms of infection after ACL reconstruction
Grafikon 1. *Simptomi infekcije nakon rekonstrukcije prednje ukrštene veze kolena*

that being in accordance with other studies [6, 13-16,23]. The most typical sign is the limited range of motion, present in 85% cases, swelling of a joint in 78%; however, a significant rubor or swelling was observed only in 30% of the cases [24]. Redness can be present in the area of the surgical approach; pus can leak from the wound [17], as it happened in our study. The macroscopic inspection of the viscous, purulent aspirate may already indicate a possible infection [17].

Infections are most frequently induced by bacterium Staphylococcus, which is found in more than two thirds of cases [6, 13, 23]. This is particularly true for the subgroup Staphylococcus Aureus because it is usually found on the skin surface. This Gram-positive bacterium was the most common cause of infection in our sample as well. Its resistance to antibiotics is a serious problem nowadays [25]. Our patients were lucky not to have Methicillin Resistant Staphylococcus Aureus (MRSA). Cephalosporines of 1st or 2nd generation are sufficient to fight against Staphylococcus Aureus [25]. In case of allergy to Cephalosporines and/or incompatibility, Clindamycin can be used. Vancomycin is indicated only in terms of second line antibiotics and in case of Cephalosporine intolerance or MRSA colonization or infection [12]. From the pharmacodynamic point of view, the best moment to introduce the first antibiotic dose is 30 minutes before the skin incision [12]. In case of infection, a positive pathogen proof cannot always be found. As for our sample, the pathogen failed to be isolated only in one case, in other words, there were 94% of the positive smears and/or punctates, whereas literature data vary from 60% to 100% [7]. It is even more difficult to be found when the patient has been treated by antibiotics. Most authors [7, 12, 13, 23] agree that antibiotics therapy should be administered for at least 4-6 weeks after the antibiogram until the CRP-level is normalized [7, 10].

Analysis of erythrocyte sedimentation and white blood cell count (WBC) is only of limited diagnostic value because almost 40% of patients presenting with acute septic arthritis have normal leukocyte account [26]. In contrast, CRP is positive in more than 95% of the patients [26], which was also true for our study sample.

Proper hygiene conditions in hospital rooms and preventive aseptic measures during surgery and postoperative care can reduce infection rate. Studies self-critically reporting a system failure in sterilization technique as a cause of increased incidence of infection after ACL reconstruction (going from 0.3% to as high as 12.2%) are scarce [27]. Surgical masks, gloves, and insufficiently sterilized instruments can also be a source of graft contamination [28]. A graft implanted in the knee joint does not have initial vascularization, so antibiotics are not effective [28, 29]. Hantes et al [29] proved that seven out of 60 (12%) microbiologically examined grafts were initially contaminated, mostly with Staphylococcus, although a postoperative infection did not develop in any of these cases. Hamstring autografts do seem to have a higher risk of infection than patellar tendon grafts. The rate of contamination is higher for hamstring grafts because of the longer graft-preparation time (nineteen minutes) than for bone-patellar tendon-bone autografts (ten minutes). In hamstring group, cultures of graft tissue from four patients (13%) were positive for bacteria. In the bone-patellar tendon-bone group, cultures from three patients (10%) were positive.

Duration of surgery can affect the rate of septic arthritis, thus the incidence of infection was three times higher in our patients who had undergone surgery lasting more than 1.5 hour either because meniscus and cartilage were operated on at the same time or because the surgeons were less experienced. Other authors [15, 16, 23, 27] have also reported a higher incidence of infection in hamstring grafts than in patellar tendon grafts. Ejerhed et al and Eriksson et al [15, 16] reported six cases of deep knee infections in 320 patients, five of them being among hamstring grafts and only one in patellar grafts.

Some of the authors tried to find the possibilities of preventing these infections [3, 30-32]. Molina et al [30] reported the incidence of positive cultures to be 58% when an ACL was accidentally dropped on the operating room floor. We also had two similar cases without ensuing infection because we treated those grafts in triple antibiotic solution followed by a sterile saline wash.

The similar results were recorded in another study [32] that surveyed leaders in sports medicine who perform ACL reconstructions to determine the preferred management when graft contamination occurs. Forty-seven of 196 (25%) surgeons reported at least one contamination during their career. Forty-three of 57 (75%) contaminated grafts were managed with cleansing of the graft and proceeding with reconstruction. Ten (18%) were managed by harvesting a different graft, and four (7%) were substituted with an allograft. No infections in any of the contaminated grafts were reported because cultures did not correlate with clinical infections [18]. Matava et al [31] recommended culture-specific antibiotics and surgical irrigation with graft retention as initial treatment and so did we. Irrigation is undoubtedly useful; otherwise, it would be difficult to explain why a patient without risk factors and graft contamination develops an infection while the patient having the graft, which was contaminated by being accidentally dropped on the floor of operative room, does not develop an infection.

Another report on contaminated rabbit patellar tendon grafts [3] found that a 30-minute soak in 4% chlorhexidine gluconate followed by a 30-minute soak in a triple antibiotic solution followed by a sterile saline wash was 100% effective in decontaminating grafts.

There are no proofs that fixation material affects infection [3, 33]. We fixed all grafts with titanium interference screws, because there is no difference between knee stability among bioabsorptive and metal screws. It has also been concluded that swelling of a knee joint is more common after the use of bioabsorptive screws [33].

If we know the causes and risk factors, we can try to prevent infections. Our experience shows that if the patients have the operative field disinfected in their rooms before surgery and if their graft is irrigated intraoperatively, they are less likely to develop an infection. After surgery, the surgeon must treat the wound properly and extract the drains applying all antiseptic measures.

The limitations of this study are connected with impossibility to explain why professional athletes, patients allergic to penicillin and hamstring grafts have higher rate of infections. We also have no data regarding the rates of bacterial inoculation during graft preparation. This study is comparable with other similar studies that make conditions for prevention of infections after anterior cruciate ligament reconstructions.

Conclusion

Infections after anterior cruciate ligament reconstructions are rare, but very serious postoperative complications which can result in a life threatening condition of the patients and compromise the final results of surgery.

The following population groups are at risk of developing septic arthritis after those procedures: professional athletes, those allergic to penicillin and the ones with immunosuppressive diseases. Staphyllococus aureus is the most common cause of infection. The incidence of infection is higher in patients with hamstring autografts than in those with patellar tendon grafts as well as in cases when the surgery is longer than 90 minutes.

Severe pain, limited range of motion, swelling of the knee joint and fever are the most common symptoms. The most reliable laboratory test is a high value of C-reactive protein.

The following preventive measures should be performed: aseptic preoperative treatment of operative field, aseptic conditions in operative rooms, irrigation of grafts before being placed into bone tunnels, experience of surgeon and proper antibiotics. Manipulation around the wound and extraction of drains should be performed by a surgeon.

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Rad je primljen 27. IX 2013.
Recenziran 4. XI 2013.
Prihvaćen za štampu 18. XII 2013.
BIBLID.0025-8105:(2014):LXVII:1-2:11-15.

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Review article
Pregledni članak
UDK 616.831-005.4-08
DOI: 10.2298/MPNS1402017Z

SONOTHROMBOLYSIS: IS THE STORY (t)OLD OR JUST THE BEGINNING

SONOTROMBOLIZA: DA LI JE OVA PRIČA ISPRIČANA ILI UPRAVO POČINJE

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Summary

Introduction. Intravenous administration of recombinant tissue plasminogen activator, fastest and widely feasible treatment in acute ischemic stroke induces arterial recanalization, a prerequisite for neurological recovery. **The Therapeutic Role of Ultrasound and Potential Mechanism of Sonothrombolysis.** Augmentation of recanalization can be achieved safely in combination with diagnostic transcranial Doppler by delivering mechanical pressure waves to the thrombus and exposing more thrombus surface to circulating drug. The addition of microspheres can further improve thrombolytic effect. **Clinical Trials.** International multicenter CLOTBUST trial showed that acute ischemic stroke patients treated with sonothrombolysis had higher rate of arterial recanalization and dramatic clinical recovery without increasing risk of symptomatic intracranial hemorrhage. A microsphere dose-escalation study called TUCSON showed that rates of recanalization and clinical recovery tended to be higher in target groups compared with controls. **Meta-analysis of clinical trials of sonothrombolysis.** Cochrane Stroke Group found that sonothrombolysis was likely to reduce death or dependency. A meta-analysis of sonothrombolysis showed that patients who received any form of sonothrombolysis had more than twofold higher likelihood of achieving complete arterial recanalization. **Perspectives for sonothrombolysis - Operator-independent device for sonothrombolysis.** The collaborative group of the CLOTBUST trial designed multi-transducer assembly to cover conventional windows used for transcranial Doppler examinations. Operator-independent device can be quickly mounted by medical personnel with no prior experience in ultrasound. Sonothrombolysis for acute ischemic stroke is now tested in a pivotal efficacy multi-national trial called CLOTBUSTER**. Conclusion.** Ultrasound is a promising tool to enhance systemic thrombolysis.

Key words: Mechanical Thrombolysis; Ultrasonic Therapy; Microbubbles; Stroke; Thrombolytic Therapy; Ultrasonography, Doppler, Transcranial; Tissue Plasminogen Activator

Sažetak

Uvod. Intravenska primena rekombinovanog tkivnog aktivatora plazminogena, najbrži i najdostupniji vid lečenja akutnog ishemijskog moždanog udara omogućava rekanalizaciju prethodno okludiranog krvnog suda, što je preduslov za neurološki oporavak. **Terapijska uloga ultrazvuka i pretpostavljeni mehanizam sonotrombolize.** Stepen rekanalizacije može se bezbedno povećati kombinacijom intravenske trombolize i dijagnostičkog transkranijanog doplera, kada predajom energije ultrazvučnih talasa trombu veća površina tromba postaje dostupna cirkulišućem leku. Aplikacijom mikromehurića dodatno se poboljšava sonotrombolitički efekat. **Kliničke studije.** Internacionalna multicentrična CLOTBUST studija je pokazala da je među pacijentima sa akutnim ishemijskim moždanim udarom, kod onih tretiranih sonotrombolizom zabeležen veći procenat rekanalizacije i izuzetnog kliničkog oporavka, bez povećanja rizika od intracerebralnog krvarenja. TUSCON studija, u kojoj su pored sonotrombolize korišćeni i mikromehurići, je pokazala da su pacijenti tretirani na ovaj način imali veći procenat rekanalizacije i kliničkog poboljšanja u odnosu na kontrolnu grupu. **Meta-analize kliničkih studija o sonotrombolizi.** Cochraneova grupa za moždani udar je zaključila da sonotromboliza smanjuje procenat smrtnog ishoda i funkcionalne zavisnosti pacijenata nakon moždanog udara. Jedna meta-analiza je pokazala da bilo koji vid sonotrombolize dvostruko povećava šansu za kompletnu rekanalizaciju. **Budućnost sonotrombolize – Uređaj za sonotrombolizu nezavisan od ispitivača.** Radna grupa CLOTBUST studije je dizajnirala uređaj sa više ultrazvučnih sondi koji pokrivaju sve standardne akustičke prozore koji se koriste pri transkranijalnom ultrazvučnom pregledu. Ovaj uređaj se može brzo i uspešno primeniti i osoba koja nema iskustva u ultrazvučnoj dijagnostici. Efikasnost i bezbednost ovog uređaja se trenutno ispituje u multicentričnoj internacionalnoj CLOTBUSTER studiji. **Zaključak.** Transkranijalni ultrazvuk je obećavajuće oruđe za poboljšanje efekata intravenske trombolize.

Ključne reči: Mehanička tromboliza; Ultrazvučna terapija; Mikromehurići; Moždani udar; Trombolitička terapija; Transkranijalna Dopler ultrasonografija; Aktivator tkivnog plazminogena

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Abbreviations

rtPA – recombinant tissue plasminogen activator
TCD – transcranial Doppler
CLOTBUST – Combined Lysis of ThromBus in brain ischemia using transcranial Ultrasound and Systemic TPA
TUCSON – Transcranial Ultrasound in Clinical SONothrombolysis
CT – computed tomography
TIBI – thrombolysis in brain ischemia
IV rtPA – Intravenous recombinant tissue plasminogen activator
TCCS – transcranial color-coded sonography
TRUMBI – Transcranial Low-Frequency Ultrasound-Mediated Thrombolysis in Brain Ischemia
sICH – symptomatic intracranial hemorrhage
NIHSS – National Institutes of Health Stroke Scale
TCCD – Transcranial color-coded duplex
mRS – modified Rankin scale
PW – pulsed-wave
US – ultrasound
MCA – middle cerebral artery
CLOTBUSTER– Combined Lysis of ThromBus using 2 MHz pulsed wave Ultrasound and Systemic TPA for Emergent Revascularization

Introduction

Intravenous recombinant tissue plasminogen activator (IV rtPA) is still the only approved treatment for acute ischemic stroke, which could be administered within the first 4.5 hours after symptom onset [1]. Treatment can be initiated fast in any emergency room equipped with a non-contrast computed tomography (CT) scanner [2]. In most medical centers in the developing countries, it is the only option for the treatment of acute ischemic stroke patients. On the other hand, transcranial Doppler (TCD) is a non-invasive, well-established and widely used ultrasound technique for fast evaluation of cerebral hemodynamics and real-time detection of arterial occlusions and recanalization during or after thrombolysis [3–7]. The high level of agreement between TCD and angiographic findings in acute ischemic stroke patients was shown in several studies [8, 9] and the patterns of intracranial arterial occlusion and recanalization on TCD are determined using the thrombolysis in brain ischemia (TIBI) grading system [8].

Various factors are associated with the outcome after acute ischemic stroke. Besides initial stroke severity, comorbidities, and patient age, the early recanalization of an acutely occluded blood vessel is associated with final infarct size, neurological improvement, and final clinical outcome [10-12]. Nevertheless, recanalization rates with IV rtPA alone are low, especially in patients who suffer major proximal occlusions [13, 14]. Several ways to improve the speed and completeness of recanalization have been studied, including the therapeutic use of ultrasound alone or in combination with IV rtPA [15]. Improved recanalization has been demonstrated with diagnostic TCD and transcranial color-coded sonography (TCCS) in combination with standard IV thrombolysis with rtPA in two randomized trials [13, 16]. Sonothrombolysis was introduced for treatment of acute intracranial occlusions at the turn of this century [17, 18].

The Therapeutic Role of Ultrasound and Potential Mechanism of Sonothrombolysis

The idea for the use of ultrasound as a thrombolytic agent is not new [14]. The ability of a mechanical pressure wave, i.e. ultrasound, to enhance thrombolysis was documented in 1976 [19] and since then has been confirmed by many experimental models [20]. However, despite numerous studies documenting a thrombolytic effect of ultrasound, the underlying mechanisms remain poorly understood [21]. The likely mechanism that emerged from these in vitro and in vivo experiments is the ability of ultrasound, through transmission of the mechanical energy momentum, to agitate flow and facilitate streaming of plasma around and through the thrombus, thus delivering more recombinant tissue plasmainogen activation (rtPA) to the target clogging sites [22-26]. In stroke patients, ultrasound can promote rtPA delivery to the areas with diminished flow near occlusion and the pressure of ultrasound waves may increase the permeation of rtPA into to the fibrin network [27].

Various ultrasound energies (0.2–2.0 W/cm^2) and frequencies (20 kHz – 2 MHz) have been tested [28, 29]. Although low kilohertz frequencies potentiate rtPA effects better, these systems (a combination of rtPA with an experimental kHz delivery system) resulted in an excessive risk of intracerebral hemorrhage in stroke patients. The clinical trial TRUMBI (Transcranial Low-Frequency Ultrasound-Mediated Thrombolysis in Brain Ischemia) was stopped prematurely because of excessive symptomatic intracranial hemorrhage (sICH) rates with sonication at 300 kHz [30]. Kilohertz frequencies were thought to induce more mechanical stretching and minimize heating [22, 31]. On the other hand, 1–2.2 MHz frequencies can also enhance rtPA-induced thrombus dissolution, utilizing different mechanisms such as fluid streaming around the clot surface, disaggregation of fibrin fibers, and delivering more tPA to the binding sites without cavitation [22, 32]. Though some concerns remain regarding tissue heating, skull absorbs most of 2 MHz ultrasound energy and this frequency is safely used for diagnostic ultrasound examinations and monitoring [32, 33].

Furthermore, it has been shown that the addition of microbubbles composed of lipid, albumin, or galactose capsules to the combination of rtPA and ultrasound additionally enhances thrombolysis [34-36]. Microbubbles agitated by the same mechanism of cavitation and microstreaming can cause localized mechanical stress on the adjacent clot. Energy delivered to the microbubbles can

lead to their oscillation in size, disruption and production of ”microjets” that are also effective in eroding a clot [21, 37, 38]. The mechanical thrombolytic effect has been confirmed in several experimental studies of only microbubbles and ultrasound, without thrombolytic drugs [39–42].

Clinical Trials

The study with low (kHz) frequency ultrasound (TRUMBI) showed a significant increase in SICH and the trial was stopped prematurely [30]. Since then, low frequency ultrasound has not been available for therapeutic purposes in clinical practice [14].

Early recanalization and dramatic recovery rates in acute ischemic stroke patients treated with rtPA were first observed during monitoring of cerebral blood flow with standard diagnostic 2-MHz TCD [17]. After identifying abnormal residual flow signals, an ultrasound beam was steadily focused on the presumed location of an intracranial thrombus, and arterial recanalization could be monitored in real time. Thus, the authors observed early recanalization and more dramatic recovery rates than expected, which suggested a potential therapeutic effect of TCD [17]. This pilot study led to the design of the phase II of CLOTBUST trial (Combined Lysis of Thrombus in Brain ischemia using transcranial Ultrasound and Systemic TPA) [13]. This randomized multi-center international clinical trial was the first properly powered clinical trial that confirmed the existence of ultrasound-enhanced thrombolysis in humans and demonstrated a positive biological effect of diagnostic ultrasound. It enrolled 126 patients with acute ischemic stroke due to occlusion of the MCA who were treated with IV rtPA therapy within 3 hours of symptom onset. All patients received IV rtPA and were randomized (1:1) to the target group receiving continuous TCD-monitoring or the control group with placebo monitoring during one hour IV rtPA infusion and one extra hour after rtPA was completed. A standard fast-track TCD examination was performed in the emergency department before rtPA bolus. TCD was used to identify the site of intracranial occlusion using TIBI grading system. Once the occlusion was diagnosed with handheld examination, the presumed clot location and residual flow around it were determined through the presence of one of the abnormal TIBI flow signals (minimal, blunted, or dampened waveforms). TCD monitoring or placebo monitoring was performed for two hours under direct visual control of the sonographer investigators. Recanalization was graded as complete, partial, or none according to TIBI criteria [8]. In both groups, follow-up measurements were performed 30, 60, 90, and 120 minutes after the rtPA bolus was given. The complete recanalization was seen in 38% of patients in the target group and in 13% of patients in the control group, p=0.002. A total of 73% of patients achieved any recanalization with rtPA plus TCD versus 50% of patients with rtPA alone within 2 hours of treatment (P<0.001).

Neurological examinations with the National Institutes of Health Stroke Scale (NIHSS) and follow-up assessments were performed by neurologists unaware of monitoring group assignment. Symptomatic ICH occurred in 4.8% in both (target and control) groups. At 3 months, 42% of patients in the target group and 29% of patients in the control group achieved favorable outcomes (modified Rankin scale (mRS) grades of 0-1, p=0.2). The CLOTBUST trial was not powered to evaluate the efficacy of ultrasound enhanced thrombolysis in improving functional outcome, but was designed to establish the safety of this treatment and to provide preliminary data for the design of a larger clinical efficacy trial. The main limitation of the CLOTBUST trial was the operator-dependency and the need for a qualified sonographer to be present at bedside to find, aim and deliver ultrasound beam to the thrombus residual flow interface [2].

Transcranial color-coded duplex (TCCD) is another ultrasound method that provides images of both cerebral arterial locations with real-time cerebral blood flow and imaging of parenchymal structures inside the brain [14, 16, 43, 44]. TCCD has also been evaluated for ultrasound enhanced thrombolysis in smaller single-center randomized clinical trials and the authors observed a similar effect in the patients with acute cerebral artery occlusion [16, 45-47]. In the Lübeck study, Eggers et al. evaluated 37 patients who were randomly selected to receive TCCS-guided pulsed-wave (PW) mode ultrasound (US) for 1 hour [16]. There were 19 patients in the target group (IV rtPA + duplex monitoring) and 18 control patients (IV rtPA alone). The patients with proximal middle cerebral artery (MCA) occlusions who underwent simultaneously ultrasound insonation and rtPA standard treatment were included in the study. Similar to the findings of the CLOTBUST trial, a trend towards higher recanalization rates was reported in the target group. Treatment with combination of IV rtPA and TCCD resulted in significantly improved recanalization; partial or complete recanalization was detected in 57.9% of patients in the target group vs. 22.2% of patients in the control group (p = 0.045). Additionally, a better functional outcome after 3 months in target patients was shown. However, tendencies for increased symptomatic cerebral bleeding (three patients in the sonothrombolysis group vs. one patient in the control group) and increased hemorrhagic transformation of infarcts were also found in patients who underwent continuous insonation [16]. The same group of authors and others have reported provocative findings that patients who are not eligible for systemic rtPA therapy may potentially benefit from continuous monitoring with ultrasound alone since, hypothetically, ultrasound may help facilitate the endogenous thrombolytic process that

leads to spontaneous recanalization in patients with acute stroke [46, 47]. In 15 patients ineligible for rtPA therapy, the recanalization after 1h occurred only in the sonothrombolysis group (62.5% in the sonothrombolysis group vs. 0% in the control group), followed by significant improvements in clinical course after 4 days and functional independence after 3 months (2 of 8 patients in the sonothrombolysis group compared with none of the 7 patients in the control group). There was no symptomatic ICH in the sonothrombolysis group [46]. However, duplex technology has some disadvantages: multiple beams at dual-emitting frequencies and higher frame rates may create standing waves, no reliable head frames for transducer fixation with most studies using handheld probes, and a higher mechanical index than TCD [48]. In the absence of a large controlled trial, there are no clear data regarding the benefit of ultrasound monitoring without rtPA. Thus, rtPA treatment should not be substituted for ultrasound alone in the patients otherwise eligible for thrombolytic therapy within 4.5 hours of symptom onset. Finally, additional studies are needed to evaluate and clarify the potential of transcranial duplex technology to enhance thrombolysis [49].

The data derived from experimental studies in the 90s have suggested that ultrasound-enhanced thrombolysis can be further amplified by microbubbles [34-36, 50]. Microbubbles composed of lipid, albumin, or galactose shells, and ranging in size from 0.5 μm to 5 μm erode the surface of clots and lower the threshold for thrombolysis by different ultrasound mediated mechanisms (e.g., enhancement of microstreaming and cavitation) [51]. Microspheres, in combination with ultrasound can lyse thrombi even without a thrombolytic drug [52]. Numerous studies have shown significant amplification of thrombolysis with the addition of microspheres to the combination of thrombolytic drug and ultrasound [53]. Molina et al. pioneered the use of gaseous microspheres in combination with CLOTBUST monitoring methods in 38 patients compared to 73 patients treated with either 2 MHz TCD and IV rtPA or IV rtPA alone [54]. Complete recanalization rate 2 h after rtPA bolus was significantly higher in the rtPA + TCD + microspheres group (54.5%) compared with rtPA + TCD (40.8%) and rtPA alone (23.9%) groups ($p = 0.038$). Symptomatic ICH rates did not differ. Another study that evaluated the safety and feasibility of TCCD ultrasound monitoring combined with microspheres and IV rtPA in patients with acute middle cerebral artery occlusion reported improved recanalization flow [55]. Complete recanalization rate was 64% in comparison to 53% of patients treated with IV rtPA only. The safety and feasibility of infusion of newer generation of microspheres were tested in patients in a pilot trial and a phase IIa study [56-58]. A multicenter microsphere dose-escalation study called TUCSON (Transcranial Ultrasound in Clinical SONothrombolysis) was aimed at determining the safety, tolerability, and activity of perflutren-lipid microspheres plus TCD insonation in sonothrombolysis [59]. The study showed a trend towards higher rates of early recanalization and clinical recovery in both microsphere doses compared with standard intravenous alteplase treatment alone. However, the study was terminated prematurely by the sponsor for administrative reasons coincidentally with the three cases of sICH in the second dose tier. Upon review, these sICH occurred in patients with severe strokes and high blood pressures in violation of rtPA treatment protocol. To date this was the last sonothrombolysis study using microspheres [15].

Meta-analysis of Clinical Trials of Sonothrombolysis

A meta-analysis of six randomized and three nonrandomized clinical studies of sonothrombolysis, which included over 400 patients, showed that patients who underwent sonothrombolysis had a 3 times higher chance for complete recanalization and a 2 times higher chance for non-disability after 3 months without increasing the risk of sICH [59]. Cochrane Stroke Group identified five eligible studies with a total of 223 patients [60]. They found that patients (among 206 patients with available data) treated with sonothrombolysis were less likely to be dead or disabled at three months (OR 0.50; 95% CI 0.27-0.91). Failure to recanalize was lower in the sonothrombolysis group (230 patients) (OR 0.28; 95% CI 0.16-0.50). There was no significant difference in cerebral hemorrhage (233 patients). Thus, authors concluded that sonothrombolysis was likely to reduce death or dependency at three months and increase recanalization without clear hazard [60]. A recently published meta-analysis of sonolysis and sonothrombolysis included 10 studies (seven randomized control trials and three case control studies) [61]. Pooled analysis of these studies for a total of 620 patients (345 patients in the treatment group and 275 patients in the control group) showed that patients who received any form of sonothrombolysis (1.8-4 MHz), with or without microspheres, and with or without IV rtPA, had more than twofold higher likelihood of achieving complete recanalization within 1-2 hours from treatment onset in comparison to patients who did not receive any form of sonothrombolysis (OR 2.95; 95% CI 1.81-4.81; $p<0.00001$). In addition, the patients treated with sonolysis/sonothrombolysis were more likely to achieve a favorable functional outcome (mRS 0-2) at three months (OR 2.20; 95% CI 1.52-3.19; $p<0.0001$). Sonolysis and sonothrombolysis alone or with microspheres were safe and carried the same risk of sICH as IV rtPA alone (OR 1.14; 95% CI 0.56-2.34; $p=0.71$).

However, according to the current recommendations, the effectiveness of sonothrombolysis for treatment of patients with acute ischemic stroke is still not well established (Class IIb; Level of Evidence B) [62].

Perspectives for Sonothrombolysis - Operator-independent Device for Sonothrombolysis

The main limitation of TCD technology is the operator-dependency and the need for a qualified sonographer to be present at bedside to find, aim and deliver ultrasound beam to the thrombus residual flow interface [2,63]. Therefore, an operator-independent device for sonothrombolysis is needed to conduct a multicenter, randomized clinical trial [64]. The collaborative group of the CLOTBUST trial first measured the outputs of all devices used [65], then designed multi-transducer assembly to cover conventional windows used for TCD examinations [66]. Further, this novel device was prospectively evaluated for safety in human volunteers [67] and showed that it was well tolerated by stroke-free volunteers and did not cause any neurological dysfunction nor did it affect blood brain barrier integrity. Subsequent phase II study in patients receiving iv rtPA showed that the operator independent device was safe and led to 40% complete MCA recanalization after 2 hours of monitoring [68].

Since this operator-independent, battery-powered device can be quickly mounted by medical personnel with no prior experience in ultrasound, the device enables us to conduct large scale sonothrombolysis trials at all levels of emergency rooms capable of administering rtPA as the standard of care, including telemedicine-supported sites. Thus, sonothrombolysis for acute ischemic stroke is now tested in a pivotal efficacy multi-national trial called CLOTBUSTER (Combined Lysis of ThromBus using 2 MHz pulsed wave Ultrasound and Systemic TPA for Emergent Revascularization, NCT01098981). All patients who will be treated with IV rtPA with NIHSS scores ≥10 points are eligible and they will wear an operator-independent ultrasound emitting device for 2 h. The proprietary device (Cerevast Therapeutics, Redmond, WA) exposes traditional TCD bone windows for sequential insonation of the 12 proximal intracranial segments that most commonly contain thromboembolic occlusions causing disabling strokes. Patients will be randomized 1:1 to continuous exposure to 2 MHz pulsed wave ultrasound versus sham exposure. Safety will be determined by the incidence of symptomatic ICH within 24 hours of treatment. Functional recovery will be determined by mRS at 3 months. CLOTBUSTER is a large simple efficacy clinical trial, the first of its kind for sonothrombolysis. Once CLOTBUSTER establishes safety and efficacy of an operator-independent ultrasound device, the next phase clinical trials can commence combining experimental microspheres with regulatory-approved rtPA therapy and safe ultrasound exposure. This exposure is needed to activate microspheres, however a proof of safety and efficacy of ultrasound is required before a complex combinatory treatment with or without rtPA can be tested any further in the clinical setting [2].

Conclusions

In a quest for stroke treatment, recanalization proved to be the first step to the success. Sonothrombolysis using diagnostic transcranial ultrasound (transcranial Doppler and transcranial color-coded duplex) in combination with recombinant tissue plasminogen activator improves recanalization of an acute intracranial artery occlusion. It can be performed at bedside using commercially available vascular diagnostic ultrasound systems without significant increase in the risk of intracranial hemorrhage. A novel operator-independent device offers a promising solution to avoid the need for an experienced sonographer to be present in the emergency room to deliver sonothrombolysis. Meanwhile, portable diagnostic 2MHz transcranial Doppler or transcranial color-coded duplex are standard equipment in many stroke units, even in developing countries, that can be used for detection of arterial occlusion as well as assessment of recanalization, emboli detection, collateralization of flow with extracranial internal carotid artery disease, alternating flow signals indicative of steal phenomenon. Pending results of ongoing studies, ultrasound remains a promising tool to enhance systemic thrombolysis, and a reliable diagnostic method for the assessment of cerebral hemodynamics in real time.

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Rad je primljen 10. XII 2013.
Recenziran 15. XII 2013.
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Review article
Pregledni članak
UDK 616.831-002.7-073
DOI: 10.2298/MPNS1402024S

RADIOLOGICAL PRESENTATION OF NEUROSARCOIDOSIS

RADIOLOŠKA PREZENTACIJA NEUROSARKOIDOZE

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Summary

Introduction. In diagnostics of neurosarcoidosis, radiological diagnostic procedures are available, non-invasive and they contribute significantly to the diagnosis of this disease. The aim of this paper is to present a brief overview of the radiological diagnostic methods, their application, and their importance in daily clinical work with these patients. **Radiological Presentation of Neurosarcoidosis**. Magnetic resonance is the method of choice in diagnostics of this disease. Computed tomography can also be helpful in patients with contraindications for magnetic resonance, although it is less precise in assessing the involvement of the periventricular white matter, hypothalamus, and cranial nerves. The number of lesions and the degree of involvement of the parenchyma and leptomeninges are better seen by magnetic resonance than by computed tomography scan. It is important to note that the magnetic resonance imaging may be normal in patients with neurosarcoidosis, especially in patients with cranial neuropathy, or in patients treated with corticosteroids. There is a number of variability in the occurrence of neurosarcoidosis on radiological images. **Conclusion**. Radiological procedures are on the very top of diagnostic pyramid of this disease due to their availability, non-invasiveness, and precision.

Key words: Magnetic Resonance Imaging; Sarcoidosis; Central Nervous System Diseases; Tomography, X-Ray Computed; Diagnosis

Sažetak

Uvod. U dijagnostici neurosarkoidoze radiološke dijagnostičke procedure su dospupne, neinazivne i značajno doprinose dijagnostici ove bolesti. Cilj ovog rada je da prikaže kratak osvrt na radiološke dijagnostičke metode i njihovu primenu, tj. značaj u svakodnevnom kliničkom radu sa ovim bolesnicima. **Radiološka prezentacija neurosarkoidoze**. U dijagnostici ove bolesti magnetna rezonancija je metoda izbora. Skener takođe može biti koristan za bolesnike sa kontraindikacijama za magnetnu rezonanciju, mada se sa manjom preciznošću mogu utvrditi zahvaćenost periventrikularne bele mase, hipotalamusa i kranijalnih nerava. Broj lezija i stepen zahvaćenosti parenhima i leptomeninga takođe su bolje vidljivi magnetnom rezonancijom, nego skenerom. Važno je napomenuti da snimak magnetnom rezonancijom može biti normalan kod bolesnika sa neurosarkoidozom, naročito kod bolesnika sa kranijalnom neuropatijom ili kod bolesnika na terapiji kortikosteroidima. Postoje brojne varijabilnosti u pojavljivanju neurosarkoidoze na radiološkim snimcima. **Zaključak**. Radiološke procedure, zbog svoje dostupnoisti, neivazivnosti i preciznosti, veoma su važne i stavljaju se na sam vrh dijagnostičke piramide za ovo oboljenje.

Ključne reči: Magnetna rezonanca; Sarkoidoza; Oboljenja centralnog nervnog sistema; Kompjuterska tomografija; Dijanoza

Introduction

Sarcoidosis is a systemic granulomatous disease most frequently affecting lungs and hilar lymph nodes. Nowadays, it is known that sarcoidosis may affect any organ in the human body, as well as the central nervous system (CNS) [1]. The golden standard in diagnostics of neurosarcoidosis is pathohistological verification of non-caseating granuloma in CNS. However, this procedure is rarely applied in practice because of invasiveness and serious complications [2]. Due to these reasons all available diagnostic methods are very important in diagnostics of this disease. Radiological diagnostic procedures are available to us, they are noninvasive and they contribute significantly to diagnostics of this disease. The aim of this paper is to present a brief review of radiological diagnostic methods, their application, and their importance in everyday clinical work with these patients.

Acknowledgement

The present work was supported by the Ministry of Education and Science the Republic of Serbia, Projects No. 175064 and 175081, 2011-2014.

Radiological presentation of neurosarcoidosis

Magnetic resonance imaging (MRI) is the method of choice in diagnostics of this disease. Computed tomography (CT) scan may also be helpful in patients with contraindications for MRI, although the involvement of periventricular white matter,

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Abbreviations

CNS – central nervous system
MRI – magnetic resonance imaging
TS – transcranial brain sonography
CT – computed tomography scan
PET – positron-emission tomography

hypothalamus and cranial nerves can be assessed with less accuracy. The number of lesions and the degree of involvement of parenchyma and leptomeninges are also more visible by MRI than by CT scan. It is very important to mention that the recording of MRI may be normal in patients with neurosarcoidosis, especially in patients with cranial neuropathy or in patients treated by corticosteroids [3, 4]. There are numerous variabilities in the occurrence of neurosarcoidosis on radiological images. The involvement of leptomeninges, which involve arachnoid and soft brain membrane, is the most frequent finding on recordings, present in about 40 per cent of patients with neurosarcoidosis. On MRI and CT scan recordings with injected contrast, this can be seen as linear and nodular enlargement along the brain outlines, extending in cortical sulci covered with a layer of pia mater (soft brain membrane). Leptomeningeal disease is usually unperceivable on recordings without contrast. The involvement can be diffuse, focal or multifocal with predilection to basal ganglions. There is no difference in the appearance comparing to meningeal carcinomatosis, lymphoma, leukemia, tuberculosis and fungus meningitis [5, 6]. In basilar leptomeningeal disease, basilar middle structures, including hypothalamus and pituitary gland infundibulum are frequently involved. These structures or leptomeninges surrounding them can be involved. The involvement of these structures can be seen as thickening on the recordings with contrast. Sarcoidosis of pituitary gland infundibulum may be similar to lymphocytic hypophisitis, tuberculosis, histyocytosis, leukemia and metastasis [7]. Similarly, the cranial nerves may be involved, where the disease frequently penetrates into superficial leptomeninges and with possible secondary infiltrations. This can be noticed as a thickening and enlargement of cranial nerves on the recording with contrast. The recordings show a poor correlation between the cranial nerves involvement and clinically neurological deficiency. The involvement of the seventh nerve, i.e. facial nerve, most frequently has a clinical manifestation, while the optic nerve is most frequently involved on the recordings. Isolated involvement of cranial nerves may imitate neuritis of different etiology, including virus infections, as well as neoplasms such as schwannoma and glioma of optic nerve [7,8].

Leptomeningeal involvement may run along the leptomeningeal layer into the perivascular space (Virchow-Robin space) surrounding the entrant cerebral vessels. Infiltration in parenchyma may appear from any cerebral surface or Virchow-Robin space, which finally connect and form granulomatous masses of different sizes. Intraparenchymal lesions are visible as perivascular enlarged lesions with or without an increase in T2 signal, with the increase reflecting the defect of brain blood barrier and the increase in T2 signal reflecting vasogenic edema due to the increased permeability. The enlargement is usually perceived as vertical in relation to the ventricles and cortical surfaces along the way of penetrating vessels. Lesions may rarely be presented as isolated enlargements of parenchymal tumefactive mass that may imitate neoplasms [9, 10].

Dura involvement is less frequently perceived than leptomeninges involvement. Dural lesions may look like enlargement of dural thickening, plaques or discrete masses and they can be seen on non-contrast recording, but not necessarily. When noticed, these changes are usually isointense with grey mass on T1 sequences of MRI and hypointense on T2 sequences of MRI. The end of dura can be seen as an intensified thickening extending from the basic mass, and the central classification can also be present. As in meningeoma, the dura and leptomeninges involvement does not normally appear together, and it is believed that arachnoid cells in the part of arachnoid mass can prevent inflammation from spreading. From the differentially diagnostic point of view, considerations of dural lesions include meningiomas, metastases, plasmacytoma, granulomatous infections, etc. [11].

Diffuse or focal area of T2 signal occurrence without increased intensity may be observed in the periventricular white mass, rarely in the cerebral stem and basal ganglions. These lesions are nonspecific and they resemble lesions likely to be seen in multiple sclerosis, vasculitis, microvascular disease and infectious disease such as Lyme disease **(Figure 1)**. These lesions are not normally correlated with clinical symptoms and they do not generally go away with treatment [12].

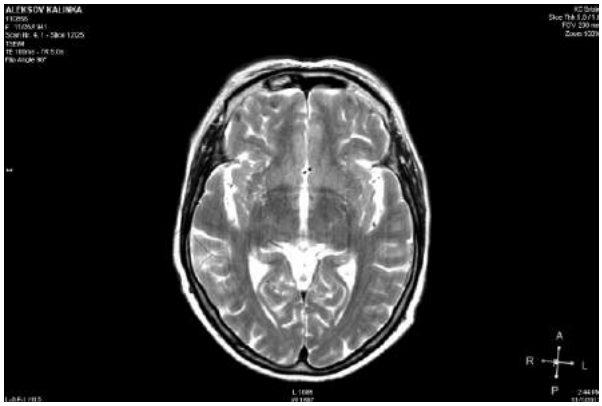

Figure 1. MRI - supratentorial multiple microangiopathic lesions, and cortical brain reductive changes
Slika 1. *MRI – supratentorijalne multipne mikroangiopatske lezije i reduktivne promene na korteksu mozga*

Figure 2. CNS CT scan - acute unilateral hydrocephalus with enlargement of the right lateral ventricle and periventricular lower density
Slika 2. *CNS CT sken – akutni unilateralni hidrocefalus sa uvećanom desnom bočnom komorom i periventrikularnom manjom gustinom*

Communicating or noncommunicating hydrocephalus is relatively rare in these patients. Communicating hydrocephalus may be secondary in leptomeninges or dura involvement with abnormal resorption of cerebral-spinal liquid. Noncommunicating or obstructive hydrocephalus may be secondary in granulomatous compression or adhesions in the ventricular system, usually in the cerebral aquaduct and in the fourth ventricle, i.e. foramen (Megendie and Lushka foramine) **(Figure 2)** [3].

Neurosarcoidosis may also affect the spinal cord and it may appear as an isolated finding or related to intracranial diseases. The most frequent manifestation is leptomeningeal involvement, perceivable as a linear and nodular thickening along the surface of the spinal cord and nerves root. In 0.3 to 0.4 per cent of patients with sarcoidosis, the intramedular part of spinal cord may be affected, which can be observed on the recordings as an intensification of T2 signal, T1 signal decrease with partial contrast injecting. Similarly to the brain, the intramedular involvement is considered to be secondary in centripetal extension of leptomeningeal disease via perivascular Virchow-Robin space. These lesions may later appear simultaneously. The lesions caused by neurosarcoidosis may affect any part of the spinal cord, but they most frequently affect its cervical part. From the differentially diagnostic point of view, considerations of intramedular lesions include neoplasms, multiple sclerosis, optic neuromielitis and tuberculosis. Radiological progress may not keep abreast with clinical improvement and there also may be improvement on recordings with the presence or progression of clinical symptoms. Spinal cord atrophy frequently appears, especially in patients with late diagnosis [13].

Positron-emission tomography (PET) is another radiological diagnostic procedure that can be applied in these patients. It must be mentioned that PET is limited to a certain degree in assessment of lesions in CNS because it can show accelerated or delayed metabolism. Accelerated metabolism in CNS is secondary in sarcoid inflammation. Delayed metabolism, on the other hand, is considered to be secondary in neuron dysfunction, where metabolic demand is decreased in affected areas in relation to high metabolic needs of the brain. In spite of limitations, PET may reveal the lesions of CNS in patients with no suspicion of sarcoidosis and it may be useful in observation of therapy reactions [14, 15]. PET imaging and scanning with gallium -67 may be useful in diagnostics of sarcoidosis, by indicating the presence of a systemic disease and identifying accessible lymph nodes for biopsy. They can also be applied to assess sarcoidosis activity and degree of involvement. PET visualization is very susceptible to increased metabolic activities of lymphoid tissues appearing in sarcoidosis, but it is nonspecific, with a wide range of different possible diagnoses including lymphoma, metastases and infections. Scanning of the whole body with gallium is less susceptible and it is specific for diagnostics of sarcoidosis, so only two of three patients have a positive gallium scan [16, 17]. When the disease involves skeletal muscles, magnetic resonance imaging and PET scan are particularly significant. In the series of Tiersen et al. including 137 patients with sarcoidosis, 6 patients were described by using 18-Fluoro-deoxyglucose (FDG) PET scan of the complete body [18].

Transcranial brain sonography (TS) is another noninvasive method used lately for diagnostic purposes in patients with sarcoidosis. TS in B-mode is capable of visualization of infratentorial and supratentorial cerebral structures. This method is widely applied in patients with Parkison's disease. The most recent research deals with the application of this ultrasound method in measuring and detection of hypoechogenicity of the substantia nigra and hyperechogenicity of nucleus ruber in patients with neurosarcoidosis. These findings are in correlation with the level of tiredness, depression, anxiety and movement disorder ("restless legs syndrome"), frequently noticed in these patients. By revealing structural changes in brain parenchyma by this method adequate therapy modality can be reached in the patients with this disease [19, 20].

Conclusion

Since it is very difficult to make pathohistological diagnosis of neurosarcoidosis, radiological diagnostics is very important in making diagnosis as fast and optimal as possible. Radiological procedures give significant contribution to the diagnostics of this disease and they are on the very top of diagnostic pyramid of this disease due to their availability, non-invasiveness, and precision.

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Rad je primljen 27. X 2013.
Recenziran 8. XII 2013.
Prihvaćen za štampu 18. XII 2013.
BIBLID.0025-8105:(2014):LXVII:1-2:24-27.

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Review article
Pregledni članak
UDK 616.89-08:615.84
DOI: 10.2298/MPNS1402028P

DEEP BRAIN STIMULATION IN PSYCHIATRY

DUBOKA MOŽDANA STIMULACIJA U PSIHIJATRIJI

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Summary

Introduction. Deep brain stimulation is a stereotactic neurosurgical method used in the treatment of Parkinson's disease and some other movement disorders. The application of deep brain stimulation in the treatment of certain psychiatric disorders has been intensively investigated taking into account the current knowledge of neurobiological basis of mood regulation, cognition, and behaviour. This paper has been aimed at presenting the available data on experience in the application of deep brain stimulation in the treatment of psychiatric disorders. It gives an overview of scientific and professional literature, bearing in mind all the contemporary approaches in the treatment of certain psychiatric disorders. Research results available so far in the treatment of treatment-resistant depression, obsessive-compulsive disorder, Gilles de la Tourette syndrome, addiction and Alzheimer's dementia, are affirmative concerning the efficacy of the method and low risk of adverse effects. Deep brain stimulation, as a relatively new neurosurgical method in the treatment of psychiatric disorders, is being intensively developed, and it is certainly going to be one of the treatments of choice, primarily of treatment-resistant disorders.

Key words: Deep Brain Stimulation; Psychiatry; Stereotaxic Techniques; Neurosurgical Procedures

Sažetak

Uvod. Duboka moždana stimulacija je stereotaksična neurohirurška metoda koja se koristi u terapiji Parkinsonove bolesti i drugih poremećaja pokreta. Uzimajući u obzir dosadašnja znanja o neurobiološkim osnovama regulacije raspoloženja, kognicije i ponašanja, primena duboke moždane stimulacije u lečenju nekih psihijatrijskih poremećaja intenzivno se istražuje. Cilj ovog rada je da prikaže raspoložive informacije o dosadašnjem iskustvu u primeni duboke moždane stimulacije u lečenju psihijatrijskih poremećaja. Dat je pregled naučne i stručne literature imajući u vidu sve savremene pristupe u lečenju pojedinih psihijatrijskih poremećaja. Do sada su dostupni rezultati istraživanja u lečenju teraporezistentne depresije, opsesivno-kompulzivnog poremećaja, Žil de la Turetovog sindroma, bolesti zavisnosti i Alchajmerove demencije, koji ilustruju efikasnosti ove metode, uz prihvatljiv rizik od neželjenih dejstava. Duboka moždana stimulacija kao relativno nova neurohirurška metoda u lečenju psihijatrijskih bolesti intenzivno se razvija i u budućnosti će sigurno predstavljati jednu od dragocenih metoda u terapiji pre svega teraporezistentnih poremećaja.

Ključne reči: Duboka moždana stimulacija; Psihijatrija; Stereotaksične tehnike; Neurohirurške procedure

Introduction

Until the mid-20th century, there were no specific medications with antipsychotic, antimanic and antidepressant effect. Some of psychiatric disorders, which are disabling and potentially lethal, were often treated using invasive methods, such as malaria pyrotherapy, hypoglycemic coma, electroconvulsive therapy and neurosurgery [1]. The first surgical attempts to treat psychotic patients, which had a limited success, date back to 1891. Back in 1937 scientists believed that abnormal models of functional and structural neuroanatomy of mood and regulation of behaviour were the consequences of dysfunctional thalamocortical communication, with the resulting introduction of methods of prefrontal leucotomy, and then lobotomy with numerous complications [2]. Prefrontal leucotomy was introduced by Prof. Dr. Slobodan Kostic, the head of the Department of Neurosurgery in Belgrade, Yugoslavia in 1947. By 1952, 339 surgical interventions had been performed. Kostic modified the classical Moniz's procedure by making it significantly simpler. The majority (90%) of patients suf-

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Abbreviations

DBS – deep brain stimulation
OCD – obsessive-compulsive disorder
NMDA – N-methyl-D-aspartate
TRD – treatment-resistant depresion

fered from schizophrenic disorder, and some of them had severe forms of psychoneurosis or were mentally retarded [3]. The first stereotactic surgery was performed in 1964 by Ilija Nagulic. He performed ablations to treat dyskinesia and in 1979, he introduced ventrolateral thalamotomy [4-6]. The discovery of psychopharmaceuticals ended the era of lobotomy. Stereotactic neurosurgical techniques enabled the targeted ablation, which reduced the development of side effects. Despite that, subcaudate tractotomy, dorsal anterior cingulotomy, anterior capsulotomy and limbic leukotomywere were still limitedly applied due to the complications such as obesity, cognitive impairment, personality changes and epilepsy. At the same time, the development of motor neuroregulation models introduced the application of deep brain stimulation (DBS) in the treatment of Parkinson's disease, essential tremor and generalized dystonia [7]. At the end of the second millennium, DBS was used in an attempt to treat treatment-resistant obsessive-compulsive disorder (OCD) in a small series of patients [8], and later on, the indication areas in psychiatry spread to treatment-resistant depression [9-11], Gilles de la Tourette syndrome [12], antipsychotic-induced tardive dystonia and dyskinesia [13-15], addiction [16] and Alzheimer's dementia [17,18].

Deep brain stimulation developed as a less invasive alternative to ablative neurosurgery in addition to the relatively well-accepted method of transcranial magnetic stimulation over the last decade. It is important both for studying the mechanism of occurrence and in the treatment of depressive episodes in Parkinson's disease [19,20]. In addition to the desired inhibitory mode of action in the grey matter, its stimulating effect was observed as well. The complex mechanism of action of this method depends on both the localization and distribution of bodies of neurons and white matter, which pervades the field of localization, and the parameters of stimulation. Besides the effect at the cellular level, DBS is believed to have a systemic effect on the behaviour through the modulatory activity of neural networks. Assumptions about the development of a number of psychiatric disorders are based on observations of altered activity in certain neural networks and those that connect different brain regions. Beneficial effects of DBS are believed to result from the changing of this activity and the mutual communication of certain neural networks [21].

Deep brain stimulation is applied by implanting one or more electric leads into certain regions of the brain through the skull using neuroimaging-guided stereotaxic techniques. Each lead usually has several electrodes at the depth of 10-20 mm. They are connected via subcutaneous extensions to the battery-powered pulse generator implanted under the skin and a device that generates stimulation. The whole system is internalized into the patient's body. Parameters such as frequency, wavelength and voltage are adjusted non-invasively and adapted by computer control [22].

Serious risks and side effects associated with DBS are rare: intracranial haemorrhage, infection, epileptic seizure and complications associated with anaesthesia [22, 23]. The literature hereby reviewed also mentions symptoms which are not directly associated with the application of DBS, but may occur later as adverse events: vegetative symptoms, headache, transient anxiety, irritability, worsening of mood as well as suicide attempt and suicide [21]. According to the available literature, cognitive impairment is not associated with DBS, although it is mentioned with other invasive methods of treatment. Malfunctioning or failure of the system for DBS is possible as well, which would require replacement of one or more components. Acute and chronic effects of deep brain stimulation depend on the indication [23].

After 25 years of application and development of this method, there are some other restrictions in addition to the aforementioned, which are not so common but potentially serious side effects for an individual. The execution of the procedure and good previous diagnostics, a potential pharmacological or other non-invasive therapy, as well as the subsequent rehabilitation and further treatment require the cooperation of a neurosurgeon, neurologist and psychiatrist, who should share a common goal, that being the welfare of the patient [24].

Obsessive-Compulsive Disorder

Although the prevalence of about 2% in the general population classifies this psychiatric disorder between depressive disorder and schizophrenia, it is still insufficiently recognized. It significantly affects the quality of life and disability of the patient. Evidence-based treatment involves administration of antidepressants with a dominant influence on the monoamine neurotransmitter systems, antipsychotics with anxiolytics as well as cognitive behavioural psychotherapy [25]. However, up to 60% of patients do not respond satisfactorily to the treatment, which makes treatment-resistant OCD a serious public health problem. Target areas for DBS are the frontal part of the internal capsule and ventral striatum, i.e. nucleus accumbens, subthalamic nucleus and lower thalamic peduncle. So far, a significant number of small case studies with favourable results in the treatment of treatment-resistant OCD, with rare side effects have been published [26-30]. Compared to other non-pharmacological treatments, DBS did not have a significant impact on cognitive impairment.

Treatment-Resistant Depression

Depression is the fourth leading cause of disability in the world according to the World Health Organization, and there are predictions that it will be the second one by 2020 [31]. Treatment of patients with depressive disorder, according to the guidelines, involves antidepressant pharmacotherapy, psychotherapy and electroconvulsive therapy. Despite the aforementioned possibilities of treatment, about two-thirds of patients do not respond to the initial antidepressant treatment, the combined pharmacotherapy gets no response in about one-third of the patients and regardless of the therapeutic approach, symptoms persist in about one-fifth of patients, i.e. they never reach full remission. Depressive disorder is often recurrent in about 60% of patients who have a good therapeutic response [22]. In recent decades, progress has been achieved in the imaging of neuroanatomical structures associated with depressive disorder and response to antidepressant therapy. In our country, the treatment of depression included the method of transcranial magnetic stimulation, both in patients suffering from Parkinson's disease and depression, and in patients with mild depressive episodes [20, 32]. Mayberg and Hamani apply DBS of the white matter cingulum and describe neuroanatomical structural changes similar to the effects of a favourable response to the treatment with antidepressants [9, 33]. Nucleus accumbens, which is involved in the neural pathways associated with reward and motivation, may also be the target of DBS due to its favourable effect on anhedonia as a key symptom of Treatment-Resistant Depression (TRD) [34]. Sartorius described the case of a female patient with TRD undergoing electroconvulsive therapy, in which remission was achieved by additional DBS of medullary stria of thalamus. This is a relatively new target location, which is normally involved in the coordination of monoamine neurotransmission [35]. There are more and more reports stating favourable results achieved in patients having treatment-resistant depressive disorder who were treated by DBS [36,37].

Gilles de la Tourette syndrome

This disorder, whose prevalence amounts to about 1% [12], is characterized by disabling vocal and motor tics, as well as symptoms similar to OCD. Its frequent association with OCD suggests a common etiologic significance of the basal ganglia dysfunction in the development of motor symptoms [21]. In smaller studies, bilateral DBS of the globus pallidus, centromedian thalamic nuclei and anterior complex of thalamic nuclei yielded favourable results in patients with this syndrome [38].

Antipsychotic-induced tardive dystonia and dyskinesia

Late extrapyramidal side effects of antipsychotic therapy are not rare, and their treatment by replacing antipsychotics with anticholinergics, anxiolytics, levodopa, botulinum toxin and physical therapy is often unsuccessful [39]. DBS proved to be a very effective and long-term solution for the treatment of primary localized or generalized dystonia and dyskinesia. Bilateral DBS of the globus pallidus is a potentially important treatment of secondary, antipsychotic-induced tardive dystonia and dyskinesia as well, which are often disabling and pharmacotherapy-resistant [13, 15, 40].

Addiction

Case reports of smokers having OCD who were treated with DBS of nucleus accumbens, also mention a favourable response in nicotine addiction [41]. In three patients unsuccessfully treated for alcoholism, Muller shows good effects of the nucleus accumbens DBS [16], which could be explained by a qualitative change of the experience of the reward associated with the intake of substance or regulation of behaviour related to the addictive behaviour, which indirectly reduces the likelihood of relapse.

Alzheimer disease

About 8% of population over 65 years of age suffer from this neurodegenerative and neuropsychiatric disease. Pharmacological therapy involves slowing down, but not prevention of further cognitive decline within disease progression. Acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists as well as antipsychotics are used for the regulation of altered behaviour [22, 25]. A potentially modulating neurophysiological effect of DBS of fornix and hypothalamus on the activity in these pathological regions is being intensively studied [17, 18].

Conclusion

Neurosurgical treatment approach in psychiatry has a long history. Previous attempts were limited by the occurrence of a number of complications. Taking into account the development of neuroanatomical, neurophysiological and neurobiochemical models of mood, thinking and behaviour on one hand and technological advances regarding the increased safety of application of deep brain stimulation on the other, opens up possibilities of relieving symptoms and improving psychosocial functioning with its application. Current results regarding efficacy and safety of this method are encouraging, but larger, randomized, placebo-controlled studies are required. More precise defining of specific effects on clearly determined brain structures in patients with different psychiatric disorders, as well as the adjustment of all variable parameter values of the technical part of the deep brain stimulation system are a part of clearly set goals for further studies of the application of deep

brain stimulation. Modern therapeutic approach to most psychiatric disorders involves a combination of pharmacotherapy, psychotherapy, as well as the application of electroconvulsive therapy. Neurosurgical approach followed by proper psychiatric rehabilitation should definitely be considered for patients who fail to respond to the aforementioned treatment options and who become disabled.

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Rad je primljen 28. V 2013.
Recenziran 10. XII 2013.
Prihvaćen za štampu 18. XII 2013.
BIBLID.0025-8105:(2014):LXVII:1-2:28-32.

PROFESSIONAL ARTICLES
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Professional article
Stručni članak
UDK 616.329-072.1-053.9
DOI: 10.2298/MPNS1402033M

OESOPHAGEAL FOOD BOLUS IMPACTION IN ELDERLY PEOPLE

ZAOSTAJANJE BOLUSA HRANE U JEDNJAKU OSOBA STARIJEG ŽIVOTNOG DOBA

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Summary
Introduction. The diagnosis of food bolus impaction in the esophagus is based on the data obtained from the patient, clinical examination, radiographic diagnosis, and endoscopy. The aim of this study was to examine the influence of possible factors causing oesophageal impaction of food boluses in elderly people. **Material and Methods.** This retrospective study included six male and eight female patients treated at the Department of Ear, Nose, and Throat Disease in Novi Sad. **Results.** Post-corrosive oesophageal stricture was diagnosed in 28.57% of patients and non-corrosive stricture was found in 21.43%. Total tooth loss was recorded in 64.29% of patients and 14.29% of patients had partial tooth loss. An impacted food bolus was located at a distance of 15-25 cm or 30-40 cm distance from the upper incisors in 42.86% of the study sample. **Discussion and conclusion**. The impaction of food boluses in the esophagus is significantly higher in women, usually after 76 years of age. There is a positive correlation between the presence of oesophageal stricture and recurrence of food bolus impaction. Partial and total tooth loss is present in a high percentage but there is no correlation with the food bolus impaction. Impaction of food bolus was equally found in the upper and lower third of the oesophagus and it was usually meat. Radiographic diagnosis should precede each esophagoscopy. Esophagoscopy with rigid oesophagoscope is a reliable method for the extraction of a bolus of food from the oesophagus in elderly patients.
Key words: Deglutition Disorders; Esophagus; Food; Aged; Radiography; Esophagoscopy

Sažetak
Uvod. Dijagnoza bolusa hrane u jednjaku postavlja se na osnovu podataka dobijenih od pacijenta, kliničkim pregledom, radiografskom dijagnostikom i endoskopijom. Cilj rada bio je da se ispita uticaj mogućih faktora koji kod osoba starijeg životnog doba uzrokuju zaostajanje bolusa hrane u jednjaku. **Materijal i metode.** Rad je retrospektivna studija koja je obuhvatila 14 pacijenata Klinike za bolesti uva, grla i nosa, Kliničkog centra Vojvodine u Novom Sadu, u periodu od 3 godine. **Rezultati.** Ispitivani uzorak činilo je 6 muškaraca i 8 žena. Postkorozivnu stenozu jednjaka imalo je 28,57% pacijenata a nekorozivnu stenozu 21,43%. Spirmanov koeficijent korelacije ukazao je da postoji statistički značajna povezanost između recidiva bolusa hrane zaostalog u jednjaku i pratećih oboljenja jednjaka ($\rho = 0,645$, $p = 0,013$). Totalnu anodonciju imalo je 64,29% a parcijalnu 14,29%. Spirmanov koeficijent korelacije ukazuje da ne postoji značajna povezanost između prisustva zuba i stranog tela ($\rho = 0,325$, $p = 0,257$). Kod istog broja pacijenta (42,86%), bolus hrane se nalazio na udaljenosti 15−25 cm ili na udaljenosti 30−40 cm od prednjih zuba. **Diskusija i zaključak.** Zaostajanje bolusa hrane u jednjaku češće se javljalo kod žena a najčešće posle 76. godine života. Postoji pozitivna korelacija između postojanja stenoze jednjaka i pojave recidiva bolusa hrane. Parcijalna i totalna anodoncija zastupljeni su u visokom procentu ali nema korelacije između ove dve pojave. Podjednako su bolusi hrane zaostajali u gornjoj i donjoj trećini jednjaka a najčešće je to bilo meso. Radiografska dijagnostika treba da prethodi svakoj ezofagoskopiji. Ezofagoskopija rigidnim ezofagoskopom je pouzdana metoda za ekstrakciju bolusa hrane iz jednjaka kod osoba starijeg životnog doba.
Ključne reči: Poremećaj gutanja; Ezofagus; Hrana; Stari ljudi; Radiografija; Ezofagoskopija

Introduction

Elderly people are at a higher risk of having dysphagia – difficulty in swallowing. It is estimated that one out of ten people over 50 years of age has dysphagia. Besides the discomfort felt while swallowing, dysphagia can result in a food bolus while eating and drinking [1]. One of the reasons is the changes in the head and neck resulting from aging as well as the changes in physiological and neurological mechanisms responsible for the function of swallowing. If the elderly people are healthy, the

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changes in the swallowing mechanism are called presbyphagia. These changes progress with the decreasing ability of the body to adjust to a physiological stress, and with the increasing co-morbidity in elderly. In comparison to younger people, healthy elderly people have reduced isometric (static) pressure of tongue. The swallowing is slow, the laryngeal and pharyngeal movements are slow too, including the laryngeal aditus closing, that is, closing of the air pathway. .

Dry oral mucosa does not involve only the mouth, it often spreads to the pharynx and the oesophagus, which leads to food obstruction. Food remains in the mouth can increase the risk of bacteria spreading, thus, oral hygiene is very important. If food stays in the oesophagus for the same reason, antiperistaltic movements can be activated and food will be returned to the pharynx. That process is called the intraoesophageal reflux.

Taste, temperature, and tactile sensors change with aging, and sarcopenia (the degenerative loss of skeletal muscle mass, a reduction in number and size of muscle fibres, transformation or selective loss of some muscle fibres), deteriorate the chewing and swallowing functions significantly [2].

However, recent studies indicate that swallowing is not jeopardized by aging itself, although medical problems and some other conditions, influenced by the swallowing, have a tendency to appear later in life [1].

The most frequent causes of the foreign bodies obstruction are: neurological disorders and stroke (Parkinson's disease, multiple sclerosis, traumatic brain injury, amyotrophic lateral sclerosis, motor neuron disease) [1,3]; structural lesion of the esophagus (neoplasm, diverticulum, post corrosive and noncorrosive stricture) [3]; mental disorders (mental retardation, alcoholism), connective tissue diseases (polymyositis, muscular dystrophy) [2,3]; iatrogenic causes (surgery) [4,5]. Among the causes are drugs, such as anticholinergics, antidepressants, antihistamines [1,2] which can have adverse effect on saliva production in the mouth or those which can lead to inflammation of the oesophageal mucous membrane, such as tetracycline, iron preparations, non-steroidal anti-inflammatory drug, potassium [2,4].

The most common symptoms are the following: dysphagia, odynophagia, hypersalivation, dyspnea and cyanosis, cough, drooling and the fixed position of the patient's head (usually bent forward) in order to alleviate the discomfort caused by the foreign body. The patients are scared, excited, and upset. They may feel pain in the larynx (if a foreign body is positioned in the upper parts of an oesophagus), behind the sternum, spreading towards the scapula or the epigastrium (if it is positioned in the lower parts) [6]. When a foreign body is in the upper oesophageal sphincter region, the patient can localize it without a problem. However, if it is localized in the upper parts of the oesophagus, it can result in predominant symptoms of the respiratory system obstruction, such as dyspnea, wheezing, and cyanosis [7] or pains caused by angina pectoris [8].

If a foreign body is in the lower parts of the oesophagus, there can be various symptoms, among which are odynophagia, choking and retrosternal pain. Odynophagia is the result of the Oesophageal distension by the food bolus, but it can also be a symptom for the Oesophageal injury such as laceration, abrasion, or perforation. Therefore, each odynophagia must be taken seriously [9].

Food bolus in the oesophagus is diagnosed according to data taken from the patient, by clinical examination, laryngeal movement test, drinking water test, radiographic testing and endoscopy. If spontaneous propulsion of food bolus does not occur, extraction from the oesophagus can be done by the flexible or, preferably, rigid endoscope. Medicamentous treatment is also one of the therapeutic options [10]. Oesophageal food boluses as well as their extraction can result in complications [11-13].

The aim of the study was to examine the possible factors causing oesophageal food bolus impaction in elderly people.

Material and Methods

This retrospective study included 14 patients treated at the Department of Ear, Nose, and Throat Disease, of the Clinical Center of Vojvodina in Novi Sad during the three-year period. All the patients were diagnosed with food bolus impaction in the oesophagus according to the anamnesis, clinical examination, radiographic diagnosis, and endoscopy. Afterwards, all of them underwent extraction of food boluses. Special attention was paid to the type and place of impacted food, the way of food bolus extraction, as well as to the presence or the absence of teeth and implants, previous Oesophagus diseases, accompanying diseases, the size of endoscopes, and recurrent boluses, if any. The spreadsheet software, *Microsoft Excel 2007* and statistical package *Statistica 5.5*, was used for the statistical data processing.

Results

The study sample consisted of 14 subjects, six men (42.86%) and eight women (57.14%). They were all between 61 and 88 years old, their average age being 76.28. Eight patients, i.e. 57.14% of the total number of subjects, were older than the average age. Of seven patients who had had esophageal food impaction at stricture sites **(Figure 1**), and thus were aware of the contemporary esophageal disease, four patients (28.57%) had post corrosive oesophageal stricture and three patients (21.43%) had non-corrosive stricture. Other patients had no knowledge of their previous oesophageal disease. No associated diseases were present in 13 patients (92.86%), whereas one patient (7.14%) had Parkinson's disease.

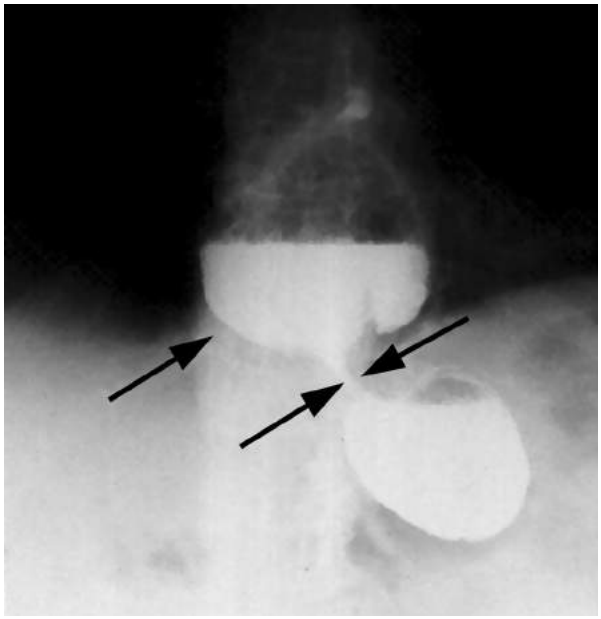

Figure 1. Post - corrosive stricture in the cardiac region, with consequent dilatation of the lower third part of the oesophagus (oesophageal contrast radiography, from the collection of the author)
Slika 1*. Postkorozivna stenoza u predelu kardije sa posledičnom dilatacijom donje trećine jednjaka (radiografija jednjaka kontrastom, iz zbirke autora)*

Spearman's coefficient correlation indicated that there was a statistically significant connection between the recurrent food bolus in the oesophagus and associated esophageal diseases ($\rho = 0.645$, $p = 0.013$). Three patients (21.43%) had their own teeth, whereas two patients (14.29%) had a partial tooth loss, and nine patients (64.29%) had total tooth loss. However, Spearman's coefficient correlation indicated that there was no significant correlation between the presence of teeth and a foreign body ($\rho = 0.325$, $p = 0.257$).

Eleven patients (78.58% of cases) had a foreign body removed with a gripper; whereas, in three patients, that is 21.34% of cases, there was a spontaneous bolus propulsion towards the oesophagus during esophagoscopy.

Six patients (42.86%) had food bolus at 15-25 cm distance from the front teeth **(Figure 2)**. Two patients (14.29%) had food bolus at 25-30 cm from the front teeth, and six patients (42.86%) had it at 30-40 cm distance **(Figure 3)**.

The most common food bolus in this research, found in ten patients (71.43%), was meat. A bone was found in two patients (14.29). Pork liver and meat with cartilage were found in one patient (7.14%), each.

The most frequently used rigid endoscope for extraction of an impacted food bolus was the 10x14x50 tube, which was used in six patients (42.86%). The 12x16x30 and 21x16x50 endoscope was used in three patients (21.43%), each. The

Figure 2. Food bolus in the upper third part of the oesophagus (oesophageal contrast radiography, from the collection of the author)
Slika 2. *Bolus hrane u gornjoj trećini jednjaka (radiografija jednjaka kontrastom, iz zbirke autora)*

10x17x30 endoscope and the 10x14x20 endoscope was used in one patient (7.14%), each.

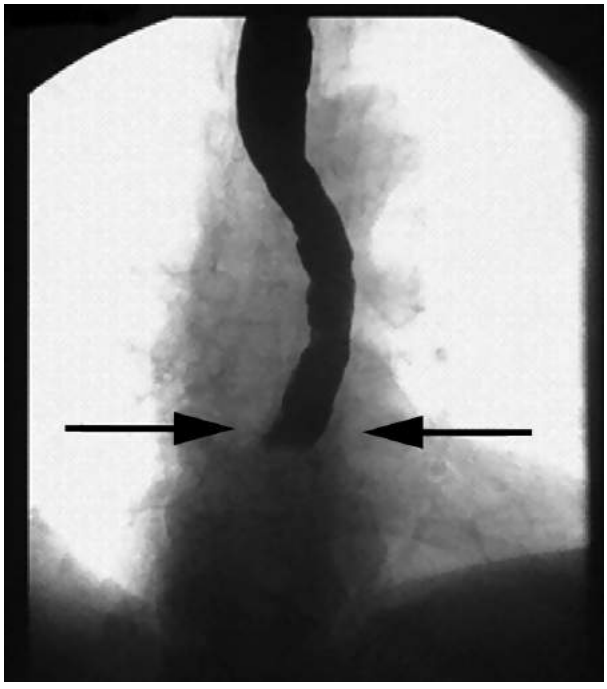

Figure 3. Food bolus in the lower third part of the oesophagus (oesophageal contrast radiography, from the collection of the author)
Slika 3. *Bolus hrane u donjoj trećini jednjaka (radiografija jednjaka kontrastom, iz zbirke autora)*

Discussion

According to Longstreth et al [14], the frequency of the foreign bodies impacted in the oesophagus increases with age, especially after the seventh decade. So in this study, more than a half of patients were older than 76. This study showed that a foreign body impaction was more frequent in women [15], whereas it is more frequent in men according to most other studies. Brooks [7] reported that the male-female ratio was 55%-45%, Longstreth et al. [13] said it was 1.7-1, and according to Williams et al. [16] it was 3:1. Kirchner et al. [17] state that the causes of bolus impaction in the oesophagus are eosinophilic oesophagitis and reflux oesophagitis with and without peptic stenosis. Although the oesophageal stenosis is the cause of the recurrence of food bolus impaction of the oesophagus, Reddy et al [18] reported the recurrence bolus rate to be 9%, stating the presence of hiatus hernia as the only reason and giving no detailed explanation of its influence on the recurrent bolus. Prasad et al. [19] also claim the hiatus hernia is the cause of the recurrence of food bolus impaction of the oesophagus.

It is interesting to say that almost a third of patients in this study had the post corrosive oesophageal stricture. Regarding the fact that the patients are elderly people, the reason for the post corrosive oesophageal stricture has been explained in details. In the post-war Republic of Yugoslavia, laundry soap was made at home, because of poverty and undeveloped chemical industry. To that purpose, sodium hydroxide, which is essential for making soap, could be bought and sodium hydroxide poisoning was rather frequent with the resulting oesophageal damage. This is exactly what happened to four patients from the study sample and how they developed post corrosive oesophageal changes [20].

The fact that nine patients (64.29%) did not have any teeth indicated that the total tooth loss may have had some influence on food bolus impaction in the esophagus. However, Spearman's coefficient correlation did not prove that there was a significant correlation between the teeth presence and a foreign body. Nevertheless, this data and the fact that saliva secretion is reduced in elderly people due to fewer acinar cells as well as weakened tongue muscles [4] account for higher frequency of foreign body impaction in elderly people. Ginsberg [8] mentions that the bad teeth condition and improperly made and/or fitted dentures are contributing factors to food bolus impaction.

Every patient from this study had their history taken and underwent clinical examination, followed by native or contrast radiographic examination. Barium and Gastrografin were used as contrast media. Williams et al [16] believe that this diagnostic procedure must be applied in all patients suspected to have foreign body impaction.

Native or contrast radiographic examination is done to show the place where food is impacted on its way through the oesophagus, to plan further intervention and to decide whether to perform oesophagoscopy, and if so, what size tube to use to extract the foreign body.

Oesophagoscopy has revealed that the most common places of food bolus obstruction are between 15 cm and 25 cm, and between 30 cm and 40 cm from the front teeth, usually, imaginary front teeth, the frequency being 42.86%, whereas the distance from to 25 cm to 30 cm from the front teeth is far less frequent. Brooks [7] has also showed that the place of the most frequent food bolus obstruction is in the upper third part of the oesophagus. In addition, his finding that the middle third part of the oesophagus is the least frequent place of foreign body impaction coincides with the findings of this study. Athanassiadi et al [3] have reported the same results. They claim that the most frequent and the least frequent place of foreign body impaction is the cervical part of oesophagus (57%) and the abdominal part of the oesophagus (17%), respectively, which is in contrast to the results obtained in this study. The reason why more patients from this study had food obstruction in the lower part of the oesophagus, is that one out of the seven patients had stenosis in the upper part (14.28%) and the other six (85.72%) in the lower third of the oesophagus.

During oesophagoscopy, eleven patients (78.57%) had their foreign body extracted, whereas, spontaneous propulsion happened in three patients only (21.43%). Williams et al. [16] have reported the opposite results, stating that spontaneous propulsion happened in 60.2% of patients. This finding corroborates the opinion that oesophagoscopy shoud not be rushed in the patients who did not have any previous oesophageal obstruction since spontaneous food bolus propulsion can happen, as claimed by Ko et al [9]. However, esophagoscopy should be performed if a patient does not have food remains which can cause complications (bone), or there is no bolus impaction. In that case spontaneous propulsion would not happen [21,22].

Meat is the most frequently found bolus in patients (71.43%), followed by a bone, pork liver, and meat with cartilage. The same finding has been reported by Brooks [7] and the authors of this study. According to Ginsberg [8], meat (beef and chicken) is also the most common bolus. Williams et al [16] have reported somewhat different results. They claim that a bone is far most common food bolus (81.4%). However, what should be taken into account here is the fact that the average age of their patients was 52 years, which is much younger age in comparison with the age of patients from this study.

Likewise, Adhikari et al [23] and Pudar [15] claim in their studies that a bone is the most common foreign body, and they have reported its frequency to be 76.1% and 42,3%, respectively.

No complications whatsoever developed in the patients with food bolus or in those who had the bolus extracted by rigid oesophagoscope.

Conclusion

Oesophageal food bolus impaction is significantly higher in women, most often in those over 76 years of age. There is a positive correlation between the presence of oesophageal stenosis and recurrence of food bolus impaction. Partial and total tooth loss is present in a high percentage but there is no correlation with food bolus impaction. The impaction of food bolus is equally found in the upper and lower third of the oesophagus and it is usually meat. Radiographic diagnosis should precede each oesophagoscopy. Oesophagoscopy with rigid oesophagoscope is a reliable method for the extraction of food bolus from the oesophagus in elderly people.

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Rad je primljen 12. XI 2013.
Recenziran 16. XII 2013.
Prihvaćen za štampu 18. XII 2013.
BIBLID.0025-8105:(2014):LXVII:1-2:33-37.

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Professional article
Stručni članak
UDK 616.31:616.527]:615.831
DOI: 10.2298/MPNS1402038P

PEMPHIGUS VULGARIS AND LASER THERAPY: CRUCIAL ROLE OF DENTISTS

PEMPHIGUS VULGARIS I LASEROTERAPIJA: PRESUDNA ULOGA STOMATOLOGA

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Summary

Introduction. Pemphigus vulgaris is a relatively rare, chronic, autoimmune vesiculobullous disorder characterized by formation of intraepithelial vesiculae and/or bullae in the skin and mucous membrane. Systemic steroids are considered to be the standard first-line therapy for pemphigus vulgaris. However, for patients unresponsive to standard therapy, the new treatment modalities are being sought. Low-level laser therapy has been accepted as an alternative or adjunctive treatment modality for many conditions in medicine and dentistry. Therefore, this study was aimed at presenting the effects of low-level laser therapy in the treatment of pemphigus vulgaris and to emphasize the crucial role of dentists in early recognition and diagnosis of pemphigus vulgaris. **Material and Methods.** The articles published until May 2013 were obtained from the Medline/PubMed online database, using following search terms and key words: "laser therapy" and "pemphigus vulgaris", "low-level laser irradiation" and "pemphigus vulgaris", "lasers" and "pemphigus vulgaris" and "pemphigus vulgaris". **Results.** Low-level laser therapy could result in immediate and significant analgesia and improved wound healing within the observation period and follow-up. Furthermore, a decrease in patients' discomfort as well as the absence of recurrence of the pemphigus vulgaris lesions has been claimed. **Conclusion.** Even though available literature suggests that low-level laser therapy can be efficiently used in treatment of oral pemphigus vulgaris, either independently or as a part of combined therapy approach, these results should be interpreted with caution since there are no solid evidence-based proofs to provide the guidelines for the treatment of pemphigus vulgaris with low-level laser therapy. Therefore, further long-term randomized controlled clinical studies are necessary in order to give any solid recommendations on the use of low-level laser therapy in the treatment of pemphigus vulgaris.

Key words: Pemphigus; Laser Therapy; Dentistry; Laser Therapy, Low-Level; Skin Diseases, Vesiculobullous; Treatment Outcome

Sažetak

Uvod. Pemfigus vulgaris relativno je retko, hronično, autoimuno, vezikulo-bulozno oboljenje, koje karakteriše stvaranje intraepitelnih vezikula (mehurića) i/ili bula (mehura) na koži i sluzokoži. Danas se terapijom izbora u lečenju pacijenata obolelih od pemfigusa smatraju sistemski kortikosteroidi. Međutim, za pacijente koji ne reaguju na standardnu terapiju, neprestano se traga za novim terapijskim rešenjima. Laseroterapija je prihvaćena kao alternativni ili dodatni vid terapije za mnoga oboljenja iz oblasti savremene medicine i stomatologije. Cilj ove studije je da predstavi efekte laseroterapije u lečenju oralnih lezija izazvanih pemfigusom vulgaris, te da podseti na važnost uloge stomatologa u ranom prepoznavanju i pravilnom dijagnostikovanju ovog obolenja. **Materijali i metode.** U razmatranje su uzete studije objavljene do maja 2013. godine, dostupne na Medline/PubMed onlajn bazi podataka. Baza podataka je pretraživana ukucavanjem ključnih reči i termina: *laser therapy* i *pemphigus vulgaris, low-level laser irradiation* i *pemphigus vulgaris, lasers* i *pemphigus vulgaris* i *pemphigus vulgaris.* **Rezultati.** Laseroterapija izaziva trenutnu i statistički značajnu analgeziju, te ubrzano zarastanje rana u datom vremenskom okviru (i tokom posmatranja, kao i tokom praćenja). Takođe, uočeno je i smanjenje tegoba kod pacijenata, kao i prestanak ponovnog pojavljivanja novih oralnih lezija nakon laseroterapije. **Zaključak.** Iako dostupna literatura predlaže upotrebu laseroterapije kao efikasne metode za lečenje oralnih lezija, bilo kao samostalan vid terapije, ili kombinovan sa drugim terapijskim postupcima, ovi rezultati se moraju vrlo oprezno interpretirati, budući da nema čvrstih dokaza koji bi dali smernice za laseroterapiju oralnog pemfigusa vulgaris. Zato su neophodne dodatne kliničke studije kako bi se dala optimalna preporuka o lečenju laseroterapijom oralnih lezija izazvanih pemfigusom vulgaris.

Ključne reči: Pemfigus; Laseroterapija; Stomatologija; Laserska terapija niskog nivoa; Vezikulobulozna oboljanja kože; Ishod lečenja

Introduction

Pemphigus is a group of relatively rare, chronic autoimmune disorders characterized by formation of intraepithelial bullae in the skin and mucous membrane [1, 2]. Pemphigus is divided into two major subtypes: pemphigus vulgaris and pemphigus foliaceus [1]. Having the incidence up to 80% of all

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Abbreviations
PV – pemphigus vulgaris
LLLT – low-level laser therapy

pemphigus cases, pemphigus vulgaris (PV) is considered the most common form of disease [2]. PV can be divided into two subgroups: the mucosal type and mucocutaneous type [3]. PV affects the oral mucosa in nearly all cases and more importantly, the oral (mainly buccal and/or palatal) mucosa is the place of the first lesions in the majority of cases [2]. It is characterized by immunoglobulin G auto antibodies against desmosome associated protein antigens (desmoglein 1 and/or 3) found in epithelial and epidermal intercellular substance. Since the desmosomes are the primary attachment mechanism between keratinocytes, this disease results in acantholysis in epidermis [1].

Typically, the patients suffering from PV have flaccid blisters (fluid filled bullae) that rupture easily provoked by even minimal trauma, further causing painful multiple erosions and ulcerations on the skin and mucous membranes, which spread to other mucosa and the skin [4]. Oral PV is usually associated with symptoms ranging from mild burning sensation to severe pain (in about 87.5% of patients with PV) affecting normal masticatory function [5]. Furthermore, due to the repeated cycles of blistering and healing, oral hygiene is usually compromised, leading to rapid breakdown of the dentition [3, 4]. A definitive diagnosis of PV is made when Nikolsky's sign is positive, in the presence of acantholysis in histopathology and by direct immunofluorescence [2].

Although a number of different treatment modalities have been recommended so far, treatment of PV is usually symptomatic, therefore showing low predictability. Most treatment modalities are conservative/pharmacological, such as systemic corticosteroids, immunosuppressant or immunomodulatory agents, corticosteroids being widely accepted as the primary treatment of choice [1]. However, corticosteroids are limited by various time and dose dependent adverse effects. One of the main drawbacks of corticosteroids is the long-term application treatment, which can be difficult on the oral mucosa, causing further frequent relapses upon the treatment's cessation and often requiring steroid-sparing agents [6, 7]. Unfortunately, steroid-sparing agents are often associated with significant toxicity. Immunosuppressants used in the treatment of severe PV may increase the risk of infection and delay healing, thus causing a problem in dental treatment procedures in this group of patients [9]. Less studied, emerging therapies include intravenous immunoglobulin, plasmapheresis, immunoadsorption, extracorporeal photochemotherapy, cholinergic agonists, rituximab, anti-CD20 monoclonal antibody therapy, tumor necrosis factor-α (TNF-α) inhibitors and other experimental therapies such as Desmoglein-3 peptides [10-12]. Since drugs used in the treatment of patients with PV have many drug-related side effects, the patients must be monitored carefully, their health status must be improved and they must be advised to exercise, diet and stop smoking. Though the majority of patients respond to these therapies, some patients will develop a recalcitrant disease [6]. Therefore, the need for better treatment alternatives was obvious, especially for patients unresponsive to standard therapy of PV.

Low-level laser therapy (LLLT; photobiostimulation) has been widely used as an alternative or supplementary treatment modality; thus, its applications in modern medicine and dentistry are numerous. The aim of this review article was to give the insight into the literature published so far regarding the effects of LLLT used for treatment of patients with PV and to remind on the crucial role of dentists in early recognition of PV.

Material and Methods

The articles published until May 2013 were obtained from the Medline/PubMed online database, using following search terms and key words: "laser therapy" and "pemphigus vulgaris", "low-level laser irradiation" and "pemphigus vulgaris", "lasers" and "pemphigus vulgaris" and "pemphigus vulgaris". Two authors performed both the screening and selection of studies independently in order to ensure impartiality when selecting the studies. Secondary sources included papers cited by articles retrieved from the above mentioned studies. The corresponding authors were contacted in case of missing and insufficient data reported originally in the studies. The authors of this study measured and compared the symptoms (pain, discomfort), signs (enhanced healing) and recurrence of the PV lesions.

Results

The author of this article knows of only three publications that deal with the effects of LLLT on

Table 1. The basic information of selected studies
Tabela 1. *Osnovni podaci o izabranim studijama*

Author and the year of the publication (reference) *Autor i godina publikacije (referenca)*	Study design *Vrsta studije*	Number of patients *Broj pacijenata*
Bhardwaj A. et al. (6)	Case report/*Prikaz slučaja*	2
Minicucci EM. et al. (7)	Case report/*Prikaz slučaja*	2
Zand N. et al. (8)	Before/after clinical trial *Pre/posle klinička studija*	10

oral pemphigus vulgaris **(Table 1)**. Minicucci et al. [7] reported two cases of oral and cutaneous PV treated with conventional steroid therapy prednisone and dapsone (diamino-diphenyl sulfone) combined with the low-level diode laser therapy and its effects on pain and faster wound healing. The following diode laser parameters were used: wavelength 660 nm, output power 100 mW, fluency 35 J/cm^{2}and time duration of 20 s per point. The laser was applied at the distance of 6 mm from the oral mucosa and the treatment was repeated daily until the pain, being the main symptom, disappeared. The immediate analgesic effect in oral lesions (70% after the first laser therapy session) and accelerated oral wound healing were evident; thus, the authors suggested LLLT as a promising supplementary treatment modality for patients with PV. On the other hand, Bhardway et al. [6] used only low-level CO_2 laser irradiation in the treatment of recalcitrant oral PV lesions (previously unsuccessfully treated with pulse therapy of methyl-prednisolone and cyclophosphamide for 6-8 months). The following laser parameters were used: wavelength 10 600 nm, continuous wave, output power of 1-1.5 W. The authors proved immediate analgesia, reduced discomfort with no recurrence of the lesions and improved wound healing within 1, 3 and 5 months of follow-up [6]. Similarly, Zand et al. reported immediate and significant analgesia following low-level CO_2 (10 600 nm, continuous wave) laser irradiation in the treatment of recalcitrant painful PV lesions [8]. Both studies employed CO_2 laser in a defocused mode to scan rapidly over oral PV lesions at the distance of 5-6 mm from oral lesions for about 5-10 s [6, 8]. However, Zand et al. used a thick layer (3-4 mm) of transparent non-anesthetic gel with high water content to reduce the beam absorption by the tissue, thus significantly reducing the output power from 1 W to 2-5 mW [8].

Discussion

Pemphigus vulgaris is a painful, and, if neglected, a potentially life-threatening blistering disease. The therapy is mainly focused on increasing oral comfort (e.g. eating, swallowing, speaking, sleeping, wearing dental prostheses…) and reducing the duration and severity of symptomatic outbreaks, especially during the periods of quiescence and exacerbation (period of increased pain and sensitivity) of PV lesions. It is widely accepted that the first line therapy for oral PV are systemic corticosteroids. However, LLLT has been introduced as a new treatment option for patients with PV lesions unresponsive to conventional therapy. LLLT is a non-destructive, non-thermal and painless procedure with no thermal damage effects visible in the oral mucosa. It has biostimulatory effects on the surrounding tissues and cells during high-level laser irradiation, such as an increase of systemic microcirculation and tissue oxygenation, cell metabolism and/or tissue regeneration and potential tissue healing, without side effects [13, 14]. LLLT has also been proven to reduce the pain of various etiologies [15]. Even though several theories have been proposed to explain the positive effects of LLLT, the exact underlying mechanism by which LLLT helps healing of the tissue and alleviation of pain is still unknown. So far, *in vitro* and *in vivo* studies have demonstrated enhanced fibroblast, keratinocyte and endothelial cells metabolism, migration and proliferation [16, 17]. Furthermore, an increase in the activity of cytokines and growth factors as well as protein synthesis and secretion following LLLT irradiation has been proved [18]. In addition, LLLT is claimed to reduce the prostaglandin E_2 level and inhibit cyclooxygenase, bradykinin and substance P activity [19, 20].

So far, LLLT has been used effectively in the treatment of oral lichen planus, leukoplakia, aphthous ulcers, epidermolysis bullosa and even oral manifestations of HIV [21-24]. Therefore, it was reasonable to expect that it would be equally efficient in oral PV therapy. The present review was aimed at evaluating the available literature on the effects of LLLT in the treatment of PV and it has been concluded that LLLT is efficient in the treatment of recalcitrant oral PV lesions, either used alone [6, 8] or as an adjunct to conventional treatment modalities [7]. LLLT resulted in the immediate and significant analgesia with enhanced wound healing, decrease in patients' discomfort and no recurrence of PV lesions during the observation period and follow-up **(Table 2)**. However, the results of this study should be interpreted with caution and evaluated more thoroughly because the literature data published on this issue are rather scarce; furthermore, a different set of laser parameters was applied and the length of observation and follow-up period were not the same.

In order to determine the real efficacy of laser therapy (the optimal set of laser irradiation parameters and well-defined duration and frequency of intervals), further carefully designed long-term clinical studies with a larger number of patients (possibly international) are necessary as well as prolonged follow-up period. It is suggested that further research should be performed with standardized outcome measures (such as patients' subjective assessment) using different wavelengths and/or laser parameter combinations in order to determine the most efficient irradiation conditions for the best PV treatment outcome. Even though the advances in laser technology have improved the site-specific delivery of laser energy, there is enough space for further improvement of the oral application of lasers, designed for different spot sizes and in variety of shapes for better handling.

After prolonged history of oral lesions, 75%-80% of the patients with PV will experience initial lesions in the oral cavity [25, 26]. Since oral PV lesions can appear similarly to other mucocutaneous disease lesions present in oral mucosa, their diagnosis can be very difficult. Therefore, the definite diagnose of PV

Table 2. Effects on laser therapy in treatment of pemphigus vulgaris
Tabela 2. *Efekti laseroterapije u lečenju pemfigusa vulgaris*

Author and the year of the publication (reference)/*Autor i godina publikacije (referenca)*	Laser device *Vrsta lasera*	Laser application *Aplikacija lasera*	Laser output power *Snaga lasera*	Main outcome measures *Analizirani pokazatelji*	Findings *Rezultati*
Bhardwaj A. et al (6)	CO_2 laser (10 600 nm)	Laser only *Samo laser*	100 mW	Symptoms: pain, discomfort *Simptomi: bol, nelagodnost*/Sign: enhanced healing *Znak: ubrzano zarastanje* Recurrence of the lesions/*Ponovno javljanje lezija*	Immediate analgesia *Trenutna analgezija* Less patients' discomfort *Smanjena nelagodnost* Accelerated oral wound healing *Ubrzano zarastanje rana u ustima* No recurrence of lesions *Nema ponovnog javljanja lezija*
Minicucci EM. et al (7)	diode laser (660 nm)	Laser+systemic corticosteroids *Laser+sistemski kortikosteroidi*	1-1.5 W	Sympom: pain *Simptom: bol* Sign: enhanced healing/*Znak: ubrzano zarastanje*	Immediate analgesia *Trenutna analgezija* Accelerated oral wound healing *Ubzano zarastanje rana u ustima*
Zand N. et al (8)	CO_2 laser (10 600 nm)	Laser only *Samo laser*	1 W	Symptom: pain *Simptom: bol*	Immediate and significant analgesia *Trenutna i značajna analgezija*

is often made with a significant delay. Oral manifestations of PV may occur independently or precede cutaneous involvement by a year or more, suggesting that oral cavity can be considered a place for potential diagnosis of PV [27, 28]. Dentists are, therefore, in a unique position to recognize the oral signs and symptoms of PV in its initial stages, to establish an early definitive diagnosis and to initiate the therapy in order to prevent the serious disease progression and morbidity that may result from the disease [29]. They can put PV disease under control and ensure patients' comfort by maintaining oral hygiene and providing prosthetic rehabilitation if necessary [30]. Apart from dentists, management of these patients requires multidisciplinary approach of other physicians (e.g. dermatologist, gastroenterologist, family physician and nurses) in order to establish an appropriate diagnostic and therapeutic plan.

Conclusion

Available literature suggests that low-level laser therapy can be used efficiently in the treatment of oral pemphigus vulgaris either independently or as an adjunct to the conventional therapy approaches. Since there have been no solid evidence-based proofs so far which would undoubtedly corroborate the effectiveness of low-level laser therapy in the treatment of oral pemphigus vulgaris, it is rather difficult to recommend the low-level laser therapy in this conclusion as superior to other available therapy options. Therefore, further long-term randomized controlled clinical studies are necessary to give a solid recommendation on the use of low-level laser therapy in the treatment of pemphigus vulgaris.

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Rad je primljen 31. VII 2013.
Recenziran 16. XII 2013.
Prihvaćen za štampu 18. XII 2013.
BIBLID.0025-8105:(2014):LXVII:1-2:38-42.

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Professional article
Stručni članak
UDK 616-006.04-052:159.97
UDK 618.19-006.6-089.168:616.89-052
DOI: 10.2298/MPNS1402043K

POST-OPERATIVE CONDITION OF BREAST CANCER PATIENTS FROM STANDPOINT OF PSYCHO-ONCOLOGY – PRELIMINARY RESULTS

STANJE PACIJENTKINJA OBOLELIH OD KARCINOMA DOJKE U POSTOPERATIVNOM PERIODU SA PSIHOONKOLOŠKOG ASPEKTA – PRELIMINARNI REZULTATI

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Summary

Introduction. Information on being diagnosed to have cancer is always shocking for the patient, and it always causes a lot of psychosocial problems during its treatment. In these moments, patients need understanding, support and someone who can help them to apprehend all available options and choices clearly. The purpose of this study is to show the psychological states of patients with breast cancer after breast surgery, the importance of the psychological support, and first experiences in psycho-oncological management of breast cancer patients. **Material and Methods.** The study sample included 46 women, their average age being 52.32 (± 8.98), who had answered questions in a questionnaire in the period after surgery. **Results.** The patients experienced fears and worries associated with almost every part of cancer treatment likely to happen in the near future. The fear of chemotherapy and radiotherapy (67%), the horror of losing hair (59%) and the fear of relapse or disease progression (57%) were evident. Moreover, the patients dreaded the forthcoming pathological results and the decisions to be made by the Oncology Commission (57%), with accompanying insomnia caused by disturbing thoughts in 39% of the patients. **Conclusion.** These findings suggest that psychological support is important in this early period after breast surgery due to the vulnerability of the patients, and because it can diminish the risk of potential escalation of distress.

Key words: Breast Neoplasms; Female; Postoperative Period; Stress, Psychological; Middle Aged; Questionnaires; Adaptation, Psychological

Sažetak

Uvod. Saznanje da im je dijagnostikovan karcinom neminovno izaziva šok kod pacijentkinja, a potom dovodi i do niza drugih psihosocijalnih problema dok traje lečenje. U tim momentima potrebna im je briga, pažnja i neko ko će im pomoći da jasnije sagledaju mogućnosti i izbore koji su pred njima. Cilj studije je da se ukaže na psihološka stanja pacijentkinja s karcinomom dojke nakon operacije, na važnost pružanja psihoonkološke podrške i prikaz prvih iskustava u radu s pacijentkinjama. **Materijal i metode**. Uzorak čini 46 pacijentkinja prosečne starosti 52,32 (± 8,98) koje su odgovorile na pitanja iz upitnika u postoperativnom periodu. **Rezultati**. Pacijentkinje doživljavaju strahove i zabrinutost u vezi sa gotovo svim događajima koji su deo procesa lečenja i koji bi trebalo da se dogode u relativno bliskoj budućnosti. Prisutni su strah od hemioterapije i zračenja (67%), užasavanje zbog gubitka kose (59%), strah da će bolest recidivirati ili metastazirati (57%). Takođe, ono zbog čega strepe jesu rezultati patohistološkog nalaza i odluke Onkološke komisije (57%), a kod većeg broja pacijentkinja prisutna je česta nesanica zbog uznemiravajućih misli (39%). **Zaključak**. Dobijeni nalazi ukazuju na to da je pružanje psihološke podrške važno i u ovom ranom periodu, nakon hirurškog zahvata, zbog vulnerabilnosti pacijentkinja, čime se smanjuje rizik od kasnije eventualne eskalacije distresa.

Ključne reči: Karcinom dojke; Žensko; Postoperativni period; Psihološki stres; Srednje godine; Upitnici; Psihološka adaptacija

Introduction

Psycho-oncology is a specific area in the field of medicine and psychology. Therefore, it is an interdisciplinary area, which started being studied in the second half of the twentieth century and it reached its full importance and expansion especially during the last couple of years [1]. There are three reasons that have probably led to its ever-growing popularity: due to the advancements of medicine, the life expectancy of people with malignancies has increased significantly, whereas the quality of their life has significantly deteriorated. Taking into consideration that treating cancer requires aggressive methods, which are exceptionally difficult for the patient and affect their social and emotional life and behavior, the focus is on preserving the overall integrity of the person, rehabilitation and returning of the patient back to their family, friends and workplace if this is possible. The other reason is that this disease affects

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not only the patients, but their family members, friends and the medical staff taking care of them as well. The third reason is the effect of the bio-psycho-social model in health care, which takes into consideration biological, psychological and social factors as well as their interaction during the development of disease.

Thus, psycho-oncology deals with the psychological reaction of patients with cancer at all stages, the reactions of their environments, families and caregivers as well as the psychological, social and behavioral factors which can affect the risk of cancer development, its treatment and outcome [2].

The very information on being diagnosed to have cancer is bound first to shock both the diseased and their family members and then it causes a wide range of other psychosocial problems during the treatment. Hospitalization, which comes quickly after hearing the diagnosis, is yet another stress factor which the patient has to go through. In most cases it is followed by a surgical intervention, chemotherapy and radiation. These interventions are outside the person's previous experience and often lead to acute anxiety, confusion, fears and even depressive manifestations [3]. In these moments, the patients need support, attention and someone who will help them see their options more clearly along with the future choices they have in store. Since the psychical state of the patients and their coping mechanisms are important for the course of the treatment (some studies state even the connection with the disease outcome) and for the adequate cooperation with the medical staff, the psychological support and the psychotherapy interventions are clearly unavoidable parts in the treatment of patients with cancer. The psychological support to the patients diagnosed with a malignant disease implies a wide range of interventions, which depend on the specific needs of every patient and whose goal is most commonly a functional adaptation to the newly developed situation. In other words, the patients have to accept the disease and seek constructive ways for further functioning, which would not lead to any kind of maladaptive behavior, i.e. it would not intensify distress but alleviate the consequences of distress, that is, the negative psycho-physiological reactions to the malignant disease. The psychological support can include both psychotherapy and counseling when the patient is in crisis and the preoperative preparation, which most commonly involves providing procedural, sensory and behavioral information [3]. The main aim of postoperative conversations is to show understanding, concern and warmth for the patient, i.e. to create such a relationship that will be of significance in the later treatment period as well so that the patients develop complete trust and ask for help more frequently should a crisis arise. In addition, the support means providing information and preparation for the chemotherapy and radiotherapy as well as giving instructions and information regarding almost all of the things likely to be expected during the treatment. The patients should be advised on which procedures to observe, i.e. what kind of life style to adopt. It also means dealing with patients in the terminal phase of the disease. The above interventions enable the patients to face their disease in the most adequate way possible by strengthening the sense of control and by decreasing the feeling that the illness is a challenge that significantly surpasses the capacity of the person who has to deal with it. Besides the techniques directed at establishing cognitive control, stress can be controlled by the relaxation techniques that affect the physiological parameters; these are, for example, guided fantasy, yoga and meditation [3]. In addition, assertive training is often used along with learning how to gain emotional literacy as a means of education. It is very important to try to overcome the stress not only for the sake of general psychological condition of the patients and their quality of life, but also for strengthening the immune system, which is necessary in the fight against malignant cells. Although it has not been proved yet, some authors believe [3] that the immune system helps the process of elimination of the initial malignant changes and that stress can contribute to the growth of tumor mass to the size which the immune system can no longer fight against easily. It is also believed that suppression of different immune system functions may weaken defence mechanisms, which also enhances the tumor growth. Some studies have even shown a certain correlation between psychological interventions and survival rates [4]. Depression is also related to a decreased number of suppressor T-cells, whose functional disorder can be associated with autoimmune diseases; it is also related with decreased activity of the killer cells (NK cells) that are important for destroying tumor cells and which are a natural defence of the organism against the tumor growth and metastases [5].

The psychological support also involves working with the family members of the diseased, who often find it more difficult to accept the disease than the patients themselves. In addition, if the diseased is a parent of the family, the family members have to adapt to the complete reorganization of the family roles resulting from this new situation. The support may include working with the medical staff in order to improve the relationship and the communication between the medical staff and the patient. Being under constant stress and therefore prone to develop the burnout syndrome due to their specific working conditions and professional expectations from themselves and others, the medical staff should be included in the stress management and counseling.

So, psycho-oncology and psycho-oncological support are important not only from the standpoint of being humane and improving the quality of the lives of people suffering from a malignant disease but also from the scientific research aspect because the findings in this area are still relatively scarce.

Having been diagnosed with a malignant disease, which is most commonly related to fatal outcome [6] and after the initial shock and intense anxiety, the female patients seek the best solution and information related to the treatment, then they visit the Institute of Oncology so that they could undergo breast surgery. It has been noticed that they are not intensively anxious about the procedure itself but about everything that comes afterwards. To be certain that the tumor will be removed completely many female patients opt for the amputation of the entire breast even though such a procedure has not been indicated.

After the surgical procedure, the patients enter the stage of recovery, when they are on their own and see their loved ones only during visiting hours and thus have more time to think about the disease itself. It seems that only in this postoperative period have the patients become aware of the disease itself as well as the uncertainty of the outcome and the fact that everything that they had to go through was actually just the beginning of a relatively long-term treatment process. Thus, being very vulnerable in this postoperative period, they are prone to develop different dysfunctional thoughts and behaviors, which can sometimes, but not necessarily, be the introduction to a state of intensive distress, which demands a combination of psychotherapeutic and psychopharmacological treatment.

Female patients with primary breast cancer are the main population group dealt with at the Ward for Oncology Rehabilitation and the psychological support given to these patients is still something new since it started being implemented recently as the main part of life quality improvement after surgeries. Therefore, this study is focused on the female patients at the early stages of their rehabilitation after their surgical treatment.

The aim of this study was to indicate the postoperative psychological states of the female patients diagnosed to have breast cancer and the importance of giving psycho-oncological support, and the presentation of the first experiences in working with these patients.

Material and Methods

The study sample consisted of 46 patients aged from 25 to 81 years, their average age being 52.32 ± 8.98 years, who had undergone surgery at the Department of Surgical Oncology of the Institute for Oncology of Vojvodina in the period from May until October 2012 and who were contacted after the surgery.

In order to get information on the psychological state of the patients after surgery, the questionnaire consisting of nine dichotomous items was used **(Appendix 1)**. The questions asked were taken from the previously conducted pilot study that used an unstructured interview, which gave data on the most upsetting things for the patients after surgical intervention as well as their needs. Information regarding the patients' opinions about the psycho-oncological support was obtained from the questionnaire which consisted of four dichotomous items **(Appendix 2)**.

Results

The obtained findings **(Table 1)** show that the patients find the possibility of having chemotherapy and radiotherapy as the most disturbing issue and something that makes them have dysfunctional thoughts (67%). It is followed by the fear and horror of a possible hair loss (59%), as well as the fear that the disease will relapse or progress (57%). Moreover, the patients are anxious about the forthcoming pathological results and the decisions to be made by the Oncology Commission (57%), while insomnia is common in a number of patients due to discomforting thoughts (39%). Politeness or impoliteness of the caregivers, according to the patients, is something that affects their current state of mind (89%). The feeling that they are not given enough information during their hospitalization and the lack of control over the ongoing situation is present in a great number of patients (61%). An interesting occurrence is the reconsidering their past habits, which makes the patients make new decisions regarding their previous lifestyles, especially regarding social relationships (83%).

By conducting an anonymous survey **(Table 2)** we asked for their viewpoints regarding the psychological support. A high percentage (89%) of patients believe that the psychological support is essential for the cancer patients, while 83% of them believe that it is the most important support at the moment of finding out about cancer diagnosis. Furthermore, 89% of them state that they will talk to their psychologist at the Department of Oncology if they go through difficult periods during their further treatment, while 61% of them would like to become a member of a group of women who have experienced similar problems in which the psychological support is provided.

Discussion

By analyzing the results of our study, it can be noticed that the patients experience fear and concern regarding almost every event which is a part of their treatment process and which is supposed to happen in near future. The feeling that the things are getting out of their control is typical for this period of acute anxiety when the patients are not fully familiarized with what a malignant disease really is and what the treatment procedure actually is, while the outcome of the whole treatment is uncertain, which intensifies the fear and concern even more. Some studies, which dealt with the psychological status of the patients after the breast cancer surgery, have shown that the post surgical period is marked with fatigue, insomnia and general loss of energy [7]. As many as 20-30% of the

Appendix 1. The questionnaire about current problems and the patients' needs after surgery
Prilog 1. *Upitnik o trenutnim tegobama i potrebama pacijentkinja nakon operacije*

There are a number of statements related to some thoughts which could arise during the post-operative period. If the following statement refers to you circle YES, and if it does not circle NO. Before you start, please write the year of your birth: _____ *Pred Vama se nalazi niz tvrdnji koje se odnose na neke misli i osećanja koja se mogu javiti u periodu nakon operacije. Ukoliko se data tvrdnja odnosi na Vas zaokružite DA, a ukoliko se ne odnosi zaokružite NE. Pre nego što počnete, molimo Vas da upišete svoju godinu rođenja. Godina rođenja:* _____
I am afraid of the possibility of getting chemotherapy or radiation therapy YES/*DA* NO/*NE* *U strahu sam od moguće hemioterapije i zračenja*
I am considering the possibility of losing my hair and that idea frightens and horrifies me YES/*DA* NO/*NE* *Razmišljam o gubitku kose i ta misao me plaši i užasava*
I'm afraid that the illness could relapse or metastasize YES/*DA* NO/*NE* *Plašim se da bi moglo doći do recidiva bolesti i/ili metastaza*
I am very afraid of the forthcoming pathohistological findings and the decision of the Oncology Commission/*Jako se plašim predstojećeg patohistološkog nalaza i odluke Onkološke komisije* YES/*DA* NO/*NE*
There are a lot of disturbing thoughts in my head; therefore I do not sleep well YES/*DA* NO/*NE* *Svašta mi se vrzma po glavi pa uglavnom jako loše spavam.*
I feel like the things are getting out of my control YES/*DA* NO/*NE* *Imam doživljaj da stvari nisu pod mojom kontrolom*
I feel like I am not being informed enough during the hospitalization YES/*DA* NO/*NE* *Imam doživljaj da ne dobijam dovoljno informacija u toku hospitalizacije*
When I get out of here I want to change myself and my attitude towards certain things, especially when it comes to relationships with other people/*Kada izađem odavde, menjaću sebe i stav prema nekim stvarima, posebno kada su odnosi sa drugim ljudima u pitanju* YES/*DA* NO/*NE*
It really is important to me how the staff is treating me because my current feelings depend on it YES/*DA* NO/*NE* *Jako mi je bitna prijatnost osoblja jer od toga zavisi kako se trenutno osećam*

patients develop a psychological disorder, most commonly anxiety or/and a depressive disorder during the first year after surgery [8, 9]. Since this study sample was small, we were not able to make a thorough assessment of the variables which would differentiate our patients and which could affect their current psychological state more or less. It is the psychosocial status of the patients they had had before they were informed about having breast cancer that contributes to the more intensive distress. It has been shown that anxiety as a personality trait as well as previous psychopathology adds to a more intense post surgical reaction. In such cases, the breast cancer diagnosis could be a precipitating factor for the relapse of the

Table 1. Acute psychological picture of a female patient after breast cancer surgery
Tabela 1. *Akutna psihološka slika pacijentkinja nakon operacije karcinoma dojke*

Dominant disorders and needs of the female patients after breast cancer surgery *Dominantne tegobe i potrebe pacijentkinja nakon operacije karcinoma dojke*	Percent of presence in our sample *Procenat prisutnosti na našem uzorku*
Fear of possible chemotherapy or radiation treatment *Strah od eventualne hemioterapije i zračenja*	67%
Anticipated fear and horror of hear loss/*Anticipirani strah i užasavanje od gubitka kose*	59%
Fear of possible metastases and/or relapses/*Strah od mogućih metastaza i/ili recidiva*	57%
Fear of forthcoming pathohistological finding and the decision of the Oncology Commission/ *Strah od predstojećeg patohistološkog nalaza i odluke Onkološke komisije*	57%
Insomnia caused by disturbing thoughts/*Nesanica izazvana uznemiravajućim mislima*	39%
The experience of lack of control over the situation *Doživljaj nedostatka kontrole nad situacijom*	61%
The experience of not receiving enough information about one's own condition during hospitalization/*Doživljaj ne dobijanja dovoljno informacija o svom stanju u toku hospitalizacije*	61%
Wish to change earlier habits, especially in social relationships *Želja za promenom ranijih navika, posebno na socijalnom planu*	83%
Wish to feel empathy of caregivers because it greatly affects their current mood *Želja za toplinom osoblja koje ih neguje, jer to bitno utiče na njihovo trenutno raspoloženje*	89%

Table 2. Patients' attitudes to the psychological support
Tabela 2*. Stavovi pacijentkinja prema psihološkoj podršci*

Survey question/*Anketno pitanje*	Yes/*Da* (%)	No/*Ne* (%)
I believe that psychological support is very important for the cancer patient *Smatram da je psihološka podrška vrlo bitna onkološkim pacijentima*	89%	11%
I believe that psychological support is most important during the moment of receiving the diagnosis/*Smatram da je psihološka podrška najbitnija u momentu saznavanja dijagnoze.*	83%	17%
If I have difficult periods during my further treatment, I will contact the psychologist at the Department of Oncology/*Ukoliko budem imala teške periode u toku daljeg lečenja, obratiću se psihologu na onkologiji*	89%	11%
I would like to be a member of a group of women with a similar problem where we could talk about our problems with experts/*Volela bih da budem učesnica u grupi žena sa sličnim problemom gde možemo sa stručnim licima da pričamo o tome šta nas muči*	61%	39%

Appendix 2. The patients' attitude towards the psychological support
Prilog 2. *Stav pacijentkinja prema psihološkoj podršci*

There are a number of statements related to the psychological support of the cancer patients. We kindly ask you to express your opinion about the subject by circling the YES or NO questions. Since the questionnaire is anonymous, please be honest. Year of birth _____
Pred Vama se nalaze tvrdnje koje se odnose na psihološku podršku onkološkim pacijentima. Zaokruživanjem DA ili NE odgovora, molimo Vas da kažete šta Vi mislite o tome. Ispitivanje je anonimno, te Vas molimo da budete iskreni. Godina rođenja: _____

I believe that the psychological support is very important to the cancer patients *Smatram da je psihološka podrška vrlo bitna onkološkim pacijentima.*	YES/*DA* NO/*NE*
I believe that the psychological support is the most important while the diagnosis is being given *Smatram da je psihološka podrška najbitnija u momentu saznavanja dijagnoze*	YES/*DA* NO/*NE*
If I have difficult periods during further treatment, I will contact the psychologist at Department of Oncology *Ukoliko budem imala teške periode u toku daljeg lečenja, obratiću se psihologu na onkologiji*	YES/*DA* NO/*NE*
I would like to be a member in the women's group with a similar problem where we could talk with experts about our mutual problems/*Volela bih da budem učesnica u grupi žena sa sličnim problemom gde možemo sa stručnim licima da pričamo o tome šta nas muči*	YES/*DA* NO/*NE*

psychological disorder [10]. Absence of social support, the early stage of life, suppressing emotions after learning about the diagnosis, stressful life events prior to the disease, as well as avoidance coping style have also been found to be important predictors of distress after surgery [10–12]. The importance of early psychological support to the breast cancer patients is corroborated by the encouraging results which show that the patients who had the supportive therapy from the beginning of the treatment and those who participated in stress management programs and learned how to express their emotions and take control have shown a more positive attitude, a lower level of maladaptive behavior, a lower subjective pain experience and a higher survival rate [13, 14].

We assume that the fear and uncertainty accompanying hospitalization can be reduced by contacting the patient after surgery, by showing the concern and offering the psychological support throughout the treatment process as well as by providing relevant information on some medical interventions along with possible psychotherapeutic interventions. Better insight into one's own capacities while confronting the new demands and encouragement to ask for psychological support throughout the possible crises may decrease the risk of escalation of distress.

In the future, we plan to conduct research on a representative sample by applying the appropriate measuring instruments. It would be aimed at assessing the importance of applied psychological techniques in stress reduction and continual follow up of the patients from the clinical and functional point of view.

Conclusion

The obtained results suggest that it is very important to provide the psychological support both immediately upon informing the patients on their diagnosis and after surgery because they are extremely vulnerable in these moments; thus, the risk of a possible escalation of distress can be decreased. Most of the patients are willing to cooperate and they show great interest at the beginning of the support therapy; their need to ventilate and talk about the disease is confirmed by our results, which is of great importance for our further work in giving support to the cancer patients.

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Rad je primljen 21. VI 2013.
Recenziran 24. X 2013.
Prihvaćen za štampu 18. XII 2013.
BIBLID.0025-8105:(2014):LXVII:1-2:43-48.

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Professional article
Stručni članak
UDK 616.379-008.64-06:617.735
DOI: 10.2298/MPNS1402049J

CORRELATION BETWEEN METABOLIC CONTROLS AND CHANGES IN RETINA IN PATIENTS HAVING DIABETES

POVEZANOST METABOLIČKE REGULACIJE SA PROMENAMA NA OČNOM DNU KOD OBOLELIH OD ŠEĆERNE BOLESTI

Mirjana A. JANIĆIJEVIĆ PETROVIĆ[1], Biljana VELJKOVIĆ[2], Katarina JANIĆIJEVIĆ[3] and Tatjana ŠARENAC VULOVIĆ[1]

Summary

Introduction. Diabetes mellitus is as old as the human race. Retinopathy, being one of complications of diabetes mellitus, is the most common cause of blindness. This study was aimed at analyzing the correlation between retinopathy and duration of disease, metabolic control, and obesity. **Material and Methods.** The study sample consisted of 135 patients divided into the experimental group of 90 patients with retinopathy and the control group of 45 patients without retinopathy. The patients were exa- mined according to standard protocols: anamneses, endocrino-logy, ophthalmology exams, biochemical analyses, and anthropometric measurements. **Results.** The average age of patients was 60.13 ± 9.29 in the experimental group, while it was 57.55 ± 4.85 in the control group. The average duration of disease was 11.71 ± 5.8 and 14.40 ± 7.68 in the control group experimental group, respectively. The following statistically essential differences between the control and experimental group were found: in duration of disease (11.71 ± 5.85; 14.40 ± 7.68; r = 0.000), in glycemia (7.02 ± 2.20; 8.34 ± 3.18; p = 0.000), in glycosylated hemoglobin *A1C (*HbA1C) (7.16 ± 1.37; 8.22 ± 2.05; r = 0.000), in triglycerides (1.92 ± 0.72; 2.63 ± 1.60; r = 0.001), and in body mass index (23.94 ± 2.65; 27.66 ± 15.13; r = 0.000). **Conclusion.** There is a positive correlation between duration of disease, glycosylated hemoglobin *A1C*, triglycerides, body mass index - obesity and retinopathy. A significant statistical correlation among those parameters has been found in patients with diabetic retinopathy.

Key words: Diabetes Mellitus; Metabolic Diseases; Diabetic Retinopathy; Hemoglobin A, Glycosylated; Triglycerides; Body Mass Index; Middle Aged; Aged

Sažetak

Uvod. Dijabetes melitus je star koliko i ljudska rasa. Retinopatija, koja je jedna od komplikacija dijabetesa, najčešći je uzrok slepila. Cilj rada bila je analiza povezanosti retinopatije sa starošću, dužinom bolesti, biohemijskim parametrima glikoregulacijske i liporegulacijske kontrole i gojaznošću. **Materijal i metode.** Posmatrali smo 135 ispitanika: eksperimentalnu grupu (90), sa retinopatijom i kontrolnu (45), bez retinopatije. Ispitivanja su vršena prema standardnim protokolima istraživanja: anamneza, endokrinološki, oftalmološki pregled, biohemijske analize, antropometrijska merenja. **Rezultati.** Prosečna starost bila je 60,13 ± 9,29 eksperimentalne, 57,55 ± 4,85 kontrolne grupe. Prosečna dužina trajanja bolesti bila je 11,71 ± 5,85 u kontrolnoj, 14,40 ± 7,68 u eksperimentalnoj grupi. Između eksperimentalne i kontrolne grupe, nađena je statistički značajna razlika u dužini bolesti (11,71 ± 5,85; 14,40 ± 7,68; r = 0,026), vrednosti glikemije (7,02 ± 2,20; 8,34 ± 3,18; p = 0,006), vrednosti glikoliziranog hemoglobina (7,16 ± 1,37; 8,22 ± 2,05; r = 0,001), vrednosti triglicerida (1,92 ± 0,72; 2,63 ± 1,60; r = 0,001), indeksa telesne mase (23,94 ± 2,65; 27,66 ± 15,13; r = 0,000). **Zaključak.** Pozitivna statistička korelacija studije postoji između dužine trajanja bolesti, vrednosti glikoliziranog hemoglobina, vrednosti triglicerida, indeksa telesne mase-gojaznosti sa retinopatijom.

Ključne reči: Diabetes melitus; Metabolička oboljenja; Diabetesna retinopatija; Glikozilirajući hemoglobin; Trigliceridi; Indeks telesna mase; Srednje godine; Stari ljudi

Introduction

Diabetes mellitus (DM) is a disease as old as the human race. It is a disease with frequency of 0.5% - 3.5% and complications which can cause serious morbidity and mortality [1]. Its etiopathogenetic division is type 1, type 2, and specific forms of gestational diabetes [2].

Oxidative stress is a biochemical mechanism that induces micro and macro angiopathy, hyperpermeability and angyo-occlusion with retinopathy [3]. The tissues that take glucose in the state of hyperglycemia independently of insulin are the retina and the lens of the eye, whereas the nerves and endothelium suffer the greatest damage [4, 5].

Non-proliferative retinopathy is indicative of ischemia of the retina, and it is diagnosed by de-

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Abbreviations

NVD – new vessels of disc
NVE – new vessels elsewhere
DM – Diabetes mellitus
BMI – body mass index
HbA1C – glycosylated hemoglobin A1C
HDL – high-density lipoprotein
LDL – low-density lipoprotein
VLDL – very low-density lipoprotein
ROC – Receiver-Operating Characteristic

tecting soft exudates, intra retinal micro vascular abnormalities, changes in the veins and arteries - micro aneurysms, hemorrhages, "cotton-wool" exudates and as focal infarction caused by occlusion of pre-capillary arterioles. Changes in the veins include dilatation, twisting the loop (looping), thickening of the beads (leading), and sausage-like segmentations [6].

Visual impairment, particularly in type 2 diabetes mellitus, is caused by maculopathy due to the involvement of fovea by edema, soft and hard exudates and ischemia [7].

Clinical characteristics of proliferative retinopathy are neovascularization of the papillae (NVD - new vessels of disc) and proliferation along the vessels (NVE - new vessels elsewhere) or both at the same time. The newly formed vessels grow from the veins as endophytic proliferations between the retina and vitreous body by using a medium as a substrate for the growth [6, 7]. Severity of the proliferative retinopathy is determined as mild, moderate or severe according to the ratio of the surface covered with vasoproliferative courts with a surface of papillae [8].

Material and Methods

The research, which included 135 subjects, was conducted at the Institute of Occupational Health, Department of Ophthalmology of the Clinical Centre in Kragujevac from November 15th, 2007 to November 15th, 2009. The inclusion criterion was retinopathy, which was diagnosed in 90 patients and they formed the experimental group; whereas the control group consisted of 45 subjects without complications.

The fundus was examined by the methods of ophthalmoscope, with Goldman's prism and panfundoskopy on the biomicroscope. The duration of disease, age, and body mass index (BMI) in obesity were obtained from the research protocols.

Biochemical analyses included fasting and postprandial glycemia. Glycosylated hemoglobin A1C (HbA1C) represented the percentage of hemoglobin that succumbed to non-enzymatic glycosylation of proteins, and was determined by chromatographic separation, photometric measurements at 415 nm (endpoint method). Total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL) - cholesterol, and triglycerides were determined early in the morning before any meal. Total cholesterol was determined by Tinder's endpoint method. HDL - cholesterol was determined by the precipitation method with fosfovolfram-acid and magnesium chloride, which quantitatively precipitated very low-density lipoprotein (VLDL) and LDL.

Cholesterol fractions of high-density lipoproteins, which remain in the supernatant after centrifugation, were measured as total cholesterol. LDL - cholesterol was calculated indirectly. Triglycerides were determined by the enzymatic - colorimetric method, the so-called endpoint method.

The BMI values were obtained from the standard protocols, i.e. the measured body weight and body height of the subject, which were then inserted into the BMI formula (BMI=body weight (kg)/body height (m^2) $^{SI\ units}$) and calculated.

The degree of risk for diabetic retinopathy as part of obesity was calculated using the standard BMI calculations and BMI balance sheet (BMI $\geq$ 30 kg/m^2 - obesity), the BMI – categories being: underweight < 18.5, normal = 18.5-24.9, overweight = 25-29.9, obesity = $\geq$ 30, obesity grade 1 = 30 to 34.9, obesity grade 2 = 35-39.9, grade 3 - morbid obesity $\geq$ 40 [9].

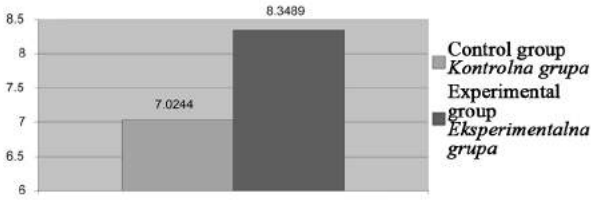
Having obtained the written consent from the subjects, the local ethics committee approved the study.

The following statistical analyses were used: methods of descriptive statistics, measures of central tendency (arithmetic mean), variability (SD), T-test, χ^2 test, Fisher's test, the method of binary logistic regression and correlation analysis [10].

Results

In the control group, the average duration of disease was 11.71 ± 5.85, and in the experimental group it was 14.40 ± 7.68 years. T-test showed that the difference in disease duration between the experimental and control group was statistically significant, being (p = 0.026). The disease lasted longer in the experimental group, which affected retinopathy.

Since the mechanisms of glucoregulation and the processes related to lipid metabolism were disrupted, it was necessary to examine their correlation with retinopathy. The priority goal of treatment was to establish adequate glucoregulation. The following parameters were used to determine

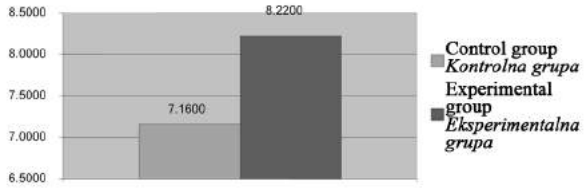


Graph 1. Glycemia (mmol/L)
Grafikon 1*. Glikemija (mmol/L)*

the quality of glucoregulation: fasting glycemia, postprandial glycemia and HbA1C values. The average value of fasting glycemia was 7.02 ± 2.20 mmol/L in the control group and it was 8.34 ± 3.18 mmol/L in the experimental group. The analysis of results showed that the difference in fasting glucose between the experimental and control group was statistically significant (p = 0.006). The experimental group had a higher level of fasting glycemia before the first meal, which can be associated with retinopathy **(Graph 1).**

The obtained value of postprandial glycemia in the control group was 10.44 ± 3.98 and in the experimental group it was 11.76 ± 4.47 mmol/L. The obtained values showed no statistically significant difference (p = 0.096) between the control and experimental group.

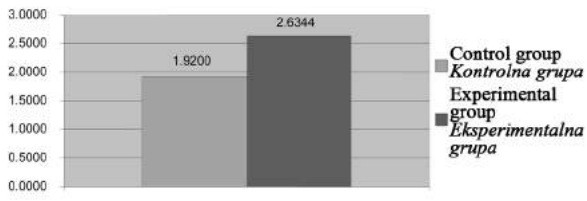
Glycosylated hemoglobin values represented a significant, reliable parameter for assessing the quality of metabolic control. The values in the experimental group were 8.22 ± 2.05, while in the control group they were 7.16 ± 1.37 mmol/L. The values of T-tests showed that there was no statistically significant difference in HbA1C between the control and experimental group (p = 0.001). The experimental group had higher HbA1C level, which proves that HbA1C values affect retinopathy (**Graph 2).**



Graph 2. HbA1c (mmol/L)
Grafikon 2. *Glikolizirani hemoglobin A1C (mmol/L)*

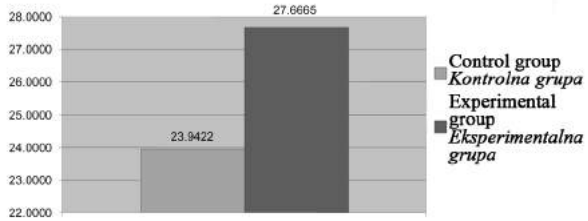
Thf -e average value of triglycerides was 1.92 ± 0.72 in the control group and in the experimental group it was 2.63 ± 1.60 mmol/L. The values of T-test suggest that there is a statistically significant difference in triglycerides between the groups (p = 0.001) and triglyceride levels may be the cause of retinopathy **(Graph 3).**

The value of cholesterol was 6.25 + 1.47 and 5.97 + 1.01 mmol/L in the experimental and control group, respectively. Considering the values of T-test, the null hypothesis can be accepted, according to which no statistically significant difference (p = 0.198) regarding total cholesterol level was found between the control and experimental group. No statistically significant difference (p = 0.088) was found in the HDL value in the blood of subjects from the control and experimental group. The average value of LDL was 3.76 ± 0.66 and 3.95 ± 0.73 mmol/L in the control and experimental group, respectively. The value of T-test shows that the difference in LDL between the experimental and control group was not statistically significant (p = 0.149).



Graph 3. The triglycerides (mmol/L)
Grafikon 3. *Trigliceridi (mmol/L)*

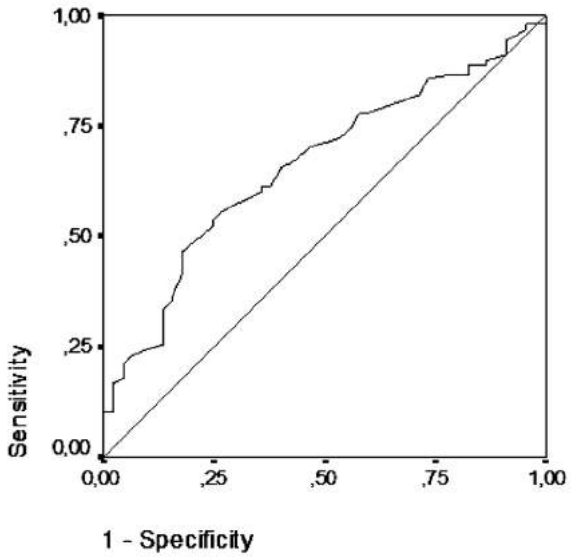
The BMI index was used to assess obesity. The average BMI was 27.66 ± 5.13 and 23.94 ± 2.65 SI – units in the experimental and the control group, respectively. The value of T-test makes it possible to accept the alternative hypothesis that there is a statistically significant difference between the control and the experimental group, which proves the positive affect of obesity on retinopathy **(Graph 4).**



Graph 4. Body Mass Index (SI - units)
Grafikon 4*. Indeks telesne mase (SI – jedinice)*

A statistically significant correlation (r = 0.753, p = 0.000) has been observed between fasting and postprandial glycemia. According to the analysis of the obtained coefficients of correlation, there is a positive direction of the relationship – the higher the fasting glycemia values, the higher postprandial glycemia values get. The absolute value of the resulting linear correlation coefficient indicates a correlation between the two parameters. Fasting glycemia values were significantly correlated with HbA1c (r = 0.541, p = 0.000). The positive sign indicated the direction of the obtained relationship, an increase in blood glucose, followed by a rise in glycosylated hemoglobin. A statistically significant linear correlation (r = 0.532, p = 0.000) was noticed between postprandial glycemia and hemoglobin. The resulting correlation coefficient indicated a significant correlation between the two parameters. The increase in postprandial glycemia level was accompanied by an increase in glycosylated hemoglobin.

By applying Receiver-Operating Characteristics (ROC) curve it was found that HbA1C might be a marker of retinopathy (r = 0.660, p = 0.002).



Graph 5. ROC curve – HbA1C
Grafikon 5. *ROC kriva – HbA1C*

The cut-off point was 7.55, the sensitivity was 0.567, and the specificity was 0.711 **(Graph 5)**.

By applying ROC curve, it was found that triglycerides might be markers of retinopathy (r = 0.640, p = 0.008). The cut off point was 2.25, the sensitivity was 0.522, and the specificity was 0.711.

By applying ROC curve, it was found that cholesterol cannot be a marker for retinopathy, HDL and LDL cannot be markers for retinopathy. By applying ROC –curve it was revealed that the duration of disease can be a marker for retinopathy (p = 0.607, p = 0.044). The cut off point was 14.5, the sensitivity was 0.511, and the specificity was 0.733. Binary logistic regression showed that the occurrence of retinopathy was affected by HbA1C, triglycerides, cholesterol, LDL. However, the application of the backward method step by step on the previous regression and the elimination of the variables one by one, starting from the one which affects retinopathy least, result in the status showing that retinopathy depends on HbA1C (p = 0.010) , triglycerides (p = 0.009), the duration of disease (p = 0.032) and obesity (p = 0.039).

The odds ratio for HbA1C was 1.389, which meant that the chance of retinopathy was increased 1.389 times, i.e. 38.9 % if HbA1C increased for the unit, provided that the other variables did not change. The odds ration for triglycerides was 1.872, which meant that the chance of retinopathy was increased 1.872 times, i.e. 87.2%, if the values of triglycerides increased by the unit, provided that the other variables did not change. The odds ratio for disease duration was 1.068, which meant that the chance of retinopathy was increased 1.068 times, i.e. 6.8%, when the duration of diabetes increased by one year, provided that the other variables did not change.

Discussion

The most common cause of blindness in working population is diabetes mellitus. The complications of proliferative retinopathy in patients having type 1 diabetes are visual impairments. In patients with type 2 diabetes, the cause of poor vision is maculopathy [11, 12]. Retinopathy is found in about 40% of patients having type 2 diabetes at the moment when the disease is being diagnosed, whereas impaired vision is found in 4.8% of these patients [13]. A great number of risk factors for developing retinopathy has been identified, such as duration of disease, poor glycemic controls, elevated triglycerides, etc; however, there is an opinion that the synergistic effect of the dominant factors is more dangerous, which was confirmed in the study - The Aus Diab Study and the Blue Mountains Eye Study [14, 15].

A statistically significant difference (T-test, p = 0.026) was found regarding the duration of disease between the experimental and control group, the average duration of disease being 14.4 ± 7.68 and 11.71 ± 5.85 years in the experimental and control group, respectively. A statistically significant correlation (r = 0.66, p = 0.02) was found between disease duration and retinopathy. Data obtained by ROC curve define the duration of disease as a marker for retinopathy. Binary logistic regression shows that the incidence of retinopathy depends on the duration of disease (p = 0.032), which coincides with the suggestions and recommendations given by the American Diabetes Association (ADA) [1, 16].

Glucoregulation quality is assessed on the basis of fasting glycemia, postprandial glycemia and glycosylated hemoglobin [16]. If glycosylated hemoglobin decreases by 1.5%, or if it is possible to reduce its value to 7 mmol/L, retinopathy is reduced as well. Studies have shown that when HbA1C is decreased by 1%, the incidence of retinopathy is reduced by 37% [17]. There was a statistically significant difference in mean fasting glucose level between the experimental and control group (T-test, p = 0.006). According to the analysis of the obtained differences, higher values of fasting glycemia were observed in the group of patients with retinopathy, being 8.34 ± 3.18, while they were 7.02 ± 2.20 in the controls.

The comparison of the values of postprandial glycemia in the experimental and control group did not show a statistically significant difference (T-test, p = 0.096). There was a statistically significant difference in the average HbA1c values between the experimental and control group (T-test, p = 0.001). Higher values of this parameter were statistically significant in the patients with retinopathy, being 8.22 ± 2.056, whereas they were 7.16 ± 1.37 in the control group. The correlation between the values of fasting glycemia and postprandial glycemia was statistically significant (r = 0.754, p = 0.000).

The result of correlation analysis was r = 0.754, which indicated a significant correlation of two parameters, meaning that the increasing values of glucose led to an increase in postprandial glucose values . The values of fasting glycemia were significantly correlated with HbA1c (r = 0.541, p = 0.000). The correlation analysis showed that the correlation coefficient r = 0.541, which indicated a significant correlation between the two parameters, meaning that the rise in glucose levels led to an increase in HbA1C. A statistically significant correlation (r = 0.66, p = 0.02) was found between retinopathy and HbA1C. The values obtained by ROC-curve make it possible to define HbA1C as the most important marker for retinopathy, which is included in the statement - The International Expert Committee [17, 18]. Binary logistic regression shows that the development of retinopathy depends on HbA1C (p = 0.10). The assessment of liporegulation quality is based on the measurements of total cholesterol, HDL - cholesterol, LDL - cholesterol and triglyceride levels [18]. No statistically significant difference in the total cholesterol values (T-test, p = 0.193) was found between the experimental and control group.

The average value of total cholesterol was 5.97 ± 1.01 and 6.25 ± 1.47 in the experimental and in the control group, respectively. Total cholesterol did not show a statistically significant correlation with retinopathy (r = 0.539, p = 0.461). No statistically significant difference (T-test, p = 0.088) was found by comparing the values of HDL - cholesterol in patients having retinopathy and those without it, the mean value of this parameter being 1.23 ± 0.24 and 1.23 ± 0.24 in the former and latter, respectively. No statistically significant correlation (r = 0.397, p = 0.052) was found between HDL - cholesterol and retinopathy, therefore the effect of HDL - cholesterol to retinopathy has not been proved. The average value of LDL - cholesterol in the patients with retinopathy was 3.95 ± 0.73, whereas it was 3.76 ± 0.66 in the control group.

The difference in LDL - cholesterol (T-test, p = 0.149) was not statistically significant between the experimental and control group. There was no statistically significant correlation (r = 0.578, p = 0.143) between LDL - cholesterol and retinopathy.

A statistically significant difference (T-test, p = 0.001) was found by comparing the levels of triglycerides in the experimental and control groups. The experimental group had higher levels of triglycerides. There was no statistically significant correlation (r = 0.640, p = 0.008) between the values of triglycerides and retinopathy, which was confirmed in the study - The Multi - Ethnic Study of Atherosclerosis (MESA) [19]. There was a statistically significant difference in BMI - obesity between the experimental and control group (T-test, p = 0.000). The average BMI in the group with retinopathy was 27.66 ± 5.13, whereas it was 23.94 ± 2.65 in the control group. The analysis of the obtained correlations shows that the effect of obesity on retinopathy increases as BMI gets higher [19].

Conclusion

The duration of illness is associated with retinopathy. There is a positive correlation between the values of the parameters of glucoregulation and retinopathy, because the increase in the values of fasting glucose, postprandial glycemmia and glycosylated hemoglobin makes it more likely for retinopathy to develop.

A correlation between triglycerides and retinopathy has also been found. Higher values of triglycerides lead to the development of retinopathy.

Retinopathy seems to occur more frequently in diabetic patients who are prone to obesity.

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Rad je primljen 10. VIII 2013.
Recenziran 16. XII 2013.
Prihvaćen za štampu 18. XII 2013
BIBLID.0025-8105:(2014):LXVII:1-2:49-54.

CASE REPORTS
PRIKAZI SLUČAJEVA

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Case report
Prikaz slučaja
UDK 616.34:616.36]-006.3-089
DOI: 10.2298/MPNS1402055A

GIANT LIVER HEMANGIOMA IN PATIENT WITH ILEAL GASTROINTESTINAL STROMAL TUMOR

VELIKI HEMANGIOM JETRE KOD PACIJENTA SA GASTROINTESTINALNIM STROMALNIM TUMOROM ILEUMA

Vasilije ANTIĆ[1], Marjan MICEV[2], Danijela BASKIĆ[3] and Violeta MLADENOVIĆ[1]

Summary

Introduction. Gastrointestinal stromal tumors are the most common mesenchymal neoplasms of the gastrointestinal tract. These tumors represent more than 80% of all mesenchymal tumors found in the gastrointestinal tract, though they account for only approximately 3% of all gastrointestinal malignancies. Literature offers case reports, which describe symptomatic gastrointestinal stromal tumors and they generally represent patients with larger tumors. **Case report.** We present the case of a small gastrointestinal stromal tumor in a 40-year-old man, with associated giant liver hemangioma and fever, and with history of abdominal discomfort and fever. Clinical examination revealed hepatosplenomegaly, palpable mass in the right lower abdomen, and signs of neurofibromatosis type 1 (*Morbus von Recklinghausen*). Computed tomography revealed a giant tumor in the right lobe of the liver. Magnetic resonance showed abscess in the hemangioma of the liver. An intestinal tumor was incidentally found and excised during surgical laparotomy. An intestinal gastrointestinal stromal tumor was revealed by histopathology and confirmed by immunohistochemistry. Although a multidisciplinary team proposed surgical removal of the liver tumor mass, the surgeons decided to follow up the patient because of a high risk of new intervention. **Conclusion**. According to the available data, this is a very rare case of small intestinal gastrointestinal stromal tumor, with symptoms of fever and giant abscess in the liver hemangioma.

Key words: Gastrointestinal Stromal Tumors; Liver Neoplasms; Hemangioma; Fever; Neurofibromatosis 1; Male; Adult; Signs and Symptoms; Diagnosis

Sažetak

Uvod. Gastrointestinalni stromalni tumori najčešće su mezenhimalne neoplazme gastrointestinalnog trakta. Iako ovi tumori čine samo oko 3% svih gastrointestinalnih maligniteta, oni se mogu naći u više od 80% svih mezenhimskih tumora gastrointestinalnog trakta. U literaturi možemo pronaći prikaze slučajeva koji opisuju simptomatske gastrointestinalne stromalne tumore većih dimenzija. **Prikaz slučaja.** Prikazan je mali gastrointestinalni stromalni tumor kod 40-godišnjeg muškarca, koji je udružen sa gigantskim hemangiomom jetre i groznicom. Istorija bolesti ovog pacijenta uglavnom se odnosi na trbušne nelagodnosti i groznicu. Klinički pregled je ukazao na hepatosplenomegaliju, opipljivu masu u donjem desnom delu abdomena, i znake neurofibromatoze tip 1 (*Morbus von Recklinghausen*). Kompjuterizovanom tomografijom otkriven je veliki tumor (hemangiom) u desnom režnju jetre, dok je magnetnom rezonancijom uočeno prisustvo apscesa u tumoru. Tokom hirurške laparotomije slučajno je otkriven i odstranjen intestinalni tumor, za koji je naknadno histopatološkom analizom uvtrđeno da pripada gastrointestinalnim stromalnim tumorima. Uprkos predlogu konzilijarnog tima da se tumor jetre hirurški zbrine, hirurzi su odlučili da prate stanje pacijenta zbog visokog rizika od nove intervencije. **Zaključak.** Prema dostupnim podacima, ovo je jedinstven slučaj gastrointestinalnog stromalnog tumora tankog creva sa simptomima groznice i prisutnim apscesom u hemangiomu jetre.

Ključne reči: Gastrointestinalni stormalni tumori; Karcinomi jetre; Hemangiomi; Groznica; Neurofibromatoza 1; Muško; Odrasli; Znaci i simptomi; Dijagnoza

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. The term GIST defines a unique group of mesenchymal neoplasms that are distinct from true smooth muscle and neural tumors [1].

Acknowledgements
Written consent was obtained from the patient for publication of this case report.

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Abbreviations

CT – computed tomography
GISTs – gastrointestinal stromal tumors
c-KIT – CD117 antigen
NF1 – neurofibromatosis type 1
MRI – magnetic resonance imaging
PDGFRA– platelet derived growth factor receptor alpha

GISTs represent more than 80% of all mesenchymal tumors found in the gastrointestinal tract, though they account only for approximately 3% of all gastrointestinal malignancies [2, 3]. It has now been well established that GISTs arise from the interstitial cells of Cajal, which are specialized pacemaker cells located around the myenteric plexus of the gut wall, particularly in the stomach and small intestine [4].

The clinical manifestations of GISTs depend on the location and size of the tumors and are often nonspecific [5, 6]. Although the literature suggests that most GISTs are symptomatic, tumors might be incidentally found at examinations performed for other indications. Case reports that can be found in the literature describing symptomatic GISTs generally represent patients with larger tumors that were symptomatic.

We present the case of a small intestinal GIST in a 40-year-old man with associated giant liver tumor, exclusively presented with fever. These data can be important for efficient diagnosis and therapy of unusual and asymptomatic cases of this neoplasm.

Case Report

A 40-year-old man was referred to our hospital with a 15-day history of fullness, fever (body temperature max 38 C degree) and discomfort in the right lower abdomen. No significant past medical history (one year before operation of left testicular hydrocele) was recorded.

On examination, the patient had a small spherical, painless, fluctuant mass of intestine palpable in the right lower abdomen. Hepatomegaly was diagnosed (2 cm below the right costal angle) with splenomegaly (1 cm below the left costal angle) and without ascites. There was a tumor in the skin of right abdomen measuring about 2 cm and a tumor in the skin of left arm measuring about 1 cm. Those tumors were strongly suspected to be neurofibromatosis but the definitive diagnosis was not investigated.

The patient had an elevated white blood cells count (WBC) (11.5 Rch 10*9/l), mild anemia (Hgb 113.1 cl g/l, MCV 84 fl), and mild thrombocytosis (568 ch 10*9/l). Signs of inflammation were positive: erythrocyte sedimentation rate (ESR) 109, fibrinogen 6.9 g/l, C-reactive protein 249 mg/l, and procalcitonin was increased 0.622 ng/ml. Necrosis of hepatocytes was present (aspartate aminotransferase /AST/ 99 IU/l, alanine aminotransferase /ALT/ 235 IU/l, gama GT 114 IU/l, alkaline phospathase 141 U/l). Iron (Fe) level was decreased to 2.6 umol/l, Ferritin amount was increased to 782 ug/l. Blood proteins were normal but albumin was decreased to 30 g/l, and globulin was increased to 49 g/l. All other laboratory data, including tumor markers (alpha-fetoprotein (AFP), cancer antigen (CA) 19-9 and carcinoembryonic antigen (CEA)), immunology and virusology findings were within normal limits. Hemoculture was positive (Staphylococcus sp., coagulase neg. sensitive to ceftriaxsone and other cephalosporin and aminoglygosides), and uroculture was negative.

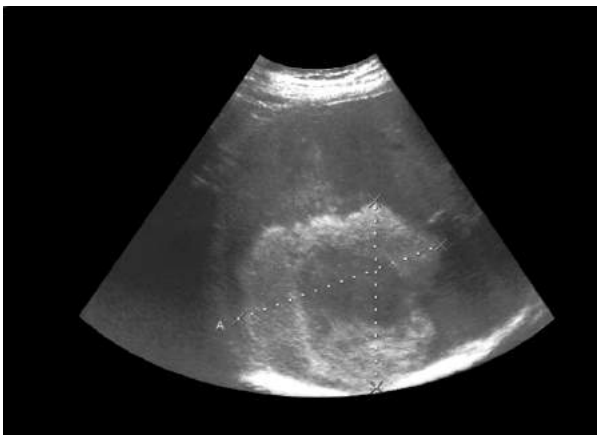

Figure 1. Ultrasound showing a giant hyper echoic tumor within the right lobe of the liver
Slika 1. *Ultrazvučni nalaz pokazuje veliki tumor (hemangiom) u desnom režnju jetre*

Ultrasound scan showed hepatomegaly (measuring 190 mm in the right lobe) and splenomegaly (measuring 160 mm). A tumor was found in the right lobe of liver, not well–defined, hyper echoic in periphery and hypo and anechoic in the center, measuring 120x100x80 mm. Another small tumor adjacent to giant mass was hyper echoic, measuring 12x10 mm, ultrasound characteristics of liver hemangioma (**Figure 1**).

Computed tomography (CT) scan showed the mass in the liver with not well – defined margins, hyper signal intensity, and central area of necrosis (measuring 137x102x113 mm) in VII and VIII segment of the liver. Two hyper signal intensity tumors close to mass were found in the liver. CT scan revealed few lymphatic nodules in hilus of the liver, measuring about 12 mm each.

Magnetic resonance imaging (MRI) showed solid multi centric tumor clearly defined (measuring 117x80x117 mm), low signal intensity on T1- weighted images, and high signal intensity on T2 – weighted images. Another small tumor was found with the same characteristic close to the biggest one, measuring 16x13 mm. The radiologist described the change to be like an infected parasite cyst, infected hemangioma or primary tumor in the liver.

In Clinical Center Serbia in Belgrade, the radiologist performed new contrast MRI and liver tumor was described as giant hemangioma. The surgeons opted for the exploratory laparotomy because the symptoms were persistent. After right subcostal and

partial left subcostal laparotomy, a moving rough nodous tumor was found in the intestines. On intraoperative examination, frozen sections revealed mesenchymal cell tumor with unknown malignant potential. The complete excision of tumor was done as well as the resection of the local peritoneum and the further 40 mm of ileum with termino-terminal ileal anastomosis (TTA).

On gross examination, the excised intramural tumor node measured 48x38x35 mm in diameters, with predominant extramural growth. The tumor appeared somehow protuberant in luminal surface, with intact mucosa, and covered with hyperaemic and rough serosis. The cut surface of the tumor showed dark red color, with well-defined borders to adjacent tissue. Histopathologically, the tumor was of obvious mesenchymal origin; it was composed of proliferating spindle and epithelioid cells with a loose interlacing bundle pattern.

Tumor cells were primitive, ovoid-to-spindle or elongated in shape, dominantly with eosinophilic cytoplasm and ovoid or elongated nuclei, but without pronounced hyperchromasia and edema, partly with hypocellular areas. Pathological examination revealed generally low to moderate cellularity, low mitotic index of 1/50 high-power fields (HPF), low nuclear anaplasia and absence of necrosis.

Immunohistochemically, the tumor showed diffuse strong cytoplasmic immunoexpresion of c-KIT (CD117 antigen), but it was negative for CD34 antigen (myeloid stem cell antigen), alpha subunit of smooth muscle actin (SMA), desmin and S-100 protein. The tumor was diagnosed as a low risk intestinal GIST and presented to multidisciplinary team as a tumor with low malignant potential and low metastatic risk.

Postoperatively, the patient was treated by transfusion of deplasmatized erythrocytes and with antibiotics according to antibiogram. So far, the patient is well and there are no signs of relapse.

The multidisciplinary team of the Clinical Centre Serbia claimed that the tumor and local peritoneum was radically excided, concluding that the tumor was in T2 stage. The check-up MRI examination was without local recidivism, but the giant mass in the liver appeared abscessing or centrally necrotizing and/or hemorrhagic, suggesting giant necrotic hemangioma. Although the surgical resection of the tumor was proposed, the decision was made to follow-up the patient because of a high risk of surgical treatment.

According to literature data, this is one of a few described cases with fever and abscess in the tumor of the liver as the first manifestations of the GIST of intestine.

Discussion

Gastrointestinal stromal tumors are usually solitary tumors. Approximately 60% of GISTs arise in the stomach, then in the small intestine (25–35%) and the colon and rectum (5–10%) [1,7]. True smooth muscle tumors tend to be predominantly in the esophagus. In rare cases, they develop outside of the gastrointestinal tract and have been reported in the mesentery, omentum, or retroperitoneum [1,7].

Gastrointestinal stromal tumors are generally found in adults over 40 years of age (their age ranging from 40 to 80 years), with average age of 60 years at presentation and a slightly male predominance. Similarly to the case reported hereby, GISTs are rarely seen in patients younger than 40 years; however, several cases have been reported in pediatric population [8].

Although some families with hereditary GISTs have been described, most cases are sporadic. The National Comprehensive Cancer Network (NCCN) Task Force Report 2007 reported GIST incidence to be approximately 14.5 per million people per year or at least 4,500–6,000 new cases per year in the United States [9].

More than 90% of GISTs result from gain-of-function mutations of the c-KIT/KIT proto-oncogene [10]. KIT encodes for the transmembrane KIT receptor tyrosine kinase. Approximately 10% of GISTs result from mutations in the KIT-related kinase gene, platelet derived growth factor receptor alpha (PDGFRA) [11]. A small percentage of GISTs are wild type, and some may also be part of familial syndromes such as von Recklinghausen neurofibromatosis (NF1) and the Carney triad (GIST, paraganglioma, and pulmonary chordoma) [12]. Patients with neurofibromatosis type 1 (NF1) have an increased prevalence of GISTs. Classically, patients with NF1 have multiple small intestinal GISTs [13]. A Swedish study reports a 500-fold increased incidence of GISTs in patients with NF1 [14].

More than 90% of GISTs stain positively for c-KIT/CD117, (the current immunohistochemical marker of choice), which correlates with our immunohistochemical analysis. Suspected GIST tumors in which CD117 immunostaining is negative should be considered for molecular analysis for KIT or PDGFRA mutations in specialized laboratories [15].

Contrast-enhanced CT is the radiologic modality of choice for evaluating primary tumors and metastasis, as well as for assessing the efficacy of treatment and follow-up. Typically, the tumor appears as a well-circumscribed, hyper dense-enhancing mass closely associated with the stomach or small intestine growing in an extra luminal manner. The tumor often demonstrates a heterogeneous pattern secondary to underlying necrosis or intratumoral hemorrhage [15].

On MRI solid portions of tumors typically show low signal intensity on T1-weighted images, intermediate to high signal intensity on T2-weighted images. According to literature data, the marked high signal seen on T2-weighted MRI should be considered as a feature strongly indicating diagnosis of GIST [15].

The liver is the most common site of metastasis, both at the time of presentation and during relapse. It is seen in 49 − 65% of the cases [16]. Different authors have described various appearances of liver metastasis. However, lesions appear similar to the primary mass in many cases. They are usually multiple, involve both lobes, and appear to be heterogeneous with peripheral enhancement.

Surgery remains the modality of choice for primary, localized, and resectable GIST. Specific tyrosine kinase inhibitors (TKIs), i.e. imatinib mesylate and, more recently, sunitinib malate have proven to be dramatically effective for unresectable, metastatic, and recurrent disease and have been approved by the United States Food Drug Administration for the abovementioned indications. Traditional cancer treatment modalities such as chemotherapy and radiotherapy have been found ineffective when treating GIST [17, 18].

As even several small GISTs have been shown to have metastatic potential, all GISTs are currently regarded as malignant unless proven otherwise. Tumor size and mitotic index are the two most important prognostic factors used for risk stratification of GIST [12]. Tumor smaller than 5 cm and less of 5 mitoses per 50 high power fields, as it was the case in our patient, have low risk for metastasis [12].

The National Comprehensive Cancer Network Soft Tissue Sarcoma Group 2007 has recommended standard guidelines for the follow-up of patients with GISTs. Those with a complete resection of the tumor should be observed with a history and physical examination every 3–6 months for 5 years and then annually, along with abdominal/pelvic CTs every 3–6 months for 3–5 years and then annually. High-risk patients should be started on imatinib, and more trials are underway to address the issue. Patients with incomplete resection, persistent gross disease (R2 resection), and metastatic disease should undergo physical examination, and abdominal/pelvic CT every 3–6 months. Less aggressive surveillance is acceptable for GISTs smaller than 2 cm and is up to the discretion of the managing physician [19]. Our patient should be followed up in recommended time every 3-6 months.

Small intestine GIST tumor with liver abscess presentation was described in few articles [20-24]. Clinical presentation of bacteriemia and liver abscess associated with GIST which became infected was described. Streptococcus milleri was detected as an indicator of possible underlying gastrointestinal neoplasm [24]. In a recent article, abscess liver nodules were negative for c-KIT and CD 34. The authors considered the possibility of liver metastasis into abscesses and, therefore, they administered imatinib mesylate to the patient [22].

On the other hand, mimicking cavernous liver angioma, as it was the case in our patient, associated with giant gastric GIST was described in one article [25].

Conclusion

According to literature, this is one of a few described cases in which fever and abscess in the tumor of the liver was the first manifestation of the gastrointestinal stromal tumors of intestine. The case report presents a gastrointestinal stromal tumor in a middle-aged patient with unique clinical features, so it could be very important in raising awareness of its timely detection in patients with atypical clinical symptoms and associated diseases that hinder its diagnosis.

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Rad je primljen 27. XI 2013.
Recenziran 10. XII 2013.
Prihvaćen za štampu 18. XII 2013.
BIBLID.0025-8105:(2014):LXVII:1-2:55-59.

LETTERS TO EDITORIAL BOARD
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COMPARISON OF ORIGINAL EUROSCORE AND EUROSCORE II RISK MODELS IN CARDIAC SURGICAL COHORT FROM VOJVODINA

I read with great interest the article by Mihajlovic et al. [1] regarding validation of the EuroSCORE model performances over a cohort of 406 consecutive patients undergoing cardiac surgical procedures at the Institute for Cardiovascular Diseases of Vojvodina from January to July 2012. Since the EuroSCORE (European System for Cardiac Operative Risk Evaluation) was introduced into daily cardiac surgical practice [2], it has been used as a measure of operative risk of adult cardiac surgery patients in more than 1300 formal citations in the medical literature [3]. Although both additive and logistic version of the EuroSCORE has remained a very good discriminatory power, some suspicions have arisen that the model may now be inappropriately calibrated for current cardiac surgery [3]. Therefore, the old EuroSCORE was renewed into EuroSCORE II (database of 22381 consecutive patients undergoing adult cardiac surgery in 154 hospitals in 43 countries over a 12-week period in 2010) in order to optimize its discriminatory power and calibration, in particular [3].

The validation of a risk model depends on the assessment of two features: discrimination and calibration. Discrimination measures the model capacity to differentiate between the individuals of a sample who suffer from an event (in this case, death after cardiac surgery) and those who do not. Discrimination can be assessed by the area under the receiver operative characteristic curve (ROC). The area under the ROC (AUC) is a percentage of randomly drawn pairs for which it is true that a patient who died had a higher risk score than a patient who survived. The discriminative power is considered to be excellent if the AUC is > 0.80, very good if > 0.75 and good (acceptable) if > 0.70 [4]. Mihajlovic et al. [1] reported unsatisfactory AUCs for both additive and logistic EuroSCORE as well as for EuroSCORE II. However, the reduced number of events and the small sample sizes induce statistical limitations. The number of at least 50 is frequently underlined as the minimum number of events needed for a stable AUC analysis. Therefore, an AUC ana-lysis with only 10 events becomes "very fragile" [5,6-discussion].

Calibration refers to the agreement between the observed events (death after cardiac surgery) and the predicted probability of occurrence of these events. A well-calibrated model is one with a high agreement between the actual (observed) number of events and the predicted (expected) number of events. The Hosmer-Lemeshow goodness-of-fit test has been the most popular test to validate calibration, measuring the differences between the expected and observed outcomes (mortality) over deciles (test results are acceptable with cohort divided in at least terciles) of risk. A well-calibrated model gives the corresponding p-value greater than 0.05 [7]. So far, Hosmer-Lemeshow statistics has been used in more than 95% of manuscripts to test the calibration of additive and logistic EuroSCORE in cardiac surgery [7]. The calibration of the EuroSCORE II was assessed by the observed/expected (O/E) ratio of mortality [3]. Ideally, this ratio equals one (the observed mortality equals expected mortality, thus the predictive model is perfectly calibrated). A value above one means that the model underestimates mortality; whereas a value below one means that the model overestimates mortality. If the 95% confidence interval of O / E ratio excludes the value 1.0, it may be considered statistically significant [7]. Surprisingly, Mihajlovic et al. [1] used chi-square test to validate calibration of the EuroSCORE models (additive, logistic and EuroSCORE II) in their sample. Thus, I wonder what the result of the EuroSCORE calibration checking would have been if the H-L test or O/E ratio of mortality had been used.

Back in 2011, VojvodinaSCORE was announced a new local model for risk stratification in cardiac surgery due to the fact that cardiac surgery cohort in Vojvodina is specific regarding the amount and type of risk factors included in daily surgical practice, as well as for different organization and tactics in perioperative treatment of the patients undergoing cardiac surgery [8]. The external validation of the locally developed model has also been predicted as well as an idea to promote VojvodinaSCORE as a national model [8]. Antunes et al. [9] were quoted to support the necessity of introducing an institutional model that could be used as a tool to provide information to clinicians and patients about the risk of in-hospital mortality in their cardiac surgery cohort. Antunes et al. [9] especially underlined that the locally derived model was strictly created for institutional use only, and it was not intended to be used in other patient populations [9];

therefore, I wonder how VojvodinaSCORE can then be promoted as the national risk stratification model in cardiac surgery.

I agree that it is possible to correct the EuroSCORE model in relation to the success of the specific hospital using following formula: expected mortality = patient logistic EuroSCORE x hospital mortality/hospital logistic EuroSCORE. However, Mihajlovic et al. [1] quoted a completely misleading reference (reference number 27 in their manuscript, [10] in this Letter) to support that statement. Namely, the quoted manuscript by Leonard and Masatu [10] examined the data on the behavior of clinicians in Tanzania which were used to measure quality and they asked whether the presence of a member of the research team had changed the behavior of clinicians (so-called Hawthorne effect). Thus, EuroSCORE models were not mentioned in that article at all. The appropriate reference would be the Editorial comment by Nashef SAM [11], the creator of the EuroSCORE models.

The authors [1] are to be congratulated for their efforts to draw our attention to the very important field in cardiac surgery practice, and that is the development and validation of risk stratification models in contemporary cardiac surgery.

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Štampu ovog časopisa ”Medicinski pregled”
pomogla je **Vlada AP Vojvodine**

Printing of this journal ”Medical Review”
has been supported by
the Government of the AP of Vojvodina

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3. Pregledni članci – do 10 strana. Predstavljaju sažet, celovit i kritički pregled nekog problema na osnovu već publikovanog materijala koji se analizira i raspravlja, ilustrujući trenutno stanje u jednoj oblasti istraživanja. Radovi ovog tipa biće prihvaćeni samo ukoliko autori navođenjem najmanje *5 autocitata* potvrde da su eksperti u oblasti o kojoj pišu.

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5. Stručni članci – do 10 stranica. Odnose se na proveru ili reprodukciju poznatih istraživanja i predstavljaju koristan materijal u širenju znanja i prilagođavanja izvornih istraživanja potrebama nauke i prakse.

6. Prikazi slučajeva – do 6 stranica. Obrađuju *retku* kazuistiku iz prakse, važnu lekarima koji vode neposrednu brigu o bolesnicima i imaju karakter stručnih radova. Prikazi slučajeva ističu neuobičajene karakteristike i tok neke bolesti, neočekivane reakcije na terapiju, primenu novih dijagnostičkih postupaka ili opisuju retko ili novo oboljenje.

7. Istorija medicine – do 10 stranica. Pišu se na poziv uredništva Medicinskog pregleda i obrađuju podatke iz prošlosti sa ciljem održavanja kontinuiteta medicinske i zdravstvene kulture, a imaju karakter stručnih radova.

8. Druge vrste publikacija (feljtoni, prikazi knjiga, izvodi iz strane literature, izveštaji sa kongresa i stručnih sastanaka, saopštenja o radu pojedinih zdravstvenih ustanova, podružnica i sekcija, saopštenja Uredništva, pisma Uredništvu, novine u medicini, pitanja i odgovori, stručne i staleške vesti i *In memoriam*).

Priprema rukopisa

Propratno pismo

– Mora da sadrži svedočanstvo autora da rad predstavlja originalno delo, kao i da nije objavljivan u drugim časopisima, niti se razmatra za objavljivanje u drugim časopisima.

– Potvrditi da svi autori ispunjavaju kriterijume za autorstvo nad radom, da su potpuno saglasni sa tekstom rada, kao i da ne postoji sukob interesa.

– Navesti u koju kategoriju spada rad koji se šalje (originalni naučni rad, pregledni članak, prethodno saopštenje, stručni članak, prikaz slučaja, istorija medicine).

Rukopis

Za pisanje teksta koristiti *Microsoft Word for Windows*. Tekst treba otkucati koristeći font *Times New Roman*, na stranici formata A4, proredom od 1,5 (i u tabelama), sa marginama od 2,5 cm i veličinom slova od 12 pt. Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana. Naslovna strana treba da sadrži kratak i jasan naslov rada, bez skraćenica, zatim kratki naslov (do 40 karaktera), puna imena i prezimena autora (najviše 6 autora) indeksirana brojkama koje odgovaraju onima kojim se u zaglavlju navode uz pun naziv i mesta ustanova u kojima autori rade. Na dnu ove stranice navesti titulu, punu adresu, e-mail i broj telefona ili faksa autora zaduženog za korespondenciju.

2. Sažetak. Sažetak treba da sadrži do 250 reči, bez skraćenica, sa preciznim prikazom problematike, ciljeva, metodologije, glavnih rezultata i zaključaka. Sažetak treba da ima sledeću strukturu:

– originalni naučni radovi: uvod (sa ciljem rada), materijal i metode, rezultati i zaključak;

– prikaz slučaja: uvod, prikaz slučaja i zaključak;

– pregled rada: uvod, odgovarajući podnaslovi koji odgovaraju onima u tekstu rada i zaključak.

U nastavku navesti do deset ključnih reči iz spiska medicinskih predmetnih naziva (*Medical Subjects Headings, MeSH*) Američke nacionalne medicinske biblioteke.

3. Sažetak na engleskom jeziku. Sažetak na engleskom jeziku treba da bude prevod sažetka na srpskom jeziku, da ima istu strukturu i da sadrži do 250 reči, bez upotrebe skraćenica.

4. Tekst rada

– Tekst originalnih članaka mora da sadrži sledeće celine:

Uvod (sa jasno definisanim ciljem rada), Materijal i metode, Rezultati, Diskusija, Zaključak, spisak skraćenica (ukoliko su korišćene u tekstu) i eventualna zahvalnost autora onima koji su pomogli u istraživanju i izradi rada.

– Tekst prikaza slučaja treba da sadrži sledeće celine: Uvod (sa jasno definisanim ciljem rada), Prikaz slučaja, Diskusija i Zaključak.

– Tekst treba da bude napisan u duhu srpskog jezika, oslobođen suvišnih skraćenica, čija prva upotreba zahteva navođenje punog naziva. Skraćenice ne upotrebljavati u naslovu, sažetku i zaključku. Koristiti samo opšte prihvaćene skraćenice (npr. DNA, MRI, NMR, HIV,...). Spisak skraćenice koje se navode u radu, zajedno sa objašnjenjem njihovog značenja, dostaviti na poslednjoj stranici rukopisa.

– Koristiti mere metričkog sistema prema Internacionalnom sistemu mera (*International System Units – SI*). Temperaturu izražavati u Celzijusovim stepenima (°C), a pritisak u milimetrima živinog stuba (mmHg).

– Ne navoditi imena bolesnika, inicijale ili brojeve istorija bolesti.

Uvod sadrži precizno definisan problem kojim se bavi studija (njegova priroda i značaj), uz navođenje relevantne literature i sa jasno definisanim ciljem istraživanja i hipotezom.

Materijal i metode treba da sadrže podatke o načinu dizajniranja studije (prospektivna/retrospektivna, kriterijumi za uključivanje i isključivanje, trajanje, demografski podaci, dužina praćenja). Statističke metode koje se koriste treba da budu jasne i detaljno opisane.

Rezultati predstavljaju detaljan prikaz podataka dobijenih tokom studije. Sve tabele, grafikoni, sheme i slike moraju da budu citirani u tekstu, a njihova

numeracija treba da odgovara redosledu pominjanja u tekstu.

Diskusija treba da bude koncizna i jasna, sa interpretacijom osnovnih nalaza studije u poređenju sa rezultatima relevantnih studija publikovanim u svetskoj i *domaćoj* literaturi. Navesti da li je hipoteza istraživanja potvrđena ili opovrgnuta. Izneti prednosti i ograničenja studije.

Zaključak u kratkim crtama mora da odbaci ili potvrdi pogled na problem koji je naveden u Uvodu. Zaključci treba da proizilaze samo iz vlastitih rezultata i da ih čvrsto podržavaju. Uzdržati se uopštenih i nepotrebnih zaključivanja. Zaključci u tekstu moraju suštinski odgovarati onima u Sažetku.

5. Literatura. Literatura se u tekstu označava arapskim brojevima u uglastim zagradama, prema redosledu pojavljivanja. Izbegavati veliki broj citata u tekstu. Za naslove koristiti skraćenice prema *Index Medicus*-u (http:// www.nlm.nih.gov/tsd/serials/lji.html). U popisu citirane literature koristiti Vankuverska pravila koja precizno određuju redosled podataka i znake interpunkcije kojima se oni odvajaju, kako je u nastavku dato pojedinim primerima. Navode se svi autori, a ukoliko ih je preko šest, navesti prvih šest i dodati et al.

Članci u časopisima:

∗ *Standardni članak*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *Organizacija kao autor*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *Nisu navedena imena autora*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *Volumen sa suplementom*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *Sveska sa suplementom*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *Sažetak u Časopisu*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije:

∗ *Jedan ili više autora*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Urednik(ci) kao autor*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *Poglavlje u knjizi*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders;1974. p. 457-72.

∗ *Rad u zborniku radova*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ *Disertacije i teze*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Elektronski materijal

∗ *Članak u Časopisu u elektronskoj formi*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monografije u elektronskoj formi*

CDI, clinical dermatology illustrated [monograph on CDROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *Kompjuterski dokument (file)*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computeried Educational Systems; 1993.

6. Prilozi (tabele, grafikoni, sheme i fotografije).

Dozvoljeno je najviše šest priloga!

– Tabele, grafikoni, sheme i fotografije dostavljaju se na kraju teksta rukopisa, kao posebni dokumenti na posebnim stranicama.

– Tabele i grafikone pripremiti u formatu koji je kompatibilan sa programom *Microsoft Word for Windows.*

– Slike pripremiti u JPG, GIF TIFF, EPS i sl. formatu

– Svaki prilog numerisati arapskim brojevima, prema redosledu njihovog pojavljivanja u tekstu.

– Naslov, tekst u tabelama, grafikonima, shemama i legendama navesti na srpskom i na engleskom jeziku.

– Objasniti sve nestandardne skraćenice u fusnotama koristeći sledeće simbole: *, †, ‡, §, ||, ¶, **, ††, ‡‡.

– U legendama mikrofotografija navesti korišćenu vrstu bojenja i uvećanje na mikroskopu. Mikrofotografije treba da sadrže merne skale.

– Ukoliko se koriste tabele, grafikoni, sheme ili fotografije koji su ranije već objavljeni, u naslovu navesti izvor i poslati potpisanu izjavu autora o saglasnosti za objavljivanje.

– Svi prilozi biće štampani u crno-beloj tehnici. Ukoliko autori žele štampanje u boji potrebno je da snose troškove štampe.

7. Slanje rukopisa

Prijem rukopisa vrši se u elektronskoj formi na stranici: **aseestant.ceon.rs/index.php/medpreg/**. Da biste prijavili rad morate se prethodno registrovati. Ako ste već registrovani korisnik, možete odmah da se prijavite i započnete proces prijave priloga u pet koraka.

8. Dodatne obaveze

Ukoliko autor i svi koautori nisu uplatili članarinu za Medicinski pregled, rad neće biti štampan. Radovi koji nisu napisani u skladu sa pravilima Medicinskog pregleda, neće biti razmatrani. Recenzija će biti obavljena najkasnije u roku od 6 nedelja od prijema rada. Uredništvo zadržava pravo da i pored pozitivne recenzije donese odluku o štampanju rada u skladu sa politikom Medicinskog pregleda. Za sva dodatna obaveštenja obratiti se tehničkom sekretaru:

Društvo lekara Vojvodine
Vase Stajića 9
21000 Novi Sad
Tel. 021/521 096; 063/81 33 875
E-mail: dlv@neobee.net

INFORMATION FOR AUTHORS

Medical review publishes papers from various fields of biomedicine intended for broad circles of doctors. The papers are published in Serbian language with an expanded summary in English language and contributions both in Serbian and English language, and selected papers are published in English language at full length with the summary in Serbian language. Papers coming from non-Serbian speaking regions are published in English language. The authors of the papers have to be Medical Review subscribers.

This journal publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 auto-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practise.

6. Case reports – up to 6 pages – deal with rare casuistry from practise important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history in the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The covering letter:

– It must contain the proof given by the author that the paper represents an original work, that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine)

The manuscript:

Use Microsoft Word for Windows to type the text. The text must be typed in font Times New Roman, page format A4, space 1.5 (for tables as well), borders of 2.5 cm and font size 12pt. The manuscript should contain the following elements:

1. The title page. The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary. The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– original and professional papers should have the introduction (with the objective of the paper), material and methods, results and conclusion

– case reports should have the introduction, case report and conclusion

– review papers should have the introduction, subtitles corresponding to those in the paper and conclusion. It is to be followed by up to 10 Key Words from the list of Medical Subject Headings, MeSH of the American National Medical Library.

3. The summary in Serbian language. The summary in Serbian should be the translation of the summary in English, it should be structured in the same way as the English summary, containing up to 250 words, without any abbreviations.

4. The text of the paper. The text of original studies must contain the following: introduction (with the clearly defined objective of the study), material and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

– The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

– The text should be written in the spirit of Serbian language, without unnecessary abbreviations, whose first mentioning must be explained by the full term they stand for. Abbreviations should not be used in the title, summary and conclusion. Only commonly accepted abbreviations (such as DNA, MRI, NMR, HIV…) should be used. The list of abbreviations used in the text, together with the explanation of their meaning, is to be submitted at the last page of the manuscript.

– All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C). and pressure in mmHg.

– No names, initials or case history numbers should be given.

Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Material and methods should contain data on design of the study (prospective/retrospective, eligibility

and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the problem mentioned in the introduction. Conclusions must be based solely on the author's own results, corroborating them. Avoid generalised and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

5. References. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by et 'al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organisation as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *Acomputer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

6. Attachments (tables, graphs, schemes and photographs). The maximum number of attachments allowed is six!

– Tables, graphs, schemes and photographs are to be submitted at the end of the manuscript, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English language.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, ||, ¶, **, † †, ‡ ‡ .

– State the type of colour used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in colour, they will have to pay additional cost.

7. Manuscript submission

The manuscripts can be submited on the web-page: **aseestant.ceon.rs/index.php/medpreg/**. The authors have to register with the journal prior to submitting their manuscript, or, if already registered, they can simply log in and begin the 5 step process.

8. Additional requirements

If the author and all co-authors have failed to pay the subscription for Medical Review, their paper will not be published.

Papers which have not met the criteria of Medical Review will not be taken into consideration. The Editorial review of the paper will be announced not later than six weeks after the submission of the paper. The Editorial Board reserves the right to make a decision regarding the publication of the paper according to the policy of Medical Review even if the review is positive. Contact the technical secretary for all additional information:

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E-mail: dlv@neobee.net