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**ČASOPIS DRUŠTVA LEKARA VOJVODINE SRPSKOG LEKARSKOG DRUŠTVA**
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## RELEVANCE OF THE HIPPOCRATIC OATH TODAY

*ZNAČAJ HIPOKRATOVE ZAKLETVE DANAS*

**Artur BJELICA[1, 2]**

**Summary**
A selection of writings on the Hippocratic Oath, with a variety of opinions, has been critically reviewed. The aim of this article was a comparative analysis of the contents of the two most widely known versions of the Oath, namely 'Classic Version' – Edelstein's translation from Greek to English, and 'Modern Version' – Lasagna's modification of the former version. Some attention has also been paid to several texts composed in a similar vein to the Hippocratic Oath. This short review of the pertinent literature shows that opinions about its relevance range from warm approval to total disapproval. A number of pros and cons were discussed, and our own preferences were clearly stated. The fact that the tradition, in which graduate medical students take some version of the Hippocratic Oath, is nurtured at (almost) all medical schools over the world supports an affirmative answer to the question posed in the title of the article.
**Key words:** Hippocratic Oath; Ethics, Medical; Codes of Ethics; History of Medicine; Attitude; Social Values; Manuscripts, Medical as Topic; Translations

**Sažetak**
U radu se daje kritički prikaz izabranih tekstova u kojima se reflektuju različita mišljenja o Hipokratovoj zakletvi. Okosnicu rada čini uporedna analiza sadržaja dveju najpoznatijih verzija Zakletve, to jest „klasične verzije" – Eldelstejnovog (*Edelstein*) prevoda sa grčkog jezika na engleski i „moderne verzije" – modifikacije prethodne verzije koju je uradio Lazanja (*Lasagna*). Određena pažnja je posvećena i jednom broju tekstova koji su takođe napisani u duhu Hipokratove zakletve. Ovaj kratak osvrt na najistaknutije izvore iz literature koji su posvećeni razmatranoj problematici pokazuje da se mišljenja o značaju Zakletve kreću od svesrdnog odobravanja do potpunog odricanja. Diskusija obuhvata neke od „za" i „protiv" argumenata, uz jasno izražene vlastite stavove o njima. Činjenica da tradicija, u kojoj diplomirani studenti medicine iskazuju svoju privrženost nekoj od verzija Hipokratove zakletve se praktikuje u (skoro) svim školama medicine širom sveta, podržava potvrdan odgovor na pitanje postavljeno u naslovu ovoga rada.
**Ključne reči:** Hipokratova zakletva; medicinska etika; eticka načela; istorija medicine; stavovi; društvene vrednosti; medicinski rukopisi kao tema; prevodi

### Introduction

The body of literature on the Hippocratic Oath is so large to make an ever-growing library. Although written some twenty five centuries ago, it is still a subject of numerous writings of medical scholars, which can be easily evidenced by Googling. It is sufficient to type "Hippocratic Oath", and the omniscient Google will find almost half a million hits. This number is related only to the amount of relevant information available in English. If we assume that the bibliography in other sixty languages into which the Hippocratic Oath has been translated [1] is also significant, the size of this virtual library becomes really impressive. However, we are going to stay only in the "English Reading Room", i.e. we will focus our attention solely on sources available in English.

If from the above number, those that only mention the term Hippocratic Oath, are excluded, it is plausible to think (but impossible to check out!) that still remains an enormous amount of pertinent literature sources. Thus, the shelves of the reading room of this virtual library are stocked with volumes of books and journals dealing with the Oath. They are mainly from the fields of medical ethics and history of medicine. Among them, there are even three books about this topic published in this century [2–4]. The other books and journals contain whole chapters, review articles, and papers of different length and significance. One should also mention numerous opinions and comments posted on popular social media websites. In the mentioned sources, one can find a wealth of opinions, ranging from those that consider that the Oath's "principles are held sacred by doctors to this day" to those that "some doctors see oath-

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taking as little more than a pro-forma ritual with little value beyond that of upholding tradition" [5].

It should be pointed out that there are different versions of the Hippocratic Oath, so that it is possible to speak about it in the plural. Namely, apart from the version usually termed 'Classical', there is also one termed 'Modern', and numerous versions written in a similar vein to the Hippocratic Oath. Although they contain the word 'Hippocratic', they are not literal translations of the Oath, but rather its adaptation to suit the values of a particular culture, like the one used by medical students in India [6] and in Russia [7]. Besides, there is opinion that "medical students are free to choose their own oaths" [8]. However, a question can be raised as to whether all these versions can be called 'Hippocratic'.

Let us recall that the Hippocratic Oath is the most widely known medical text of the Greek heritage, authored by Hippocrates, the founder of a school of medicine on the Greek island of Kos, or by his closest associates [9, 10]. It is a code of ethics which "provides first statements of a moral of conduct to be used by physicians" [11], separating medicine from religion. Along this line, the famous American anthropologist Margaret Mead wrote: "For the first time in our tradition there was a complete separation between killing and curing. Throughout the primitive world, the doctor and the sorcerer tended to be the same person. ... With the Greeks, the distinction was made clear. One profession, the followers of Asclepius, were to be dedicated completely to life under all circumstances, regardless of rank, age, or intellect – the life of a slave, the life of the Emperor, the life of a foreign man, the life of a defective child" [12].

The Oath was originally written in the Ionic Greek, probably in the late fifth century Before Christian Era [1]. Its best known translation into English was done by Ludwig Edelstein, a classical scholar and historian of medicine. This translation is usually called 'Classical version' [13], whereas the (modified) version written by Louis Lasagna is known as 'Modern version' [14]. However, it should be pointed out that there is a significant number of references in which, instead of 'classical', it is called the 'original', which is not correct because there are various translations from the Greek. Therefore, the word 'original' could be appropriate only for the version written in Greek, although it can be rightly supposed that, in its long history, the 'pristine' text could have been subjected to alterations.

Below, we present the full texts of the 'Classical' and 'Modern' versions of the Oath, not only to compare their contents, but also for the purpose of discussing their significance at the present time. In doing so, we will review critically different opinions on the subject matter and also tackle some points which, in our opinion, have not been treated appropriately in the available literature.

**Hippocratic Oath: Classical Version** [13]

"I swear by Apollo Physician and Asclepius and Hygieia and Panaceia and all the gods and goddesses, making them my witnesses, that I will fulfill according to my ability and judgment this oath and this covenant:

To hold him who has taught me this art as equal to my parents and to live my life in partnership with him, and if he is in need of money to give him a share of mine, and to regard his offspring as equal to my brothers in male lineage and to teach them this art - if they desire to learn it - without fee and covenant; to give a share of precepts and oral instruction and all the other learning to my sons and to the sons of him who has instructed me and to pupils who have signed the covenant and have taken an oath according to the medical law, but no one else.

I will apply dietetic measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice.

I will neither give a deadly drug to anybody who asked for it, nor will I make a suggestion to this effect. Similarly I will not give to a woman an abortive remedy. In purity and holiness I will guard my life and my art.

I will not use the knife, not even on sufferers from stone, but will withdraw in favor of such men as are engaged in this work.

Whatever houses I may visit, I will come for the benefit of the sick, remaining free of all intentional injustice, of all mischief and in particular of sexual relations with both female and male persons, be they free or slaves.

What I may see or hear in the course of the treatment or even outside of the treatment in regard to the life of men, which on no account one must spread abroad, I will keep to myself, holding such things shameful to be spoken about.

If I fulfill this oath and do not violate it, may it be granted to me to enjoy life and art, being honored with fame among all men for all time to come; if I transgress it and swear falsely, may the opposite of all this be my lot."

**Hippocratic Oath: Modern Version** [14]

"I swear to fulfill, to the best of my ability and judgment, this covenant:

I will respect the hard-won scientific gains of those physicians in whose steps I walk, and gladly share such knowledge as is mine with those who are to follow.

I will apply, for the benefit of the sick, all measures [that] are required, avoiding those twin traps of overtreatment and therapeutic nihilism.

I will remember that there is art to medicine as well as science, and that warmth, sympathy, and understanding may outweigh the surgeon's knife or the chemist's drug.

I will not be ashamed to say "I know not," nor will I fail to call in my colleagues when the skills of another are needed for a patient's recovery.

I will respect the privacy of my patients, for their problems are not disclosed to me that the world may

know. Most especially must I tread with care in matters of life and death. If it is given me to save a life, all thanks. But it may also be within my power to take a life; this awesome responsibility must be faced with great humbleness and awareness of my own frailty. Above all, I must not play at God.

I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person's family and economic stability. My responsibility includes these related problems, if I am to care adequately for the sick.

I will prevent disease whenever I can, for prevention is preferable to cure.

I will remember that I remain a member of society, with special obligations to all my fellow human beings, those of sound mind and body as well as the infirm.

If I do not violate this oath, may I enjoy life and art, respected while I live and remembered with affection thereafter. May I always act so as to preserve the finest traditions of my calling and may I long experience the joy of healing those who seek my help."

**A brief comparative analysis of two versions**

According to dictionaries, an oath, in its noble meaning, is a solemn promise, often invoking a divine witness, regarding one's future action or behavior. The abandonment of ancient Greek gods and goddesses as witnesses, the Classical version, deprived the Oath of much of its solemnity. Instead of deities, Lasagna's formulation called upon personal virtues of the oath taker (I swear to fulfill, to the best of my ability and judgment, this covenant). While not pretending to be quite serious, one can invoke as a witness something that is neither divine nor personal. Thus, in their poem in prose entitled "Hippocratic oath translated into poetry", R. Philipp and D. Hart say: "I swear by the music of the expanding universe and by the eloquence of the good in all of us that I will excite the sick and the well by the severity of my kindness to a wholeness of purpose" [15].

The second part of both versions is concerned with the relations between the physician and his teachers, as well as the students he will be teaching one day. In the Modern version, the respect to the seniors and readiness to share the knowledge "with those who are to follow" are clearly stated in a succinct way. In the Classical version, this matter is more elaborated, and the corresponding sentence is much longer. The oath taker declares that he is obliged to his teacher as much as to his own parents, and promises to give him material support in case of need. This high regard and readiness to help extends also to the teacher's offspring. The neophyte physician is ready to teach them the art of medicine ("if they desire to learn it") the same way as his own sons. This implies that medical professionals could be primarily members of the family's male lineage. This holds for Hippocrates himself, whose father was also a physician, whereas his two sons and son-in-law were his pupils [1]. Although this was quite normal in the time of Hippocrates, by the modern views it is neither acceptable nor compliant with reality. Namely, the percentage of female physicians is growing in many countries. For example, in the United States of America, they made only 9.7 % in 1970 and 32.4% in 2010 [16].

It seems that the tradition of practicing medicine, mainly reserved for the members of 'medical clans', has survived to the present day. On the one hand, this may be a desirable trend, as the members of younger generations grow up in a favorable milieu, which could be beneficial for the medical profession. However, this tradition can be criticized on the grounds that some gifted young people may be thus hindered or prevented from learning the art of medicine. True enough, there is a possibility for "pupils who have signed the covenant and have taken an oath according to the medical law, but no one else". One can understand that from this stems the requirement for a 'medical license' at the present time.

The rest of the sections are concerned with the physician-patient relationship, stating that the physician, although being aware of his limitations, will always act in the patient's best interests. This is a typical paternalistic attitude, since the physician assumes the role of the parent (father), who knows best what suits his patient (child). However, this is not consistent with fundamental principles of modern medical ethics, by which the physician-patient dyad should function in a cooperative way [17, 18].

The following part of the classical text "… I will keep them from harm…" may be considered only as a hint of the well known principle "First, do no harm" ("Primum non nocere"), which is often (wrongly) associated with the Hippocratic Oath. In fact, it has been stated in the collection of medical writings called 'Hippocratic Corpus' (in the book "Epidemics") [19].

Obviously, the above principle is one of the core obligations of every physician. However, as pointed out by Robert H. Shmerling from the Harvard Medical School: "The fact is that when difficult, real-time decisions must be made, it's hard to apply the "first, do no harm" dictum because estimates of risk and benefit are so uncertain and prone to error" [20]. It is quite probable that many medical practitioners had to face such a situation. The most important thing is that they must not inflict harm intentionally!

The strong readiness of the physician to do everything "for the benefit of the sick" (mentioned twice in the classical and once in the modern text) means more than "do no harm". In contrast to the old version, in which the physician's empathy for his patients is not stated explicitly, Lasagna expressed it in a beautiful way as "warmth, sympathy, and understanding may outweigh the surgeon's knife or the chemist's drug".

Abortion, euthanasia ("physician-assisted death"), and surgery are the three issues that have been most frequently in the focus of attention of medical ethicists and other interested authors. While in the classical text the physician swears not to practice abortion ("I will not give to a woman an abortive remedy")

and euthanasia ("I will neither give a deadly drug to anybody who asked for it"), these life-and-death issues, though not mentioning explicitly either abortion or euthanasia, Lasagna worded with subtle care ("Most especially must I tread with care in matters of life and death…But it may also be within my power to take a life; this awesome responsibility must be faced with great humbleness and awareness of my own frailty. Above all, I must not play at God."). Abortion and euthanasia are topics of hot debates among not only medical ethicists and healthcare professionals, but also among law and religious authorities, as well as people from all walks of life. While abortion has been legalized in many countries, euthanasia is allowed only in a few European countries (Netherlands, Belgium, Luxembourg, Switzerland), and in some states of the United States of America [16, 18].

As far as surgery is concerned, one may understand that the oath taker was not going to practice it ("I will not use the knife … but will withdraw in favor of such men as are engaged in this work."). By this, the physician admits his incompetence in the art of surgery, and there is no mentioning of the possible specialization. Hence, a question arises as to how then the surgeons were trained, since there is evidence in the Hippocratic Corpus that "Greek doctors were in fact aggressive surgeons" [21]. In both versions, the oath taker declares to respect the privacy of his patient, and this confidentiality principle is also contained in the majority of modified versions. Thus, according to a survey of the contents of oaths in United States of America medical schools in 2000, the principle of "Protecting patient confidentiality" is ranked first, as it was present in 91% of the oaths, followed by the "Loyalty to colleagues, profession and teachers" (87%), while "Avoiding sexual misconduct" (2.8%) and "Prohibition of abortion" (0.7%) were at the end of the list in the oaths that "maintain ethical values in the traditional Hippocratic oath" [22]. Such low percentages of the oaths addressing the last two issues may seem somewhat surprising.

It is interesting to see how the Oath is treated in legislation, i.e. how the breaches of the Oath's principles are sanctioned. Dimitrios Gakis observed that "in ancient Athens if somebody was treating inappropriately a supplicant, the penalty was death!" [23]. In general, this statement does not tell what behavior is referred to as inappropriate treatment. In today's healthcare practice, there may arise many specific situations, especially in the domain of the very sensitive physician-patient relationship, abortion, euthanasia, etc., that may lead to court cases. There is an interesting opinion that "the Hippocratic Oath exerts a powerful influence on modern legal controversies implicating medical ethics, leading courts to adopt an overly doctor-centered view of these disputes" [24]. This questionable statement is supported by the presumed dignification of the medical profession and by the opinion that "the Oath treats the patient as subordinate to the physician." In their book, Pellegrino and Thomasma [25] put the focus on the patient's autonomy. This matter is formulated in the form of the principles known as "Pellegrino's Precepts". In the linguistic sense, this shift from the term 'oath' to 'precept' can be understood as a weakening of the obligation of the physician to stick strictly to the pledge.

**On the contemporary relevance of the Oath**

As pointed out in the Introduction, the literature search shows that the Hippocratic Oath is a very controversial subject. Generally, opinions range from warm approval to total disapproval. It seems that every single bit of the Oath has been subjected to detailed analysis and interpretations. The majority of objections are related to the Classical version, which is claimed to be outdated, although at the time it was, supposedly, 'modern'.

Below, we are going to discuss some pros and cons related to the Oath, while trying to formulate our own position in this matter. The choice of topics selected for discussion is very limited as it was made with the only purpose to illustrate the diversity of views of a number of authors.

One of the starting points in a significant number of writings on the subject is concerned with the formulation of the oath opening, i. e. with the choice of the oath witnesses. While D. Graham says: "To invoke the gods and goddesses as witnesses to an oath is certainly a more serious undertaking than making a pledge to a personal conscience that can easily be ignored" [26], H. Herrell's opinion is that "few students today would take swearing by Apollo and Asclepius seriously" [27]. On the other hand, H. Kantarjian and Steensma [21] put it this way: "Today, we face (and may swear by) old and new deities, including one perhaps more powerful and capable of extremes of good and evil than any other: money." It is true that nobody can deny that money is a powerful incentive, but one would like to believe that humanistic values will prevail, at least in certain situations.

In his article, "The Myth of the Hippocratic Oath", Robert H. Shmerling has expressed his opinions (some of which may seem a bit contradictory) on a number of relevant issues, and, among the others he stated the following: "In fact, the modern-day Hippocratic Oath covers only a few issues relevant to the ethical practice of medicine" [20]. Although this observation is true, it is possible to criticize it on the grounds that one should not expect that an oath, bearing in mind its specific character, is supposed to address the whole multitude of ethical issues that a physician can encounter in his/her practice. All these aspects, including those concerned with medical research, are appropriately covered in the corresponding declarations of the World Medical Association [18, 28].

In her long and well articulated article, Emily Woodbury [29] stated that "the importance of a unique medical morality cannot be understated." She also points out that "this myriad of interpretations"

concerning the Hippocratic Oath and medicine in general "necessitates a unified philosophical grounding for medicine and an agreement within the medical professional community on ethical constraints". She concluded that "the Hippocratic Oath fails to meet those demands", so that it should be abandoned, announcing thus a "post-Hippocratic era". It is interesting to note that although advocating strongly the replacement of the Oath with Pellegrino's Precepts, Woodbury proposes to discard two (the 5th and 11th) of the 13 precepts. This is evidence on how difficult it is to take a clear stand on a controversial topic.

A similar opinion that the Hippocratic Oath is outdated and that it should be replaced with Pellegrino's Precepts has been recently expressed in an online article [30]. The author claims that "the Oath sees the patient as a subordinate to the doctor" and advocates for taking patient's opinion into consideration. Although not giving the source of data, the author gives the following statement: "as of the year 2016, all (100%) of students swear upon some version of an oath upon graduating from medical school".

It is interesting to note that there are few articles concerning the opinions of physicians about the influence of the Hippocratic Oath on their personal attitude towards the professional practice. This was the subject of a recent extensive polling on the impact of medical oaths and other professional codes on the "physicians' professional formation and practice", carried out by Antiel et al. [31]. The survey included 1032 United States practicing physicians who returned a completed questionnaire, and the data were analyzed by taking into account a number of factors. Practically all respondents (97%) participated in the ceremony of taking the oath, which was a version of the Hippocratic Oath in 85% of cases. To the question on the extent to which their practice was influenced by the oath, the answers were as follows: "a lot" (26%), "somewhat" (37%), "not very much" (24%), and "not at all" (13%). It is also interesting to note that in relation to other sources of moral guidance the respondents marked "personal sense of right and wrong" (92%), "great moral teachers" (35%), and "specific traditions" (28%).

The argument that "today's doctors face a number of important ethical issues that are not included in the Hippocratic Oath" [20], although being true, cannot be used as a basis for making it more complete. That would result in a very long text which could not serve its purpose any more. Anyway, one cannot expect that a small number of ethical guidelines could address all possible aspects of the physician's practice.

Although the wordings of the statements that are sworn by the physicians may differ to a great extent, they always express very positive attitudes about the physician's work. The awareness that their colleagues all over the world attend similar ceremonies and pronounce similar words can induce the feeling that they are members of a wholesome fraternity (Gens una sumus). Although this may seem an exaggeration, we would like to believe that there is a grain of truth in this premise.

This short review of the pertinent literature indicates the existence of a great variety of opinions about the relevance of the Hippocratic Oath. Despite of this, it appears that the tradition that graduate students take a medical oath – different versions of the Hippocratic Oath or the oaths composed in a similar vein – is nurtured at (almost) all medical schools over the world. So, to make a choice from this rich menu is not an easy task. If one is inclined to respect tradition that has passed down to us throughout so many centuries ("Tradition means obligation!"), he will choose the Classical version, despite the right criticisms related to the attitudes towards some crucial aspects (abortion and euthanasia). The Modern version, could be recommended as the "most appropriate", while Pellegrino's Precepts are less acceptable because of the fact that the replacement of the term "oath" with "precepts" may seem as weakening the obligation. Finally, all those "self-composed" and jocular versions could not be considered to be a valid substitute for the Oath.

## Conclusion

In conclusion, the shortest answer to the question in the title of the paper is a big "yes". The Hippocratic Oath is alive and well today, and will, hopefully, be so in the future.

## References

1. Jotterand F. The Hippocratic oath and contemporary medicine: dialectic between past ideals and present reality? J Med Philos. 2005;30(1):107-28.

2. Miles SH. The Hippocratic oath and the ethics of medicine. New York; Oxford: University Press; 2004.

3. Tallis R. Hippocratic oaths: medicine and its discontents. London: Atlantic; 2004.

4. Dossetor JB. Beyond the Hippocratic oath. Edmonton: University of Alberta Press; 2005.

5. Tyson P. The Hippocratic oath today [Internet]. 2001 [cited 2019 Jan 13]. Available from: www.pbs.org/wgbh/nova/article/hippocratic-oath-today/?utm_source=promourl&utm_medium=direct&utm_campaign=nova_2019.

6. Pai SA, Pandya SK. A revised Hippocratic oath for Indian medical students. Natl Med J India. 2010;23(6):360-1.

7. Tishchenko PD. Resurrection of the Hippocratic oath in Russia [Internet]. 2008 [cited 2019 Jan 13]. Available from: http://www.zpu-journal.ru/en/articles/detail.php?ID=330.

8. Bailey M. So long Hippocrates. Medical students choose their own oaths [Internet]. 2016 [cited 2019 Jan 13]. Available from: http://www.statnews.com/2016/09/21/hippocratic-oath-medical-students.

9. Carrick P. Medical ethics in the ancient world. Washington, D.C.: Georgetown University Press; 2001.

10. Bjelica A. A short journey through the history of medical ethics. Med Pregl. 2017;70(3-4):119-22.

11. Oath and law of Hippocrates/Physician/Oath - Scribd [Internet]. 2016 [cited 2019 Jan 13]. Available from: https://www.scribd.com/document/Oath-and-Law-of-Hippocrates.

12. American Hippocratic Registry - History and meaning of the oath [Internet]. 2016 [cited 2019 Jan 13]. Available from: www.ahregistry.us/history-and-meaning-of-the-oath.html.

13. Edelstein L. The Hippocratic oath: text, translation, and interpretation. Baltimore: Johns Hopkins Press; 1943.

14. Lasagna L. Hippocratic oath: modern version [Internet]. 1964 [cited 2019 Jan 13]. Available from: https://www.pbs.org/wgbh/nova/doctors/oath_modern.html.

15. Philipp R, Hart D. An ethical code for everybody in health care: Hippocratic oath translated into poetry. BMJ. 1998;316(7142):1460.

16. Strasser AR. Despite growing number of female doctors and lawyers, women's pay still lags behind [Internet]. 2012 [cited 2019 Jan 13]. Available from: https://thinkprogress.org/despite-growing-number-of-female-doctors-and-lawyers-womens-pay-still-lags-behind-9b43f25c0335/.

17. Emanuel EJ, Emanuel LL. Four models of the physician-patient relationship. JAMA. 1992;267(16):2221-6.

18. Bjelica A. An outline of medical ethics. Novi Sad, Serbia: Faculty of Medicine; 2015.

19. The Internet Classics Archive. Of the epidemics by Hippocrates [Internet]. [cited 2019 Jan 13]. Available from: http://classics.mit.edu/Hippocrates/epidemics.html.

20. Shmerling RH. First, do no harm [Internet]. 2015 [updated 2015 Oct 14; cited 2019 Jan 13]. Available from: https://www.health.harvard.edu/blog/first-do-no-harm-201510138421.

21. Kantarjian H, Steensma DP. Relevance of the Hippocratic oath in the 21st century [Internet]. 2014 [cited 2019 Jan 13]. Available from: http://www.ascopost.com/issues/october-15-2014/relevance-of-the-hippocratic-oath-in-the-21st-century.aspx.

22. Kao AC, Parsi KP. Content analyses of oaths administered in U.S. medical schools in 2000. Acad Med. 2004;79(9):882-7.

23. Gakis D. The Hippocratic oath today. MOJ Surgery. 2016;3(2):35.

24. Hasday LR. The Hippocratic oath as literary text: a dialogue between law and medicine. Yale J Health Policy Law Ethics. 2002;2(2):299-323.

25. Pellegrino ED, Thomasma DC. For the patient's good. New York: Oxford University Press; 1988.

26. Graham D. Revisiting Hippocrates: does an oath really matter? JAMA. 2000;284(22):2841-2.

27. Herrell H. The Hippocratic oath: a commentary and translation [Internet]. 2000 [cited 2019 Jan 13]. Available from: http://utilis.net/hippo.htm.

28. Volkmer S. International ethics applicable to health care professionals [Internet]. 2010 [cited 2019 Jan 13]. Available from: https://www.law.berkeley.edu/files/IntlMedlEthicspaper(final)11June10.pdf.

29. Woodbury E. The fall of the Hippocratic oath: why the Hippocratic oath should be discarded in favor of a modified version of Pellegrino's precepts. Georgetown University Journal of Health Sciences. 2012;6(2):9-17.

30. Dalvidap. Hippocratic oath [Internet]. 2016 [cited 2019 Jan 13]. Available from: https://rampages.us/univ200hippocraticoath/author/dalvidap.

31. Antiel RM, Curlin FA, Hook CC, Tilburt JC. The impact of medical school oaths and other professional codes of ethics: results of a national physician survey. Arch Intern Med. 2011;171(5):469-71.

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# ORIGINAL STUDIES
# *ORIGINALNI NAUČNI RADOVI*

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## NOVEL DIAGNOSTIC AND THERAPEUTIC APPROACHES TO THE TREATMENT OF OVARIAN CANCER

*SAVREMENI DIJAGNOSTIČKO-TERAPIJSKI PRISTUP U LEČENJU KARCINOMA JAJNIKA*

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**Summary**

**Introduction.** Ovarian cancer is an intra-abdominal, chemosensitive, chronic disease and according to current protocols, it is primarily treated with surgery followed by adjuvant chemotherapy. In Serbia, 820 cases of ovarian cancer are newly diagnosed annually. The aim of the study is to present the results of surgical treatment in 304 patients with ovarian cancer, treated during a 15-year period (2003 – 2017) at the Clinic of Gynecology and Obstetrics, Clinical Center of Vojvodina in Novi Sad. **Material and Methods.** Before the operation, clinical, gynecological, ultrasonography examination and analysis of cancer antigen 125 blood concentrations were performed in all patients. Based on basic diagnostics, additional pelvic, abdominal and thoracic computed tomography or magnetic resonance imaging studies, together with colonoscopy if needed, were performed. The selection of the type and extent of surgical procedure was based on intraoperative assessment of the stage of disease, intraoperative histopathological confirmation of ovarian cancer, wish for fertility preservation and general patient's condition. Exclusion criteria were histopathologically confirmed benign or borderline ovarian tumors, i. e. absence of cancer in the final microscopic specimen. **Results.** The patients' age ranged from 19 – 88 years, with a median of 53.4 years. According to the International Federation of Gynecology and Obstetrics staging, most patients had stage III – 98 (33.1%) and epithelial ovarian cancer – 240 (84.2%). The most common surgical procedures were hysterectomy with bilateral adnexectomy and omentectomy, whereas cytological analysis was performed in 138 (45.4%) treated patients. Complications were recorded in 13 (4.3%) operated patients with inflammation and wound seroma being the most common (4 patients – 1.3% of cases). **Conclusion.** Ovarian cancer treatment is planned individually, depending on the stage of the disease, histological tumor type, patient's general condition, wish for fertility–sparing treatment and technical capacity of the institution where the treatment is performed.

**Key words:** Ovarian Neoplasms; Diagnostic Imaging; CA-125 Antigen; Biomarkers, Tumor; Morphological and Microscopic Findings; Neoplasm Staging; Surgical Procedures, Operative; Postoperative Complications; Prognosis

**Sažetak**

**Uvod.** Karcinom jajnika je intraabdominalno, hemiosenzitivno, hronično oboljenje koje se primarno leči hirurški, nakon čega sledi dopunska hemioterapija prema važećim protokolima. U Srbiji se godišnje otkrije oko 820 novih slučajeva karcinoma jajnika. Cilj istraživanja je prikaz rezultata lečenja kod 304 operisane pacijentkinje od karcinoma jajnika u 15-godišnjem periodu (2003–2017) na Ginekološko-akušerskoj klinici Kliničkog centra Vojvodine u Novom Sadu. **Materijal i metode.** Kod svih pacijentkinja pre operacije izvršen je klinički, ginekološki, ultrazvučni pregled i određivanje koncentracije tumorskih markera CA 125 iz krvi. Na osnovu ove osnovne dijagnostike izvršeni su dopunski pregledi skenerom ili magnetnom rezonancom karlice, abdomena i grudnog koša a prema potrebi i kolonoskopija. Izbor vrste i obima hirurškog postupka izvršen je na osnovu intraoperativne procene stadijuma bolesti, histopatološke potvrde da se radi o karcinomu jajnika u toku operacije, želje za rađanjem i opšteg stanja pacijentkinje. Kriterijum za isključenje iz istraživanja je patohistološki potvrđen benigni ili graničnomaligni (*borderline*) tumor jajnika odnosno odsustvo karcinoma na definitivnom mikroskopskom preparatu. **Rezultati.** Uzrast pacijentkinja kretao se između 19 i 88 godina, u proseku 53,4 godine. Najviše pacijentkinja bilo je prema kriterijumima *International Federation of Gynecology and Obstetrics* u III stadijumu bolesti 98 (33,1%) i grupi epitelijalnih karcinoma jajnika 240 (84,2%). Najčešće sprovedena operacija bila je histerektomija sa obostranom adneksektomijom, omentektomijom i citološkom analizom koja je izvršena kod 138 (45,4%) operisanih pacijentkinja. Komplikacije su zabeležene kod 13 (4,3%) operisanih pacijentkinja a najčešće su bili zastupljeni inflamacija i serom rane u četiri slučaja (1,3%). **Zaključak.** Lečenje karcinoma jajnika planira se individualno u zavisnosti od stadijuma bolesti, histološke vrste tumora, opšteg stanja pacijenkinje, želje za očuvanjem fertilne sposobnosti i tehničkih mogućnosti ustanove u kojoj se sprovodi lečenje.

**Ključne reči:** ovarijalne neoplazme; dijagnostički imidžing; CA-125 antigen; tumorski biomarkeri; morfološki i mikroskopski nalazi; klasifikacija karcinoma; operativne hirurške procedure; postoperativne komplikacije; prognozaski nalazi; klasifikacija karcinoma; operativne hirurške procedure; postoperativne komplikacije; prognoza

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***Abbreviations***

| | |
|---|---|
| CGO | – Clinic of Gynecology and Obstetrics |
| US | – ultrasound |
| CT | – computed tomography |
| MRI | – magnetic resonance imaging |
| FIGO | – International Federation of Gynecology and Obstetrics |
| CA | – cancer antigen |
| AFP | – alpha fetoprotein |
| hCG | – human chorionic gonadotropin |
| BRCA | – breast cancer gene |

## Introduction

Ovarian cancer is an intra-abdominal, chemosensitive chronic disease and according to current protocols, it is primarily treated with surgery followed by adjuvant chemotherapy [1]. The incidence of newly diagnosed ovarian cancer worldwide is 4% of all malignant tumors in female population, and it is twice higher in economically developed countries. In Serbia, 820 cases of ovarian cancers are newly diagnosed every year, and it is the leading cause of death among all malignant gynecological tumors [2]. It affects the elderly population, and in more than 80% of cases it is diagnosed after the age of 60 years [3]. The first symptoms are nonspecific, including the sensation of abdominal pressure and pain, bloating, loss of appetite, nausea, increased abdominal circumference, defecation problems etc. [4]. There are no successfully organized screening programs for ovarian cancer yet. The diagnosis is based on imaging, which comprises ultrasonography (US) and color Doppler, computed tomography (CT) and magnetic resonance imaging (MRI) [5]. Preoperative analysis of specific tumor marker concentrations (cancer antigen (CA) 125, human epididymis protein (HE) 4, CA 19.9, alpha fetoprotein (AFP), beta human chorionic gonadotropin (hCG) etc.) can aid the diagnosis [6, 7]. Definite diagnosis is based on histopathological analysis of tissue specimen following laparoscopy or laparotomy [1–3]. Nowadays, distinction between two different entities: low-grade serous carcinoma (LGSC) and high-grade serous carcinoma (HGSC), which have different precursors, biological behavior and molecular diversity, is of significant importance. Most low-grade cancers have a mutation of Kirsten rat sarcoma viral oncogene homolog (KRAS) and v-Raf murine sarcoma viral oncogene homolog (BRAF) genes, with the assumption that serous borderline tumors are precursors of this disease. High-grade tumors have a tumor protein (TP) 5 mutation, about 50% have breast cancer gene (BRCA) 1 and BRCA2 abnormalities and are not related to borderline tumors [8, 9]. Two most important prognostic factors are tumor dissemination at the moment of diagnosis and volume of residual tumor after surgical treatment [10]. Assessment of ovarian cancer dissemination or stage of the disease is performed intraoperatively by detailed examination of all intra-abdominal organs and obtaining biopsy specimens for histopathological examination from all suspicious sites and serous surfaces of pelvic and abdominal cavity (peritoneum, diaphragm domes, liver, spleen, small and large intestine etc.) according to up to date International Federation of Gynecology and Obstetrics (FIGO) classification [1–5]. The aim of the study is to present the results of surgical treatment in 304 patients with ovarian cancer treated during a 15-year period (2003 – 2017) at the Clinic of Gynecology and Obstetrics (CGO), Clinical Center of Vojvodina in Novi Sad.

## Material and Methods

The study included 304 patients operated for ovarian cancer. Before the surgery, clinical, gynecologic, ultrasonography examination and analysis of tumor marker CA 125 blood concentrations were performed in all patients. Based on the test results, additional diagnostic tests, including pelvic, abdominal and thoracic computed tomography (CT) or magnetic resonance imaging (MRI), additional blood levels of tumor markers tests (CA19,9, AFP, beta hCG etc.), as well as colonoscopy, gastroscopy etc., were performed. Indications for surgical treatment with intraoperative ex tempore diagnostics included patients with: suspicion of ovarian cancer based on imaging tests (US, CT, MRI): presence of papillary proliferations on the inner tumor capsule larger than 3 mm, honeycomb and solid portions within the cystic tumors, predominantly solid tumors, presence of ascites, increased number of septations larger than 3 mm, etc. In all patients, bowel preparation was performed 24 – 48 hours prior the surgery. Two hours before the surgery, lower extremities were bandaged, and anticoagulant therapy with Fraxiparin and one dose of antibiotics (Cephalosporin 1 – 2 g) were administered. Apart from standard blood and urine laboratory tests, preoperative preparation included chest X–ray, electrocardiography (ECG), examination by internal medicine specialist and anesthesiologist, as well as reservation of decanted erythrocytes if hemoglobin levels were below 100 g/l and organization of intraoperative histopathological ex tempore analysis. The selection of type and extent of surgical procedure was based on intraoperative assessment of FIGO stage of the disease, intraoperative histopathological confirmation of ovarian cancer, wish for fertility preservation, and general patient's condition. In all cases where different intra-abdominal organs were involved (small and large intestines, liver, spleen, peritoneum, diaphragm), an abdominal surgeon joined the surgery. Assessment of ovarian cancer dissemination to surrounding tissues (stage of the disease) was performed based on intraoperative and histopathological findings of biopsies of different pelvic and abdominal organs according to FIGO classification for ovarian cancer from 2009. Histopathological confirmation of cancer was based

on intraoperative ex tempore findings and definite histopathological examination of all obtained tumor tissue specimens. Inclusion criterion was a confirmed ovarian cancer on definite histopathological specimen, while exclusion criteria were histopathologically confirmed benign or borderline tumors. In all patients with advanced stages of the disease (FIGO III and IV) with involvement of intra-abdominal organs (colon, liver, spleen, peritoneum, diaphragm domes, urinary bladder, or kidney), an abdominal surgeon and urologist joined the surgery. After the surgery and final histopathological reports, all patients were presented at the Gynecologic-Oncologic Committee at our Clinic, and then at the Institute of Oncology in Sremska Kamenica. The decision on adjuvant chemotherapy was considered according to current protocols and recommendations in all cases where FIGO stage was IB or higher. After completion of therapy, follow ups were performed at the Outpatient Department of CGO of the Clinical Center of Vojvodina and Institute of Oncology in Sremska Kamenica.

## Results

In the period from 2003 – 2017, 304 ovarian cancer patients underwent surgery at the CGO of the Clinical Center of Vojvodina in Novi Sad. The age distribution of operated patients is shown in **Graph 1**. Most surgical procedures were performed in 2017, a total of 34. The age of patients ranged from 19 to 88 years (mean age 53.4 years). According to the FIGO classification, there were 92 (30.6%) patients with FIGO I stage, 53 (16.5%) with stage II, 98 (33.1%) with stage III, and 61 (19.8 %) patients with stage IV. Based on histopathological type, ovarian cancers were classified into the following groups: epithelial 240 (84.2%), germ cell 21 (5.4%), stromal sex cord tumors 22 (5.6%), sarcomas 2 (0.4%) and metastatic tumors 19 (4.4%). **Table 1** shows the types of performed surgical procedures. The most frequent surgical procedure was total abdominal hysterectomy with bilateral adnexectomy, and total omentectomy in 138 (45.4%) patients. **Table 2** shows the distribution of complications in the operated patients and the most frequent was wound inflammation in 4 (1.3%) patients. In 109 (35.8%) patients, besides hysterectomy, adnexectomny, and omentectomy, radical surgical procedures also included lymphadenectomy and surgical excision of involved organs (colon, liver, spleen, urinary bladder, kidney, and peritoneum). Only explorative laparotomy with biopsy followed by histopathology and adjuvant chemotherapy was done in 15 (4.9%) operated patients with advanced stage (FIGO III and IV) of ovarian cancer**. Figure 1** and **Figure 2** show different intraoperative findings and surgical procedures in advanced FIGO III and IV stages of ovarian cancer.

**Table 1.** Types of surgical procedures according to FIGO staging
***Tabela 1.*** *Vrsta sprovedenog hirurškog postupka u odnosu prema FIGO stadijumu bolesti*

| Type of surgery<br>*Vrsta operacije* | FIGO Stage of the disease<br>*FIGO stadijum bolesti* | | | | Percentage<br>*Procenat* |
|---|---|---|---|---|---|
| | I | II | III | IV | % |
| Unilateral adnexectomy Biopsy + Citology<br>*Jednostrana adneksektomija biopsija + citologija* | 15 | 4 | 0 | 0 | 6.3 |
| Hysterectomy + Bilateral adnexectomy<br>*Histerektomija + obostrana adneksektomija* | 19 | 0 | 4 | 0 | 7.6 |
| Hysterectomy + Bilateral adnexectomy + Omentectomy<br>*Histerektomija + obostrana adneksektomija + omentektomija* | 53 | 24 | 38 | 23 | 45.4 |
| Hysterectomy + Bilateral adnexectomy + Omentectomy + Hemicolectomy + Splenectomy/*Histerektomija + obostrana adneksektomija + Omentektomija + hemikolektomija + splenektomija* | 0 | 5 | 32 | 14 | 16.7 |
| Hysterectomy + Bilateral adnexectomy + Omentectomy + Lymphadenectomy + Nephrectomy + Urinary bladder resection<br>*Histerektomija + obostrana adneksektomija + omentektomija + limfadenektomija + nefrektomija + resekcija mokraćne bešike* | | | 1 | | 0.3 |
| Hysterectomy + Bilateral adnexectomy + Omentectomy + Hemicolectomy + Splenectomy + Liver resection/*Histerektomija + obostrana adneksektomija + omentektomija + hemikolektomija + splenektomija + resekcija jetre* | | | | 3 | 1 |
| Hysterectomy + Bilateral adnexectomy + Omentectomy + Lymphadenectomy + Peritonectomy/*Histerektomija + obostrana adneksektomija + omentektomija + limfadenektomija + peritonektomija* | 6 | 19 | 22 | 7 | 17.8 |
| Exploratory laparotomy + Biopsy<br>*Eksplorativna laparotomija + biopsija* | 0 | 0 | 5 | 10 | 4.9 |
| Total/*Ukupno* | 93 | 52 | 102 | 57 | 100 |

Legend: FIGO - International Federation of Gynecology and Obstetrics

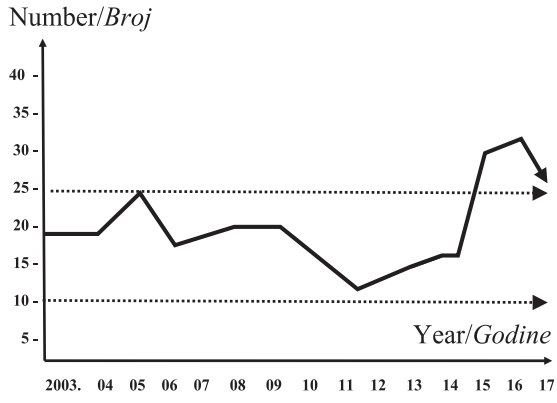
**Table 2.** Types of complications after ovarian cancer surgery
***Tabela 2.*** *Vrsta komplikacije posle hirurškog lečenja karcinoma jajnika*

| Type of complication/*Vrsta komplikacije* | Number/*Broj* | %/*Procenat* |
|---|---|---|
| Bleeding + relaparotomy/*Krvarenje + relaparotomija* | 3 | 1.1 |
| Wound dehiscence/*Dehiscencija rane* | 3 | 1.1 |
| Seroma + wound inflammation/*Serom + inflamacija rane* | 4 | 1.3 |
| Sepsis + pleural empyema/*Sepsa + empijem pleure* | 1 | 0.4 |
| Injury of ureter and bladder/*Povreda uretera i mokraćne bešike* | 2 | 0.8 |
| Total/*Ukupno* | 13 | 4.3 |

## Discussion

The aim of surgical treatment of ovarian cancer is complete tumor reduction, with residual microscopic cancer cells in the abdominal cavity. It has been proven that patients with complete cytoreduction have better prognosis compared to those with minimal residual tumors [11]. According to different studies, optimal cytoreductive surgery is performed in about 20 - 30% of all ovarian cancers. Definition of "optimal" and "maximal" cytoreductive surgery is still controversial. Nowadays, it is considered that optimal surgical cytoreduction can be defined only if there are no macroscopically visible remains. The aim of cytoreductive surgery is to enhance the effects of cytostatics on possible residual tumor cells [12, 13]. When planning the treatment of ovarian cancers, special circumstances and situations must be considered: sparing surgery which preserves woman's fertility, surgery of ovarian cancer with low malignant potential (borderline tumors), surgical treatment of epithelial and germ cell ovarian cancer adjusted to different FIGO stages, use of laparoscopic technique and surgical treatment of ovarian cancer in pregnancy [2]. Considering the fact that ovarian cancer is an intra-abdominal disease which may disseminate to all serous surfaces, organs and topographic parts of the pelvic and abdominal cavity, the attitude - surgeon as a prognostic factor is being often mentioned in the literature [14]. The success of surgical treatment strongly depends on the experience, knowledge and treatment conditions in the referent institution, as well as general patient's condition. Only a well trained surgical team can perform all necessary interventions on different abdominal organs, including large and small bowel, liver, spleen, lymph nodes, diaphragm etc. and be a reliable "prognostic factor" in ovarian cancer surgical treatment [11–14].

The study presents results of surgical treatment in 304 patients of average age of 53.4 years. Most patients had FIGO III stage of the disease 98 (33.1%) and epithelial ovarian cancer 240 (84.2%). According to up to date references, about 70% of ovarian cancer cases are diagnosed in advanced stages (FIGO III and IV) [1–3, 14, 15]. This was not the case in our study, where 52.3% of cases were diagnosed at FIGO stage III and IV, while 47.4% at early FIGO stage I and II. This can be explained by




**Graph 1.** Age distribution of 304 patients operated for ovarian cancer at the CGO, Clinical Center of Vojvodina, Novi Sad, from 2003 to 2017
***Grafikon 1.*** *Distribucija 304 operisane pacijentkinje od karcinoma jajnika prema godinama na Klinici za ginekologiju i akušerstvo Kliničkog centra Vojvodine u Novom Sadu, u periodu 2003–2017.*

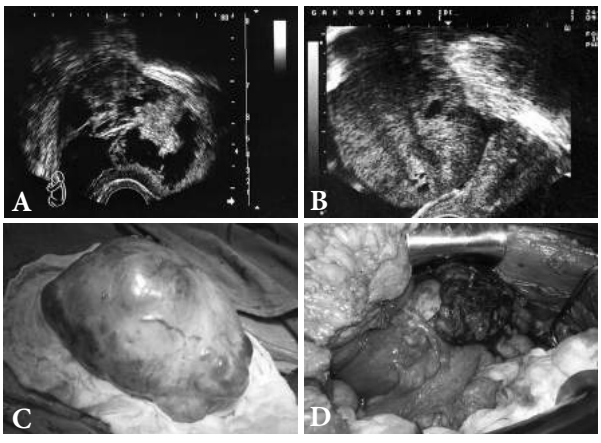



**Figure 1.**A and B – characteristic ultrasonography images of ovarian cancer with intracystic proliferations and solid portions; C – serous cystadenocarcinoma FIGO stage IB (low grade); D – intraoperative finding of pelvic organs infiltration FIGO stage IIIC
***Slika 1.*** *A i B – ultrazvučne karakteristike karcinoma jajnika sa intracističnim proliferacijama i solidnim delovima; C – serozni tip cistadenokarcinoma jajnika stadijuma I B (nizak stepen malignosti); D – intraoperativni nalaz infiltracije organa male karlice kod stadijuma III C karcinoma jajnika*

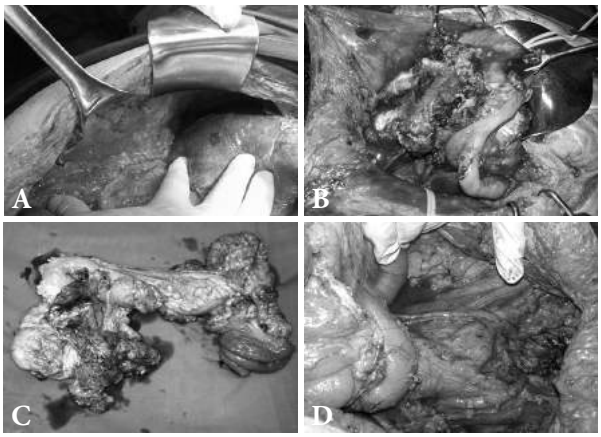



**Figure 2.** Surgical procedures in advanced ovarian cancer stages III and IV: A – peritonectomy of diaphragmatic domes above the liver; B – peritonectomy of vesicouterine peritoneum; C – complete colectomy with peritonectomy; D – complete pelvic peritonectomy
***Slika 2.*** *Hirurški postupci kod uznapredovalih stadijuma karcinoma jajnika stadijum III I IV: A – peritonektomija kupole dijafragme iznad jetre, B – peritonektomija vezikouterinog peritoneuma; C – kompletna kolektomija sa peritonektomijom; D – kompletna karlična peritonektomija*

the fact that more patients with cystic ovarian tumors, over 60 mm in the longest diameter, are relatively early operated by laparoscopy with intraoperative ex tempore diagnosis, so early stage ovarian cancers are discovered faster and earlier [4–6]. The most commonly performed operations were hysterectomy with bilateral adnexectomy, omentectomy and sampling of peritoneal lavage for cytological analysis, conducted in 138 (45.4%) operated patients. This is also the standard surgical procedure for ovarian cancer in patients who fulfilled their reproductive function [10]. Radical surgical procedures were performed in 119 (34.9 %) patients with removal of uterus, adnexa, tubes and omentum, but also included removal of diaphragm domes and pelvic peritonectomy, pelvic lymphadenectomy, splenectomy, nephrectomy, hemicolectomy, liver resection etc. These results are in accordance with current trends in surgical treatment of ovarian cancer with the aim of achieving maximal surgical tumor reduction, including interventions (resections) of affected organs of the upper abdomen. In developed countries, such extensive operations are performed in centers specialized for this type of surgery involving a multidisciplinary team [15–18]. Complications were recorded in a total of 13 (4.3 %) patients. Most common were minor complications such as inflammation and wound seroma in 4 (1.3%) cases. Relaparotomy was performed in 3 (1.1%) patients due to bleeding caused by fall of vascular ligatures. In 1 (0.4%) patient with germ cell ovarian cancer, infection of abdominal organs occurred after the surgery, accompanied by sepsis and pleural empyema, which was successfully treated by reoperation, abdominal and thoracic cavity drainage and administration of antibiotics based on an antibiogram from the obtained microbiology samples.

## Conclusion

During the 15-year period (2003 – 2017), 304 patients underwent surgery for ovarian cancer at the Clinic of Gynecology and Obstetrics. The average age of patients was 53.4 years, and most patients had International Federation of Gynecology and Obstetrics stage III - 98 (33.1%) and 240 (84.2%) had epithelial ovarian cancer. Hysterectomy with bilateral adnexectomy and omentectomy were the most common surgical procedures, whereas cytologic analysis was performed in 138 (45.4%) patients; radical surgeries with resection of the upper abdominal organs were performed in 25 (35.8%) patients. Complications were recorded in 13 (4.3 %) patients, inflammation and wound seroma (4, 1.3%) being the most common. Ovarian cancer treatment is planned individually, depending on the stage of the disease, histological tumor type, patient's general condition, wish for fertility-sparing treatment, and technical capacity of the institution where the treatment is performed.

## References

1. Djurdjevic S. Hirurško lečenje karcinoma jajnika. In: Rakić S, editor. Zbornik radova 57. Ginekološko akušerska nedelja SLD; 2013 Jun 6-7; Beograd, Srbija. Beograd: Ginekološko akušerska sekcija SLD; 2013. p. 386-98.

2. Nieuwenhuyzen-de Boer GM, Hofhuis W, Reesink-Peters N, Ewing-Graham PC, Schoots IG, Beltman JJ, et al. Evaluation of effectiveness of the PlasmaJet surgical device in the treatment of advanced stage ovarian cancer (PlaComOv-study): study protocol of a randomized controlled trial in the Netherlands. BMC Cancer. 2019;19(1):58.

3. Doubeni CA, Doubeni AR, Myers AE. Diagnosis and management of ovarian cancer. Am Fam Physican. 2016;93 (11):937-44.

4. Yauy K, Imbert-Bouteille M, Bubien V, Lindet-Bourgeois C, Rathat G, Perrochia H, et al. Ovarian clear cell carcinoma in Cowden syndrome. J Natl Compr Canc Netw. 2019;17(1):7-11.

5. Smith-Bindman R, Poder L, Johnson E, Miglioretti DL. Risk of malignant ovarian cancer based on ultrasonography findings in a large unselected population. JAMA Intern Med. 2019;179(1):71-7.

6. Pantelić M. Značaj tumorskih markera CA 125 i HE4, konvencionalne i dopler transvaginalne sonografije u dijagnostici karcinoma jajnika [disertacija]. Novi Sad: Univerzitet u Novom Sadu, Medicinski fakultet; 2016.

7. Mehri JS, Farnaz S, Ali DT, Parvin MG, Elaheh O, Marziyeh P, et al. Diagnostic value of tumor biomarkers CA125 and CA72-4 in differentiation of epithelial ovarian cancer and endometrioma. Biomed Res. 2018;29(8):1697-701.

8. Washington C, Gunderson CC, Moore KN. Update in the use and evaluation of poly (ADP-ribose) polymerase inhibitors in epithelial ovarian cancer - current and pending clinical research. Curr Opin Obstet Gynecol. 2019;31(1):4-11.

9. Li C, Bonazzoli E, Bellone S, Choi J, Dong W, Menderes G, et al. Mutational landscape of primary, metastatic, and recurrent ovarian cancer reveals c-MYC gains as potential target for BET inhibitors. Proc Natl Acad Sci U S A. 2019;116(2):619-24.

10. Ye S, You Y, Yang J, Cao D, Bai H, Huang H, et al. Comparison of the pure and mixed-type clear cell carcinoma of the ovary: a clinicopathological analysis of 341 Chinese patients. Int J Gynecol Cancer. 2014;24(9):1590-6.

11. Fotopoulou C, Savvatis K, Kosian P, Braicu IE, Papanikolaou G, Pietzner K, et al. Quaternary cytoreductive surgery in ovarian cancer: does surgical effort still matter? Br J Cancer. 2013;108(1):32-8.

12. Sehouli J, Vergote I, Ferron G, Reuss A, Meier W, Greggi S, et al. Randomized controlled phase III study to evaluate secondary cytoreductive surgery in platinum-sensitive recurrent ovarian cancer. Int J Gynecol Cancer. 2017;27(Suppl 4):1662.

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BIBLID.0025-8105:(2019):LXXII:1-2:11-16.

13. Suzuki K, Takakura S, Saito M, Morikawa A, Suzuki J, Takahashi K, et al. Impact of surgical staging in stage I clear cell adenocarcinoma of the ovary. Int J Gynecol Cancer. 2014;24(7):1181-9.

14. Cordeiro Vidal G, Babin G, Querleu D, Guyon F. primary debulking surgery with a plasma device surgery system, for advanced ovarian cancer. Gynecol Oncol. 2017;144(1):223-4.

15. Dickson BC, Childs TJ, Colgan TJ, Sung YS, Swanson D, Zhang L, et al. Uterine tumor resembling ovarian sex cord tumor - a distinct entity characterized by recurrent NCOA2/3 gene fusions. Am J Surg Pathol. 2019;43(2):178-86.

16. van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med. 2018;378(3):230-40.

17. Lee J, Curtin JP, Muggia FM, Pothuri B, Boyd LR, Blank SV. Timing is everything: intraperitoneal chemotherapy after primary or interval debulking surgery for advanced ovarian cancer. Cancer Chemother Pharmacol. 2018;82(1):55-63.

# PROFESSIONAL ARTICLES
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## CYCLOPS SYNDROME – A COMPLICATION AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

*KIKLOP SINDROM KAO KOMPLIKACIJA POSLE REKONSTRUKCIJE PREDNJEG UKRŠTENOG LIGAMENTA*

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**Summary**

**Introduction.** Cyclops syndrome is one of the causes of failure of anterior cruciate ligament reconstruction. The aim of the study was to examine the quality of life of patients who had this complication and its consequences till the return to unrestricted (sports) activities. **Material and Methods.** During an eighteen-year follow-up of 4330 patients, cyclops syndrome was found in 71 patients (1.64%). This study included 60 of them, who agreed to fill out a questionnaire and functional scoring scales. **Results and Discussion.** The mean Tegner score was 5.95 and Lysholm score was 86.13 points. After the arthroscopic removal of cyclops lesion, excellent results were found in 22 patients (36.7%), good in 19 (31.7%), poor in 16 (26.7%) and very poor in three cases (5%). On average, athletes lose 10 months from injury to anterior cruciate ligament reconstruction. It takes at least 6 months to return to competitive sports. If cyclops lesion occurs, it takes approximately 10 months to arthroscopy, and on average 3 months of postoperative recovery. **Conclusion.** Cyclops lesion is a complication that significantly compromises the outcome of anterior cruciate ligament reconstruction, in terms of functional scores, subjective symptoms, the intensity of sports activities, and quality of life. Arthroscopic removal of the cyclops lesion leads to satisfactory postoperative results, but athletes lose 2.5 years on the whole, from injury to return to unrestricted sports activities.

**Key words:** Anterior Cruciate Ligament Reconstruction; Range of Motion, Articular; Reconstructive Surgical Procedures; Postoperative Complications; Quality of Life; Recovery of Function; Arthroscopy; Surveys and Questionnaires

**Sažetak**

**Uvod.** *Kiklop* sindrom predstavlja jedan od uzroka neuspeha rekonstrukcije prednjeg ukrštenog ligamenta. Cilj istraživanja je da utvrdi kakav je kvalitet života pacijenata koji su imali ovu komplikaciju i koliko gube od povratka nerestriktivnim (sportskim) aktivnostima. **Materijal i metode.** Tokom osamnaestogodišnjeg perioda praćenja 4 330 pacijenata, *kiklop* lezija je pronađena kod 71 pacijenta (1,64%). Ovom studijom ih je obuhvaćeno 60 koji su pristali da popune anketni upitnik, sa dodatkom funkcionalnih bodovnih skala. **Rezultati.** Prosečna vrednost *Tegner* skora iznosi 5,95, a *Lišolmove* bodovne skale 86,13 bodova. Odličnom ocenom, nakon artroskopskog uklanjanja *kiklop* lezije, ocenjeno je 22 pacijenta (36,7%), dobrom 19 (31,7%), lošom 16 (26,7%) i veoma lošom tri pacijenta (5%). Sportista prosečno gubi 10 meseci od povrede ligamenta do njegove rekonstrukcije. Potom je potrebno najmanje šest meseci da bi se vratio takmičenjima. Kad pacijent ima *kiklop* leziju, do ponovne operacije protekne prosečno još 10 meseci, nakon čega se prosečno oporavlja još tri meseca. **Zaključak.** *Kiklop* lezija kao komplikacija u značajnoj meri kompromituje rezultat rekonstrukcije prednjeg ukrštenog ligamenta, po pitanju bodovnih skala, subjektivnih tegoba pacijenata, intenziteta sportskih aktivnosti i kvaliteta života. Artroskopsko uklanjanje kiklop lezije dovodi do zadovoljavajućih postoperativnih rezultata, ali sportista ukupno gubi prosečno skoro 2,5 godine od povrede do povratka nerestriktivnim aktivnostima.

**Ključne reči:** rekonstrukcija prednjeg ukrštenog ligamenta; opseg pokreta zgloba; rekonstruktivne hirurške procedure; postoperativne komplikacije; kvalitet života; oporavak funkcije; artroskopija; istraživanja i upitnici

## Introduction

Anterior cruciate ligament (ACL) reconstruction is an effective surgical procedure with 75% to 90% of patients reporting good or excellent outcomes [1, 2]. Complications after ACL reconstruction are rare, but with the increase in the number of reconstructions, their number is also increasing. Arthrofibro-

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***Abbreviations***

ACL – anterior cruciate ligament
MRI – Magnetic Resonance Imaging
BTB – bone-patellar tendon-bone
KOOS – Knee injury Osteoarthritis Outcome Score
SD – standard deviation

sis is one of the potential complications. The scar tissue in the knee joint may cause pain and limitation of movement. It may occur in primary arthrofibrosis without a known pattern. Secondary arthrofibrosis is caused by immobilization and infection [3, 4] or poor surgical technique, causing graft friction due to positioning of the tibial fixation tunnel too anteriorly [5], inadequate notchplasty or too large size of the graft [6, 7].

Cyclops lesion is also called localized anterior arthrofibrosis, because of its location in front of the graft tibial attachment. It is often detected by magnetic resonance imaging (MRI) as asymptomatic, almost in 25% of all reconstructions [8]. This syndrome causes a progressive knee extension deficit, with or without pain and instability. Even a 5-degree loss of knee extension may significantly limit the patient's sports activities, presenting a difficulty returning to their previous level. Considering the fact that ACL injuries and cyclops syndrome are most common among young physically active athletes, it is very important to examine all aspects of the injury: causes, mechanisms, risk factors, treatment and rehabilitation [9, 10]. Successful arthroscopic reconstruction, postoperative follow-up and aggressive rehabilitation significantly reduce the duration of treatment, rehabilitation, costs of treatment, and provide faster return of patients to daily and work activities [6, 7, 11, 12].

The aims of this study were to examine the quality of life of patients with cyclops lesion, the time necessary to return to unrestricted (sports) activities, and whether there were statistically significant differences between sex and age of the respondents.

## Material and Methods

A descriptive-retrospective study was conducted at the Department of Orthopedic Surgery and Traumatology with the approval of the Ethical Committee of the Clinical Center of Vojvodina. The study included 60 patients with cyclops syndrome after ACL reconstruction performed at the Clinic in the period from January 2000 to May 2018.

Of the 4330 patients who underwent bone-patellar tendon-bone (BTB) ACL reconstruction technique during an 18-year period, this complication was found in 71 patients (1.64%). A survey questionnaire was sent by e-mail to all volunteer respondents [13].

A modified Knee injury Osteoarthritis Outcome Score (KOOS) was used in the data collection [14] as well as Tegner [15] and Lysholm scores [16]. Questions related to problems specific to this type of injury have been added. The questionnaire was designed to assess the short-term and long-term effects of knee joint injuries and it was divided into four parts. The first included general information about the level of sports activities before and after injury, type of sport, mechanism of injury, time from injury to diagnosis of ACL rupture, time from injury to reconstruction, concomitant injuries, time from ACL reconstruction to arthroscopy and symptoms that were the reason to seek help again. The second segment covered issues related to pain and constraints during various activities. The third part was related to the post-operative level of sports activities, while the fourth referred to the quality of life after surgery and the way they experienced their injuries.

The respondents had the opportunity to give their suggestions at the end of the questionnaire. The segment on the quality of life contained 6 questions related to: perceptions on their current quality of life, difficulties after surgery, awareness of limitations and lifestyle changes in order to avoid activities that could potentially be harmful.

All patients were contacted by telephone to explain the purpose of the research, and answers to the questionnaire were forwarded via e-mail. We performed a selection and separation of medical data (medical history, computer database) of all patients with cyclops syndrome after ACL reconstruction.

Out of the total number of respondents, 52 were males (86.7%) and 8 females (13.3%). The youngest respondent, at the time of the research, was 18 and the oldest 50 years old. The average age was 26.7 years (± 6.472). At the time of injury, the average age of the respondents was 22.6 years (± 5,726), ranging from 14 to 42 years. The average height was 184.93 cm (ranging from 158 to 206 cm), while the average weight was 85.85 kg (ranging from 59 to 130 kg).

In 58 patients, the injuries occurred during sports. One patient was injured in the workplace, and in one case the injury was a result of a traffic accident. There was no statistically significant difference in the cause of injuries between male and female respondents (Sig = 0.005 < 0.05).

It was found that 42 examinees (70%) injured their right knee, while left-sided injuries were found in 18 patients (30%). The dominant jumping leg was left in 40 subjects, and the right leg in 20 patients.

Only four respondents had a positive family history of ACL rupture. In all cases, the patient's father was injured. In the remaining 56 patients, no one in the family had a similar injury.

A contralateral ACL injury was found in 11 patients, i. e. 18.3% of the total number of participants. There were 24 patients with concomitant injuries. Out of that number, 11 had a rupture of the medial meniscus, 9 of the lateral meniscus, and 4 patients of both menisci.

Before ACL injury, 30 respondents (50%) were professionally engaged in sports, 27 (45%) were recreational players, while 3 patients did not engage in sports (5%). By analyzing data on the level of

sports activity before injury, the obtained results showed that 12 of them were international athletes, 14 were national and 13 were regional athletes.

Within the descriptive statistics, the variables were determined for parametric features: mean value, standard deviation, minimum and maximum. For nonparametric features, the incidence of certain categories was investigated. In the data analysis and hypothesis testing, a paired sample T-test was used as well as regression analysis.

## Results

Data on the current level of sports activity showed that at present 5 athletes compete at international level, 7 at republic, 9 at regional, 24 at recreational level, while 12 patients stopped their sports activities.

The average time interval since ACL reconstruction to the arthroscopic debridement of the cyclops lesion was 10.3 months, namely 1 month was the shortest interval, up to 6 years, that was the longest interval.

The most frequent subjective symptom before re-arthroscopy was the inability to fully extend the knee and it was found in 76.7% of cases.

Of all the respondents, 29 had some difficulties during high energy activities, 28 had partial limitations, and 3 patients described their activities as very difficult.

The pain was graded according to the type of knee activity, with 23 patients experiencing pain when pivoting, 14 when extending, 32 when flexing, and 11 when walking on a flat surface, 24 during long standing, and 25 during long sitting.

During the first month after the second look arthroscopy, more than a third of the respondents, 22 (36.7%) started running, 11 (18.3%) continued training, and after six months 42 (70%) athletes returned to training, and 18 did not. Even a year after the repeated arthroscopic surgery, 23 respondents did not return to non-restricted sports activities (as much as 38.3%).

**Table 1** shows the degree of severity of symptoms after arthroscopy in regard to the activities. It has been demonstrated that arthroscopic removal of the cyclops lesion significantly reduced patients' symptoms (pain and limitations during: changing the direction, training, competition, landing, jumping, sprint, workout at gym), because half of patients had no symptoms, and pain always persisted only in 3.3% of cases.

The median Tegner score was 5.95; the minimum was 2, and the maximum 10 (standard deviation (SD) 2.204). The average score among the female respondents was 5.85, ranging from 3 to 9 (SD 1.8). Among the male respondents, the average score was 5.96, ranging from 2 to 10, with a SD of 2.274. It was found that there was no statistically significant difference between the sexes (Sig = 0,003 < 0.05).

The average Lysholm score was 86.13. The minimum was 50, and the maximum 100. The average score among the female respondents was 85.63, ranging from 72 to 95. Among the male respondents, the average score was 86.21, ranging from 50 to 100. Also, there was no statistically significant difference between the sexes (Sig = 0,026 < 0.05).

After the arthroscopic removal of the cyclops lesion, according to Lysholm score, excellent results were achieved in 22 patients (36.7%), good in 19 (31.7%), poor in 16 (26.7%) and very poor in three cases (5%).

Fifteen respondents (25%) continued training with the same intensity as before the injury, and 13 respondents (21.7%) were training with higher intensity. The number of patients who have reduced training intensity was 15 (25%), 17 of them (28.3%) stated that they did not practice sports actively, while activity decreased in seven patients (12.7%). Two years after surgery, three patients stopped practicing sports (5.4%).

The time span from arthroscopy to return to full competition was 3.3 months, on average. Only 23.3% returned to competition in the first 3 months. By the seventh month, 31 patients continued with competitive activity. Six respondents needed more than a year to achieve a competitive level. Out of the total number of respondents, 23 were no longer engaged in sports.

Knee surgery affected the quality of life to some degree in 80% of our respondents. The majority of patients were aware of their knee problems (63.4%), and 71.7% of respondents have changed their way of life to some extent in order to avoid activities that were potentially harmful to their health. Around 65% of participants in our study presented with some knee problems. The most frequent was the impact on the quality of life and daily functioning in a mild form. Considering sport activities, between 30% and 50% of the respondents did not have any difficulties. After competitions, 15 of 60 patients did not have any knee problems. During the usual training practice, 20 of them also had no difficulties. Between 40 and 60% of patients reported some limitations during changing the direction of movement, landing on injured leg, jumping, sprint, and exercises at gym.

Analyzing the questionnaire answers, there were no statistically significant differences in all age groups (Sig = 0,004 < 0.05).

## Discussion

According to available literature, knee injuries account for about 30% of all sports injuries [17]. The incidence of ACL injuries is constantly increasing. Over the last three decades, all of the structures of the knee joint are more frequently injured, as well as ACL. The higher increase of injuries is the result of increased involvement of modern men in sports, both professional and amateur [1, 17, 18].

The most common activities that cause these injuries are skiing, football, handball, basketball, volleyball and traffic accidents (up to 20%) [19]. Regarding the situation in which the injury occurred, our results show a deviation from the literature data, as 96.6% of our patients sustained sports injuries, most often during playing soccer [20, 21].

**Table 1.** Difficulties associated with activities
***Tabela 1.*** *Tegobe povezane sa aktivnostima*

| Problem<br>*Problem* | Never<br>*Nikad* | Rare<br>*Retko* | Sometimes<br>*Ponekad* | Often<br>*Često* | Always<br>*Uvek* | No data<br>*Bez podataka* |
|---|---|---|---|---|---|---|
| Competition/*Takmičenje* | 15 | 17 | 14 | 5 | 2 | 7 |
| Training/*Trening* | 20 | 17 | 14 | 1 | 2 | 6 |
| Patellar pain/*Bol čašice* | 19 | 17 | 16 | 4 | 2 | 2 |
| Hypoesthesia/*Utrnutost* | 25 | 11 | 6 | 4 | 13 | 1 |
| Changing direction/*Promena pravca* | 28 | 12 | 11 | 5 | 1 | 3 |
| Landing/*Doskok* | 28 | 12 | 12 | 3 | 2 | 3 |
| Jumping/*Odraz* | 27 | 12 | 12 | 2 | 4 | 2 |
| Betting/*Stav* | 32 | 13 | 8 | 2 | 1 | 4 |
| Sprint/*Sprint* | 32 | 10 | 9 | 1 | 4 | 4 |
| Gym exercises/*Vežbe u teretani* | 27 | 16 | 7 | 2 | 4 | 4 |

The ACL reconstruction is today one of the most commonly performed surgical procedures. In the United States alone, more than 200,000 of these procedures are performed annually [18]. The main goals of the surgery are to remove the symptoms, gain full knee stability throughout the movement, and return to the previous level of sports activities. This is achieved in 75 – 90% of operated patients [1, 2, 22]. Immediately after surgery, instead of immobilization, it begins with early, controlled knee joint movements. The main tasks of rehabilitation protocols are to prevent swelling of the knee joint, establish good muscular control, and restore the full range of motion and prevent arthrofibrosis and patellar pain [9]. The early introduction of exercises prevents the development of complications such as arthrofibrosis and patellar pain. It is necessary to insist on achieving the full knee extension in the first three postoperative weeks, because it leads to optimal positioning of the graft and prevents excessive bleeding followed by an increase in the production of scar tissue [4, 10].

Complications following ACL reconstruction are relatively rare [4]. One of the potential complications is cyclops lesion. Cyclops syndrome was first described by Jackson and Schaefer in 1990 [7]. They defined it as loss of extension of the knee after ACL reconstruction, caused by intra-articular nodular proliferation of the fibrovascular tissue, originally from ACL graft. This syndrome was named after Cyclops, one-eyed giants from Greek mythology. The fibrous formation is arthroscopically resembling a head with reddish-blue areas that looks like eye of a Cyclop [23] (**Figure 1**). This lesion consists of interposition of fibrous tissue in front of the tibial insertion of the new ligament, which will work as an end point during extension, thus limiting the last degrees of motion. The clinical picture varies from painless strokes to the acoustic phenomenon ("click") at the end of the movement, to the painful mechanical blocking the full extension [23]. Although pathophysiology and the cause of the occurrence are unknown, there are more theories about what leads to this lesion [23–25]. According to the first theory, the nodule is created from bone and cartilaginous residues, after drilling bone tunnels in the joint [23]. Another theory argues that cause happen to be a reparative process that occurs as a reaction to the residual living tissue of a ruptured ACL [24]. According to the third theory, repeated contact of the graft in the intercondylar notch ruptures its front fibers, causing fibrosis scarring [25]. The risk of cyclops syndrome is doubled when the tibial and/or femoral tunnel is placed too anteriorly [5, 23]. Patients with narrow intercondylar notch also have a higher tendency to develop this lesion [25], since the formation of the cyclops can be induced by contact, due to the incompatibility in the size of notch and graft, causing its impingement.

This syndrome is more common: in people who have undergone a ligament reconstruction with bone-patellar tendon-bone (BTB) graft than with hamstring tendons [26], in patients who had ACL reconstruction within the first four weeks after the injury, as well as those who had signs of inflammation at the time of surgery. It is most commonly developed around the distal remnant of the ruptured ACL due to an inflammatory reaction [27].

Cyclops syndrome most commonly occurs in the early postoperative period, in the first two months

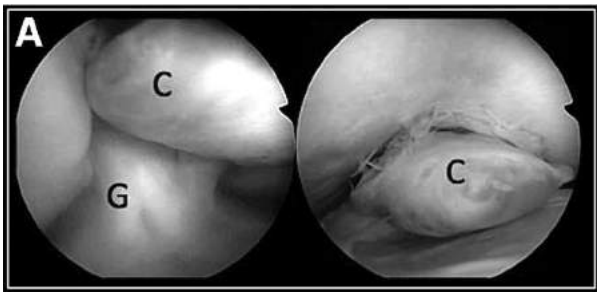


**Figure 1.** Arthroscopy: C – cyclops lesion; G – bone-patellar tendon-bone graft
***Slika 1.*** *Artroskopija: C – kiklop lezija; G – kost-čašična tetiva-kost kalem*

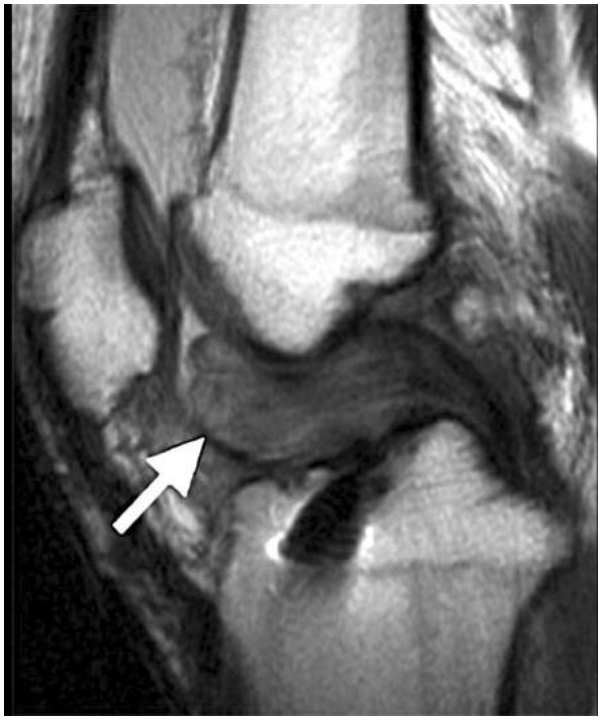

**Figure 2.** MRI image of cyclops lesion
***Slika 2.*** *Dijagnostika kiklop lezije magnetnom rezonancijom*

after the surgery [28], but there are also cases of delayed-onset lesions [29], even four years after reconstruction. Although this syndrome was primarily observed in people who had ACL reconstruction, cyclops can also occur after ACL rupture, but without surgery [27–29]. There is also a statistically significant correlation between the occurrence of cyclops lesion and knee extension deficiency in the 3rd and 6th weeks after ACL reconstruction. The stiffness of the back thigh muscles in the early postoperative stage may predict the occurrence of this complication [30].

Beside the cyclops lesions, there are also cyclopoid formations, with arthroscopic and MRI findings of cyclops, but without clinical manifestations and without deficiency in the knee extension [8, 29–32]. Histomorphological analysis shows a difference in the histological structure of the cyclops and cyclopoid nodules. Cyclops lesions are most commonly made of fibrous and cartilaginous tissue, coated with a synovial membrane, affected by ossification [31]. There are signs of bone formation with the activity of osteoblasts and osteoclasts. The tissue is well vascularized. There is no infiltration of inflammatory or granulocytic tissue [31]. Cyclopoid scarring formations are made of fibrous and granulocytic tissues, with areas of cartilaginous tissue, but without osseous tissue. A well-vascularized granulocyte tissue is surrounded by a mature, well-organized fibrous capsule. Cyclopoid formations do not contain grafted cells [31].

The occurrence rate of cyclops syndrome in the literature varies from 1.2% to 25% [4, 7, 8, 31–34]. In our sample of over 4000 surgeries, the incidence was 1.64%. Although we used BTB graft, the reason for low incidence may lie in the fact that most of our patients underwent surgery at least three weeks after injury, when the full range of knee movements was achieved and the possibility of inflammatory processes and fibrosis was reduced.

Cyclops lesion can be prevented by adequate removal of all ruptured ligament fibers, positioning the bone tunnels in bones, avoiding fiber damage [11, 12] and early rehabilitation, which aims to achieve full extension and flexion of at least 90 degrees during the first postoperative month [9, 10]. If the lesion causes pain and movement restriction, predominantly in knee extension, arthroscopic knee debridement is necessary [6, 7, 11, 12].

In order to treat cyclops adequately, it needs to be recognized as soon as possible. The diagnosis is based on clinical symptoms and MRI findings **(Figure 2)**. Patients complain of pain and progressive loss of extension with cracking or popping noises in the knee and painful terminal extension when walking or running. Among our respondents, the most common reasons for visiting the doctor and performing arthroscopy after ACL reconstruction were pain in 29 patients, loss of extension in 38, and loss of knee flexion in 15 patients. Swelling appeared in 18 subjects, and knee squint in 14 patients. The results of our research do not differ significantly from the results in the available literature [2, 6 – 8, 23], as others also reported that the most common symptoms that indicate second-look arthroscopy were: pain, swelling, and lack of terminal knee extension.

Of the 60 respondents who participated in our study, 52 were male (86.7%). In most other studies, this complication is more common in males [7, 17, 23, 31, 32]. The average age of our patients at the time of ACL injury was 22.6 years. The average age of male patients was 22.7 years, while it was 21.1 years in female patients. Our results are similar to those of a Japanese study of cyclops lesions [25], where the average age was 21.6 years, but in most others, the patients' age ranged between 27 – 30 years [23, 31, 32]. The reason why patients of all ages are found in the literature is that athletes start their professional career earlier, the life expectancy has generally increased with the promotion of healthy life and healthy aging, and people remain physically active at older age as well.

Cyclops syndrome is treated arthroscopically, because methods of physical medicine and rehabilitation do not provide satisfactory results [7, 23, 31, 32]. The rehabilitation is long and hard, whereas the results are inadequate and short-termed, as confirmed in our study. Even when an increase in the range of motion is achieved, the deficit returns shortly after the end of rehabilitation. It is necessary to surgically remove the mechanical obstacle in the

joint. After arthroscopic removal of nodules, postoperative rehabilitation follows. In most cases, immediately after the surgery, the knee mobility increases, and after kinesiotherapy the full range of motion is achieved [32], which was also the case on our sample.

The gap between ACL reconstruction and rearthroscopy in our patients was 10.3 months on average (from 1 month to 6 years). This period in other studies ranges from 9 - 21 months [23, 31, 32].

We evaluated the surgical status results using functional scales. The average Lysholm score in our patients was 86.13 points (50 – 100). Out of 60 patients, 68.4% were ranked as good or excellent. In the literature, the postoperative Lysholm score in the cyclops syndrome ranges between 91.5 and 94.1 points [11, 33], while in other surgical procedures used for the elimination of knee adhesions, only 82 points [12]. In our earlier papers [35–38], this value ranged between 93 and 97 points, which indicated that cyclops lesion is a complication that significantly compromises the average results of ACL reconstruction.

The mean value of Tegner score after arthroscopy in our patients was 5.95. We did not find the results of postoperative Tegner score in any study dealing with cyclops following ACL reconstructions. After the arthroscopic removal of all adhesions, the average postoperative Tegner score was 5 [12]. Otherwise, the average values of this scoring scale after ACL reconstruction range from 7.6 to 8.2 [36, 37]. These values are significantly better than in our study, which also indicates that the cyclops syndrome significantly affects the level of activity after ACL reconstruction.

The available literature is scarce regarding data about return to sport, considering the level and intensity of post-arthroscopic sports activities. Such information are found only in a Chinese study [33], where from 45 patients, only 6 athletes (13%), were unable to deal with their usual sports activities, due to loss of extension. Of the 60 respondents who participated in our study, 46 (80%) recovered full knee extension, and 37 knee flexion. Activities that require significant strength, such as lifting weight and participation in sports competitions, are partially complicated for 28 patients, very difficult for 3 patients, while 29 examinees reported no difficulty in these activities.

The average recovery time after arthroscopy and return to light sports activity or starting running in our respondents was two months. Fifty percent of them started running in the first two months after arthroscopy. In the first 6 months, 82% began running smoothly. The remaining 18% were non-athletes. On average, 2.15 months have passed since arthroscopy to return to training.

In the first three post-arthroscopic months, 45% of patients returned to training, and 70% after sixth months. The most comprehensive study examining the period needed to return to competition was our earlier study, when we examined the same parameters in patients with bilateral ACL reconstructions [35]. In that study, 87% of athletes returned to training after ACL reconstruction of one knee, and 75% continued competing. After surgery of the contralateral knee, 81% returned to training, but only 53% returned to full competition [35].

A comprehensive review on the return to sports activities after ACL reconstruction, which included 48 studies, with a total of 5770 participants and average follow-up period of 41.5 months [18], reported that 82% of participants had returned to sports activities at some level, 63% returned to the level of participation before the injury, and only 44% returned to competitive sport. Fear of recurrence is the most common reason for postoperative reduction or a cessation of participation in sports. Despite high chances for operative success, a relatively low rate of return to competitive sport supports the fact that psychological factors can influence the degree of return to sports activities after injury [18].

Reconstruction of ACL is considered to be a "quality of life" surgery, as it helps patients return the quality of life to the level before the injury. However, cyclops syndrome causes a progressive deficit of knee extension, with or without pain and instability. A loss of just 5 degrees can significantly limit the patient's sporting performance and prevent the return to sports. Analyzing the data of the study, the results show that in 80% of our patients, knee surgery has to some extent affected the patients' quality of life. The majority of patients are aware of their knee problems (63.4%), and 71.7% of respondents have changed their way of life to some extent in order to avoid activities that are potentially harmful to their health.

Our research has several limitations. One of the disadvantages is that patients were contacted by telephone or email, so we could not directly explain anything possibly unclear in the questionnaire. In addition to a small sample, we also had a great disproportion between the sexes. We only interviewed eight females, which affected the credibility of the examined correlations. In addition, there were some problems in designing the questionnaire itself. As the questions in the KOOS questionnaire are not specific to the cyclops syndrome, it was necessary to modify it, which affected the loss of statistical calculation of each individual segment of the questionnaire. One of the limitations is the time interval from the injury to surgical intervention and the moment of conducting the study and filling the questionnaire. The main problem is that for a large part of the questions patients were asked to retrospectively recall specific information about the activities and symptoms, so the presence of bias in the methodology cannot be excluded.

This research could provide guidelines for further studies to deal with the quality of life after cyclops syndrome, especially because a small number of papers deal with this topic, from the as-

pect of quality of life and the impact on sports activities of patients with this complication.

## Conclusion

Cyclops lesion is a rare but a potential complication after anterior cruciate ligament reconstruction. This syndrome causes a progressive deficit of knee extension, significantly limiting the patient's sporting performance and does not respond to rehabilitation treatment. Answers to questionnaire questions indicate that there are no statistically significant differences in age or sex distribution of examinees. Cyclops lesion significantly compromises the result of reconstruction, in terms of scale, subjective symptoms, the intensity of sports activities and the quality of life. After reoperation, the patients' symptoms significantly reduced, but results of the activity scale and return to sport were worse than in patients who underwent reconstruction without this complication. The arthroscopic removal of the cyclops lesion leads to satisfactory postoperative results, but athletes lose altogether about 2.5 years from injury to return to unrestricted activities.

## References


1. Bach BR. Revision ACL reconstruction: indications and technique. In: Miller M, Cole B, editors. Textbook of arthroscopy. Philadelphia: Elsevier; 2004. p. 675-86.

2. George MS, Dunn WR, Spindler KP. Current concepts review: revision anterior cruciate ligament reconstruction. Am J Sports Med. 2006;34(12):2026-37.

3. Ristić V, Maljanović M, Harhaji V, Milankov M. Infections after reconstructions of anterior cruciate ligament. Med Pregl. 2014;67(1-2):11-5.

4. Ristić V, Vranješ M, Obradović M, Bjelobrk M, Harhaji V, Milankov M. Complications of anterior cruciate ligament reconstructions. Med Pregl. 2017;70(11-12):449-58.

5. Ristić V, Ristić N, Harhaji V, Bjelobrk M, Milankov V. Radiographic analysis of tibial tunnel position after anterior cruciate ligament reconstruction. Med Pregl. 2018;71(1-2):15-20.

6. Howell SM, Clark JA, Farley TE. Serial magnetic resonance study assessing the effects of impingement on the MR image of the patellar tendon graft. Arthroscopy. 1992;8(3):350-8.

7. Jackson DW, Schaefer RK. Cyclops syndrome: loss of extension following intra-articular anterior cruciate ligament reconstruction. Arthroscopy. 1990;6(3):171-8.

8. Facchetti L, Schwaiger BJ, Gersing AS, Guimaraes JB, Nardo L, Majumdar S, et al. Cyclops lesions detected by MRI are frequent findings after ACL surgical reconstruction but do not impact clinical outcome over 2 years. Eur Radiol. 2017:27(8):3499-508.

9. Shelbourne KD, Nitz P. Accelerated rehabilitation after anterior cruciate ligament reconstruction. Am J Sports Med. 1990;18(3):292-9.

10. Shelbourne KD, Patel DV, Martini DJ. Classification and management of arthrofibrosis of the knee after anterior cruciate ligament reconstruction. Am J Sports Med. 1996;24(6):857-62.

11. Baldwin K, Harper C, Eckenrode BJ, Sennett B, Tjoumakaris F. The arthroscopic treatment of cyclops syndrome. Curr Orthop Pract. 2011;22(4):327-32.

12. Millet PJ. Arthrofibrosis of the knee. In: Feagin JA, Steadman JR, editors. The crucial principles in care of the knee. Part II. Philadelphia: Wolters Kluwer; Lippincott Williams and Wilkins; 2008. p. 163-84.

13. Asocijacija za sportsku traumatologiju i artroskopsku hirurgiju Srbije. Upitnik o kvalitetu života posle rekonstrukcije prednjeg ukrštenog ligamenta kolena [Internet]. [cited 2018 Jun 15]. Available from:

http://www.astas.rs /dokumenti/ upitnik o kvalitetu života posle rekonstrukcije prednjeg ukrštenog ligamenta kolena.pdf.

14. Roos EM, Lohmander LS. The knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes. 2003;1:64.

15. Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. Clin Orthop Relat Res. 1985;(198):43-9.

16. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. Am J Sports Med. 1982;10(3):150-4.

17. Muellner T, Kdolsky R, Grossschmidt K, Schabus R, Kwasny O, Plenk H Jr. Cyclops and cyclopoid formation after anterior cruciate ligament reconstruction: clinical and histomorphological differences. Knee Surg Sports Traumatol Arthrosc. 1999;7(5):284-9.

18. Herrington L, Wrapson C, Matthews M, Matthews H. Anterior cruciate ligament reconstruction, hamstring versus bone-patella tendon-bone grafts: a systematic literature review of outcome from surgery. Knee. 2005;12(1):41-50.

19. Wang J, Ao Y. Analysis of different kinds of cyclops lesions with or without extension loss. Arthroscopy. 2009;25(6):626-31.

20. Ristić V, Ristić S, Maljanović M, Đan V, Milankov V, Harhaji V. Risk factors for bilateral anterior cruciate ligament injuries. Med Pregl. 2015;68(5-6):192-7.

21. Ristić V, Ninković S, Harhaji V, Milankov M. Causes of anterior cruciate ligament injuries. Med Pregl. 2010;63(7-8):541-5.

22. Milankov M, Miličić A, Savić D, Stanković M, Ninković S, Matijević R, et al. Revision anterior cruciate ligament reconstruction due to knee instability. Med Pregl. 2007;60(11-12):587-92.

23. Sonnery-Cottet B, Lavoie F, Ogassawara R, Kasmaoui H, Scussiato RG, Kidder JF, et al. Clinical and operative characteristics of cyclops syndrome after double-bundle anterior cruciate ligament reconstruction. Arthroscopy. 2010;26(11):1483-8.

24. Delince P, Krallis P, Descamp PY, Fabeck L, Hardy D. Different aspects of the cyclops lesion following anterior cruciate ligament reconstruction: a multifactorial etiopathogenesis. Arthroscopy. 1998;14(8):869-76.

25. Fujii M, Furumatsu T, Miyazawa S, Okada Y, Tanaka T, Ozaki T, et al. Intercondylar notch size influences cyclops formation after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc. 2015;23(4):1092-9.

26. Vinagre G, Kennedy NI, Chahla J, Cinque ME, Hussain ZB, Olesen ML, et al. Hamstring graft preparation techniques for anterior cruciate ligament reconstruction. Arthrosc Tech. 2017;6(6):e2079-84.

27. Kulczycka P, Larbi A, Malghem J, Thienpont E, Vande Berg B, Lecouvet F. Imaging ACL reconstructions and their complications. Diagn Interv Imaging. 2015;96(1):11-9.

28. Irisawa H, Takahashi M, Hosokawa T, Nagano A. Cyclops syndrome occurring after chronic partial rupture of the anterior

cruciate ligament without surgical reconstruction. Knee Surg Sports Traumatol Arthrosc. 2007;15(2):144-6.

29. Nuccion S, Hame SL. A symptomatic cyclops lesion 4 years after anterior cruciate ligament reconstruction. Arthroscopy. 2001;17(2):E8.

30. Pinto FG, Thaunat M, Daggett M, Kajetanek C, Marques T, Guimares T, et al. Hamstring contracture after ACL reconstruction is associated with an increased risk of cyclops syndrome. Orthop J Sports Med. 2017;5(1):1-5.

31. Veselko M, Rotter A, Tonin M. Cyclops syndrome occuring after partial rupture of the anterior cruciate ligament not treated by surgical reconstruction. Arthroscopy. 2000;16(3):328-31.

32. McMahon PJ, Dettling JR, Yocum LA, Glousman RE. The cyclops lesion: a cause of diminished knee extension after rupture of the anterior cruciate ligament. Arthroscopy. 1999;15(7):757-61.

33. Ahn JH, Yoo JC, Yang HS, Kim JH, Wang JH. Second-look arthroscopic findings of 208 patients after ACL reconstruction. Knee Surg Sports Traumatol Arthrosc. 2007;15(3):242-8.

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BIBLID.0025-8105:(2019):LXXII:1-2:17-24.

34. LaPrade RF, Spiridonov SI, Coobs BR, Ruckert PR, Griffith CJ. Fibular collateral ligament anatomical reconstructions: a prospective outcomes study. Am J Sports Med. 2010;38(10):2005-11.

35. Ristić V, Ristić S, Maljanović M, Milankov V, Harhaji V, Đuričin A. Quality of life after bilateral anterior cruciate ligament reconstructions. Med Pregl. 2015;68(9-10);308-15.

36. Ristić V, Ninković S, Harhaji V, Stanković M, Savić D, Milankov M. Reconstruction of anterior cruciate ligament by using two different techniques. Med Pregl. 2010;63(11-12):845-50.

37. Ninković S, Miličić A, Savić D, Stanković M, Radić S, Milankov M. Correlation between radiological and clinical findings after anterior cruciate ligament reconstruction. Med Pregl. 2006;59(9-10):421-5.

38. Ninković S, Avramov S, Harhaji V, Obradović M, Vranješ M, Milankov M. Influence of different levels of sports activities on the quality of life after the reconstruction of anterior cruciate ligament. Med Pregl. 2015;68(3-4):116-21.

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# PROGNOSTIC VALUE OF AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA – A SINGLE CENTRE EXPERIENCE

## *PROGNOSTIČKI ZNAČAJ STAROSNO USKLAĐENOG MEĐUNARODNOG PROGNOSTIČKOG INDEKSA KOD PACIJENATA SA REFRAKTORNIM DIFUZNIM B KRUPNOĆELIJSKIM LIMFOMOM – ISKUSTVO JEDNOG CENTRA*

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**Summary**

**Introduction.** The research aimed to evaluate the impact of age-adjusted international prognostic index and time to the first relapse on overall survival and progression-free survival from the beginning of the second line of treatment in patients with relapsed/refractory diffuse large B-cell lymphoma. **Material and Methods.** The research included 36 patients with relapsed/refractory diffuse large B-cell lymphoma treated at the Oncology Institute of Vojvodina, Serbia, from January 2013 to December 2015. Patients were stratified according to age-adjusted international prognostic index score at the time of relapse into patients with low risk (score 0 – 1) and patients with high risk (score 2 – 3), as well as according to the time of the first relapse: early relapse (≤ 12 months) and late relapse (> 12 months). **Results**. In the group of patients with a score of 0 – 1, the median overall survival was 44 months compared with 6 months in patients with score of 2 – 3, hazard ratio 0,4 (confidence interval 0,16 – 0,99), p = 0,03. In patients with early relapse, the median overall survival was 7 months compared with 25 months in patients with late relapse, hazard ratio 0,55 (confidence interval 0,25 – 1,19), p = 0,12. In patients with early relapse, median progression-free survival was 0 months compared with 10 months in patients with late relapse, hazard ratio 0,34 (confidence interval 0,12 – 1,00), p = 0,0017. **Conclusion.** The impact of age-adjusted international prognostic index score significantly affects overall survival in patients with relapsed diffuse large B-cell lymphoma. The time to the first relapse impacts progression-free survival calculated from the time of the second-line treatment initiation.

**Key words:** Prognosis; Indexes; Lymphoma, Large B-Cell, Diffuse; Recurrence; Disease-Free Survival; Lymphoma, Non-Hodgkin; Age Factors

**Sažetak**

**Uvod**. Cilj ovog istraživanja je procena uticaja *Age-adjusted International Prognostic Index* i vremena do pojave prvog relapsa na ukupno preživljavanje i vreme do progresije bolesti od započinjanja druge linije lečenja kod bolesnika sa relapsnim ili refrakternim difuznim B-krupnoćelijskim limfomom. **Materijal i metode**. U istraživanje je uključeno 36 bolesnika koji su u periodu od januara 2013. do decembra 2015. godine lečeni u Institutu za onkologiju Vojvodine zbog relapsnog ili refrakternog difuznog B-krupnoćelijskog limfoma. Bolesnici su grupisani prema vrednosti *Age-adjusted International Prognostic Index* skora u relapsu na bolesnike sa niskim rizikom (skor 0-1) i bolesnike sa visokim rizikom (skor 2-3) i vremenu do pojave prvog relapsa: rani relaps (do 12 meseci) i kasni relaps (preko 12 meseci). **Rezultati**. Medijana ukupnog preživljavanja u grupi bolesnika sa niskim rizikom (skor 0-1) iznosila je 44 meseca u odnosu na grupu bolesnika sa visokim rizikom (skor 2-3) gde je medijana ukupnog preživljavanja iznosila 6 meseci, odnos hazarda 0,4 (interval poverenja 0,16–0,99), p = 0,03. Medijana ukupnog preživljavanja u grupi bolesnika sa ranim relapsom iznosila je sedam meseci u odnosu na medijanu ukupnog preživljavanja bolesnika sa kasnim relapsom koja je iznosila 25 meseci, odnos hazarda 0,55 (interval poverenja 0,25-1,19), p = 0,12. U grupi bolesnika sa ranim relapsom medijana vremena do progresije bolesti iznosila je 0 meseci u odnosu na grupu bolesnika sa kasnim relapsom kod kojih je medijana vremena do progresije bolesti iznosila 10 meseci, odnos hazarda 0,34 (interval poverenja 0,12–1,00), p = 0,0017. **Zaključak**. Vrednost relapsnog *Age-adjusted International Prognostic Index* skora značajno utiče na ukupno preživljavanje bolesnika sa relapsnim difuznim B-krupnoćelijskim limfomom, dok vreme do prvog relapsa značajno utiče na vreme do progresije bolesti nakon započinjanja druge linije lečenja kod bolesnika sa relapsnim ili refrakternim difuznim B-krupnoćelijskim limfomom.

**Ključne reči:** prognoza; indeksi; difuzni B krupnoćelijski limfom; relaps; preživljavanje bez bolesti; ne-Hočkinov limfom; uzrast

## Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common Non-Hodgkin lymphoma (NHL) and accounts for 30 – 40% of all NHLs [1]. Since 1970, the standard therapeutic option in the treatment of DLBCL has been a chemotherapy regimen with cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP)

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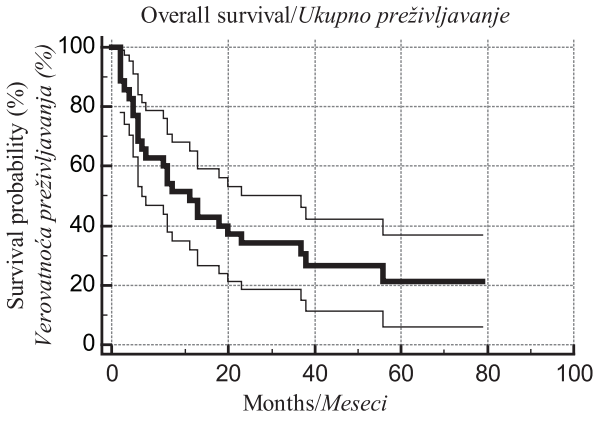
***Abbreviations***

aaIPI – age-adjusted international prognostic index
OS – overall survival
PFS – progression-free survival
DLBCL – diffuse large B-cell lymphoma
HR – hazard ratio
CI – confidence interval
CR – complete response
PR – partial response
SD – stable disease
PD – progressive disease
NHL – Non-Hodgkin lymphoma
CHOP – cyclophosphamide, adriamycin, vincristine, prednisone
R-CHOP – rituximab plus cyclophosphamide, adriamycin, vincristine, prednisone
ASCT – autologous stem cell transplantation
CORAL – Cardiovascular Outcome in Renal Atherosclerotic Lesions
CAR – chimeric antigen receptor
GCB – germinal center B-cell
R-ICE – rituximab, ifosfamide, carboplatin, etopside

which is associated with a 50% complete remission (CR) [2]. The current standard is immunochemotherapy with rituximab plus cyclophosphamide, adriamycin, vincristine, and prednisone (R-CHOP) which is associated with a 60% CR [3]. Even after achieving a CR, 30 – 40% of patients relapse [4]. Among patients who relapse or who are refractory to first-line treatment, 40% are eligible for high-dose chemo with autologous stem cell transplantation (ASCT) [5]. After ASCT, 50% of patients relapse [6] with a median survival of 3 months [7]. The treatment of choice in patients who are not eligible for high-dose chemo with ASCT (60%) [5] is GemOx (gemcitabine-oxaliplatin), bendamustine, gemcitabine, dexamethasone, and cisplatin (GDP), lenalidomide (activated B-cell - non–germinal center B-cell (GCB) and ibrutinib (non-GCB) [8–12].

This research aimed to estimate the overall survival (OS) and progression-free survival (PFS) in patients with relapsed DLBCL. We have also examined the impact of age-adjusted International Prognostic Index (aaIPI) and time to the first relapse on the OS and PFS after the beginning of the second line treatment; the impact of time to disease relapse after the first line of treatment (early or late relapse) on OS, and time to disease progression after the second line of treatment.




**Graph 1.** Overall survival of all patients from the beginning of the second-line treatment
***Grafikon 1.*** *Ukupno preživljavanje u ukupnoj populaciji bolesnika nakon započinjanja druge linije terapije*

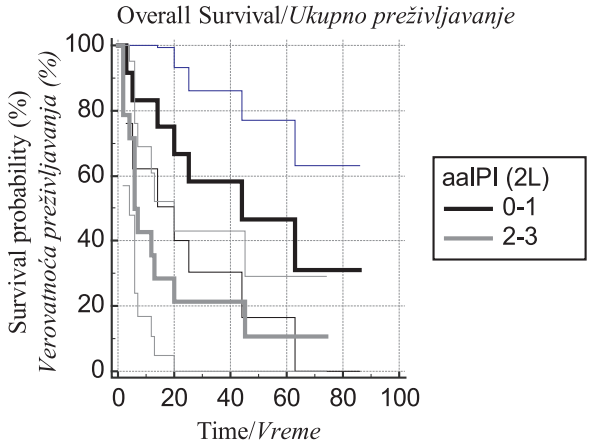
## Material and Methods

The research included patients with relapsed DLBCL who were treated at the Oncology Institute of Vojvodina, Serbia from January 2013 to December 2015. The data were obtained from the medical histories of patients and the following characteristics were analyzed: sex, age at the time of diagnosis, germinal center B-cell (GCB)/non-GCB subtype [14], initial treatment, time of disease relapse (early relapse ≤ 12 months from the end of the first-line treatment, late relapse > 12 months from the end of the first line of treatment). The same parameters were evaluated at the time of the first and the second relapse. The OS was calculated from the time of initiation of the second-line treatment until death or the last follow-up visit. The PFS was calculated from the start of the second-line treatment until disease progression.

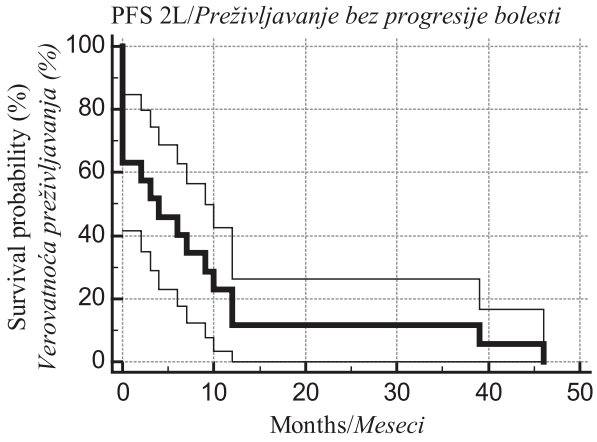
The primary endpoint of our study was to estimate OS and PFS from the initiation of treatment post-relapse using Kaplan–Meier curves. The statistical data analysis was performed by using MedCalc statistical software (version 18.10).

## Results

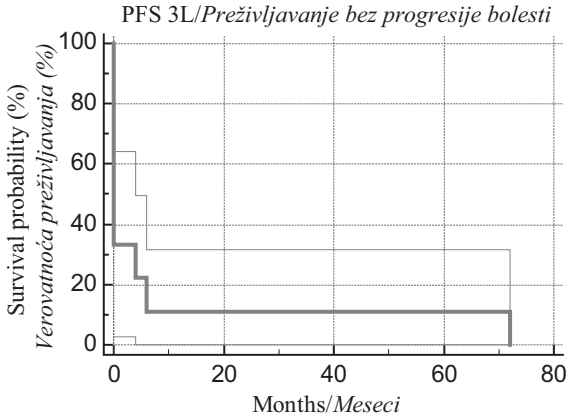
The research included 36 patients, with average age of 56 years, ranging from 22 to 78 years. Sixteen out of 36 (44%) were male, 20 (55%) were female. According to Ann Arbor classification at the time of diagnosis,




**Graph 2.** Median overall survival in patients with aaIPI 0 – 1 (low risk) versus aaIPI 2 – 3 (high risk)
***Grafikon 2.*** *Medijana ukupnog preživljavanja u grupi bolesnika sa Age-adjusted international prognostic index skorom 0-1 (nizak rizik) u odnosu na bolesnike sa skorom 2-3 (visok rizik)*



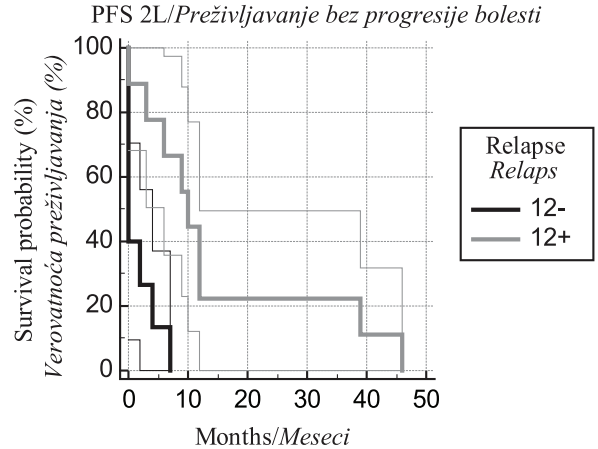

**Graph 3.** Progression free survival in overall patients from the beginning of the second-line treatment
***Grafikon 3.*** *Preživljavanje bez progresije bolesti u ukupnoj populaciji bolesnika nakon započinjanja druge linije terapije*




**Graph 5.** Median time to disease progression in patients who were treated with third-line therapy
***Grafikon 5.*** *Medijana preživljavanja bez progresije bolesti kod pacijenata koji su primali treću terapijsku liniju*

4 patients had stage I (11%), 6 had stage II (16%), 13 had stage III (36%) and 13 stage IV (36%). Thirteen patients had GCB subtype, while 11 had non-GCB. According to aaIPI at the time of initial diagnosis: 13 patients were low risk (0 - 1), while 19 were high risk patients (2 - 3). All patients were treated with R-CHOP regimen in the first line of treatment, 15 (41%) with six cycles, whereas 21 (58%) received eight cycles. After the first line of treatment, 23/36 (33%) had a CR, 18 (50%) had a partial response (PR), 1 (2.7%) patient had a stable disease (SD), while 5 (13.8%) had a progressive disease (PD).

At the time of the first relapse, Ann Arbor stage was available for 33 patients, 6 (18%) had stage I, 7 (21%) had stage II, 7 (21%) had stage III, while 13 (39%) had stage IV. AaIPI score at the time of relapse




**Graph 4.** Median progression free survival in patients with late relapse versus early relapse
***Grafikon 4.*** *Medijana preživljavanja bez progresije bolesti u grupi bolesnika sa kasnim relapsom u odnosu na grupu bolesnika sa ranim relapsom*

was available for 26 patients; 13 were low risk (0 - 1) while the remaining 13 (50%) were high risk patients (2 - 3). Late relapse occurred in 21/36 (58%), while 14 (42%) patients had an early relapse. In the second-line treatment, 12/32 (37.5%) patients were treated with platinum-based regimen, 12 (37.%) with ifosfamide-based regimen, while 8 (25%) patients were treated with one of various CHOP-like regimens. Data on response to treatment were collected for 30 patients: CR and PR were achieved in 9 (30%) and 10 (33%) patients, respectively; SD was not registered in any patient, while PD occurred in 11 (36.6%). Among patients who achieved CR or PR, 3 eventually received ASCT.

Data on Ann Arbor stage were available for 18 patients after the second relapse staged from I to IV: 2 (11.1%), 3 (16.6%), 2 (11.1%) and 11 (61.1%), respectively. AaIPI score was collected for 18 patients with second relapse: 10 (55.5%) were low risk (0 - 1), while 8 (44.5%) were high risk (2 - 3). In the third-line treatment 4 (22%) out of 18 patients were treated with ifosfamide-based regimen, 8 (44.4%) received one of CHOP-like regimens, 3 (16.6%) platinum-based regimen, while 2 (11.1%) received cyclophosphamide, vincristine sulfate, adriamycin, dexamethasone (hyper CVAD). Response to treatment was collected for 16 patients: CR, PR, SD and PD occurred in 6 (37.5%), 1 (6.25%), 1 (6.25%), 8 (50%) patients, respectively.

In overall patients, median OS (5-year follow-up) was 18 months (7 - 44) **(Graph 1).** Median OS in the group of patients with aaIPI 0 - 1 (low risk) was 44 months in comparison to aaIPI 2 - 3 (high risk patients) with median OS 6 months hazard ratio (HR) 0,4 (confidence index (CI) 0,16 - 0,99), p = 0,03 **(Graph 2).** Median OS in early-relapsed patients was 7 months, versus 25 months in late-relapsed patients, HR 0,55 (CI 0,25 - 1,19), p = 0,12.

In overall patients, median PFS was 4 months (0 - 9) **(Graph 3)**. In early-relapse subgroup of patients, median PFS was 0 months, versus 10 months in late-relapse subgroup, HR 0,34 (CI 0,12 - 1,00),

p = 0,0017 **(Graph 4).** Median PFS of patients who were treated with third-line treatment was 0 months (0 - 4) **(Graph 5)**.

## Discussion

Patients with refractory or relapsed DLBCL after first-line treatment are candidates for salvage treatment [15]. The overall response rate to various salvage protocols is 42–64% [16–20]. Patients who achieve a response to salvage therapy receive high dose chemo with ASCT [21]. All our patients were treated with R-CHOP as the first-line regimen. At first relapse, different salvage protocols were used. The median OS from the beginning of salvage treatment was 18 months, while survival at 5 years was 27%, regardless of the salvage protocol used. The (CORAL) study reported 62% of patients treated with R-CHOP protocol. At first relapse, patients were treated with R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) or R-DHAP (rituximab, dexamethasone, cisplatin, cytarabine) and after achieving a response they proceeded to ASCT. The OS at 3 years was 49% [22]. Paul et al. performed a study where all patients were treated with CHOP regimen at first-line and ICE salvage protocol; the OS at 4 years was 34% [23]. Rachel et al. reported 5-year OS (38%) in patients treated with various salvage protocols and eventually ASCT [24]. We observed a significant difference in OS among our patients with low-risk aaIPI 0 - 1 (45%, median OS 44 months) in comparison to patients with high-risk aaIPI 2 - 3 (10% - median OS 6 months). Three-year OS in low-risk patients in CORAL trial was 62%, versus 32% in high-risk patients ($p < .001$) [22]. Another trial also reported a significant difference in 4-year OS in patients with low, intermediate and high risk, (74% v 49% v 18%, respectively) [23]. Rachel at al. reported that median OS in low-risk patients was 27 versus 5 months in high-risk patients ($p < .001$) [24]. According to our data, after a 3-year follow up, PFS was 16%, calculated from the start of the second-line treatment. There was a significant difference in PFS after initiation of the second-line treatment. Three-year PFS in patients with late relapse was 22%, median PFS 10 months, compared to early-relapsed patients with a second relapse in the first months of the second-line treatment (median 0 months). The CORAL trial reported 3-year PFS, post-second-line treatment initiation, to be 37% in overall patient population, and it did not differ in the subpopulation with late relapse. In early-relapse patients, PFS was 23% [22].

Our results are comparable to the data reported by above mentioned authors and confirm the fact that patients with relapsed/refractory DLBCL have a very poor prognosis [22–24]. SCHOLAR-1 trial reported that OS of patients who relapsed in less than 12 months post ASCT, with all treatments available, was 6,3 months [25]. Chimeric antigen receptor (CAR)-T cell therapy proved effective in patients with relapsed/refractory DLBCL [25]. ZUMA trial treated patients with refractory DLBCL with axicabtagene ciloleucel (anti-CD19 CAR T-cell) [26]. The treatment response rate was 82% and CR was achieved in 54% patients. After 15,4 month follow up, 42% of patients still responded to the treatment, while 40% still had CR [26]. In JULIET trial, patients with relapsed/refractory DLBCL were treated with tisagenlecleucel [27]. The overall response rate was 54%, 40% had CR, while 13% had PR. The median duration of response was not achieved after 19 months of follow up [27]. Polatuzumab vedotin (anti-CD79 antibody-drug conjugate) in combination with bendamustine and rituximab vs. bendamustine alone in relapsed/refractory DLBCL patients who were not eligible for ASCT accomplished significantly longer OS and PFS [28]. A CR was achieved in 40% of patients who were treated with polatuzumab vedotin in combination with bendamustine and rituximab in comparison to 13% of patients who were treated with bendamustine and rituximab [28].

## Conclusion

The age-adjusted international prognostic index score calculation significantly influences the overall survival in patients with relapsed/refractory diffuse large B-cell lymphoma. Time to the first relapse significantly impacts the time to disease progression after the second-line treatment initiation in these patients, so this subpopulation warrants novel therapeutic options in the future.

## References

1. Al-Hamadani M, Habermann TM, Cerhan JR, Macon WR, Maurer MJ, Go RS. Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: a longitudinal analysis of the National Cancer Data Base from 1998 to 2011. Am J Hematol. 2015;90(9):790-5.

2. DeVita VT Jr, Canellos GP, Chabner B, Schein P, Hubbard SP, Young RC. Advanced diffuse histiocytic lymphoma, a potentially curable disease. Lancet. 1975;1(7901):248-50.

3. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346(4):235-42.

4. Coiffier B, Thieblemont C, Van Den Neste E, Lepeu G, Plantier I, Castaigne S, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood. 2010;116(12):2040-5.

5. Nowakowski GS, Chiappella A, Witzig TE, Spina M, Gascoyne RD, Zhang L, et al. ROBUST: lenalidomide-R-CHOP versus placebo-R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. Future Oncol. 2016;12(13):1553-63.

6. Hamadani M, Hari PN, Zhang Y, Carreras J, Akpek G, Aljurf MD, et al. Early failure of frontline rituximab-containing

chemo-immunotherapy in diffuse large B cell lymphoma does not predict futility of autologous hematopoetic cell transplantation. Biol Blood Marrow Transplant. 2014;20(11):1729-36.

7. Vose JM, Bierman PJ, Anderson JR, Kessinger A, Pierson J, Nelson J, et al. Progressive disease after high-dose therapy and autologous transplantation for lymphoid malignancy: clinical course and patient follow-up. Blood. 1992;80(8):2142-8.

8. Corazzelli G, Capobianco G, Arcamone M, Ballerini PF, Iannitto E, Russo F, et al. Long term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant ineligible patients with refractory/relapsing B-cell lymphoma. Cancer Chemother Pharmacol. 2009;64(5):907-16.

9. Weidmann E, Kim SZ, Rost A, Schuppert H, Seipelt G, Hoelzer D, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin lymphoma. Ann Oncol. 2002;139(8):1285-9.

10. Crump M, Baetz T, Couban S, Belch A, Marcellus D, Howson-Jan K, et al. Gemcitabine, dexamethasone and cisplatin in patients with recurrent and refractory aggressive histology B-cell non-Hodgkin lymphoma: a phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer. 2004;101(8):1835-42.

11. Wiernik PH, Lossos IS, Tuscano JM, Justice G, Vose JM, Cole CE, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2008;26(30):4952-7.

12. Wilson WH, Young RM, Schmitz R, Yang Y, Pittaluga S, Wright G, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med. 2015;21(8):922-6.

13. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993;329(14):987-94.

14. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000;403(6769):503-11.

15. Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood. 2015;125(1):22-32.

16. Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in rituximab era. J Clin Oncol. 2010;28(27):4184-90.

17. Crump M, Kuruvilla J, Couban S, MacDonald DA, Kukreti V, Kouroukis CT, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014;32(31):3490-6.

18. Kewalramani T, Zelenetz AD, Nimer SD, Portlock C, Straus D, Noy A, et al. Rituximab and ICE as a second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood. 2004;103(10):3684-8.

19. Sieniawski M, Staak O, Glossmann JP, Reineke T, Scheuss H, Diehl V, et al. Rituximab added to an intensified salvage chemotherapy program followed by autologous stem cell transplantation improved the outcome in relapsed and refractory aggressive non-Hodgkin lymphoma. Ann Hematol. 2007;89(2):107-15.

20. Vellenga E, van Putten WL, van 't Veer MB, Zijlstra JM, Fibbe WE, van Oers MH, et al. Rituximab improves the treatment results of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20+ NHL: a prospective randomized HOVON trial. Blood. 2008;111(2):537-43.

21. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995;333(23):1540-5.

22. Hagberg H, Gisselbrecht C; CORAL study group. Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study. Ann Oncol. 2006;17 Suppl 4:iv31-2.

23. Hamlin PA, Zelenetz AD, Kewalramani T, Qin J, Satagopan JM, Verbel D, et al. Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B-cell lymphoma. Blood. 2003;102(6):1989-96.

24. Lerner RE, Thomas W, Defor TE, Weisdorf DJ, Burns LJ. The International Prognostic Index assessed at relapse predicts outcomes of autologous transplantation for diffuse large-cell non-Hodgkin's lymphoma in second complete or partial remission. Biol Blood Marrow Transplant. 2007;13(4):486-92.

25. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-8.

26. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-44.

27. Schuster SJ, Bishop MR, Tam C, Borchmann P, Jaeger U, Waller EK, et al. Sustained disease control for adult patients with relapsed or refractory diffuse large B-cell lymphoma: an updated analysis of Juliet, a global pivotal phase 2 trial of tisagenlecleucel. Blood. 2018;132 Suppl 1:1684.

28. Sehn LH, Herrera AF, Matasar M, Kamdar M, Assouline S, Hertzberg M, et al. Polatuzumab vedotin (pola) plus bendamustine (B) with rituximab (R) or obinutuzumab (G) in relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): updated results of a phase (Ph) Ib/II study. Blood. 2018;132 Suppl 1:1683.

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# PSYCHOTIC SYMPTOMS IN PARKINSON'S DISEASE: ETIOLOGY, PREVALENCE AND TREATMENT

*PSIHOTIČNI SIMPTOMI U PARKINSONOVOJ BOLESTI – ETIOLOGIJA, PREVALENCIJA I TERAPIJA*

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**Summary**

**Introduction.** Parkinson's disease is the second most common neurodegenerative disease with as many as 50 – 70% of patients experiencing psychotic symptoms during the course of the illness. Our aim was to provide an evidence-based review on the etiology, prevalence and management of psychotic symptoms in Parkinson's disease. **Material and Methods.** We used references from the "Medline" database published from 1999 to 2019. **Results.** The most common psychotic symptoms in Parkinson's disease are visual hallucinations, which occur in 25 - 30% of patients, acoustic hallucinations in about 20%, and delusions in around 5% of these patients. The etiology of psychotic symptoms is not fully clarified, but researchers suggest a complex interrelationship of factors associated with the disease itself and the factors associated with antiparkinsonian medications. After exclusion of other etiologic causes of psychotic symptoms, it is necessary to revise the type and dose of antiparkinsonian drugs. Although pimavanserin has recently been approved by the United States Food and Drug Administration, the current treatment of choice for psychotic symptoms in Parkinson's disease is still quetiapine. Only patients who do not tolerate or do not respond to quetiapine are treated with clozapine, which has been proven more effective, but with significant side effects. **Conclusion.** Timely diagnosis and adequate treatment of psychotic symptoms in Parkinson's disease are essential, because they dramatically affect the quality of life of patients and their families. Therefore, it is necessary to establish more effective tools for screening and treatment of psychotic symptoms in Parkinson's disease.

**Key words:** Parkinson Disease; Psychotic Disorders; Hallucinations; Antiparkinson Agents; Drug-Related Side Effects and Adverse Reactions; Risk Factors; Quality of Life

**Sažetak**

**Uvod.** Poznato je da u Parkinsonovoj bolesti, drugoj po učestalosti u grupi neurodegenerativih bolesti, čak 50–70% pacijenata doživljava psihotične simptome. Cilj aktuelnog istraživanja je da obezbedi pregled podataka iz literature koji se odnose na etiologiju, prevalenciju i tretman psihotičnih simptoma u Parkinsonovoj bolesti. **Materijal i metode.** Identifikovali smo reference koristeći bazu podataka *Medline* za period od 1999. do 2019. godine. **Rezultati.** Najčešći psihotični simptomi u Parkinsonovoj bolesti jesu optičke halucinacije koje se javljaju kod 25–30% pacijenata, akustičke halucinacije koje se javljaju kod oko 20% pacijenata i sumanutosti koje se javljaju kod oko 5% pacijenata. Etiologija psihotičnih simptoma nije u potpunosti razjašnjena, ali istraživači ukazuju na kompleksan međusobni odnos faktora povezanih sa samom bolešću i faktora povezanih sa antiparkinsoničnim lekovima. Nakon isključivanja drugih etioloških faktora, kod pojave psihotičnih simptoma u Parkinsonovoj bolesti, potrebno je revidirati doze i vrstu ordiniranih antiparkinsonika. Iako je atipični antipsihotik *pimavanserin* nedavno odobren za lečenje psihotičnih simptoma u Parkinsonovoj bolesti od američke Uprave za hranu i lekove, aktuelni tretman izbora za ovu indikaciju je i dalje antipsihotik *kvetiapin*. Samo kod pacijenata kod kojih postoji problem sa efikasnošću ili tolerabilnošću kvetiapina uvodi se *klozapin*, koji je dokazano efikasniji, ali koji ima i značajne neželjene efekte. **Zaključak**. Pravovremena dijagnoza i adekvatan tretman psihotičnih simptoma u Parkinsonovoj bolesti su neophodni jer dramatično nepovoljno utiču na kvalitet života pacijenata i njihovih porodica. Zbog toga je neophodno uspostaviti efikasnije algoritme za skrining i lečenje psihotičnih simptoma u Parkinsonovoj bolesti.

**Ključne reči:** Parkinsonova bolest; psihotični poremećaji; halucinacije; antiparkinsonici; nuspojave i neželjene reakcije izazvane lekovima; faktori rizika; kvalitet života

## Introduction

Parkinson's disease (PD) is a common neurodegenerative disease diagnosed based on motor impairment. It usually occurs in people older than 65 years, but it is estimated that 5% of patients are diagnosed before the age of 40 years [1, 2]. PD predominantly affects subcortical brain structures and the cerebral cortex is affected during disease progression. The histopathological substrate of this disorder is hypofunction of dopaminergic neurons in substantia nigra, but serotonergic and noradrenergic nerve pathways are also affected [3].

In addition to the primary motor symptoms, there are non-motor symptoms that have been recognized as a possible complication of long-term treatment, but often remain unrecognized and untreated [4, 5]. Psychiatric symptoms of PD, such as psychosis, mood

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***Abbreviations***
PD – Parkinson's disease

disorders, dementia and anxiety lead to further disability and may have a greater impact on the quality of life than motor symptoms. Risk factors for psychosis in PD include duration of illness, presence of dementia, sensory impairments or insomnia, use of dopamine agonists, and perhaps the angiotensin converting enzyme of dopamine transporter genes [6].

## Material and Methods

The aim of this study was to examine the etiology, prevalence and treatment strategies for psychotic symptoms in PD. References were identified using "Medline" database in the period between 1999 and 2019. Classification of studies, in relation to their quality, was performed using the guideline for levels of evidence established by the American Academy of Neurology.

## Results

It has been found that psychotic symptoms occur in less than 10% of PD patients who do not use antiparkinsonian agents [7–10]. However, psychotic symptoms can occur in as many as 15 to 40% of patients using antiparkinsonian drugs [11–13].

There are specific risk factors for the occurrence of psychotic symptoms in PD patients which include exposure to antiparkinsonian drugs, older age, executive functions disorders, comorbid diagnosis of dementia, severity and duration of the disease, comorbid depression, visual disturbances, polypharmacotherapy and hereditary predisposition to psychiatric disorders [14–19].

There are criteria for diagnosis of psychosis in PD [20]: 1. occurrence of at least one of the symptoms: hallucinations, illusions, delusions; 2. occurrence of psychotic symptoms after the onset of PD; 3. the symptoms are recurrent or persist for at least four weeks; 4. exclusion of psychiatric disorders and other medical conditions as possible causes of psychotic symptoms.

Psychotic symptoms may lead to disability and cause a significant problem for patients and their families [21, 22]. These symptoms usually occur after more than 10 years of antiparkinsonian treatment. It is estimated that patients with PD, in contrast to individuals with schizophrenia, usually have insight into their psychotic symptoms [14–16].

The most common psychotic symptoms are visual hallucinations, occurring in one-quarter to one-third of all patients with PD. Auditory hallucinations occur in approximately 20%, while delusions occur in 5% of patients [23, 24]. Visual hallucinations in PD are usually complex, well-established and most often imply human beings or animals. They are often recurrent and stereotype, occurring in dark or dim light in the evening. Unlike hallucinations in schizophrenia, hallucinations in PD are without emotional content [25]. In addition to visual and auditory, there are so-called "minor" hallucinations where the patient feels someone's presence or sees somebody passing through his peripheral visual field. There is also "selective diplopia" as a specific type of hallucination [26].

Isolated delusions rarely exist in PD, however, it is estimated that 10% of patients experience delusions in addition to hallucinations [27]. One of the most common delusions is partner's infidelity. Additionally, literature describes "Capgras syndrome" - experiencing that acquaintances are replaced by similar persons, "Fragola syndrome" - experiencing that acquaintances are disguised as strangers and "reduplicative paramnesia" when patients have the impression of duplicated place or location [28].

The etiology of psychotic symptoms in PD is not fully clarified, but researchers suggest a complex interaction of factors associated with the disease itself and factors associated with antiparkinsonian drugs [14]. It has been proven that all classes of antiparkinsonian drugs (dopamine receptor agonists, N-methyl D-aspartate (NMDA) receptor antagonists, levodopa, monoamine oxidase B inhibitors of catechol-O-methyltransferase and antimuscarinic drugs) may induce psychotic symptoms [15]. There is a classification of antiparkinsonian drugs in terms of their potency to cause psychotic symptoms and some controlled studies support these claims. Levodopa and dopamine agonists, two drugs of first choice for the treatment of motor symptoms of PD are also associated with the appearance of psychotic symptoms. Controlled studies show that psychotic symptoms are more likely to occur during the use of dopamine agonists than during the use of levodopa [29, 30]. Levodopa, as the drug which has the lowest potency to induce psychotic symptoms, should be used in patients with PD and suffering from psychosis [31, 32]. Dopaminergic drugs lead to excessive stimulation or hypersensitivity of mesolimbic D2 and D3 receptors and may induce psychosis. Serotonergic and dopaminergic system imbalance is also associated with the onset of psychosis in PD [33].

In addition to the effects of dose and duration of the drug treatment, there is a strong interaction between antiparkinsonian medications themselves and comorbid vulnerability for the development of psychotic symptoms such as cognitive deficits and visual disturbances. Risk factors for the development of psychotic symptoms in PD include primary deficits of processing visual information (reduced visual acuity deficit in recognizing colors and contrast, optic nerve damage and functional abnormalities of the brain). There are additional factors, such as sleep disturbances, structural brain abnormalities and genetic factors that may contribute to the occurrence of psychotic symptoms in PD [14]. It is necessary to rule out other possible causes of psychotic symptoms in PD, including infection, intoxication, endocrine disorders, acute metabolic imbalance and certain medications, before starting the treatment [34, 35].

The first step in the treatment of psychotic symptoms is dose reduction or withdrawal of benzodiazepines and tricyclic antidepressants. The next step

is to reduce the dose of antiparkinsonian drugs with respect to their potency for inducing psychotic symptoms. This sequence implies anticholinergics first, then amantadine, dopaminergic agonists, monoamine oxidase-B (MAO-B), catechol O-methyltransferase (COMT) and eventually levodopa. However, these interventions may lead to motor symptoms worsening, so the main aim is to achieve an optimal balance between motor and psychotic symptoms of PD [2]. The treatment of psychotic symptoms in PD is challenging, because the treatment of motor symptoms leads to exacerbation of psychotic symptoms, and the treatment of psychotic symptoms leads to worsening of motor symptoms [35].

When it is necessary the introduce antipsychotics, professionals should avoid classical antipsychotics such as haloperidol due to increased risk of extrapyramidal side-effects causing worsening of motor symptoms [18]. It is important to point out that extrapyramidal syndrome induced by conventional antipsychotics withdraws after 4 to 16 weeks after the discontinuation of antipsychotic therapy [36]. That is the main reason for introduction of atypical antipsychotics from the beginning.

The course of psychosis in PD is not sufficiently explored and there is no empirical evidence about the duration of psychosis treatment. One study showed that psychotic relapses occurred in 83% of fully recovered patients after a gradual withdrawal of antipsychotic drugs [36].

According to literature and clinical experience, the current treatment of choice for psychotic symptoms in PD is still quetiapine - 25 to 300 mg per day, with an average maintenance dose of 75 mg. It is known that quetiapine is well tolerated, safe and effective. However, quetiapine has not shown efficacy better than placebo in two placebo-controlled trials [37, 38]. While clozapine has proven the most effective, its introduction is recommended only for patients who do not tolerate or do not respond to quetiapine, due to considerable side effects [35]. Three adequately designed, placebo controlled trials in which low dose clozapine was used in PD showed a reduction of psychotic symptoms, without motor-symptoms worsening [31, 38, 39]. There is some evidence justifying the introduction of olanzapine and risperidone as well, but more pronounced extrapyramidal side effects can be expected, in comparison with quetiapine. Another study showed that both olanzapine and clozapine significantly reduced psychotic symptoms and did not lead to worsening of motor symptoms [40]. However, two placebo-controlled trials did not identify differences in efficiency between olanzapine and placebo. In addition, olanzapine is associated with a significant worsening of motor symptoms [41, 42]. One interesting study showed risperidone as more effective in reducing psychotic symptoms than clozapine, without motor side effects [43]. Recent meta-analysis of trials on treatment of psychotic symptoms in PD concluded that only clozapine can be fully recommended [44]. We have to point out that pimavanserin, 5-hydroxytryptamine receptor serotonin 2A inverse agonist was recently approved by the United States Food and Drug Administration for the treatment of PD psychosis and may prove to be a more targeted therapy without the downsides of atypical antipsychotics [45, 46].

## Conclusion

New definitions and medications have raised the research interest and led to expansion of the literature concerning psychosis in patients with Parkinson's disease, with the main interests being the etiology and treatment. Timely diagnosis and adequate treatment of psychotic symptoms is essential, because these symptoms dramatically affect the quality of life of the patients and their families. It is known that patients often do not report psychotic symptoms spontaneously to their clinicians. Therefore, it is necessary to establish more effective instruments for screening and treatment strategies for psychotic symptoms in Parkinson's disease, taking into account the importance of this phenomenon.

## References

1. Kehagia AA. Neuropsychiatric symptoms in Parkinson's disease: beyond complications. Front Psychiatry. 2016;7:110.

2. Latoo J, Mistry M, Dunne FJ. Diagnosis and management of psychosis in Parkinson's disease. Prog Neurol Psychiatry. 2012;16(5):7-10.

3. Mitchell AJ. Neuropsychiatry and behavioral neurology explained. London: Saunders; 2004.

4. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30(12):1591-601.

5. Hermanowitcz N, Edwards K. Parkinson's disease psychosis: symptoms, management, and economic burden. Am J Manag Care. 2015;21(10 Suppl):5199-206.

6. Factor SA, Steenland NK, Higgins DS, Molho ES, Kay DM, Montimurro J, et al. Disease-related and genetic correlates of psychotic symptoms in Parkinson's disease. Mov Disord. 2011;26(12):2190-5.

7. Fenelon G, Goetz CG, Karenberg A. Hallucinations in Parkinson disease in the prelevodopa era. Neurology. 2006;66(1):93-8.

8. Cummings JL. Neuropsychiatric complications of drug treatment in Parkinson's disease. In: Huber SJ, Cummings JL. Parkinson's disease: neurobehavioral aspects. New York: Oxford University Press; 1992. p. 313-27.

9. Baldwin RC, Byrne EJ. Psychiatric aspects of Parkinson's disease. BMJ. 1989;299(6690):3-4.

10. Lang AE, Blair RD. Parkinson's disease in 1984: an update. Can Med Assoc J. 1984;131(9):1031-7.

11. Aarsland D, Bronnick K, Ehrt U, De Deyn PP, Tekin S, Emre M, et al. Neuropsychiatric symptoms in patients with Parkinson's disease and dementia: frequency, profile and associated care giver stress. J Neurol Neurosurg Psychiatry. 2007;78(1):36-42.

12. Barnes J, David AS. Visual hallucinations in Parkinson's disease: a review and phenomenological survey. J Neurol Neurosurg Psychiatry. 2001;70(6):727-33.

13. Slawek J. Levodopa in the treatment of Parkinson disease - yesterday and today. Neurol Neurochir Pol. 2012;46(1):63-75.

14. Zahodne LB, Fernandez HH. Pathophysiology and treatment of psychosis in Parkinson's disease: a review. Drugs Aging. 2008;25(8):665-82.

15. Papapetropoulos S, Mash DC. Psychotic symptoms in Parkinson's disease. From description to etiology. J Neurol. 2005;252(7):753-64.

16. Lang G. Psychosis in Parkinson's disease: phenomenology, frequency, risk factors and current understanding of pathophysiologic mechanisms. CNS Spectr. 2008;13(3 Suppl 4):18-25.

17. Marsh L, Williams JR, Rocco M, Grill S, Munro C, Dawson TM. Psychiatric comorbidities in patients with Parkinson disease and psychosis. Neurology. 2004;63(2):293-300.

18. Henderson MJ, Mellers JDC. Psychosis in Parkinson's disease: 'between a rock and a hard place'. Int Rev Psychiatry. 2000;12(4):319-34.

19. Pacchetti C, Manni R, Zangaglia R, Mancini F, Marchioni E, Tassorelli C, et al. Relationship between hallucinations, delusions, and rapid eye movement sleep behavior disorder in Parkinson's disease. Mov Disord. 2005;20(11):439-48.

20. Ravina B, Marder K, Fernandez HH, Friedman JH, McDonald W, Murphy D, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. Mov Disord. 2007;22(8):1061-8.

21. Fuchs GA. Psychoses in idiopathic Parkinson's disease - risk factors in the course of disease. Psychoneuro. 2008;34(8)361-6.

22. Forsaa EB, Larsen JP, Wentzel-Larsen T, Goetz CG, Stebbins GT, Aarsland D, et al. A 12-year population-based study of psychosis in Parkinson disease. Arch Neurol. 2010;67(8):996-1001.

23. Fenelon G, Alves G. Epidemiology of psychosis in Parkinson disease. J Neurol Sci. 2010;289(1-2):12-7.

24. Chou Kl, Messing S, Oakes D, Feldman PD, Breier A, FriedmanJH. Drug-induced psychosis in Parkinson disease: phenomenology and correlations among psychosis rating instruments. Clin Neuropharmacol. 2005;28(5):215-9.

25. Beaulieu-Boire I, Lang AE. Behavioral effects of levodopa. Mov Disord. 2015;30(1):90-102.

26. Nebe A, Ebersbach G. Selective diplopia in Parkinson's disease: a special subtype of visual hallucination? Mov Disord. 2007;22(8):1175-8.

27. Moro A, Munhoz RP, Moscovich M, Arruda WO, Teive HA. Delusional misidentification syndrome and other unusual delusions in advanced Parkinson's disease. Parkinsonism Relat Disord. 2013;19(8):751-4.

28. Stewart JT. Fregoli syndrome associated with levodopa treatment. Mov Disord. 2008;23(2):308-9.

29. Weintraub D, Morales KH, Duda JE, Moberg PJ, Stern MB. Frequency and correlates of co-morbid psychosis and depression in Parkinson's disease. Parkinsonism Relat Disord. 2006;12(7):427-31.

30. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. JAMA. 2000;284(15):1931-8.

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BIBLID.0025-8105:(2019):LXXII:1-2:30-33.

31. Ecker D, Unrath A, Kassubek J, Sabolek M. Dopamine agonists and their risk to induce psychotic episodes in Parkinson's disease: a case-control study. BMC Neurol. 2009;9:23.

32. Holroyd S, Currie L, Wooten GF. Prospective study of hallucinations and delusions in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2001;70(6):734-8.

33. Wolters EC. Dopaminomimetic psychosis in Parkinson's disease patients: diagnosis and treatment. Neurology. 1999;52(7 Suppl 3):S10-3.

34. Thomsen TR, Panisset M, Suchowersky O, Goodridge A, Mendis T, Lang AE. Impact of standard of care for psychosis in Parkinson disease. J Neurol Neurosurg Psychiatry. 2008;79(12):1413-5.

35. Weintraub D, Hurtig HI. Presentation and management of psychosis in Parkinson's disease and dementia with Lewy bodies. Am J Psychiatry. 2007;164(10):1491-8.

36. Jesic MP, Jesic A, Filipovic JB, Zivanovic O. Extrapyramidal syndromes caused by antipsychotics. Med Pregl. 2012;65(11-12):521-6.

37. Ondo WG, Tintner R, Voung KD, Lai D, Ringholz G. Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. Mov Disord. 2005;20(8):958-63.

38. Rabey JM, Prokhorov T, Miniovitz A, Dobronevsky E, Klein C. Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration. Mov Disord. 2007;22(3):313-8.

39. The French Clozapine Parkinson Study Group. Clozapine in drug-induced psychosis in Parkinson's disease. Lancet. 1999;353(9169):2041-2.

40. Morgante L, Epifanio A, Spina E, Zappia M, Di Rosa AE, Marconi R, et al. Quetiapine and clozapine in Parkinsonian patients with dopaminergic psychosis. Clin Neuropharmacol. 2004;27 (4):153-6.

41. Breier A, Sutton VK, Feldman PD, Kadam DL, Ferchland I, Wright P, et al. Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease. Biol Psychiatry. 2002;52(5):438-45.

42. Ondo WG, Levy JK, Vuong KD, Hunter C, Jankovic J. Olanzapine treatment for dopaminergic-induced hallucinations. Mov Disord. 2002;17(5):1031-5.

43. Ellis T, Cudkowicz ME, Sexton PM, Growdon JH. Clozapine and risperidone treatment of psychosis in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 2000;12(3):364-9.

44. Frieling H, Hillemacher T, Ziegenbein M, Neundörfer B, Bleich S. Treating dopamimetic psychosis in Parkinson's disease: structured review and meta-analysis. Eur Neuropsychopharmacol. 2007;17(3):165-71.

45. Samudra N, Patel N, Womack KB, Khemani P, Chitnis S. Psychosis in Parkinson disease: a review of etiology, phenomenology and management. Drugs Aging. 2016;33(12):855-63.

46. Black KJ. Treatment of Parkinson's disease psychosis. Med Int Rev. 2017; 27(109):266-71.

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# EVALUATION OF THE AGE AT ORCHIOPEXY

*PROCENA UZRASTA U KOM SE IZVODI ORHIDOPEKSIJA*

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**Summary**

**Introduction**. Undescended testis is the most common congenital anomaly of the male urogenital tract. The main issues associated with this condition are decreased fertility and an increased risk for testicular cancer, which are minimized if early orchiopexy is performed. The objective of this study is to evaluate the age at orchiopexy at the Institute of Child and Youth Health Care of Vojvodina and to compare it to international guidelines (American Urological Association, Canadian Urological Association and European Association of Urology). **Material and Methods.** A retrospective study included 457 patients operated on between 2010 and 2015. The recorded data were analyzed by Microsoft Excel Office 365 using means, medians, minimums, maximums and standard deviations where appropriate. The patient age and current recommendations for timing of orchiopexy were analyzed as well. **Results.** The mean age at orchiopexy was 69.47 months, and the median age was 64 months. Considering each year separately, no significant differences between mean and median age at orchiopexy were found. The percentage of orchiopexies performed before 24 months was 29% and 5% were performed before 12 months of age. The mean age at orchiopexy was 51.47 months later than recommended by current international guidelines. **Conclusion.** This study confirmed that the age at orchiopexy in our sample was significantly delayed than recommended. It is necessary for all medical practitioners involved in child health care to share new information, trends and diagnostic-therapeutic algorithms about undescended testis and consequences of late treatment.

**Key words:** Orchiopexy; Cryptorchidism; Infant; Child, Preschool; Age Factors; Early Diagnosis; Time-to-Treatment; Physician's Role; Practice Guideline

**Sažetak**

**Uvod.** Nespušteni testis je najčešća kongenitalna anomalija urogenitalnog trakta kod dečaka. Najznačajniji problemi koji se dovode u vezu sa ovim stanjem su poremećaji fertiliteta i povišen rizik obolevanja od karcinoma testisa, a čija pojava se značajno umanjuje izvođenjem orhidopeksije u ranom uzrastu. Cilj studije bio je utvrditi uzrast u kom se izvodi orhidopeksija na Institutu za zdravstvenu zaštitu dece i omladine Vojvodine, kao i uporediti ove rezultate sa međunarodnim preporukama (Američko, Kanadsko i Evropsko udruženje urologa). **Materijal i metode.** U retrospektivnu studiju uključeno je 457 pacijenata operisanih (orhidopeksija) od 2010. do 2015. godine. Prikupljeni podaci analizirani su pomoću programa *Microsoft Excel Office 365*, a predstavljeni kao prosečne vrednosti uzrasta, medijane, najniže i najviše vrednosti, kao i standardne devijacije. Vršeno je i poređenje dobijenih vrednosti sa najnovijim preporukama za pravovremeno operativno lečenje nespuštenih testisa. **Rezultati.** Prosečni uzrast u trenutku operacije iznosio je 69,47 meseci (medijana 64 meseca). Vrednosti ovih parametara nisu se značajno razlikovale u godinama posmatranja. Kod 29% dece orhidopeksija je urađena tokom prvih 24 meseca života, a u toku prvih 12 meseci kod 5% pacijenata. U poređenju sa aktuelnim preporukama, operisana deca su bila u proseku 51,47 meseci starija od preporučenog uzrasta. **Zaključak.** Rezultati studije ukazuju da se orhidopeksija izvodi u značajno kasnijem uzrastu u odnosu na najnovije preporuke. Neophodno je da svi zdravstveni radnici uključeni u rad sa decom budu u toku sa najnovijim saznanjima, trendovima i dijagnostičko-terapijskim algoritmima u lečenju nespuštenog testisa, odnosno sa posledicama kasnog terapijskog tretmana.

**Ključne reči:** orhidopeksija; nespušteni testis; odojče; predškolsko dete; uzrast; rana dijagnoza; vreme do lečenja; uloga lekara; preporuke

## Introduction

Undescended testis occurs in 1 – 4% of full-term and in 1 – 45% of premature infants. It is the most common congenital anomaly affecting the male urogenital tract.

This condition negatively affects the development of the testis [1–3]. The main issues associated with undescended testis are decreased fertility and an increased risk for developing testicular cancer. This is due to the body's core temperature, which is not optimal for further development and functioning of the testis, whose optimal temperature is 33 degrees Celsius, such as in the normal scrotal position [2, 4].

The undescended testis has a normal histological structure at birth. This means that germ cells are the prominent cells in the seminiferous tubules (testicular parenchyma). In the undescended testis, Sertoli and

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***Abbreviations***

AUA – American Urological Association
CUA – Canadian Urological Association
EAU – European Association of Urology
SD – standard deviation

Leydig cells are not affected by increased temperature, whereas germ cells progressively decline. That is why the histological structure shows an apparent increase in the number of Leydig cells. There is also thickening of the basement membrane. By two years of age, 40% of undescended testes completely lose their germ cells [2, 5, 6].

Screening for undescended testis is done at every routine well child visit, when the finding is recorded in the medical history, and by physical examination. In medical history it is important to emphasize the corrected age and positive family history of an undescended testis. The corrected gestational age gives a more accurate representation of the developmental stage of a preterm infant than the actual age. It is calculated by subtracting the number of weeks of prematurity from the actual age.

Standard physical examination is done in supine and upright positions. For neonates and infants, physical examination is completed in a supine frog-legged position (**Figure 1**). It must be performed at comfortable room temperature and with warm hands to minimise cremasteric reflex activation [3, 5].

During physical examination, a fine distinction must be made between a true undescended testis and a retractile testis. A true undescended testis either cannot be manually positioned into the scrotum, or if it is positioned into the scrotum it immediately retracts. Retractile undescended testis can be manually placed into the scrotum and stays in the scrotum for some time before retracting again [3]. Our professionals informally call a true undescended or gliding testis retractile, whereas retractile testes are referred to as migrating testes. In everyday professional communication this can be a confusing and serious problem.

A true undescended testis has never been visualized in the scrotum by the physician or parents. On the other hand, retractile testis was present in the scrotum at birth and parents report seeing the testicle in the scrotum periodically [3].

Retractile testis is considered as a normal variant, where the cause for retraction is an overactive cremasteric muscle. These patients require close follow-up. The majority of retractile testes reside in the normal scrotal position after puberty. This is due to higher concentrations of androgens which diminish the cremasteric reflex. On the other hand, a minority of them progress to so-called acquired or ascended testes which require surgical treatment by orchiopexy [3].

If the testis does not spontaneously descend before six months of (corrected) age, the patient must be immediately referred to a pediatric urologist or pediatric surgeon. The decision is based solely on the medical history and physical examination [3].

During the last years, many researchers have done a great work summarizing new knowledge about this subject. In order to minimize the risk of suboptimal fertility and increased risk for testicular cancer, the American Urological Association (AUA) recommends orchiopexy between 6 and 16 months of age, the Canadian Urological Association (CUA) between 6 and 12 months, and the European Association of Urology (EAU) between 12 and 18 months of age [1, 2, 7].

An undescended testis is usually treated by open or laparoscopic orchiopexy, with a one- or two-stage Fowler-Stephens procedure. Hormonal therapy is very rarely used for acquired undescended testis [3, 5, 8, 9].

The purpose of this retrospective study is to evaluate the average age at orchiopexy at the Institute of Child and Youth Health Care of Vojvodina and to make a comparison with current international guidelines.

## Material and Methods

This retrospective review was performed after obtaining permission from the institutional Ethics Committee. Data were analyzed for 457 patients that were hospitalized for an undescended testis. These patients underwent exploration and subsequent orchiopexy between January 2010 and December 2015 at the Clinic of Pediatric Surgery of our Institute.

The data were analyzed by Microsoft Excel Office 365 for: mean, median, minimum and maxi-

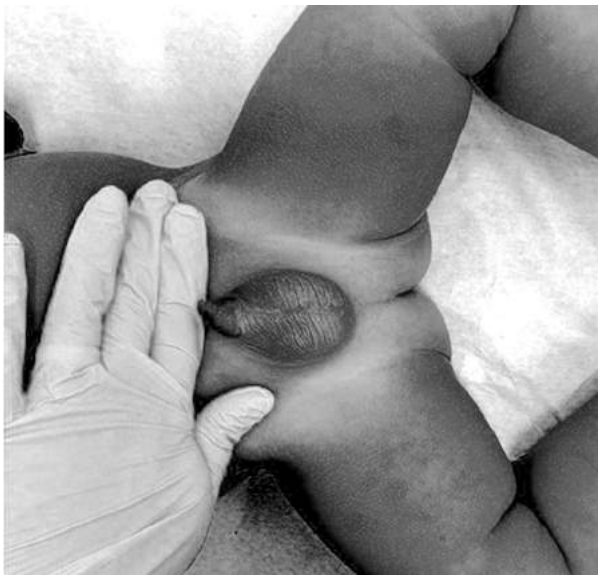


**Figure 1.** Proper testicular examination in the supine, frog-legged position
***Slika 1.*** *Pravilan način pregleda testisa u ležećem, žabljem položaju deteta*

**Table 1.** Mean, median, minimum and maximum age at orchiopexy (months) and SD for surgeries performed between January 2010 and December 2015
***Tabela 1.*** *Prosečne vrednosti, medijana, najmanje i najviše vrednosti, kao i standardne devijacije (SD) uzrasta (izražene u mesecima) dece operisane od januara 2010. do decembra 2015. u trenutku izvođenja orhidopeksije.*

| N<br>*Broj* | Missing data<br>*Nedostaju podaci* | Mean<br>*Srednja* | Median<br>*Medijana* | Minimum Age<br>*Najmlađi* | Maximum Age<br>*Najstariji* | SD/*SD* |
|---|---|---|---|---|---|---|
| 457 | 2 | 69.47 | 64 | 8 | 332 | 49.23 |

**Table 2**. Mean, median, minimum and maximum age at orchiopexy (months) and SD by year of surgery from January 2010 to December 2015
***Tabela 2.*** *Prosečne vrednosti, medijana, najmanje i najviše vrednosti, kao i standardne devijacije (SD) uzrasta (izražene u mesecima) dece operisane od januara 2010. do decembra 2015. u trenutku izvođenja orhidopeksije, prikazane po godinama posmatranja.*

| Year<br>*Godina* | N<br>*Broj* | Missing data<br>*Nedostaju podaci* | Mean<br>*Srednja* | Median<br>*Medijana* | Minimum Age<br>*Najmlađi* | Maximum Age<br>*Najstariji* | SD/*SD* |
|---|---|---|---|---|---|---|---|
| 2010 | 81 | 0 | 63.58 | 50 | 8 | 332 | 51.29 |
| 2011 | 80 | 1 | 72.01 | 67 | 9 | 186 | 51.25 |
| 2012 | 73 | 0 | 68.86 | 66 | 10 | 219 | 45.63 |
| 2013 | 94 | 1 | 68.63 | 54 | 8 | 197 | 50.74 |
| 2014 | 67 | 0 | 71.31 | 79 | 12 | 172 | 46.68 |
| 2015 | 62 | 0 | 73.94 | 67 | 12 | 186 | 49.56 |

mum ages at orchiopexy; standard deviation (SD); mean and median ages at orchiopexy by year of operation individually; number and percentage of orchiopexies performed on patients younger than 24 months (as recommended by the AUA, CUA and EAU) and younger than 12 months (as recommended by the CUA and AUA).

## Results

A total of 457 patients were included in this study. Data for 2 patients was incomplete. For patients who underwent surgery between 2010 and 2015, the mean age at orchiopexy was 69.47 months, and the median age was 64 months (SD+/- 49.23 months, range 8 – 332 months) **(Table 1)**. Considering each year separately, no significant difference was found between mean and median age at orchiopexy **(Table 2)**.

The results in **Table 3** show that 124 (29%) orchiopexies were performed in patients younger than 24 months. Considering each year individually, no significant difference was found. The results in **Table 4** show that only 29 (5%) orchiopexies were performed in patients younger than 12 months.

Finally, the results in **Graph 1** represent the age (months) at which orchiopexy was performed at our institution and comparison with the recommended timing for orchiopexy by the CUA, AUA and EAU. The mean age at orchiopexy was 51.47 months later than recommended by current international guidelines.

## Discussion

The optimal time for surgical treatment of an undescended testis has been debated for decades. It was speculated that earlier orchiopexy would lead to better fertility, and recommended age at orchiopexy has steadily declined. In the 1950's, the age at orchiopexy was 10 – 15 years, in the 1970's it was 5 – 6 years, in the late 1970's and early 1980's it declined to 2 years of age. Current consensus for the optimal age for performing orchiopexy is between 12 and 18

**Table 3.** Orchiopexies performed before 24 months of age
***Tabela 3.*** *Orhidopeksije koje su izvedene tokom prva 24 meseca života deteta.*

| Year/*Godina* | Patients < 24 months/*Pacijenti < 24 meseci* | N/*Broj* | Percentage/*Procenat* |
|---|---|---|---|
| 2010 | 23 | 81 | 28.40% |
| 2011 | 23 | 79 | 29.11% |
| 2012 | 17 | 73 | 23.29% |
| 2013 | 27 | 93 | 29.03% |
| 2014 | 16 | 67 | 23.88% |
| 2015 | 18 | 62 | 29.03% |
| January 2010 to December 2015<br>*Januar 2010 do decembar 2015.* | 124 | 455 | 29.00% |

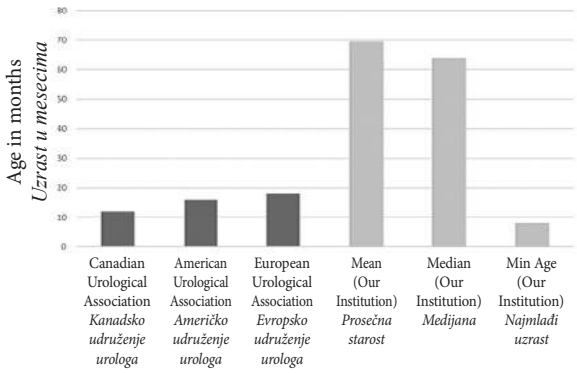
**Table 4.** Orchiopexies performed before 12 months of age
***Tabela 4.*** *Orhidopeksije koje su izvedene tokom prvih 12 meseca života deteta*

| Year/*Godina* | Patients < 12 months/*Pacijenti < 12 meseci* | All patients/*Svi pacijenti* | Percentage/*Procenat* |
|---|---|---|---|
| 2010 | 5 | 81 | 6.17% |
| 2011 | 7 | 79 | 8.68% |
| 2012 | 7 | 73 | 9.59% |
| 2013 | 6 | 93 | 6.45% |
| 2014 | 1 | 67 | 1.49% |
| 2015 | 3 | 62 | 4.84% |
| January 2010 to December 2015/*Januar 2010 do Decembar 2015.* | 29 | 455 | 5.00% |

months [11–13]. Guidelines from AUA, CUA and EAU were considered in our study [3, 5, 7, 10].

Our sample consisted of 455 patients operated on between 2010 and 2015. The mean age at orchiopexy was 69.47 months, and the median age was 64 months. Our results indicate that the mean age at orchiopexy was 51.47 months and the median age was 32 months later than recommended. These results are not unusual, because the other authors found a similar gap between the current guidelines and clinical practice. Williams et al. (2018) found that the median age at orchiopexy in some United States hospitals (New Jersey, Maryland and Florida) was between 48 and 60 months. A number of papers published worldwide have observed the average age at orchiopexy between 19 and 61 months, which almost corresponded with our findings [7, 13, 14].

Our sample has shown that 124 patients (29%) underwent orchiopexy before 24 months of age and only 29 patients (5%) before 12 months. Again, our




**Graph 1.** Maximum recommended age at orchiopexy (months) by the CUA, AUA and EAU. Mean, median, minimum age at orchiopexy (months) for surgeries performed between January 2010 and December 2015
***Grafikon 1.*** *Najstariji preporučeni uzrast za izvođenje orhidopeksije (izražen u mesecima) prema preporukama Kanadskog, Američkog i Evropskog udruženja urologa. Prosečna starost, medijana i najmlađi uzrast u kom se izvodi orhidopeksija (izražen u mesecima) kod dece operisane između januara 2010. i decembra 2015.*

results reflect those found in the literature. Williams et al. reported that between 1999 and 2008, 43% of patients were operated on before 24 months. They also reported that in an institution in West Virginia, 21% and 30% of patients were operated on before 12 months and 24 months, respectively [7].

We found no significant age difference at orchiopexy when we considered each year separately. We also analyzed the percentage of orchiopexies performed before 24 months of age and 12 months of age for each year individually, and found no statistically significant difference. These results are very similar with the previous study performed in our institution which covered the period from 2007 to 2014 [14].

Finally, we compared our results with the mean age at orchiopexy recommended by the leading world associations. We found that the mean age at which orchiopexy was performed was 69.47 months, and median age was 64. This shows that the age at orchiopexy is later than recommended by the leading urologic associations.

The possible reason for the discrepancy between current guidelines and clinical practice is inadequate triage, as suggested by Romao [15]. He recommends pediatric urologists to educate family physicians and pediatricians in order to improve their skills in physical examination and referral practice. Physical examination of testes can be particularly challenging due to the natural anxiety of the child during such an examination. It must be performed at every well-child visit as recommended by Mau [3].

Current pediatric urology referral guidelines recommend urologists to perform physical examinations in cases with a presumed undescended testis, without ordering additional tests. However, some primary care physicians still order additional tests before referral to pediatric urologists and this results in a delayed diagnosis and treatment [3, 15].

Another possible reason to explain the discrepancy between the current guidelines and practice is the lack of conviction concerning the recent guidelines. As Niedzielski has remarked, the age at orchiopexy has declined steadily in the last decades [11]. Since general practitioners have a lot of guidelines to follow, some of them are not informed about new recommendations about the age at which orchiopexy should be performed

[11]. Romao recommends that pediatric urologists should update primary care physicians about changes in the guidelines. Primary care physicians and pediatricians are the ones that have the first contact with the patient and refer them to the urologists and pediatric surgeons [15].

The confusion about the timing of testicular descent as well as the causes may also contribute to delayed referral to a pediatric urologist. The timing of testicular descent has been debated for years and this is reflected in the changes in guidelines that followed new discoveries every few years. However, some primary care physicians still believe that an undescended testis can spontaneously descend after six months of age. They persistently wait for the testicle to descend after six months [3, 11].

## Conclusion

This study confirmed that in our sample the age at orchiopexy was significantly delayed than recommended by the leading world pediatric urology associations. It is necessary for all medical practitioners involved in the care of children to share new information, trends and diagnostic-therapeutic algorithms about undescended testis and consequences of late treatment.

## References

1. Barthold JS, Gonzalez R. The epidemiology of congenital cryptorchidism, testicular ascent and orchiopexy. J Urol. 2003;170(6 Pt 1):2396-401.

2. Epstein JI. The lower urinary tract and male genital system. In: Kumar V, Abbas AK, Fausto N, Aster JC, editors. Robbins and Cotran pathological basis of disease. 8th ed. Philadelphia, PA: Sauders Elsevier; 2010. p. 984-85.

3. Mau EE, Leonard MP. Practical approach to evaluating testicular status in infants and children. Can Fam Physician. 2017;63(6):432-5.

4. Hrivatakis G, Astfalk W, Schmidt A, Hartwig A, Kugler T, Heim T, et al. The timing of surgery for undescended testis. Dtsch Aeztebl Int. 2014;111(39):649-57.

5. Braga LH, Lorenzo AJ. Cryptorchidism: a practical review for all community health care providers. Can Urol Assoc. 2017;11(1-2 Suppl 1):S26-32.

6. The reproductive system. In: Betts JG, DeSaix P, Johnson E, Johnson JE, Korol O, Kruse DH, et al. Anatomy and physiology [monograph on the Internet]. Houston, Texas: OpenStax College, Rice University; 2017 [cited 2019 Jan 15]. Available from: https://opentextbc.ca/anatomyandphysiology/chapter/27-1-anatomy-and-physiology-of-the-male-reproductive-system/.

7. Williams K, Baumann L, Shah A, Abdullah F, Johnson EK, Oyetunji TA. Age at orchiopexy for undescended testis in the United States. J Pediatr Surg. 2018;53(1):86-9.

8. Mehendale VG, Shenoy SN, Shah RS, Chaudhari NC, Mehendale AV. Laparoscopic management of impalpable undescended testis: 20 years' experience. J Minim Access Surg. 2013;9(4):149-53.

9. Hutson JM. Undescended testis, torsion, and varicocele. In: Coran AG, Caldamone A, Adzick NS, Kurmmel TM, Laberge JM, Shamberger R, editors. Pediatric surgery. 7th ed. Philadelphia, PA: Saunders Elsevier; 2012. p. 1003-19.

10. van Brakel J, de Muinck Keizer-Schrama SM, van Casteren NJ, Hasebroek FW, Dohle GR. Scrotal ultrasound findings in previously congenital and acquired unilateral undescended testis and their contralateral normally descended testis. Andrology. 2015;3(5):888-94.

11. Niedzielski JK, Oszukowska E, Slowikowska-Kilczer J. Undescended testis - current trends and guidelines: a review of the literature. Arch Med Sci. 2016;12(3):667-77.

12. Hadziselimovic F, Herzog B. Cryptorchidism. Pediatr Surg Int. 1987;2(3):132-41.

13. Bradshaw CJ, Corbet-Burcher G, Hitchcock R. Age at orchidopexy in the UK: has new evidence changed practice? J Pediatr Urol. 2014;10(4):758-62.

14. Dobanovački D, Vučković N, Slavković A, Lučić Prostran B, Lakić T, Gajić I. Variations in timing of elective orchidopexy. Med Pregl. 2016;69(3-4):106-9.

15. Romao RL. Pediatric urologists must advocate for improved quality of care in patients with cryptorchidism. Can Urol Assoc. 2017;11(1-2 Suppl 1):S33.

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# CASE REPORTS
## *PRIKAZI SLUČAJEVA*

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Case report
*Prikaz slučaja*
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# PLEURAL EFFUSION CAUSED BY POLYOSTOTIC FIBROUS DYSPLASIA INVOLVING THE RIBS, THE STERNUM AND THE THORACIC SPINE ASSOCIATED WITH MULTIPLE CYSTIC DEGENERATIONS – A CASE REPORT

*PLEURALNA EFUZIJA PROUZROKOVANA POLIOSTOTSKOM FIBROZNOM DISPLAZIJOM SA ZAHVATANJEM REBARA, STERNUMA I TORAKALNE KIČME PRAĆENA MULTIPLOM CISTIČNOM DEGENERACIJOM – PRIKAZ SLUČAJA*

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**Summary**

**Introduction.** Fibrous dysplasia is a noninherited benign skeletal disorder associated with abnormal bone development. Single bone involvement, the monostotic form, accounts for 70 – 80% of cases, while the polyostotic form, with multiple bone involvement, accounts for 20 – 30% of cases. Cystic degeneration and occasional aneurysmal bone cyst formation may be found in fibrous dysplasia lesions, particularly in the costal lesions. **Case Report.** A 51-year-old man presented with acute shortness of breath after sustaining simple chest wall injury. Chest computed tomography showed multiple massive osteolytic rib lesions, as well as a massive left-sided pleural effusion with compression atelectasis of the lung parenchyma. Osteolytic lesions of the anterior 2nd and 7th thoracic vertebral body were found, along with a well defined osteolytic lesion in the body of the sternum. Video-assisted thoracoscopy of the left pleural space was performed and frozen sections, collected using endoscopic biopsy forceps of the cystic wall and solid parts of the tumors, were sent for ex tempore histopathological analysis. Results showed fibrous dysplasia with suspected malignancy. Talc pleurodesis was performed based on the obtained results. At present, the patient is asymptomatic with his daily routine uninterrupted by his medical condition. **Conclusion.** Treatment of pleural effusion caused by a cyst rupture of unresectable degenerated polyostotic fibrous dysplasia of the ribs represents a surgical challenge. Surgical drainage of the cysts followed by chemical pleurodesis seems to be a reasonable solution in cases where pulmonary functions are impacted by combined effects of pleural effusion and cystic compression.

**Key words:** Fibrous Dysplasia, Polyostotic; Pleural Effusion; Pleurodesis; Thoracoscopy; Thoracic Surgery, Video-Assisted; Diagnosis; Morphological and Microscopic Findings

**Sažetak**

**Uvod.** Fibrozna displazija predstavlja nenasledni poremećaj razvoja skeleta. Zahvaćenost jedne kosti, monostotska bolest, zastupljena je u 70−80% slučajeva, dok je zahvaćenost više kostiju, poliostotska bolest, zastupljena u 20−30% slučajeva. Cistična degeneracija i formiranje aneurizmatske koštane ciste mogu biti komplikacije fibrozne displazije, posebno kod lezija koje zahvataju rebra. **Prikaz slučaja.** Prikaz slučaja bolesnika, starog 51 godinu, sa akutno nastalim dispnoičnim tegobama ispoljenim nakon blage traume grudnog koša. Kompjuterizovana tomografija toraksa opisivala je multiple masivne osteolitične lezije rebara i masivni levostrani pleuralni izliv sa kompresivnom atelektazom pluća kao posledicom. Nađene su i osteolitične lezije tela drugog i četvrtog torakalnog pršljena, kao i jasno definisana osteolitična lezija tela sternuma. Tokom videoasistirane torakoskopske procedure, koristeći bioptička klešta, bioptirani su zid ciste i solidna tumorska komponenta koje su poslate na eks tempore patohistološki pregled. Rezultati su ukazivali na fibroznu displaziju sa mogućom malignom alteracijom. U ovim okolnostima hemijska pleurodeza je izvedena talkom. Bolesnik je aktuelno bez tegoba sa nultim stepenom invalidnosti. **Zaključak**. Tretman pleuralne efuzije nastale rupturom cistično izmenjene neresektabilne poliostotske fibrozne displazije rebara, predstavlja hirurški izazov. U slučajevima kada pleurana efuzija zajedno sa kompresivnim efektom cisti utiče na plućnu funkciju, hirurška drenaža ciste praćena hemijskom pleurodezom može biti optimalno terapijsko rešenje.

**Ključne reči:** poliostotska fibrozna displazija; pleuralna efuzija; pleurodeza; torakoskopija; video-asistirana grudna hirurgija; dijagnoza; morfološki i mikroskopski nalazi

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***Abbreviations***
CT – computed tomography
VATS – video-assisted thoracoscopy

## Introduction

Fibrous dysplasia is a noninherited benign skeletal disorder with abnormal bone development. Abnormal differentiation of osteoblasts leads to the replacement of normal marrow and cancellous bone by immature woven bone with fibrous stroma. Single bone involvement, the monostotic form, accounts for 70 – 80% of cases, while the polyostotic form, with multiple bone involvement accounts for 20 – 30% of cases. In the polyostotic form, up to 75% of the whole skeleton may be involved [1]. The most commonly affected areas are bones of the lower and upper extremities, pelvis, ribs and skull. Lumbar spine, clavicle and cervical spine are rarely involved, and only a few cases of sternum involvement have been reported in the literature [2, 3]. McCune-Albright syndrome is a polyostotic disorder associated with pigmented skin lesions and multiple endocrine dysfunctions [4]. A combination of muscular myxomas and fibrous dysplasia is a rare condition known as Mazabraud's syndrome [5]. The incidence of malignant transformation is ~0.5%, mostly in males with polyostotic disease. Osteosarcoma accounts for 50% of all malignancies in fibrous dysplasia [6]. Cystic degeneration with occasional formation of aneurysmal bone cysts can be found in fibrous dysplasia lesions, especially in the costal lesions [7].

## Case Report

A 51-year-old man presented with acute shortness of breath after sustaining a simple chest wall injury. The pateient was referred to the Thoracic Surgery Clinic, with a chest X-ray showing large multifocal rib tumors and left-sided pleural effusion reaching the posterior aspect of the 6th rib.

The patient's medical history showed bilateral rib masses that were accidentally diagnosed after a traffic accident which took place 42 years before. A chest X-ray made 22 years before was provided. Changes on the ribs were identified as giant bilateral bone calluses, attributed to childhood rib fractures. Chest computed tomography (CT) was done 15 years ago in another medical center, but no medical history was presented.

On admission, all vital signs were within normal limits. A physical examination revealed stiff painless bilateral palpable masses in the chest wall. The breath sounds were decreased on the left side, followed by wheezing heard at the end of both inspiratory and expiratory phases.

Chest CT showed multiple massive expansile osteolytic rib lesions. On the right side, the 1st, 2nd, 4th and 7th ribs were affected and on the left side the 2nd, 5th, 7th and 11th ribs were affected **(Figures 1 and 2)**. All rib expansile osteolytic lesions were associated with sclerotic margins, partially with cortical thinning and endosteal scalloping, mostly fluid-filled with a massive anterior solid part. After intravenous contrast administration, the solid part was demarcated better and

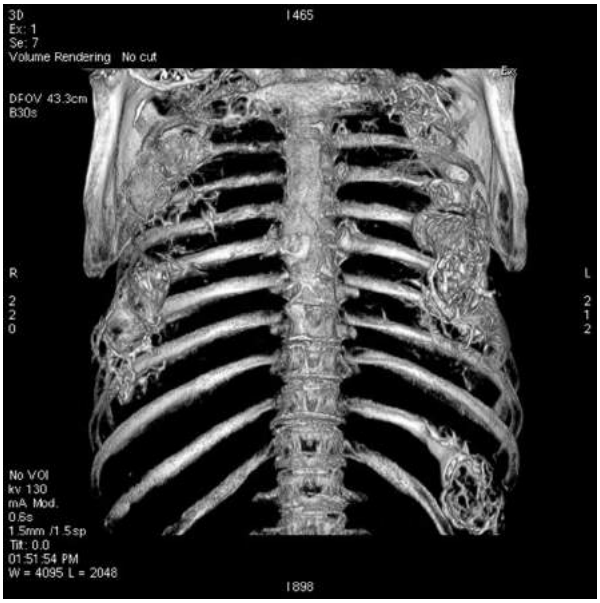


**Figure 1.** Computed tomography shows multiple rib tumors
***Slika 1.*** *Kompjuterizovana tomografija: multipli tumori rebara*

showed a moderate, heterogeneous contrast enhancement with cystic cavities inside. The described masses entered the thoracic cavity, with no signs of infiltration into the surrounding structures. A massive left-sided pleural effusion with compression atelectasis of lung parenchyma was detected **(Figure 3)**. On the right side, there were no signs of pleural effusion. Osteolytic lesions of the anterior part of the 2nd and 7th thoracic vertebral body were described, along with a well defined osteolytic lesion in the body of the sternum **(Figure 4)**.

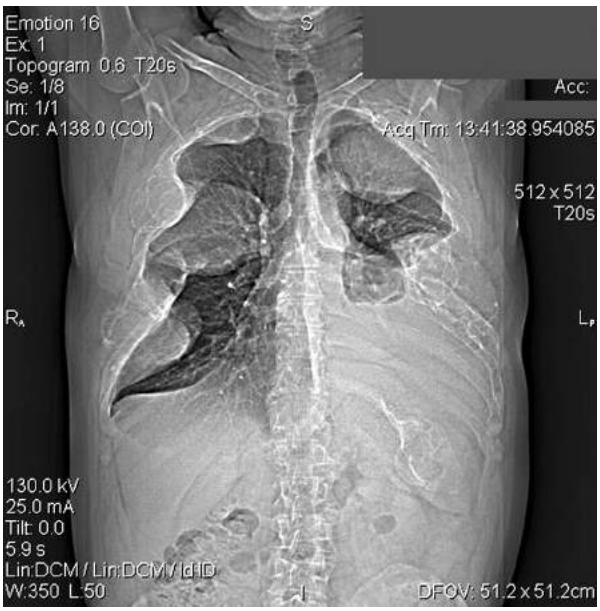


**Figure 2.** Volume rendering image shows rib lesions
***Slika 2.*** *Prikaz zapremine rebarnih lezija*

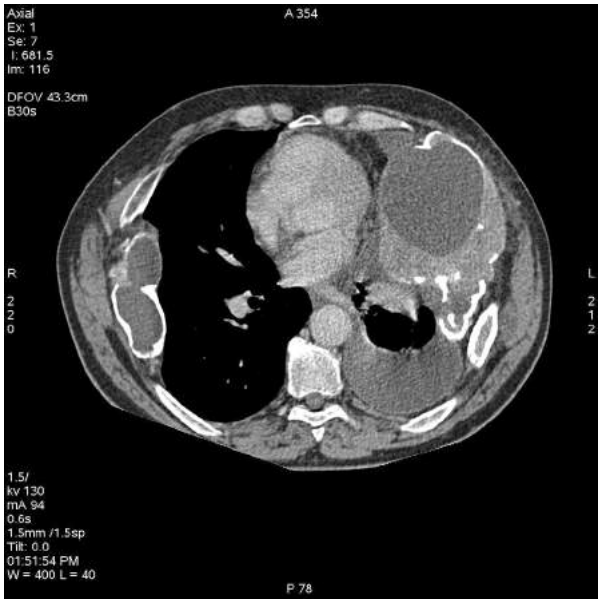


**Figure 3.** Computed tomography shows multiple massive expansile osteolytic rib lesions with left sided pleural effusion
***Slika 3.*** *Kompjuterizovana tomografija: multiple masivne ekspanzivne osteolitičke lezije rebara sa levostranim pleuralnim izlivom*

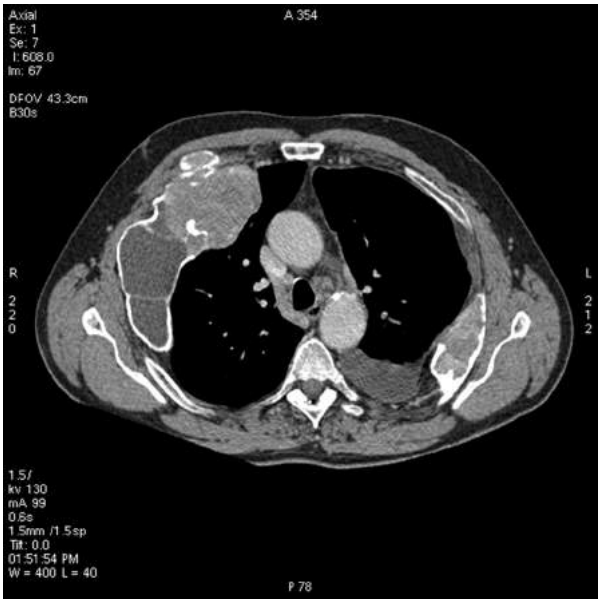


**Figure 4.** Computed tomography shows multiple osteolytic ribs, sternum and vertebral body lesions
***Slika 4.*** *Kompjuterizovana tomografija: multiple osteolitične lezije rebara, sternuma i pršljenskih tela*

Preoperative laboratory testing showed normal findings. Forced spirometry showed a severe reduction of the lung capacities and volumes as a result of left lower lobe atelectasis, induced by the compressive effect of the pleural effusion and reduction of endothoracic volume due to the tumor growth.

A video-assisted thoracoscopy (VATS) of the left pleural space was performed. After placement of ports, 2000 ml of serous fluid was aspirated. Almost the entire parietal pleura was covered by a thick white membrane, overlaying 6 solid prominent rib tumors, 1 cm in diameter. At least three large rib tumor masses were found, measuring up to 10 cm in diameter with evident compression of the lung tissue **(Figure 5)**. The left lower lung lobe was atelectatic. Two large cystic formations were surgically opened, presenting multiple cavities predominantly filled with serous fluid **(Figure 6)**. The frozen sections, collected using endoscopic biopsy forceps of the cystic wall and solid parts of the tumors, were sent for ex tempore histopathological analysis. Results showed fibrous dysplasia with suspected malignancy. Talc pleurodesis was performed based on the results. One chest tube was inserted and the incision was closed with a single skin suture. Dur-

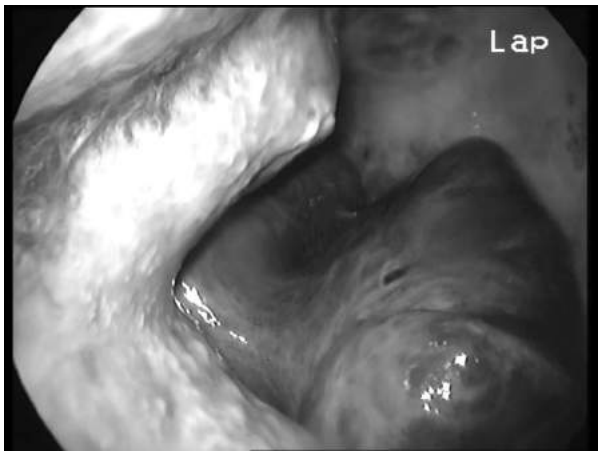


**Figure 5.** Video-assisted thoracoscopy shows the thoracic cavity with multiple rib tumors
***Slika 5.*** *Video asistirana torakoskopija: pleuralna šupljina sa multiplim tumorima rebara*

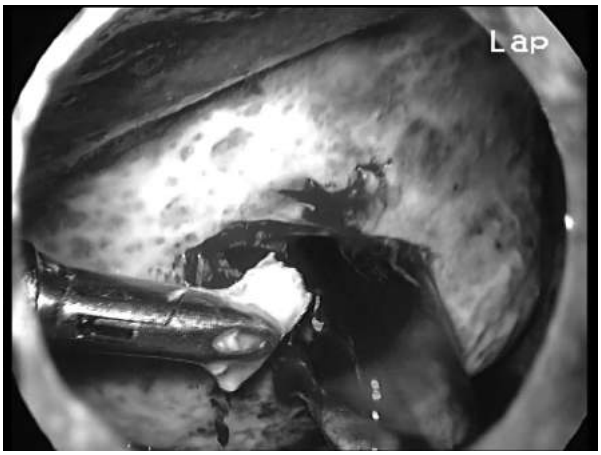


**Figure 6.** Video-assisted thoracoscopy: biopsy forceps tissue sampling
***Slika 6.*** *Video asistirana torakoskopija: uzimanje uzoraka bioptičkim kleštima*

ing the postoperative period, the control chest X-rays showed an incomplete re-expansion in the apex of the left pleural space. Consequently, a second chest tube was inserted through the first intercostal space, followed by the talc slurry re-pleurodesis. The chest tubes were removed on the 6th postoperative day. Definitive histophatological examination of the affected tissue showed fibrous dysplasia associated with multiple cystic transformations. A control spirometry was done two months after the surgery, showing significant improvements in the pulmonary function. Control chest X-ray showed no signs of pleural re-effusion. At present, the patient is asymptomatic with his daily routine uninterrupted by his present medical condition.

## Discussion

Symptoms accompanying fibrous dysplasia, if present, are usually mild, and depend on the location and size of the tumors. In our case, although the polyostotic form was found in some rare locations, including sternum and thoracic veretebra, the main symptoms were caused by massive costal lesions. Dyspnea was induced by two mechanisms, compression by the tumor tissue and pleural effusion. Generally, bone lesions stop growing after skeletal maturity. However, costal lesions tend to keep growing, especially if cystic or aneurysmal transformation has occurred [1].

In the series of ten patients with fibrous dysplasia, Aida et al. [8] reported that stable and asymptomatic lesions in patients with histopathologically verified fibrous dysplasia should be simply monitored. Surgery should be considered for the confirmation of the disease by biopsy, correction of deformity, failure of nonsurgical therapy, prevention of pathologic changes, and elimination of symptomatic lesions. Traibi et al. [9] suggested that in the monostotic form affecting the rib, it should be resected, whenever technical requirements are met. Bisphosphonate therapy is recommended in cases where surgical resection is not possible, or in polyostotic forms [1]. In a population study, Chapurlat et al. [10] showed that bisphosphonate therapy shows positive effects on bone density and pain management. However, in cases where new symptoms and lesion growth are verified, diagnostic procedures for excluding malignant transformation should be taken into the account.

In our patient, although rib lesions have been known to exist for more than 40 years, cystic degeneration occurred during adulthood. The probable cause of cyst rupture, followed by pleural effusion and symptoms of dyspnea, was the chest trauma. Surgery was performed in order to obtain a biopsy sample, resolve the pleural effusion, and eliminate the symptoms. The mechanical compression of the lung parenchyma was reduced by opening the cystic cavities during VATS procedure. Chemical pleurodesis was preformed due to the presence of intrapleural cystic tumor formations, combined with pleural effusion and suspected malignancy. The VATS procedure combined with pleurodesis showed satisfactory postoperative pulmonary function test results. After a review of the medical literature, we did not manage to find any case reporting on a pleural effusion associated with fibrous dysplasia of the ribs with multiple cystic transformations.

## Conclusion

Treatment of pleural effusion caused by a cyst rupture of unresectable degenerated polyostotic fibrous dysplasia of the ribs represents a surgical challenge. Surgical drainage of the cysts followed by chemical pleurodesis seems to be a reasonable solution in cases where pulmonary functions are impacted by combined effects of pleural effusion and cystic compression. Chemical pleurodesis may be beneficial in symptoms control by prevention of recurrent pleural effusions.

## References

1. Mahadevappa A, Patel S, Ravishankar S, Manjunath GV. Monostotic fibrous dysplasia of the rib: a case report. Case Rep Orthop. 2012;2012:690914.

2. Leet AI, Magur E, Lee JS, Wientroub S, Robey PG, Collins MT. Fibrous dysplasia of the spine: prevalence of lesions and association with scoliosis. J Bone Joint Surg Am. 2004;86-A(3):531-7.

3. Prada EJ, Hassan KH, Brandi ML, Falchetti A. Polyostotic form of fibrous dysplasia in a 13 years old Colombian girl showing clinical and biochemical response to neridronate intravenous therapy. Clin Cases Miner Bone Metab. 2009;6(3):264-5.

4. Albright F, Butler AM, Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females: report of five cases. N Engl J Med. 1937;216(17):727-46.

5. Zoccali C, Teori G, Prencipe U, Erba F. Mazabraud's syndrome: a new case and review of the literature. Int Orthop. 2009;33 (3):605-10.

6. DiCaprio MR, Enneking WF. Fibrous dysplasia: pathophysiology, evaluation, and treatment. J Bone Joint Surg Am. 2005;87(8):1848-64.

7. Ozkaya S, Findik S, Demir H, Yuksel C, Atici AG. Polyostotic fibrous dysplasia of the ribs: an unusual cause of chest pain and dyspnea. Int Med Case Rep J. 2009;2:23-5.

8. Ayadi-Kaddour A, Ben Slama S, Marghli A, Mehouachi R, Djilani H, Kilani T, et al. Fibrous dysplasia of the rib. Ten case reports. Rev Chir Orthop Reparatrice Appar Mot. 2008;94(3):301-7.

9. Traibi A, El Oueriachi F, El Hammoumi M, Al Bouzidi A, Kabiri el H. Monostotic fibrous dysplasia of the ribs. Interact Cardiovasc Thorac Surg. 2011;14(1):41-3.

10. Chapurlat RD, Gensburger D, Jimenez-Andrade JM, Ghilardi JR, Kelly M, Mantyh P. Pathophysiology and medical treatment of pain in fibrous dysplasia of bone. Orphanet J Rare Dis. 2012;7(Suppl 1):S3.

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Case report
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# HYPOTHYROIDISM AFTER FINE NEEDLE ASPIRATION BIOPSY OF THYROID NODULES – A CASE REPORT

## *HIPOTIROIDIZAM KAO POSLEDICA ASPIRACIONE BIOPSIJE TANKOM IGLOM NODUSA ŠTITASTE ŽLEZDE – PRIKAZ SLUČAJA*

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**Summary**

**Introduction.** Fine needle aspiration biopsy is a non-surgical invasive diagnostic method for the cytological evaluation of the thyroid gland. Complications of fine needle aspiration biopsy are rare. **Case Report.** A female patient, 64 years of age, underwent left-sided nodulectomy in 2006, due to a follicular adenoma of the thyroid gland. In September of 2016, ultrasonography of the thyroid gland confirmed a node in the right lobe, approximately 10 mm in the longest diameter. The thyroid-stimulating hormone level was within the reference range (1,8 mIU/L), as well as calcitonin and carcinoembryonic antigen levels, but with elevated anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies, so fine needle aspiration was indicated. The cytological finding indicated a suspected follicular lesion and total thyroidectomy with an ex tempore biopsy was proposed in November of 2016. Prior to the surgery, hormone levels were measured and high thyroid-stimulating hormone levels were recorded (79 mIU/L). Further investigation showed low levels of free thyroid hormone concentrations, and levothyroxine was initiated at a dose of 75 mcg per day and the surgical treatment was delayed. The indicated dose of levothyroxine resulted in satisfactory values of the thyroid gland free hormones, and in February 2017, right-sided lobectomy was performed, whereas the histopathological findings indicated lymphocytic thyroiditis. Levothyroxine replacement therapy showed satisfactory results in the postoperative period. Further outpatient ultrasonographic monitoring showed a residual thyroid tissue, with slightly non-homogeneous echostructure in the left thyroid bed, 12 x 11 x 32 mm in size. Regular follow-up was suggested. **Conclusion.** Hypothyroidism has not been reported as a fine needle aspiration complication in the available literature.

**Key words:** Hypothyroidism; Biopsy, Fine-Needle; Thyroid Nodule; Thyroid Gland; Diagnosis; Ultrasonography; Morphological and Microscopic Findings; Postoperative Complications

**Sažetak**

**Uvod**. Ultrasonografski kontrolisana aspiraciona biopsija tankom iglom – *fine needle aspiration* nehirurška je invazivna dijagnostička metoda za citološku evaluaciju nodusa štitaste žlezde. Komplikacije pri ovoj biopsiji su retke. **Prikaz slučaja**. Bolesnica, stara 64 godine, operisana je 2006. godine zbog folikularnog adenoma štitaste žlezde u predelu levog režnja, kada je urađena levostrana nodulektomija. U septembru 2016. godine ultrasonografskim pregledom je verifikovan nodus u desnom režnju štitaste žlezde najvećeg promera 10 mm, a vrednost tirostimulišućeg hormona (1,8 mlIU/l) u okviru referentnih vrednosti kao i vrednosti kalcitonina i karcinoembrionalnog antigena, uz povišene vrednosti antitela na tiroksin periosidazu i antitiroglobulinskih antitela, te je indikovana biopsija. Citološki nalaz ukazivao je na suspektnu folikularnu leziju; predložena je totalna tiroidektomija sa biopsijom eks tempore u novembru 2016. godine. Pre operacije kontrolisane su vrednosti hormona, kada su registrovane visoke vrednosti tireostimulišućeg hormona (79 mlIU/l), uz niske vrednosti slobodnih hormona štitaste žlezde, te uvedena supstitucija levotiroksinom u dozi od 75 mcg dnevno i odloženo operativno lečenje do normalizacije vrednosti slobodnih hormona. Hormonski status štitaste žlezde kontrolisan je u više navrata; navedena doza levotiroksina dovela je do zadovoljavajućih vrednosti slobodnih hormona štitaste žlezde, te je u februaru 2017. godine bolesnici urađena desnostrana lobektomija, a patohistološki nalaz ukazivao je na limfocitni tiroiditis. Postoperativno, vrednosti hormona štitaste žlezde na dotadašnjoj terapiji ukazuju na zadovoljavajuću supstituciju levotiroksinom. U daljem ambulantnom praćenju ultrasonografski potvrđeno je postojanje rezidualnog tkiva štitaste žlezde u loži levog režnja lako nehomogene ehostrukture bez izdvajanja nodusa dimenzija 12 x 11 x 32 mm. Predloženo je dalje praćenje. **Zaključak**. Hipotiroidizam do sada nije opisan u literaturi kao komplikacija nakon biopsije tankom iglom.

**Ključne reči:** hipotireoidizam; aspiraciona biopsija tankom iglom; tireoidni čvor; štitna žlezda; dijagnoza; ultrasonografija; morfološki i mikroskopski nalazi; postoperativne komplikacije

## Introduction

Thyroid gland nodules are common clinical findings. Fine needle aspiration (FNA) is a non-surgical invasive diagnostic method for the cytological evaluation of the thyroid gland. Complications of FNA are rare. To the best of our knowledge, this is the first report of hypothyroidism, most likely being the consequence of the FNA procedure.

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***Abbreviations***

FNA – fine needle aspiration
TSH – thyroid-stimulating hormone
CEA – carcinoembryonic antigen
TPO – thyroid peroxidase antibodies
TG – thyroglobulin
AP – anteroposterior
CC – craniocaudal

## Case Report

A female patient, 64 years of age, presented with a nodule in the area of the left lobe of the thyroid gland in 2005. Thyroid-stimulating hormone (TSH) and free thyroid hormone levels were in the reference range, with high antithyroid antibody titer. She underwent left-sided nodulectomy in 2006, due to a follicular adenoma of the thyroid gland in the left lobe region. Annual ultrasound check-ups and TSH level measurements were conducted. In September of 2016, ultrasonography of the thyroid gland confirmed a hypoechoic nodule in the right lobe of thyroid gland, 6 x 10 mm, anteroposterior (AP) x craniocaudal (CC) in size **(Figure 1)**. The patient was afraid of having a malignant disease. At that time, the TSH level was within the reference range (1,8 mIU/L) as well as calcitonin and carcinoembryonic antigen (CEA) levels, but with elevated antibodies to thyroid peroxidase (TPO) and antithyroglobulin (TG). The cytological finding indicated a suspected follicular lesion and total thyroidectomy with an ex tempore biopsy was proposed in November of 2016. Prior to the surgery, thyroid hormones checkup was performed and high TSH levels were recorded (79 mIU/L) **(Table 1)**, as well as low values of free thyroid hormones.

Thyroid ultrasonography was performed and hypothyroidism was established, but no morphological changes were registered. Levothyroxine replacement therapy, at a dose of 75 mcg per day, was initiated and the surgical treatment was delayed. The patient denied pain, swollen neck, or any other illness after FNA. The indicated dose of levothyroxine resulted in satisfactory levels of the thyroid gland free hormones, and in February 2017, the patient underwent right-sided lobectomy; the histopathological findings indicated lymphocytic thyroiditis. The postoperative thyroid hormone levels in the previous therapy indicated satisfactory substitution with levothyroxine. Further outpatient ultrasound monitoring showed a residual thyroid tissue in the left lobe, 12 x 11 x 32 mm in size, with slightly non-homogeneous echostructure. Further follow-up was suggested.

## Discussion

Therapeutic punctures of the thyroid gland used to be performed using instruments that resemble modern aspiration needles, first described in the famous research of Kitab at-Tasrif (The Method of Medicine), the most influential book of Arabic medieval medicine.

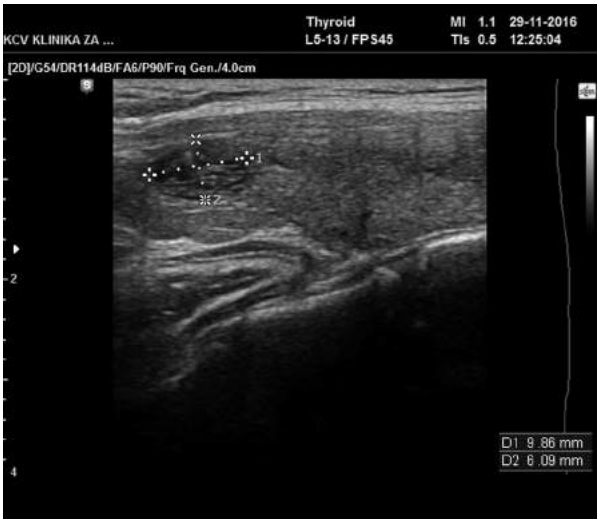


**Figure 1.** Nodule in the right lobe of the thyroid gland
***Slika 1.*** *Nodus u predelu desnog režnja štitaste žlezde*

His description resembles the modern FNA biopsy of the thyroid gland [1]. Since 1994, many studies have evaluated the efficacy and safety of FNA, so the use of FNA has rapidly increased at the beginning of 2010 [2]. FNA plays a central role in the assessment of the malignant nature of the thyroid gland nodules. FNA biopsy should be selective, since systemic FNA of all nodules, regardless of size or appearance, is superfluous and even leads to unnecessary invasive diagnosis. Quick diagnosis can mean early detection of cancer, giving more options for treatment, and diagnosing benign nodules can reduce the number of unnecessary surgeries [3]. Medical history data and ultrasonographic characteristics of nodules are used in deciding whether FNA biopsy is necessary. In our case report, the ultrasonographic properties of the nodules did not require FNA to be done immediately, but it was nevertheless indicated, since the nodules were not verified at previous ultrasound controls and because the patient expressed fear of a potentially malignant disease. Complications related to blood extravasation are more common in patients with a deep lesion or when the lesion has a cystic component that is > 50% of the overall size of the lesion. The risk is slightly higher in cystic compared to solid nodules. The most common manifestation of bleeding is local pain, mild dysphagia (probably the result of unintentional esophageal puncture), and sometimes visible local edema. Acute or delayed diffuse swelling of the thyroid gland, after which in some cases patients need corticosteroid therapy, is rarely associated with compromised airways. There may also be paralysis of recurrent laryngeal nerves, cervical radiculopathy [4]. Our patient denied pain or edema after FNA, and they probably have not occurred. One study showed post aspiration thyrotoxicosis that occurred in 1% of patients, and the origin is unknown.

In our case, there is a possibility that the patient had a sub-clinical post-aspiration thyrotoxicosis that was not confirmed due to the lack of clinical symp-

**Table 1.** Levels of the thyroid-stimulating hormone, free T3, free T4 levels before and after fine needle aspiration, as well as before and after surgery
***Tabela 1.*** *Vrednosti tireostimulišućeg hormona, slobodnog T3, slobodnog T4 pre i nakon FNA, kao i pre i nakon operacije*

| | TSH (mIU/l) *TSH (mIU/l)* | Free T4 (pmol/l) *Slobodni T4 (pmol/l)* | Free T3 (pmol/l) *Slobodni T3 (pmol/l)* |
|---|---|---|---|
| Level before FNA/*Vrednost pre FNA* | 1,8 | 14,4 | 4,26 |
| Level after FNA/*Vrednost nakon FNA* | 79 | 5,3 | 2,4 |
| Level before surgery (levothyroxine 75 mcg/day) *Vrednost pre operacije (levotiroksin 75 mcg/dan)* | 2,8 | 16,2 | 4,70 |
| Level after surgery (levothyroxine 75 mcg/day) *Vrednost posle operacije (levotiroksin 75 mcg/dan)* | 4,2 | 19,9 | / |

Legend**:** FNA – fine needle aspiration; TSH – thyroid-stimulating hormone; T3 – triiodothyronine; T4 – thyroxine
*Legenda**:** FNA – aspiraciona biopsija tankom iglom; TSH – tirostimulišući hormon; T3 – triiodotironin; T4 – tiroksin*

toms. Other rare complications that are the subject of several case reports include the development of fibrovascular tumors, such as hemangioma or pseudoaneurysm [4].

If our patient had these complications, they would be histopathologically confirmed, but these findings indicated lymphocytic thyroiditis.

Fine needle aspiration can also destroy thyroid gland follicles, which leads to the release of TG into the circulation. Leakage of fluid from the cystic nodes to the surrounding thyroid tissue (perinodular) or other tissues close to the thyroid gland (perithyroid) is a potential post-FNA complication, which may cause acute thyroiditis. Mild thyroiditis and/or subsequent fibrosis of the thyroid tissue should not be excluded. In our patient, the thyroid gland had no cystic component. Hypothyroidism may have occurred as a result of subacute thyroiditis that was not verified after FNA, but the absence of neck pain makes it less likely, and thyroid tissue fibrosis has not been proven histopathologically. Leakage of ethanol is described after percutaneous injection of ethanol (usually through a thin needle under ultrasound guidance), which is a therapeutic method for cystic degeneration of nodules.

Ethanol leakage may cause local pain and fibrosis in the surrounding tissues, which is caused by an increase in intranodal pressure after ethanol injection. Usage of local anesthetics, especially lidocaine, or parasitic cyst rupture, may cause an anaphylactic reaction.

Local anesthetics are used only prior to FNA in some patients. Cases of thyroid gland cysticercosis are also reported, but these are usually cases with the involvement of the thyroid gland in generalized cysticercosis. However, other parasitic cysts might more easily be mistaken for simple thyroid cystic nodules, because their primary lesion may be in the thyroid gland. Primary hydatid cysts of the thyroid gland caused by echinococcosis, although rare, have been reported, and its dissemination may be a potential complication. Our patient did not have a cystic component, and local anesthetics were not used. Thyroid FNA may be complicated with cerebral embolism, especially in elderly patients or patients predisposed to thrombophilic conditions. Blindness was described as a consequence of thromboembolism in one patient. Despite the lack of direct evidence, it is recommended that thyroid FNA of nodules in the immediate vicinity of the carotid artery should be performed under ultrasound control, especially if there is evidence of carotid artery atherosclerosis. In our patient, FNA was performed under ultrasound control. Thromboembolism of the thyroid artery may cause sudden hypothyroidism, but this would lead to ischemia of the thyroid gland tissue that should have been verified by an ultrasound examination which is done when hypothyroidism is diagnosed or post-surgical finding is established. Malignant scarring after FNA is rarely described, but most often in medullar carcinoma of the thyroid gland or thyroid lymphoma, and extremely rare in other malignant thyroid diseases [5, 6]. In our patient, malignant cell scattering was not possible, since it was not a malignant thyroid disease. A case of a 35-year-old woman who was admitted to the hospital after a three-day vocal roughness, laryngeal stridor and dyspnea without fever, was reported after FNA was performed, which was confirmed with retropharyngeal cellulitis [7, 8]. A 35-year-old man was examined because of painless edema, which gradually increased on the right side of the neck after FNA. He had no symptoms of thyroid function disorder, no obstructive symptoms and no history of chronic disease or surgery. He was diagnosed with abscess in the area of the right thyroid gland. Thyroid abscess and acute suppurative thyroiditis have been described as rare complications of thyroid FNA. A transition phase of hyperthyroidism has also been reported due to the secretion of thyroid gland hormone in connection with mass destruction of tissue associated with abscess [9]. The medical history of our patient and a histopathological examination showed no data indicating the existence of cellulitis, abscess or other purulent infection. Hashimoto thyroiditis is part of the spectrum of autoimmune thyroid disease and is characterized by the destruction of thyroid cells by various cell and antibody induced immune processes. This condition is the most common

cause of hypothyroidism [3, 10–12]. Although our patient had Hashimoto thyroiditis for more than 10 years, TSH values during regular controls were normal and the absence of symptoms of hypothyroidism indicated a still preserved function of the thyroid gland before performing FNA. Considering that hypothyroidism in our patient has progressed rapidly, within a period of two months after FNA, in our opinion hypothyroidism was not the result of autoimmune thyroiditis alone, most likely the consequence of the FNA procedure itself.

## Conclusion

Hypothyroidism has not been described in literature as a complication after fine needle aspiration. The medical history, surgery and histopathological findings after surgery did not clarify the etiology of the sudden development of hypothyroidism in our patient. We seriously consider that the cause of hypothyroidism was fine needle aspiration. According to guides, routine control of thyroid hormone status after fine needle aspiration is not indicated.

## References

1. Abu al-Qasim al-Zahrawi (Abulcasis). The Kitab al-Tasrif (The Method of Medicine).

2. Ha EJ, Suh CH, Baek JH. Complications following ultrasound-guided core needle biopsy of thyroid nodules: a systematic review and meta-analysis. Eur Radiol. 2018;28(9):3848-60.

3. https://www.myvmc.com/investigations/fine-needle-aspiration-biopsy-fna/ [assessed 27 Jan 2019].

4. https://www.insideradiology.com.au/thyroid-fna-hp/ [assessed 27 Jan 2019].

5. Polyzos SA, Anastasilakis AD. Clinical complications following thyroid fine-needle biopsy: a systematic review. Clin Endocrinol (Oxf). 2009;71(2):157-65.

6. Polyzos SA, Anastasilakis AD. Rare potential complications of thyroid fine needle biopsy. Hippokratia. 2011;15(2):116-9.

7. Sato K, Izumi T, Toshima M, Nagai T, Muroi K, Komatsu N, et al. Retropharyngeal abscess due to methicillin-resistant Staphylococcus aureus in a case of acute myeloid leukemia. Intern Med. 2005;44(4):346-9.

8. Cesareo R, Naciu A, Barberi A, Pasqualini V, Pelle G, Manfrini S, et al. A rare and severe complication following thyroid fine needle aspiration: retropharyngeal cellulitis. Int J Endocrinol Metab. 2016;14(4):e39174.

9. Mohamed AAR, Al Quarshi TA, Mohamed AA, Saud AMA. Thyroid abscess rare complication of thyroid FNA: case report and literature review. Sch J Med Case Rep. 2018;6(2):101-7.

10. Dilas LT, Bajkin I, Icin T, Paro JN, Zavisic BK. Iodine and thyroid gland with or without nuclear catastrophe. Med Pregl. 2012;65(11-12):489-95.

11. Dilas LT, Icin T, Paro JN, Bajkin I. Autoimmune thyroid disease and other non-endocrine autoimmune diseases. Med Pregl. 2011;64(3-4):183-7.

12. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev. 2014;13(4-5):391-7.

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# TYPE III ROACH SCALE STURGE-WEBER SYNDROME ASSOCIATED WITH AN EXTRACRANIAL LIPOMA - A CASE REPORT

## *VARIJANTA TIPA III STARDŽ-VEBEROVOG SINDROMA PO ROUČU UDRUŽENA SA EKSTRAKRANIJALNIM LIPOMOM – PRIKAZ SLUČAJA*

**Stefan STOJANOSKI[1, 2], Duško KOZIĆ[1, 2], Miloš LUČIĆ[1, 2] and Katarina KOPRIVŠEK[1, 2]**

**Summary**
**Introduction.** Sturge-Weber syndrome is a neurocutaneous disorder characterized by neurological features such as headaches, developmental delay, mental retardation and seizures, facial anomalies such as port-wine stain and glaucoma which is the most common ocular manifestation. The main neuroimaging findings in patients with Sturge-Weber syndrome are leptomeningeal angiomatosis and corticopial calcifications associated with underlying cortical atrophy. The purpose of this report is to present a rare case of a patient with seizures whose magnetic resonance imaging findings suggested a Sturge-Weber syndrome variant. **Case Report.** We report a case of a 14-year-old boy with a two year history of well controlled generalized tonic clonic seizures with visual aura, who was admitted to our institution for neuroimaging examination. Neuropsychological testing showed normal cognitive and psychomotor development. Electroencephalography revealed unilateral runs of right occipital spikes with secondary generalization. Neuroimaging findings showed focal cerebral leptomeningeal enhancement in the right parasagittal occipital region associated with focal cortical atrophy, whereas susceptibility weighted imaging showed hypointense intracortical calcification and hyperplastic enhanced ipsilateral choroid plexus. The computed tomography confirmed cortical calcifications. Also, an overlying parieto-occipital subcutaneous lipoma was found in the innervation field of the ophthalmic nerve. **Conclusion.** Magnetic resonance imaging is the key imaging modality that confirmed the clinical suspicion of Sturge-Weber syndrome based on a physical and neurological examination. Neither magnetic resonance imaging nor clinical examination is sufficient for a correct diagnosis.
**Key words:** Sturge-Weber Syndrome; Lipoma; Seizures; Magnetic Resonance Imaging; Angiomatosis; Neuroimaging; Calcinosis; Diagnosis

**Sažetak**
**Uvod.** Stardž-Veberov sindrom je neurokutani poremećaj za koji su karakteristične neurološke tegobe kao što su: glavobolje, zaostajanje u razvoju, mentalna retardacija i epileptički napadi, anomalije lica kao što je mrlja boje *porto* vina i glaukom, kao najčešća očna manifestacija. Glavni neuroradiološki znaci kod pacijenata sa Stardž-Veberovim sindromom su leptomeningealna angiomatoza i kortikopijalne kalcifikacije udružene sa atrofijom moždanog parenhima ispod promene. Svrha ovog rada je prikaz retkog slučaja čiji neuroimidžing nalaz ukazuje na to da se radi o varijanti Stardž-Veberovog sindroma. **Prikaz slučaja.** Četrnaestogodišnji mladić sa dvogodišnjom istorijom, dobro kontrolisanih generalizovanih tonično-kloničnih napada sa vizualnom aurom, primljen je u našu ustanovu radi neuroimidžing pregleda. Neuropsihološko testiranje je otkrilo normalan kognitivni i psihomotorni razvoj. Elektroencefalografijski nalaz je prikazao unilateralnu patološku aktivnost okcipitalno desno sa sekundarnom generalizacijom. Nalaz na magnetno-rezonantnom imidžingu prikazao je leptomeningealno prebojavanje u okcipitalnoj regiji parasagitalno desno i kortikopijalne kalcifikacije, uz atrofiju parenhima ispod promene, kao i hipertrofiju istostranog horoidnog pleksusa bočne moždane komore. Pregled kompjuterizovanom tomografijom endokranijuma potvrdio je da se radi o kortikopijalnim kalcifikacijama. Dodatni nalaz je bio supkutani lipom parijetookcipitalno desno u regiji inervacije oftalmičkog nerva. **Zaključak.** Magnetna rezonancija je ključna radiološka metoda za potvrdu klinične sumnje na Stardž-Veberov sindrom, bazirane na kliničkom i neuropsihološkom ispitivanju.
**Ključne reči:** Stardž-Veberov sindrom; lipom; konvulzije; magnetna rezonanca; angiomatoza; neuroimidžing; kalcifikacije; dijagnoza

## Introduction

Leptomeningeal angiomatosis and corticopial calcifications are among the main features of Sturge-Weber syndrome (SWS). SWS is a neurocutaneous disorder characterized by facial, ocular and cerebral vascular anomalies. Clinical presentation of SWS includes neurological features such as headaches, developmental delay, mental retardation and primarily seizures, as well as port-wine stain

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***Abbreviations***

SWS – Sturge-Weber syndrome
MRI – Magnetic Resonance Imaging
T1W – T1 weighted
T2W – T2 weighted
FLAIR – Fluid-attenuated inversion recovery
SWI – Susceptibility weighted imaging
CT – Computed tomography
MA – Meningioangiomatosis
WISC – Wechsler Intelligence Scale for Children

(PWS), mostly unilateral, in the innervation field of the ophthalmic nerve (V1), sometimes including the maxillary (V2) and mandibular (V3) nerves. It can also be bilateral; glaucoma is the most common ocular manifestation, probably due to vascular eye abnormalities. According to Roach, there are three types of SWS; type I includes facial and leptomeningeal angiomatosis with or without glaucoma; type II includes facial angiomatosis with or without glaucoma and no intracranial manifestations, and type III includes only leptomeningeal angiomatosis without facial and ocular lesions [1–4]. The purpose of this article is to present an unusual case of a young male patient with seizures whose neuroimaging findings suggested type III SWS associated with extracranial lipoma in the innervation field of the ophthalmic nerve and to discuss possible differential diagnosis of this unique finding.

## Case Report

A 14-year-old boy, with a two-year history of well controlled generalized tonic clonic seizures with visual aura was admitted to our institution for neuroimaging examination. He was diagnosed with

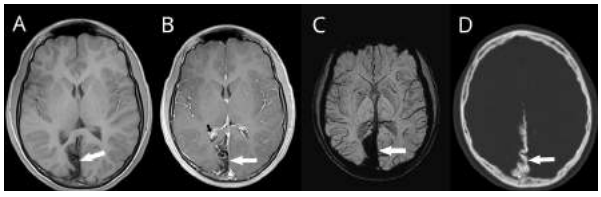


**Figure 1.** T1W before (A) and after (B) gadolinium administration in the axial plane; White arrows indicate leptomeningeal enhancement in the right parasagittal occipital region; Black arrow in B indicates hyperplastic enhanced ipsilateral choroid plexus; SWI (C) and CT (D) confirming the presence of "tram-like" corticopial calcifications in the same location

***Slika 1.*** *T1W pre (A) i nakon (B) primene gadolinijumskog kontrastnog sredstva u transverzalnoj ravni; bele strelice ukazuju na leptomeningealno postkontrastno pojačanje intenziteta signala okcipitalno parasagitalno desno, dok crna strelica (B) ukazuje na hiperplastični istostrani horoidni pleksus. SWI (C) i kompjuterizovana tomografija (D) potvrđuju prisustvo "šinastih" kortikopijalnih kalcifikacija na istoj lokaciji*

Legend: SWI - Susceptibility weighted imaging

*Legenda: SWI – imidžing magnetne susceptibilnosti*

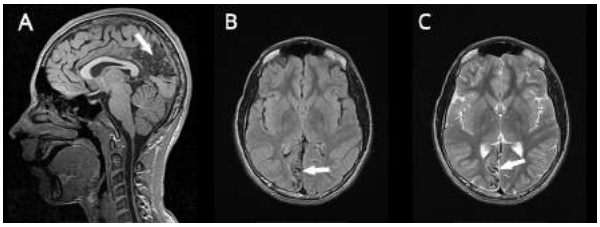


**Figure 2.** T1W in the sagittal plane (A), FLAIR (B) and T2W (C) images in the axial plane; White arrows indicate suspected abnormal leptomeningeal vessels in the right parasagittal, occipital region with focal atrophy of the surrounding cortex

***Slika 2.*** *T1W u sagitalnoj (A), FLAIR (B) i T2W (C) u transverzalnoj ravni. Bele strelice ukazuju na suspektnu abnormalnu leptomeningealnu vaskulaturu u okcipitalnoj regiji parasagitalno desno, uz fokalnu atrofiju parenhima ispod promene*

Legend: FLAIR – Fluid attenuated inversion recovery

*Legenda: FLAIR – fluidni atenuirani inverzni oporavak*

epilepsy and treated with valproic acid since the age of twelve. The seizure frequency was very low, with only two reported attacks per year, with similar semiology and duration. On admission, his neurological and physical states were unremarkable. Neuropsychological testing revealed normal cognitive and psychomotor development, with intelligence quotient (IQ) score of 126 on Wechsler Intelligence Scale for Children (WISC). Electroencephalography (EEG) was performed two days earlier and it revealed unilateral runs of right occipital spikes with secondary generalization. The Magnetic Resonance Imaging (MRI) showed a focal cerebral leptomeningeal enhancement in the right parasagittal occipital region (**Figure 2A**), associated with focal cortical atrophy (**Figures 1 and 2B**) and susceptibility weighted imaging (SWI) hypointense intracortical calcification (**Figure 2C**). As associated findings, hyperplastic enhanced ipsilateral choroid plexus and an overlying parietooccipital subcutaneous lipoma in the innervation field of ophthalmic nerve, were found (**Figure 3**). Non-enhanced computed tomography (CT) scans, performed subsequently, confirmed the presence of intracortical calcification (**Figure 2D**), revealing a (gyral) "tram-track" pattern, obscured by blooming susceptibility effect on SWI scans (**Figure 2C**). The ophthalmological examination, performed due to radiologically suspected SWS, did not reveal any ocular and retinal abnormality, including glaucoma.

## Discussion

Even though the exact etiology of SWS remains unclear, it is proposed that the main pathophysiological mechanism in the affected regions of the brain is the absence of well-functioning superficial cortical venous system, thus blood is redirected centrally via medullary veins, resulting in venous hyperemia and hypertension [5].

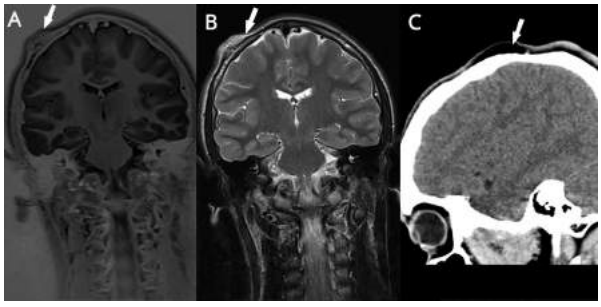


**Figure 3.** T1W (A) and T2W (B) in the coronal plane, and CT (C) in the sagittal plane; Arrows show a subcutaneous mass in the right parietooccipital region, with signal intensity and density of the fatty tissue, suggesting the presence of a subcutaneous lipoma

***Slika 3.*** *T1W (A) i T2W (B) u koronalnoj, kao i kompjuterizovana tomografija (C) u sagitalnoj ravni. Strelice ukazuju na supkutanu masu parijetookcipitalno desno, sa intenzitetom signala i denzitetom koji odgovara masnom tkivu, što ukazuje na prisustvo supkutanog lipoma*

Neurological manifestations of SWS include seizures (75–90%), developmental delay (50–75%), headaches (40–60%) and hemiplegia (30%). The seizures are usually focal, arising from the areas of affected parenchyma, mostly parietooccipital. The early onset of seizures, larger unilateral lesions or bilateral disease, are risk factors for developing pharmacoresistant epilepsy and intellectual impairment [5–7]. Our patient had the first seizure attack at the age of twelve, and did not develop any other neurological or psychological disorders in the follow up years. On the contrary, his WISC score was 126, which puts him in the superior group. His mild neurological and normal neurocognitive status did not correlate with the pial angiomatosis and cortical atrophy extent, detected by MRI, affecting almost the whole medial surface of the right occipital lobe. These results prove that there is a big discrepancy between neuroimaging findings and clinical presentation in suspected cases of SWS variant, and neither clinical examination nor MRI alone is sufficient to make the correct diagnosis.

Regardless that the neuroimaging findings in our patient were highly suggestive of type III Roach variant of SWS, one should keep in mind, that similar imaging features could be present in other congenital pial angiomatosis related disorders and/or angioproliferative diseases. First of all, the meningioangiomatosis (MA) should be considered in differential diagnosis, especially in pediatric patients and young adults with seizures [8]. MA is a rare benign lesion of unknown etiology, usually affecting cerebral cortex and leptomeninges, but can also involve the brain stem and thalamus [9]. It can occur sporadically or associated with neurofibromatosis type II (NF II) [10]. In our patient, the diagnosis of MA was ruled out, based on the lack of perilesional vasogenic edema in the surrounding brain parenchyma, which was reported as typical for MA.

The MRI features in our patient differ from previously reported cases of pediatric and young adults with SWS, in detected additional findings. Intracranial convexity lipoma, as a rare associative finding to focal leptomeningeal enhancement and corticopial calcifications, was described in unique case of Morana et al. The clinical presentation in their two non-related pediatric patients was similar to our patient [11]. To the best of our knowledge, extracranial subcutaneous lipoma, overlaying angiomatous pial malformation in SWS has never been reported before. More interestingly, lipoma was completely within the innervation field of the right ophthalmic nerve. We believe that combined neuroimaging findings, such as pial angiomatosis and corticopial calcifications with atrophy of underlying brain parenchyma, in association with ipsilateral parietooccipital subcutaneous lipoma and seizures, without mental retardation and developmental delay, have not been reported yet, indicating a possibility of a rare manifestation of neurocutaneous disorder. The whole spectrum of clinical phenotypes associated with pial angiomatosis related disorders has still to be clearly defined.

## Conclusion

Magnetic resonance imaging is one of the key imaging modalities that confirms the clinical suspicion of Sturge-Weber syndrome based on physical and neurological examinations. However, neither magnetic resonance imaging nor clinical examination alone is sufficient for a correct diagnosis of Sturge-Weber syndrome. In all pediatric and young adult patients, with clinical presentation of seizures, headaches, developmental delay or mental retardation and pial angiomatosis and cortical calcifications confirmed by magnetic resonance imaging, type III Sturge-Weber syndrome should be considered.

## References

1. Roach ES. Neurocutaneous syndromes. Pediatr Clin North Am. 1992;39(4):591-620.

2. Comi AM, Fischer R, Kossoff EH. Encephalofacial angiomatosis sparing the occipital lobe and without facial nevus: on the spectrum of Sturge-Weber syndrome variants? J Child Neurol. 2003;18(1):35-8.

3. Taddeucci G, Bonuccelli A, Polacco P. Migraine-like attacks in child with Sturge-Weber syndrome without facial nevus. Pediatr Neurol. 2005;32(2):131-3.

4. Piram M, Lorette G, Sirinelli D, Herbreteau D, Giraudeau B, Maruani A. Sturge-Weber syndrome in patients with facial port-wine stain. Pediatr Dermatol. 2012;29(1):32-7.

5. Comi AM. Presentation, diagnosis, pathophysiology, and treatment of the neurological features of Sturge-Weber syndrome. Neurologist. 2011;17(4):179-84.

6. Thomas-Sohl KA, Vaslow DF, Maria BL. Sturge-Weber syndrome: a review. Pediatr Neurol. 2004;30(5):303-10.

7. Siri L, Giordano L, Accorsi P, Cossu M, Pinelli L, Tassi L, et al. Clinical features of Sturge-Weber syndrome without facial nevus: five novel cases. Eur J Paediatr Neurol. 2013;17(1):91-6.

8. Wiebe S, Munoz DG, Smith S, Lee DH. Meningioangiomatosis. A comprehensive analysis of clinical and laboratory features. Brain. 1999;122(Pt 4):709-26.

9. Arcos A, Serramito R, Santín JM, Prieto A, Gelabert M, Rodríguez-Osorio X, et al. Meningioangiomatosis: clinical-radiological features and surgical outcome. Neurocirugia (Astur). 2010;21(6):461-6.

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Prihvaćen za štampu 22. II 2019.
BIBLID.0025-8105:(2019):LXXII:1-2:47-50.

10. Koutsopoulos AV, Yannopoulos A, Stathopoulos EN, Evangeliou A, Panayiotides JG, Kafousi M, et al. Meningioangiomatosis with predominantly cellular pattern. Case report. Neuropathology. 2003;23(2):141-5.

11. Morana G, Mancardi MM , Baglietto MG, Rossi A. Focal leptomeningeal enhancement and corticopial calcifications underlying a parietal convexity lipoma: a rare association of findings in 2 pediatric epileptic patients. J Child Neurol. 2011;26(5):634-7.

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# CENTRAL AND PERIPHERAL VESTIBULAR SIGNS SIMULTANEOUSLY PRESENT IN A PATIENT WITH INSTABILITY – A CASE REPORT

## *CENTRALNI I PERIFERNI VESTIBULARNI ZNACI ISTOVREMENO PRISUTNI KOD PACIJENATA SA NESTABILNOŠĆU – PRIKAZ SLUČAJA*

**Dušan PAVLOVIĆ**

**Summary**

**Introduction.** Cerebellar ataxia, neuropathy, vestibular areflexia syndrome is a rare neurodegenerative disease with instability as the main presenting symptom. Patients with this syndrome often present with central and peripheral vestibular signs. This slowly progressive disease usually starts after 60 years of age and it takes 11 years to diagnose it. **Case Report.** Here I present a 62-year-old woman with instability lasting for 7 years, but deteriorating in the last two years with two episodes of falls, diplopia when looking to the right, paresthesia in the extremities and clumsiness with hands. Clinical examination revealed dysarthria, positive Romberg test, left hand dysmetria, gaze evoked and downbeat nystagmus, positive head impulse test, absent vestibulo-ocular reflex at video head impulse test, no response to caloric stimulation, no smooth pursuit and dysmetric and prolonged saccades at videonystagmography, positive visually enhanced vestibulo ocular reflex test, normal head magnetic resonance imaging, subclinical signs of polyneuropathy at electroneurography and negative autoimmune and paraneoplastic cerebellar antibodies. **Conclusion.** Instability is the first symptom in patients with cerebellar ataxia, neuropathy, vestibular areflexia syndrome. Easy to perform, positive visually enhanced vestibulo-ocular reflex test points to a concomitant central and peripheral vestibular disorder. Negative autoimmune and paraneoplastic antibodies rule out other cerebellar diseases. However, normal head magnetic resonance imaging findings without expressed signs of peripheral sensory neuropathy are in concordance with a slowly progressive form of this syndrome.

**Key words:** Vestibular Diseases; Cerebellar Ataxia; Autonomic Nervous System Diseases; Peripheral Nervous System Diseases; Head Impulse Test; Vestibular Function Tests; Reflex, Vestibulo-Ocular; Dizziness; Postural Balance; Signs and Symptoms

**Sažetak**

**Uvod.** Cerebelarna ataksija, neuropatija, vestibularna arefleksija sindrom retko je neurodegenerativno oboljenje sa nestabilnošću kao glavnim simptomom. Kod pacijenata sa ovim sindromom prisutna je kombinacija centralnih i perifernih vestibularnih znakova. Obično počinje u šezdesetim godinama i obično prođe 11 godina do postavljanja dijagnoze ovog sporo progresivnog oboljenja. **Prikaz pacijenta.** Prikazujem ženu staru 62 godine sa nestabilnošću koja traje sedam godina, a pogoršava se poslednje dve, sa dve epizode pada, diplopijom pri pogledu udesno, parestezijom u ekstremitetima i „šeprtljavošću" u rukama. Klinički pregled otkriva dizartriju, pozitivan Rombergov test, dismetriju levom rukom, pogledni nistagmus i nistagmus nadole, pozitivan *head-impulse* test, odsustvo vestibulookularnog refleksa na video *head-impulse* testu, odsustvo odgovora na kalorijskom testu, izostanak glatkog praćenja i dismetrične i produžene sakade na video-nistagmografiji, pozitivan vizuelno pojačani vestibulo okularni refleks test, normalan nalaz magnetne rezonancije glave, supkliničke znake polineuropatije na elektroneurografiji i negativna autoimuna i paraneoplastična cerebelarna antitela. **Zaključak.** Nestabilnost je prvi simptom pacijenata sa sindromom cerebralne atakcije, neuropatije i vestibularne arefleksije. Vizuelno pojačani vestibulo okularni refleks test se lako izvodi, a kada je pozitivan ukazuje na istovremeni centralni i periferni vestibularni poremećaj koji je vrlo karakterističan za ovo oboljenje. Negativna autoimuna i paraneoplastična antitela isključuju druga cerebelarna oboljenja. Još uvek dobar nalaz magnetne rezonancije glave i neizraženi znaci periferne senzorne neuropatije su u saglasnosti sa sporo progresivnom formom ovog sindroma.

**Ključne reči:** vestibularni poremećaji; cerebralna ataksija; poremećaji autonomnog nervnog sistema; poremećaji perifernog nervnog sistema; head impulse test; testovi vestibularne funkcije; testovi vestibulookularnog refleksa; vrtoglavica; ravnoteža; znaci i simptomi

## Introduction

Presence of bilateral vestibulopathy was reported in a group of patients with cerebellar ataxia in 1991 [1]. Later, this was described as cerebellar ataxia and bilateral vestibulopathy (CABV) syndrome with a very characteristic clinical sign – positive visually enhanced vestibulo-ocular reflex test (VVOR) [2]. In 2011, Szmulewicz recognized and described sensory neuropathy in all patients with CABV syndrome. Because it results from the same pathological process and also contributes to patients' instability and represents an integral part of the same syndrome, it was renamed to cerebellar ataxia neuropathy and vestibular areflexia syndrome (CANVAS) [3].

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***Abbreviations***

CANVAS – cerebellar ataxia, neuropathy, vestibular areflexia syndrome
VVOR – visually enhanced vestibulo-ocular reflex
VOR – vestibulo-ocular reflex
CABV – cerebellar ataxia and bilateral vestibulopathy
VHIT – video head impulse test
MRI – magnetic resonance imaging
SCA3 – spinocerebellar ataxia type 3
FRDA – Friedreich ataxia

The age of CANVAS onset is at the 60's, with a mean duration of symptoms of 11 years at the time of diagnosis [3, 4]. The main symptoms of CANVAS are instability, oscillopsia, dizziness and intrinsic falls. Signs of cerebellar involvement are gaze evoked or downbeat nystagmus, saccadic smooth pursuit, gait ataxia, dysarthria and appendicular ataxia. Bilateral vestibulopathy is readily seen with positive head impulse test, while video head impulse test (VHIT) shows absent vestibulo ocular reflex (VOR) and hudge overt saccades. The caloric test shows absent or reduced response [3, 4].

In patients with CANVAS, a highly characteristic clinical sign is positive VVOR test. During slow passive head turning (0,5 Hz) two systems enable sharp target at retina: smooth pursuit and vestibulo-ocular reflex. As both systems are affected in patient with CANVAS, VVOR test is positive: saccadic eye movements compensate for non functioning smooth pursuit and VOR [2].

Peripheral neuropathy is mainly sensory and clinical signs of reduced pin prick sensation, reduced vibration sensation and absent ankle reflex are usually present. Sometimes clinical signs of peripheral neuropathy lag signs of cerebellar disorder and bilateral vestibulopathy, so electro-neurography testing reveal absent sensory nerve action potential (SNAP) (3-5). On the ground of electrophysiological measurements it couldn't be distinguished if sensory deficit is due to peripheral neuropathy or neuronopathy. Autopsy revealed dorsal root ganglionopathy and ganglionopathy of the cranial nerves: Scarpa's ganglion (84% reduction in cell bodies), geniculate and trigeminal ganglia as well, but spiral ganglion and auditory nerve were intact. CANVAS patients always have normal hearing for their age (6-7).

Autonomic dysfunction can be seen in these patients as a result of autonomic small fiber neuropathy. Orthostatic hypotension and hypohidrosis are usual manifestations, but persistent cough is present in some patients and may be attributed to vagal neuronopathy and denervation hypersensitivity of the upper airways and esophagus [8].

Magnetic resonance imaging (MRI) shows cerebellar atrophy that preferentially affects the anterior and dorsal vermis (lobules VI, VIIa and VIIb) and laterally predominantly affects crus I. At the initial stage of the disease, MRI is not very sensitive and may show normal results [3].

## Case Report

Here I present a 62-year-old woman with instability lasting for 7 years, but deteriorating in the last two years, with two episodes of falls without loss of consciousness. Recently, she noticed diplopia when looking to the right. She reported slight headaches in the occipital region, paresthesia in the extremities and clumsy hands.

Clinical examination revealed slight dysarthria, positive Romberg test and slight dysmetria of the left hand. Muscle strength and tone were normal, reflexes present, sensations of touch, pain, temperature in both upper and lower extremities were normal and only shorten sensation of vibration in the right leg was revealed. Her cognitive functions were normal.

The patient presented with gaze evoked nystagmus and sometimes downbeat nystagmus as well. Head impulse test was positive at both sides, while VHIT showed absent VOR. The caloric test was without any labyrinth response. Videonystagmography showed no smooth pursuit, saccades had prolonged latencies to the right and were dysmetric with lateropulsion to the right (hypermetria to the right and hypometria to the left). The VVOR test was positive. Head MRI showed normal findings. Electroneurography showed subclinical signs of polyneuropathy, predominantly axonal and sensitive. Testing for paraneoplastic and autoimmune antibodies was negative.

## Discussion

Positive VVOR test indicates simultaneous nonfunctioning smooth pursuit system and vestibulo-ocular reflex, which is the main clinical sign in patients with CANVAS [2]. The presented patient showed a combination of the cerebellar oculomotor signs, like gaze evoked nystagmus, downbeat nystagmus, saccadic pursuit and dysmetric saccades, while absence of the VOR indicated the presence of bilateral vestibulopathy. However, good MRI findings without signs of peripheral sensory neuropathy were in concordance with a slowly progressive form of this syndrome [4, 5]. Autoimmune and paraneoplastic cerebellar ataxia were excluded with laboratory tests. The major differential diagnosis of CANVAS are spinocerebellar ataxia type 3 (SCA3), Friedreich ataxia (FRDA), multiple system atrophy of cerebellar type, and Wernicke encephalopathy [3]. SCA 3 and FRDA can also manifest with bilateral vestibulopathy and cerebellar atrophy and sensory neuropathy, but SCA 3 shows familial involvement, fourth ventricle enlargement and motor neuropathy, while FRDA usually manifests before the age of 25 years and with normal head MRI, but atrophic spinal cord at spinal MRI.

## Conclusion

Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome is rare, idiopathic, slowly pro-

gressive neurodegenerative disorder. It is probably a late onset recessive disorder.

Instability is the first symptom. Patients with cerebellar ataxia, neuropathy, and vestibular areflexia syndrome have a very characteristic positive visually enhanced vestibulo-ocular reflex test which indicates concomitant central and peripheral vestibular deficit. The nerve conduction measures should be performed in patients showing combination of central and peripheral vestibular signs. Unfortunately, there is still no medical therapy for this condition and only supportive measures are recommended.

## References

1. Bronstein AM, Mossman S, Luxon LM. The neck-eye reflex in patients with reduced vestibular and optokinetic function. Brain. 1991;114(Pt 1A):1-11.

2. Migliaccio AA, Halmagyi GM, McGarvie LA, Cremer PD. Cerebellar ataxia with bilateral vestibulopathy: description of a syndrome and its characteristic clinical sign. Brain. 2004;127(Pt 2):280-93.

3. Szmulewicz DJ, Waterston JA, Halmagyi GM, Mossman S, Chancellor AM, McLean CA, et al. Sensory neuropathy as part of the cerebellar ataxia neuropathy vestibular areflexia syndrome. Neurology. 2011;76(22):1903-10.

4. Szmulewicz DJ, Waterston JA, MacDougall HG, Mossman S, Chancellor AM, McLean CA, et al. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS): a review of the clinical features and video-oculographic diagnosis. Ann N Y Acad Sci. 2011;1233:139-47.

5. Szmulewicz DJ, Seiderer L, Halmagyi GM, Storey E, Roberts L. Neurophysiological evidence for generalized sensory neuronopathy in cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome. Muscle Nerve. 2015;51(4):600-3.

6. Szmulewicz DJ, Merchant SN, Halmagyi GM. Cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome: a histopathologic case report. Otol Neurotol. 2011;32(8):e63-5.

7. Szmulewicz DJ, McLean CA, Rodriguez ML, Chancellor AM, Mossman S, Lamont D, et al. Dorsal root ganglionopathy is responsible for the sensory impairment in CANVAS. Neurology. 2014;82(16):1410-5.

8. Wu TY, Taylor JM, Kilfoyle DH, Smith AD, McGuinness BJ, Simpson MP, et al. Autonomic dysfunction is a major feature of cerebellar ataxia, neuropathy, vestibular areflexia 'CANVAS' syndrome. Brain. 2014;137(Pt 10):2649-56.

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BIBLID.0025-8105:(2019):LXXII:1-2:51-53.

# UPUTSTVO ZA AUTORE

Časopis ***Medicinski pregled*** objavljuje radove koji prethodno nisu objavljeni niti poslati u drugi časopis. U Časopisu mogu biti objavljeni radovi iz različitih oblasti biomedicine, koji su namenjeni lekarima različitih specijalnosti.

Od 1. januara 2013. godine *Medicinski pregled* je počeo da koristi usluge *e-Ur* − Elektronskog uređivanja časopisa. Svi korisnici sistema − autori, recenzenti i urednici, moraju biti registrovani korisnici sa jednom elektronskom adresom.

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U postupku prijave neophodno je da se pošalje saglasnost i izjava autora i svih koautora da rad nije delimično ili u celini objavljen ili prihvaćen za štampu u drugom časopisu.

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Primaju se samo radovi koji su napisani na engleskom jeziku, uz sažetak rada i naslov rada koji treba da budu napisani na engleskom i srpskom jeziku.

Radove koji su pristigli u časopis *Medicinski pregled* pregleda jedan ili više članova Uređivačkog odbora Časopisa. Oni radovi koji su napisani prema pravilima Časopisa šalju se na anonimnu recenziju kod najmanje dva recenzenta, stručnjaka iz odgovarajuće oblasti biomedicine. Načinjene recenzije radova pregleda glavni urednik ili članovi Uređivačkog odbora i one nisu garancija da će rad biti prihvaćen za štampu. Materijal koji je pristigao u časopis ostaje poverljiv dok se rad nalazi na recenziji, a identitet autora i recenzenata su zaštićeni, osim u slučaju ako oni odluče drugačije.

U časopisu *Medicinski pregled* objavljuju se: uvodnici, originalni članci, prethodna ili kratka saopštenja, pregledni članci, stručni članci, prikazi slučajeva, članci iz istorije medicine i drugi članci.

**1. Uvodnici** – do 5 strana. Sadrže mišljenja ili diskusiju o posebno značajnoj temi za Časopis, kao i o podacima koji su štampani u ovom ili nekom drugom časopisu. Obično ih piše jedan autor po pozivu.

**2. Originalni članci** – do 12 strana. Predstavljaju rezultate istraživanja autora rada i njihovo tumačenje. Istraživanje treba da bude obrađeno i izloženo na način da se može ponoviti, a analiza rezultata i zaključci jasni da bi se mogli proveriti.

**3. Pregledni članci** – do 10 strana. Predstavljaju sistematsko, sveobuhvatno i kritičko izlaganje problema na osnovu analiziranih i diskutovanih podataka iz literature, a koji oslikavaju postojeću situaciju u određenom području istraživanja. Literatura koja se koristi u radu mora da sadrži najmanje 5 radova autora članka iz uže naučne oblasti koja je opisana u radu.

**4. Prethodna ili kratka saopštenja** – do 4 strane. Sadrže izuzetno važne naučne rezultate koje bi trebalo objaviti u što kraćem vremenu. Ne moraju da sadrže detaljan opis metodologije rada i rezultata, ali moraju da imaju sva poglavlja kao originalni članci u sažetoj formi.

**5. Stručni članci** – do 10 strana. Odnose se na proveru ili prikaz prethodnog istraživanja i predstavljaju koristan izvor za širenje znanja i prilagođavanja originalnog istraživanja potrebama postojeće nauke i prakse.

**6. Prikazi slučajeva** – do 6 strana. Opisuju retke slučajeve iz prakse. Slični su stručnim člancima. U ovim radovima prikazuju se neuobičajeni oblici i tokovi oboljenja, neočekivane reakcije na primenjenu terapiju, primene novih dijagnostičkih procedura ili retke i nove bolesti.

**7. Članci iz istorije medicine** – do 10 strana. Ovi članci opisuju događaje iz prošlosti sa ciljem da omoguće očuvanje medicinske i zdravstvene kulture. Imaju karakter stručnih članaka.

**8. Ostali članci** – U časopisu Medicinski pregled objavljuju se feljtoni, prikazi knjiga, izvodi iz strane literature, izveštaji sa kongresa i stručnih sastanaka, saopštenja o radu pojedinih zdravstvenih organizacija, podružnica i sekcija, saopštenja Uredništva, pisma Uredništvu, novosti u medicini, pitanja i odgovori, stručne i staleške vesti i članci napisani u znak sećanja (*In memoriam).*

**Priprema rukopisa**

Kompletan rukopis, uključujući tekst rada, sve priloge i propratno pismo, treba poslati na elektronsku adresu koja je prethodno navedena.

Propratno pismo:

– mora da sadrži izjavu svih autora da se radi o originalnom radu koji prethodno nije objavljen niti prihvaćen za štampu u drugim časopisima;

– autori svojim potpisom preuzimaju odgovornost da rad ispunjava sve postavljene uslove i da ne postoji sukob interesa i

– autor mora navesti kategoriju članka (originalni rad, pregleni rad, prethodno saopštenje, stručni rad, prikaz slučaja, rad iz istorije medicine, itd.).

**Rukopis**

**Opšta uputstva**

Tekst rada treba da bude napisan u programu *Microsoft Word* za *Windows*, na A4 formatu stranice (sve četiri margine 2,5 cm), proreda 1,5 (isto važi i za tabele), fontom *Times New Roman*, veličinom slova 12 *pt*. Neophodno je koristiti međunarodni sistem mernih jedinica (*SI*), uz izuzetak temperature (° *C*) i krvnog pritiska (*mmHg*).

Rukopis treba da sadrži sledeće elemente:

**1. Naslovna strana**

Naslovna strana treba da sadrži: kratak i sažet naslov rada, bez skraćenica, skraćeni naslov rada (do 40 karaktera), imena i prezimena autora (ne više od 6) i afilijacije svih autora. Na dnu strane treba da piše ime, prezime i titula autora zaduženog za korespondenciju, njena/njegova adresa, elektronska adresa, broj telefona i faksa.

**2. Sažetak**

Sažetak ne može da sadrži više od 250 reči niti skraćenice. Treba da bude strukturisan, kratak i sažet, sa jasnim pregledom problema istraživanja, ciljevima, metodama, značajnim rezultatima i zaključcima.

Sažetak originalnih i stručnih članaka treba da sadrži uvod (sa ciljevima istraživanja), materijale i metode, rezultate i zaključak.

Sažetak prikaza slučaja treba da sadrži uvod, prikaz slučaja i zaključak.

Sažetak preglednih članaka treba da sadrži Uvod, podnaslove koji odgovaraju istima u tekstu i Zaključak.

Navesti do 10 ključnih reči ispod sažetka. One su pomoć prilikom indeksiranja, ali autorove ključne reči mogu biti izmenjene u skladu sa odgovarajućim deskriptorima, odnosno terminima iz *Medical Subject Headings*, *MeSH*.

Sažetak treba da bude napisan na srpskom i engleskom jeziku. Sažetak na srpskom jeziku trebalo bi da predstavlja prevod sažetka na engleskom, što podrazumeva da sadrži jednake delove.

**3. Tekst članka**

Originalni rad treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima istraživanja), Materijal i metode, Rezultati, Diskusija, Zaključak, spisak skraćenica (ukoliko su

korišćene u tekstu). Nije neophodno da se u posebnom poglavlju rada napiše zahvalnica onima koji su pomogli da se istraživanje uradi, kao i da se rad napiše.

Prikaz slučaja treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima), Prikaz slučaja, Diskusija i Zaključak.

**Uvod**

U poglavlju Uvod potrebno je jasno definisati predmet istraživanja (prirodu i značaj istraživanja), navesti značajne navode literature i jasno definisati ciljeve istraživanja i hipoteze.

**Materijal i metode**

Materijal i metode rada treba da sadrže podatke o vrsti studije (prospektivna/retrospektivna, uslove za uključivanje i ograničenja studije, trajanje istraživanja, demografske podatke, period praćenja). Detaljno treba opisati statističke metode da bi čitaoci rada mogli da provere iznesene rezultate.

**Rezultati**

Rezultati predstavljaju detaljan prikaz podataka koji su dobijeni istraživanjem. Sve tabele, grafikoni, sheme i slike moraju biti citirani u tekstu rada i označeni brojevima po redosledu njihovog navođenja.

**Diskusija**

Diskusija treba da bude koncizna, jasna i da predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi. U poglavlju Diskusija potrebno je naglasiti da li su postavljene hipoteze potvrđene ili nisu, kao i istaknuti značaj i nedostatke istraživanja.

**Zaključak**

Zaključci moraju proisteći isključivo iz rezultata istraživanja rada; treba izbegavati uopštene i nepotrebne zaključke. Zaključci koji su navedeni u tekstu rada moraju biti u saglasnosti sa zaključcima iz Sažetka.

**4. Literatura**

Potrebno je da se literatura numeriše arapskim brojevima redosledom kojim je u tekstu navedena u parentezama; izbegavati nepotrebno velik broj navoda literature. Časopise bi trebalo navoditi u skraćenom obliku koji se koristi u *Index Medicus* (*http://www.nlm.nih.gov/tsd/serials/lji.html*). Pri citiranju literature koristiti Vankuverski sistem. Potrebno je da se navedu svi autori rada, osim ukoliko je broj autora veći od šest. U tom slučaju napisati imena prvih šest autora praćeno sa *et al*.

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

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.

∗ Bez 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 (urednici) kao autor (autori)

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.

∗ Zbornik radova sa kongresa

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.

∗ Disertacija

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

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

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

∗ Monografija u elektronskom formatu

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.

∗ Kompjuterska datoteka

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

**5. Prilozi (tabele, grafikoni, sheme i slike)**

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG*, *GIF*, *TIFF*, *EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legende slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

**6. Dodatne obaveze**

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

## *INFORMATION FOR AUTHORS*

***Medical Review*** publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

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Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

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**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.

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**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 self-citations.

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

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**Preparation of the manuscript**

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

**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:**

**General instructions.**

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), margins set to 2.5 cm and font size 12pt. 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.

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), materials 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.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

**3. The text of the paper.**

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials 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.

**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.

**Materials 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 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

**4. 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 organization 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.

∗ *A computer file*

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

**5. Attachments (tables, graphs, schemes and photographs).**

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, 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

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

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

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