

СРПСКИ АРХИВ

ЧАСОПИС СРПСКОГ ЛЕКАРСКОГ ДРУШТВА ОСНОВАН 1872. ГОДИНЕ

ЗА ЦЕЛОКУПНО ЛЕКАРСТВО

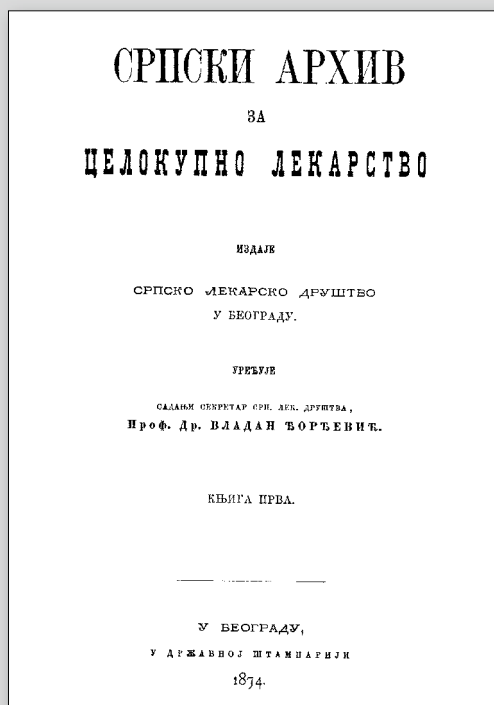


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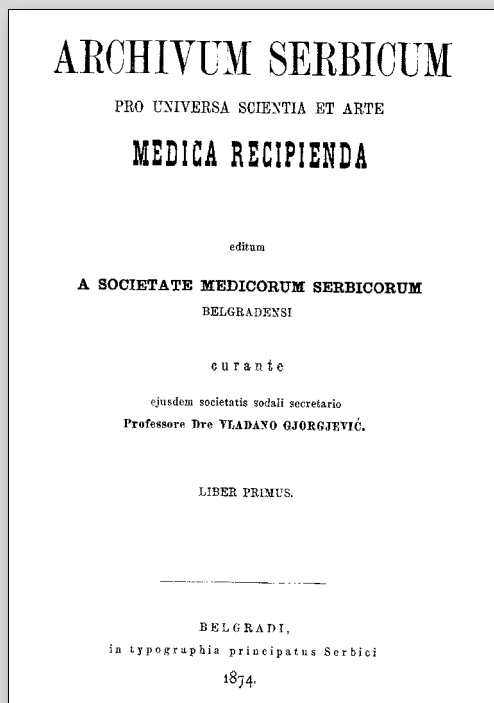
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Факсимил текста на српском језику на првој страници прве свеске часописа, објављене 1874. године (две године после оснивања часописа).



Facimile of the text in Latin language of the title page of the first Journal edition published in 1874 (two years after the Journal was founded)

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Complications in Cochlear Implantation at the Clinical Center of Vojvodina

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SUMMARY

Introduction The first modern cochlear implantation in Serbia was performed on November 26, 2002 at the Center for Cochlear Implantation of the Clinic for Ear, Nose and Throat Diseases, Clinical Center of Vojvodina.

Objective The aim of the paper is the analysis of intraoperative and postoperative complications. Major complications include those resulting in the necessity for revision surgery, explantation, reimplantation, severe disease or even lethal outcomes. Minor complications resolve spontaneously or can be managed by conservative therapy and do not require any prolonged hospitalization of the patient.

Methods In the 2002–2013 period, 99 patients underwent surgical procedures and 100 cochlear implants were placed. Both intraoperative and postoperative complications were analyzed in the investigated patient population.

Results The analysis encompassed 99 patients, the youngest and the oldest ones being one year old and 61 years old, respectively. The complications were noticed in 11 patients, i.e. in 10.5% of 105 surgical procedures. The majority of procedures (89.5%) were not accompanied by any post-surgical complications. Unsuccessful implantation in a single-step procedure (4.04%) and transient facial nerve paralysis can be considered most frequent among our patients, whereas cochlear ossification (1.01%) and transient ataxia (2.02%) occurred rarely. Stimulation of the facial nerve (1.01%), intraoperative perilymph liquid gusher (1.01%), device failure and late infections (1.01%) were recorded extremely rarely.

Conclusion Complications such as electrode extrusion, skin necrosis over the implant or meningitis, which is considered the most severe postoperative complication, have not been recorded at our Center since the very beginning. Absence of postoperative meningitis in patients treated at the Center can be attributed to timely pneumococcal vaccination of children.

Keyword: cochlear implantation; intraoperative complications; postoperative complications

INTRODUCTION

The first successful cochlear implantation in Serbia has been performed at the Center for Cochlear Implantation of the Clinic for Ear, Nose and Throat Diseases, Clinical Center of Vojvodina. The first modern cochlear implant, Nucleus 24, was placed on November 26 of 2002 in a 40-year-old female patient with postlingual hearing impairment. The surgery was performed by Prof. Dr. J. Jori and Prof. J. G. Kiss from the ENT Clinic, Szeged, Hungary, and Prof. Dr. Dragan Dankuc from the ENT Clinic, Novi Sad, Serbia.

Subsequently, for the first time in Serbia, Dragan Dankuc, under the assistance of Prof. Dr. J. Jori, has performed the first implantation of an artificial inner ear – a cochlear implant Nucleus 24 [1]. Ever since, the cochlear implant surgery in Novi Sad has been exclusively performed by an experienced team led by eminent professors Zoran Komazec, Dragan Dankuc, Ljiljana Vlaški, Slobodanka Lemajić Komazec, specialized surdopedagogists Spomenka Nedeljkov, Ivana Sokolovac and Oliver Vajs, as well as engineers Tibor Mendrei and Vladimir Mrdjanov [2].

OBJECTIVE

The paper's objective is to analyze possible intraoperative and postoperative complications. Major complications may result in the necessity for revision surgery, explantation, reimplantation, severe disease or even lethal outcomes. Minor complications, on the other hand, can resolve spontaneously and do not require any prolonged hospitalization of the patient.

METHODS

In the 2002–2013 period, 99 patients underwent surgical procedures and 100 cochlear implants were placed. In four patients, the single-stage surgery was not applicable because of intraoperative complications, thus successful implantation was accomplished in a second procedure. In one patient, the late postoperative complications have required the revision surgery (reimplantation), whereas one female patient underwent bilateral cochlear implantation.

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RESULTS

The analysis encompassed 99 patients, the youngest and the oldest ones being one year old and 61 years old, respectively. The patient population included 11 (11.1%) adults and 88 (88.9%) children as the majority of the patient population.

Both intraoperative and postoperative complications were analyzed in the investigated patient population. The complications were noticed in 11 patients, i.e. in 10.5% of 105 surgical procedures. Implant placement in a single-stage procedure was not possible in four cases because of acute otitis media in one patient, diagnosed during surgery, and the ossification of the cochlea that prevented electrode array placement in the remaining three patients (Figure 1A-B). The second surgery was successfully performed in all four patients, without any subsequent complications. Transient facial nerve paresis was recorded in four (4.04%) patients, which completely subsided two months post surgery after appropriate therapeutic treatment. Transient ataxia was observed in two (2.02%) patients [3].

Some rare complications, such as facial nerve stimulation associated with electro-stimulation of the cochlea, late complication occurring one year post surgery, device failure identified at fitting session and late infection, were observed in one (1.01%) patient each. All complications were successfully managed by incision and drainage, while preserving the functionality of the device (Table 1).

DISCUSSION

The youngest patient was only one year old (i.e. 14.7 months) at the moment of surgery. In 27 (30.7%) children, the surgery was performed at the age below three, whereas 50 (56.8%) children underwent implantation procedure at

the age under four years old. The aims of early implantation are to reduce the hearing deprivation period and to improve the development of auditory performance [4].

In adult patients with postlingual deafness, comprehensive evaluation of the ratio between potential benefit and risks associated with surgery itself and potential comorbidities should be performed. However, age is not the criterion for excluding a patient from implantation procedure unless other risk factors are present [5, 6].

Complications associated with cochlear implantation can be categorized as major and minor ones. Major complications include those resulting in the necessity for revision surgery, explantation, reimplantation, severe disease or even lethal outcomes. Minor complications resolve spontaneously or can be managed by conservative therapy, and do not require any prolonged hospitalization of the patient [7, 8].

Cohen et al. [9] characterized implant-related complications as *major* if they required revision surgery, and *minor* if they resolved with minimal or no treatment. A survey reported 55 major (12%) and 32 minor (7%) complications.

Webb et al. [10] reporting their experience with 153 patients found 13.7% major and minor complications.

Table 1. Complications of cochlear implants at the Center for Cochlear Implantation of the Clinic for Ear, Nose and Throat Diseases, Clinical Center of Vojvodina

Complications	Number
Without complications	94
Unsuccessful implantation	4
Transient paresis of n. VII	4
Cochlea ossification	3
Transient ataxia	2
Unwanted stimulation of n. VII	1
Perilymph gusher	1
Device failure	1
Late infection of incision site	1

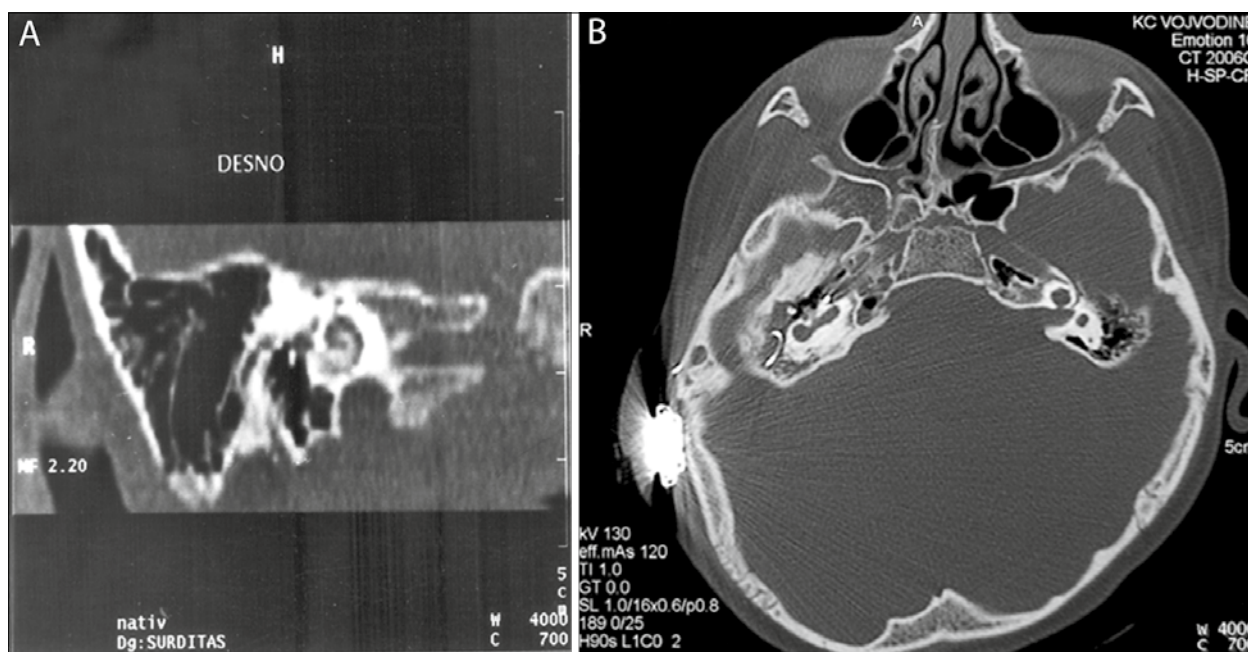


Figure 1. CT images: A) ossification of cochlea; B) congenital malformation

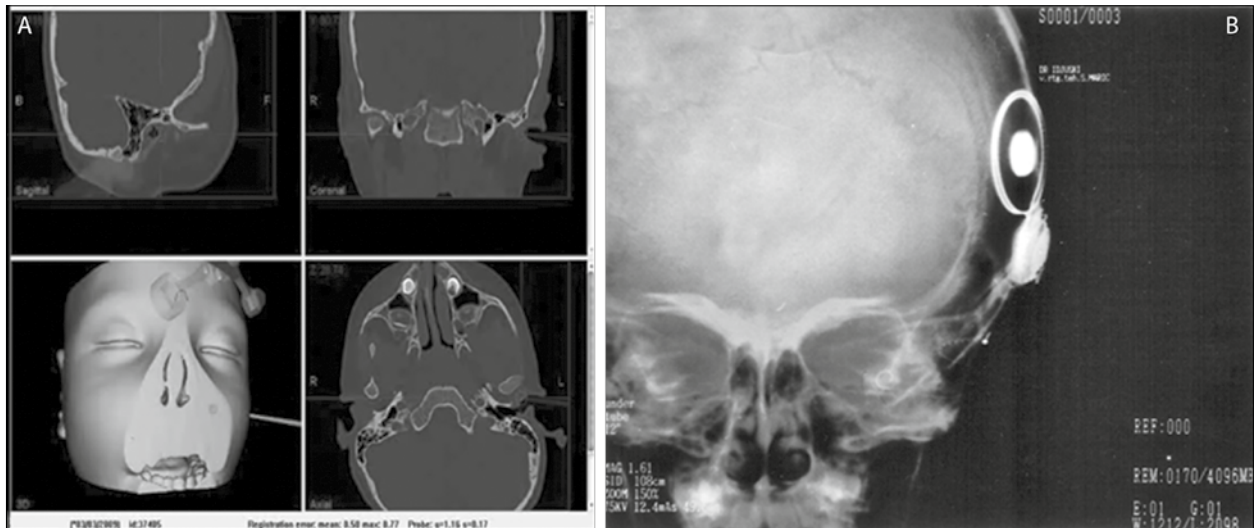


Figure 2. A) The surgical navigation system; B) Transorbital RTG – Hass

Hoffman and Cohen [11] noted that in later follow-up 220 (8%) major and 119 (4.3%) minor complications occurred among 2,751 implantations.

At our Center for Cochlear Implantation of the Clinical Center of Vojvodina, complications were observed in 11 patients, that is 10.05% of performed surgical procedures [12]. This incidence corresponds with the incidence rates reported from related centers worldwide, which is around 10%. In four (4.04%) patients treated at our Center, the single-stage surgery had not been initially possible, thus implantation was postponed and successfully accomplished in the second stage. In one patient, successful implantation using another type of electrode was performed on the same side. In three other patients, the second-stage surgery was performed on the other side with favorable outcome.

In cases of congenital malformations of the inner ear in two of our pediatric patients, the placement of the electrode into the altered cochlea could not be accomplished in spite of the surgical navigation system (Figure 2A-B).

Transient postoperative peripheral facial nerve paresis was observed in four (4.04 %) patients. This condition is considered a minor complication and is explained by transient edema of the facial nerve in the fallopian canal induced by the heating of its immediate surrounding structures during posterior tympanotomy. This impairment of nerve function was transient in all our patients. The symptoms resolved completely within the first month post surgery after conservative corticosteroid therapy without any need for subsequent surgical nerve decompression.

Major complications include facial nerve paralysis and implant exposure due to skin flap necrosis. Necrosis of the skin flap can lead to wound infection and device extrusion, necessitating scalp flap revision, and, when intractable infection is present, device removal with or without replacement.

Transient ataxia was observed in two (2.02%) patients, who presented with symptoms of postoperative instability and nausea. The patients responded well to symptomatic therapy and recovered rapidly without any consequences.

This complication might be explained by perilymph and endolymph leakage during the formation of the cochleostoma. After the surgery, upon reestablishment of the homeostasis of the semicircular canals, ataxia resolves spontaneously without need for any specific therapy.

Postoperative facial nerve stimulation was observed in one (1.01%) female patient. According to the available literature, this major complication of cochlear implantation occurs in some 0.31–14% of cases. Switching off the electrodes that directly stimulate the nerve might be the potential solution in such cases; however, this can result in reduced sound perception, which was the case in our patient. Thus, implantation of the second ear was performed to accomplish satisfactory overall hearing performance through bilateral stimulation at sub-maximal level. Instead of electrode remapping, facial nerve stimulation can be managed by botulinum toxin injections; however, this therapeutic option requires repeated administration at three- to six-month intervals [13, 14].

Extensive intraoperative perilymph gusher was observed in one (1.01%) patient. This is considered a minor complication, and was successfully managed during surgical procedure without affecting the outcome.

Function of external sound processor may be lost due to direct trauma, exposure to water and most frequently normal wear and tear of connecting lead-wires linking the sound processing unit with the magnetically retained antenna that relays information and power to the internal device. An internal device failure typically presents as either an immediate cessation of function or intermittency associated with reduced quality of sound and a period of diminishing function over days to weeks. Reports of painful stimulation have been noted, but are rare. Device failure is the most common indication for revision surgery and cochlear reimplantation.

Device failure at mapping session occurred in one (1.01%) patient. Such failures are considered major complications, as they inevitably require second surgery, which was successfully performed in our patient.

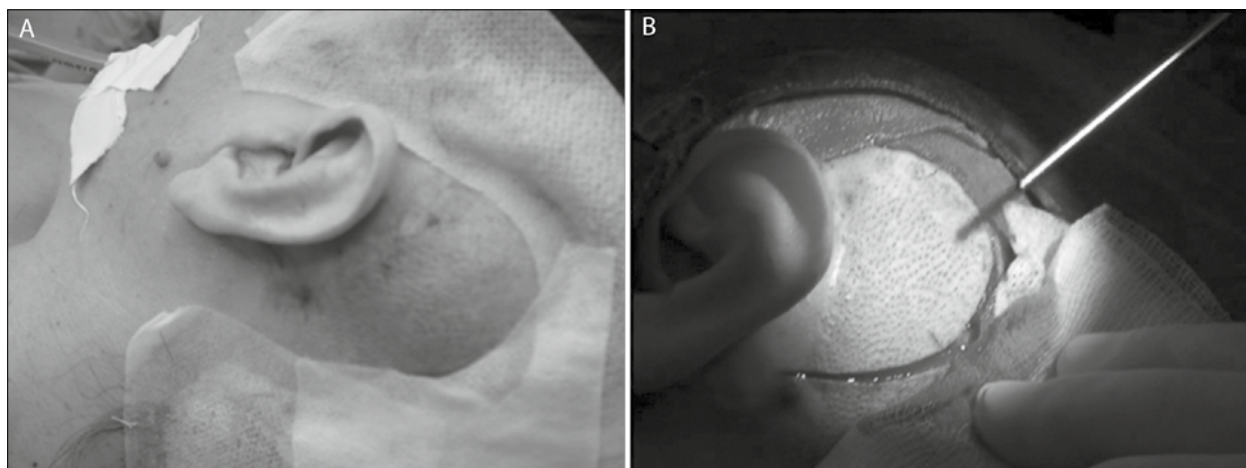


Figure 3. Implant region: A) skin infection; B) skin incision

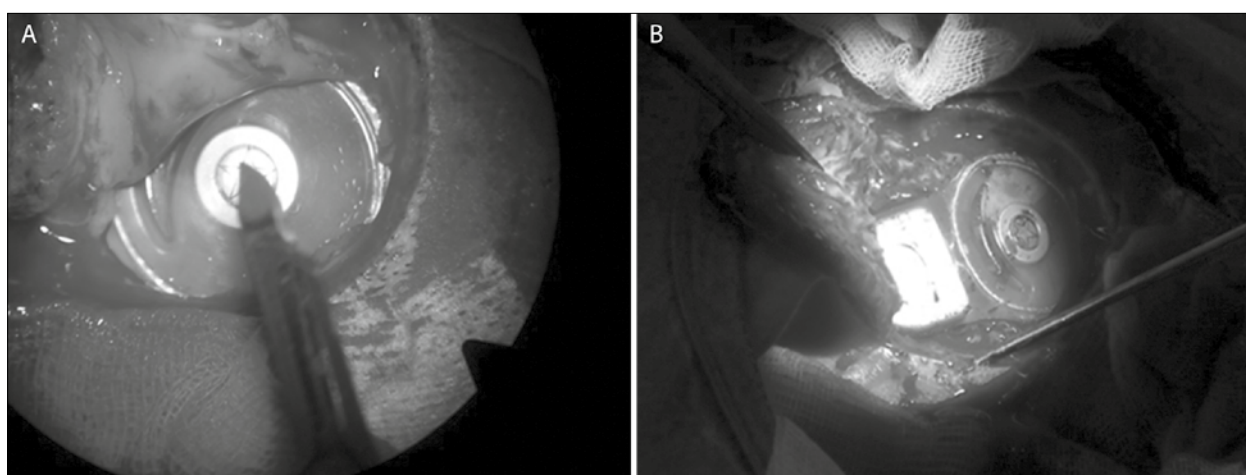


Figure 4. A) Infection with biofilm formation; B) Exposed implant with biofilm

Infection and flap breakdown require reimplantation less frequently [15]. Luetje and Jackson [16] reported a 9% rate of device failure in a review of 55 children.

Cochlear implants are rarely complicated by microbial infections. When such infections do occur, they can be difficult to treat with conventional antibiotic therapy, and may consequently require surgical removal of the implant [17, 18, 19]. Several studies have demonstrated that infections of cochlear implants are due to biofilm formation [20, 21]. A biofilm-related infection is difficult to treat, as biofilm formation results in increased bacterial resistance both to the body's immune response and to antibiotic therapy [22, 23]. Numerous studies have demonstrated that antimicrobial resistance is considerably increased when bacteria grow in biofilm mode [24, 25].

The increased antibiotic resistance of bacteria growing in a biofilm has been attributed to a number of factors, including decreased antibiotic penetration, altered metabolism of bacteria growing in biofilm and expression of biofilm-specific antibiotic resistance genes.

Skin infection in implant region was noticed as a late complication in one (1.01%) adult patient several months post surgery (Figure 3A-B). Prophylactic perioperative application of antibiotics can greatly reduce such infec-

tions, but other authors also reported the occurrence of this complication at the incidence of some 1%. In our patient, the infection was successfully managed by drainage and antibiotic therapy while preserving the functionality and position of the implant. In our case, the patient will have the infected implant temporarily removed and bathed in 3% hydrogen peroxide solution for approximately 30 minutes, in an attempt to eradicate the bacterial biofilm (Figure 4A-B). After this period of disinfection, the implant is replaced as before and the patient is discharged on a high-dose course of appropriate antibiotics (Figures 5A-B and 6A-B).

The risk of bacterial infection of an implanted device producing labyrinthitis or meningitis and associated reactive fibrosis and destruction of neural elements appears to be low. Reefhuis et al. [26] conducted a study of 4,264 children implanted between 1997 and 2002 and found 29 cases of bacterial meningitis of all implanted children. This rate of meningitis caused by *Streptococcus pneumoniae* was 30 times the incidence in the general population.

Complications reported in the literature, such as electrode extrusion, skin necrosis over the implant, or meningitis, which is considered the most severe postoperative complication, have not been recorded at our Center since

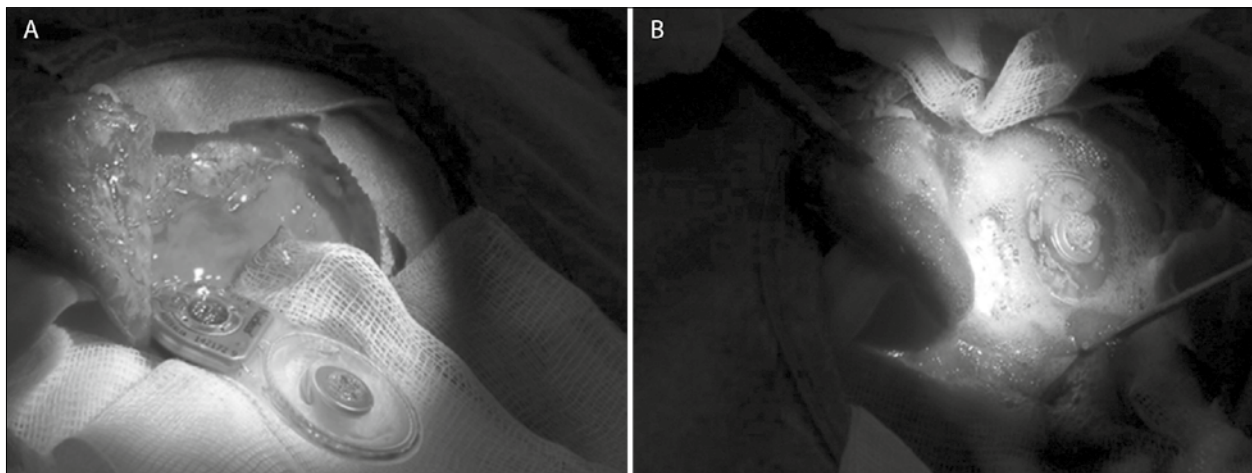


Figure 5. A) Infected implant removed; B) Implant bathed in a 3% hydrogen peroxide solution

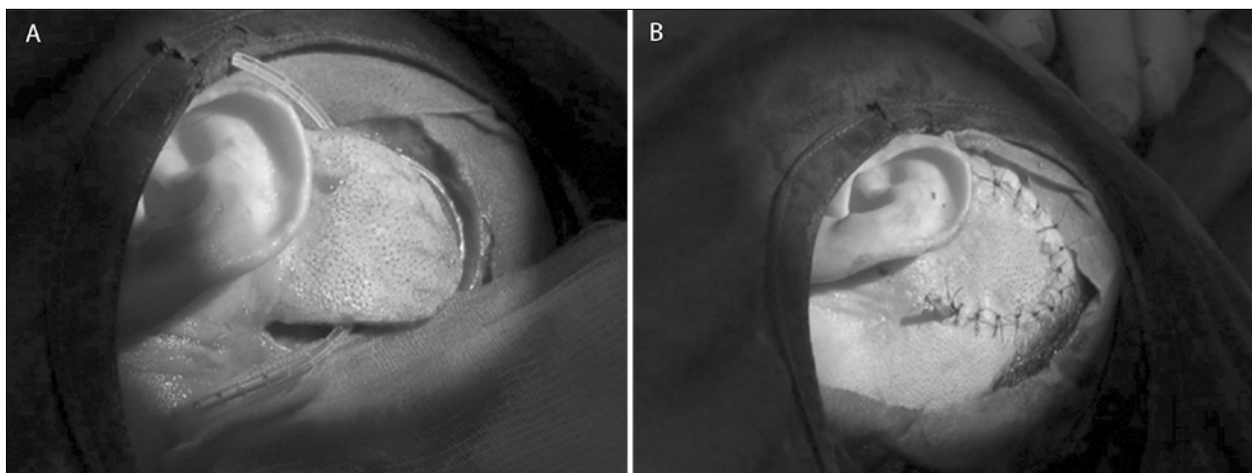


Figure 6. A) The implant is replaced; B) Drainage with local antibiotics

the very beginning. Absence of postoperative meningitis in patients treated at the Center can be attributed to timely pneumococcal vaccination of children.

CONCLUSION

The majority of our patients, i.e. 84 (84.9%), manifested prelingual hearing loss, whereas postlingual type of deafness was observed in 15 (15.1%) cases.

At our Center for Cochlear Implantation of the Clinical Center of Vojvodina, the majority of procedures (89.5%) were not accompanied by any post-surgical complications.

REFERENCES

1. Dankuc D. Kohlearni implant. Uvodnik. *Med Pregl.* 2005; 58(7-8):329-32. [PMID: 16296573]
2. Komazec Z, Dankuc D, Vlaški LJ, Lemajić-Komazec S, Nedeljkov S, Sokolovac I. Kohlearna implantacija na Klinici za bolesti uva, grla i nosa Kliničkog centra Vojvodine. *Med Pregl.* 2007; 60(11-12):643-8. [DOI: 10.2298/MPNS0712643K] [PMID: 18666611]
3. Komazec Z, Lemajić-Komazec S, Dankuc D, Vlaški LJ. Kohlearna implantacija – rizici i komplikacije. *Med Pregl.* 2008; 61(Suppl 2):27-30. [PMID: 18924587]
4. Valencia DM, Rimell FL, Friedman BJ, Oblander MR, Helmbrecht J. Cochlear implantation in infants less than 12 months of age. *Int J Pediatr Otorhinolaryngol.* 2008; 72(6):767-73. [DOI: 10.1016/j.ijporl.2008.02.009] [PMID: 18403026]
5. Baumgartner WD, Pok SM, Egelerler B, Franz P, Gstöttner W, Hamzavi J. The role of age in pediatric cochlear implantation. *Int J Pediatr Otorhinolaryngol.* 2002; 62(3):223-8. [DOI: 10.1016/S0165-5876(01)00621-8] [PMID: 11852125]

6. Yeagle JD, Ceh KM, Francis HW. Geriatric cochlear implantation. *Operative Techniques in Otolaryngology-Head and Neck Surgery*. 2010; 21(4):266-71. [DOI: 10.1016/j.otot.2010.03.003]
7. Black IM, Bailey CM, Albert DM, Leighton SE, Hartley BE, Chatrath P, et al. The Great Ormond Street Hospital paediatric cochlear implant programme 1992–2004. A review of surgical complications. *Cochlear Implants Int*. 2007; 8(2):53-67. [DOI: 10.1179/cim.2007.8.2.53] [PMID: 17549805]
8. McJunkin J, Jeyakumar A. Complications in pediatric cochlear implants. *Am J Otolaryngol*. 2010; 31(2):110-3. [DOI: 10.1016/j.amjoto.2008.11.012] [PMID: 20015728]
9. Cohen NL, Hoffman RA, Stroschein M. Medical or surgical complications related to the Nucleus multichannel cochlear implant. *Ann Otol Rhinol Laryngol Suppl*. 1988; 135:8-13. [PMID: 3140706]
10. Webb RL, Lehnhardt E, Clark GM, Laszig R, Pyman BC, Franz BK. Surgical complications with the cochlear multiple-channel intracochlear implant: experience at Hannover and Melbourne. *Ann Otol Rhinol Laryngol*. 1991; 100(2):131-6. [DOI: 10.1177/000348949110000208] [PMID: 1992899]
11. Hoffman RA, Cohen NL. Surgical pitfalls in cochlear implantation. *Laryngoscope*. 1993; 103(7):741-4. [DOI: 10.1288/00005537-199307000-00006] [PMID: 8341098]
12. Dankuc D, Šegan D, Komazec Z, Vlaški Lj, Lemajić Komazec S, Sokolovac I. Cochlear implant surgery at the Clinical center of Vojvodina – ten year experience. *Med Pregl*. 2014; 67(Suppl 1):25-31. [DOI:10.2298/MPNS14S1025D]
13. Kim CS, Chang SO, Oh SH, Lee HJ. Complications in cochlear implantation. *International Congress Series*. 2004; 1273:145-8. [DOI: 10.1016/j.ics.2004.07.055]
14. Kubo T, Matsuura S, Iwaki T. Complications of cochlear implant surgery. *Operative Techniques in Otolaryngology-Head and Neck Surgery*. 2005; 16(2):154-8. [DOI: 10.1016/j.otot.2005.03.007]
15. Alexiades G, Roland JT Jr, Fishman AJ, Shapiro W, Waltzman SB, Cohen NL. Cochlear reimplantation: surgical techniques and functional results. *Laryngoscope*. 2001; 111(9):1608-13. [DOI: 10.1097/00005537-200109000-00022] [PMID: 11568614]
16. Luetje CM, Jackson K. Cochlear implants in children: what constitutes a complication? *Otolaryngol Head Neck Surg*. 1997; 117:243-7. [DOI: 10.1016/S0194-5998(97)70181-5] [PMID: 9334772]
17. Cunningham CD 3rd, Slattery WH 3rd, Luxford WM. Postoperative infection in cochlear implant patients. *Otolaryngol Head Neck Surg*. 2004; 131(1):109-14. [DOI: 10.1016/j.otohns.2004.02.011] [PMID: 15243566]
18. Howard NS, Antonelli PJ. Complications of cochlear implant placement with minimal hairshave. *Am J Otolaryngol*. 2004; 25:84-7. [DOI: 10.1016/j.amjoto.2003.11.003] [PMID: 14976651]
19. Tambyraja RR, Gutman MA, Megerain CA. Cochlear implant complications: utility of federal database in systematic analysis. *Arch Otolaryngol Head Neck Surg*. 2005; 131(3):245-50. [DOI: 10.1001/archotol.131.3.245] [PMID: 15781766]
20. Antonelli PJ, Lee JC, Burne RA. Bacterial biofilms may contribute to persistent cochlear implant infection. *Otol Neurotol*. 2004; 25(6):953-7. [DOI: 10.1097/00129492-200411000-00015] [PMID: 15547425]
21. Pawlowski KS, Wawro D, Roland PS. Bacterial biofilm formation on a human cochlear implant. *Otol Neurotol*. 2005; 26:972-5. [DOI: 10.1097/01.mao.0000169047.38759.8b] [PMID: 16151345]
22. Hoyle BD, Jass J, Costerton JW. The biofilm glycocalyx as a resistance factor. *J Antimicrob Chemother*. 1990; 26(1):1-5. [DOI: 10.1093/jac/26.1.1] [PMID: 2211430]
23. Buret A, Ward KH, Olson ME, Costerton JW. An in vivo model to study the pathobiology of infectious biofilms on biomaterial surfaces. *J Biomed Mater Res*. 1991; 25(7):865-74. [DOI: 10.1002/jbm.820250706] [PMID: 1918103]
24. Lewis K. Riddle of biofilm resistance. *Antimicrob Agents Chemother*. 2001; 45(4):999-1007. [DOI: 10.1128/AAC.45.4.999-1007.2001] [PMID: 11257008]
25. Anderson GG, O'Toole GA. Innate and induced resistance mechanisms of bacterial biofilms. *Curr Top Microbiol Immunol*. 2008; 322:85-105. [DOI: 10.1007/978-3-540-75418-3_5] [PMID: 18453273]
26. Reefhuis J, Honein MA, Whitney CG, Chamany S, Mann EA, Biernath KR, et al. Risk of bacterial meningitis in children with cochlear implants. *N Engl J Med*. 2003; 349(5):435-45. [DOI: 10.1056/NEJMoa031101] [PMID: 12890842]

Компликације кохлеарне имплантације у Клиничком центру Војводине

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КРАТАК САДРЖАЈ

Увод Прва савремена кохлеарна имплантација у Србији урађена је 26. новембра 2002. године у Центру за кохлеарну имплантацију Клинике за болести ува, грла и носа Клиничког центра Војводине у Новом Саду.

Циљ рада Сврха овог рада је анализа интраоперационих и постоперационих компликација. Велике компликације су све оне које доводе до потребе за поновном операцијом, експлантацијом и реимплантацијом или доводе до тешког обољења, односно смрти болесника. Мале су све остале компликације које се могу санирати спонтано или конзервативним лечењем и не захтевају продужену хоспитализацију болесника.

Методе рада У периоду 2002–2013. године оперисано је 99 болесника и при том уграђено 100 кохлеарних имплантата. Интраоперационе и постоперационе компликације анализирани су у испитиваној групи болесника.

Резултати Анализом је обухваћено 99 болесника, од којих је најмлађи имао једну, а најстарији 61 годину. Компликације

су се јавиле код 11 испитаника од 105 (10,5%) извршених операција. Већина операција (89,5%) прошла је без компликација. Од чешћих компликација забележене су неуспешна имплантација у првом акту (4,04%) и пролазна одузетост фацијалног живца. Од ређих компликација јавиле су се осификација кохлеје (1,01%) и пролазна атаксија (2,02%). Врло ретке су биле стимулација фацијалног живца (1,01%), интраоперационо појачано истицање перилимфе (1,01%), квар апарата и касна инфекција (1,01%).

Закључак Компликације попут екструзије електроде, некрозе коже изнад имплантата и менингитис, који се сматра најтежом постоперационом компликацијом у Центру за кохлеарну имплантацију од почетка његовог рада, нису забележене. Чињеница да се менингитис није јављао код болесника оперисаних у нашем центру може се објаснити увођењем правовремене вакцинације деце применом пнеумококне вакцине.

Кључне речи: кохлеарна имплантација; интраоперационе компликације; постоперационе компликације

Changes in Cervical Lordosis and Cervicovertebral Morphology in Different Ages with the Possibility of Estimating Skeletal Maturity

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SUMMARY

Introduction During growth, proportions of craniofacial and cervical structures are changed. Craniofacial and cervicovertebral structures are morphologically and functionally connected, but their each other's influence is still unknown.

Objective The aim of this study was to determine the changes in cervical lordosis and cervicovertebral morphology in different age periods and the possibility of estimating skeletal maturity, based on the percentage of anterior cervical vertebrae body height sum in the total anterior C2–C5 height.

Methods The study included lateral radiographs of 120 patients of both sexes, divided into three different age groups: eight, 12–13 and 17–18 years of age. Five craniofacial and 15 cervical parameters were measured and analyzed.

Results The results showed significant correlation between cervical lordosis angle and age, gender, anterior and posterior body height of C3, C4, C5, anterior C4–C5 and posterior C2–C3, C3–C4, C4–C5 intervertebral space, anterior body height of C2–C5. Overall values of all cervical body heights were more present in the total height of the spine in females, while all intervertebral spaces were more present in males. The percentage of anterior and posterior C2, C3, C4, C5 body height sum compared to total C2–C5 height increases with age.

Conclusion The cervical lordosis becomes more curved and vertebral bodies occupy more space in females, while intervertebral spaces occupy more in males. Skeletal maturity could be estimated following vertebral percentage distribution in the total anterior C2–C5 part.

Keywords: spinal curvatures; lordosis; growth; maturity

INTRODUCTION

During prenatal and postnatal period proportions of cervical structures change [1, 2]. Cervicovertebral morphology is influenced by factors such as age [3], gender [3-7], ethnic origin [5, 8] and craniofacial morphology [6, 7, 9].

The change in cervicovertebral morphology is a process lasting from birth to full maturity, passing through all stages of skeletal development [1]. Every stage can be seen on lateral cephalogram which was used to assess skeletal maturity using the cervical vertebral maturation (CVM) method [10, 11, 12]. However, validity, reliability and reproducibility of the CVM method were analyzed in several studies. It was suggested that this method was subjective and that it should be used with some other parameters that estimate skeletal maturity [13-18].

Cervical curve begins to form during fetal development, but it does not assume its natural form until after birth. It changes when it begins to bear the weight of the head. Also, lordotic curve results partly from difference in the anterior and posterior intervertebral space heights [19].

OBJECTIVE

Our aim was to determine the changes in cervical lordosis in different age groups, to compare

the differences in cervicovertebral morphology between genders, and to determine the possibility of estimating skeletal maturity based on the percentage of anterior cervical vertebrae C2–C5 body height sum in comparison to the total anterior height of that part of the cervical spine.

METHODS

The study included lateral cephalograms of 120 (71 female, 49 male) patients treated at the Clinic of Orthodontics, School of Dental Medicine, University of Belgrade. The Ethical Committee of the School of Dental Medicine, University of Belgrade, approved this research (No. 36/14 – 2013).

The inclusion criteria were white subjects of Serbian population of both sexes with the visibility of the C1–C5 cervical vertebrae. Total sample was divided into three different age groups: I (eight-year-olds – pre-puberty), II (12- and 13-year-olds – accelerated period of growth) and III (17- and 18-year-olds – final phase of growth); each group consisted of 40 subjects. None of the subjects had a history of previous orthodontic treatment, craniofacial and cervical vertebra anomalies, trauma, or systemic muscle or temporomandibular joint disorders.

Lateral cephalograms were made using a standardized technique on a ProMax® device

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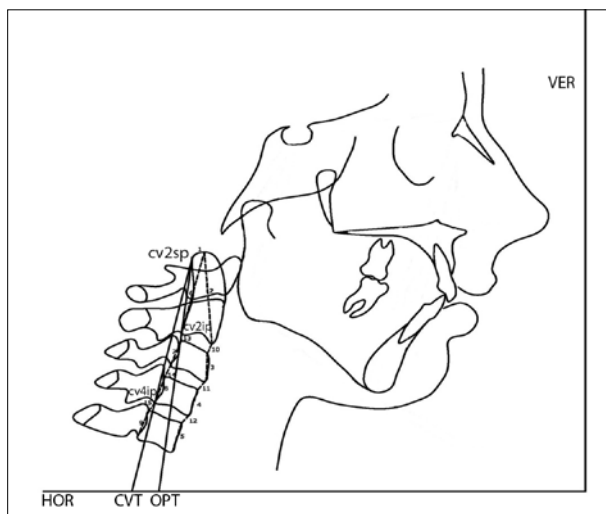


Figure 1. Cephalometric points, angular and linear measurements used for lateral cephalogram analysis

Ver – true vertical line projected on the film; Hor – true horizontal line drawn by constructing a line perpendicular to the true vertical line; cv2sp – postero-superior points of C2 vertebral bodies; cv2ip – postero-inferior points of C2 vertebral bodies; OPT – tangent of odontogenic process through cv2sp and cv2ip; CVT – tangent through cv2sp and cv4ip

(enlargement factor 10%), Planmeca, Helsinki, Finland. The patients were in standing position, with the head in the natural head position, and with the teeth in occlusion [20]. All radiographs were traced manually, using acetate paper, and all measurements were taken by single observer (E.L.). On each radiograph cervical parameters (Figure 1, Table 1) were measured and used to assess cervicovertebral morphology in different age groups and genders.

Statistical analysis

All statistical analyses were performed in IBM SPSS Statistics for Windows Software (Version 20.0, Armonk, NY, USA). The results were presented as frequency, percent and mean $\pm$ SD. The analysis of variance and Kruskal–Wallis test were used to compare three groups while t-test and Mann–Whitney U-test were used to compare two groups of patients. Bonferroni correction was used for multiple comparisons. Pearson correlation was performed to assess associations of OPT/CVT angle and other variables. All p-values less than 0.05 were considered significant.

RESULTS

Total sample consisted of 71 female and 49 male patients divided into three different age groups. This age distribution was made in order to see the cervicovertebral morphology in different age periods.

The results showed the trend of OPT/CVT angle increase from group I to group III and statistically higher value in female patients. A comparison between age groups showed statistically significant increase in older groups compared to younger ones (Table 2).

The parameters with statistically significant correlation with OPT/CVT angle are presented in Table 3. Correlation coefficients are presented in an interval from the smallest to the largest and showed weak to moderate correlation.

Tables 4 and 5 show values and comparisons between age group I compared to age group II, and age group II com-

Table 1. Description of cervical parameters

(1) OPT/CVT (°)	Angle of cervical curvature – lordosis; down open angle between OPT: tangent of odontogenic process through cv2sp and cv2ip and CVT: tangent through cv2sp and cv4ip
(2–5) ABH C2–C5 (mm)	Anterior height of the cervical vertebra bodies – the distance between antero-superior and antero-inferior points of C2–C5 vertebral bodies
(6–9) PBH C2–C5 (mm)	Posterior height of the cervical vertebra bodies – the distance between postero-superior and postero-inferior points of C2–C5 vertebral bodies
(10–12) AIS C2–C5 (mm)	Anterior intervertebral space of the cervical vertebrae – the anterior distance between C2–C5 bodies
(13–15) PIS C2–C5 (mm)	Posterior intervertebral space of the cervical vertebrae – the posterior distance between C2–C5 bodies
%ABHC/AH C2–C5	Percentage of anterior body heights of C2, C3, C4 and C5 in total anterior height of the C2–C5 part
%PBHC/PH C2–C5	Percentage of posterior body heights of C2, C3, C4 and C5 in total posterior height of the C2–C5 part
%AIS C2–C3/AH C2–C5	Percentage of anterior intervertebral space height C2–C3, C3–C4, C4–C5 in total anterior height of the C2–C5 part
%PIS C2–C3/PH C2–C5	Percentage of posterior intervertebral space height C2–C3, C3–C4, C4–C5 in total posterior height of the C2–C5 part
% Σ ABH C/AH C2–C5	Percentage of anterior C2, C3, C4, C5 body heights sum in total anterior height of the C2–C5 part
% Σ PBH C/PH C2–C5	Percentage of posterior C2, C3, C4, C5 body heights sum in total posterior height of the C2–C5 part
% Σ AIS/AH C2–C5	Percentage of anterior intervertebral space height sum in total anterior height of the C2–C5 part
% Σ PIS/PH C2–C5	Percentage of posterior intervertebral space height sum in total posterior height of the C2–C5 part

Table 2. Changes of cervical lordosis angle according to age and gender

Variable OPT/CVT (°)	Age groups ^a						
	Overall	I	I vs II	II	II vs III	III	I vs III
Total (n=120)	4.03 $\pm$ 3.07	2.51 $\pm$ 3.14	*	4.63 $\pm$ 2.06		4.95 $\pm$ 3.33	**
Male (n=49) ^b	3.02 $\pm$ 3.31	1.40 $\pm$ 3.52		3.83 $\pm$ 2.36		3.63 $\pm$ 3.65	
Female (n=71) ^b	4.73 $\pm$ 2.70*	3.18 $\pm$ 2.74	*	5.27 $\pm$ 1.55*		5.83 $\pm$ 2.84*	**

^a ANOVA; ^b Student's t-test;

* p<0.05; ** p<0.01

For a description of the variables, refer to Table 1.

n – number of patients

Table 3. Correlation of cervical lordosis angle (OPT/CVT) with different parameters

Variable	R
Gender	0.274**
Age	0.326**
ABH C3, C4, C5	0.269**–0.278**
PBH C3, C4, C5	0.246**–0.255**
AIS C4–C5	-0.189*
PIS C2–C3, C3–C4, C4–C5	-0.217**–0.328**
ABH C2–C5	0.255**
% Σ AH C/C2–C5	0.225*
% Σ PH C/C2–C5	0.339**
% Σ AIS/C2–C5	-0.225*
% Σ PIS/C2–C5	-0.339**

R – coefficient of correlation

* $p < 0.05$, ** $p < 0.01$

pared to age group III. Comparison between group I and group III was not described because of large age difference and expected statistical significance. Statistically significant increase of anterior and posterior C2, C3, C4 and C5 body heights between age groups is shown in Table 4. All anterior intervertebral spaces were statistically smaller in group III compared to group II, while posterior intervertebral spaces were statistically smaller in group II compared to group I. Therefore, there was general trend of cervical vertebrae body growth from group I to group III and decrease of the intervertebral space. There was a significant increase of total C2–C5 anterior and posterior height. According to sex, overall linear values were greater in males, except the values of the anterior body heights of the vertebrae C3, C4 and C5. Statistically significant difference between sexes was found in anterior and posterior body height of the vertebrae C2 and posterior intervertebral space C3–C4.

The results showed that the biggest part of the cervical spine C2–C5 was vertebra C2, average $44.12 \pm 2.09\%$ of the anterior height and $42.35 \pm 2.35\%$ of the posterior height of the part C2–C5. The rest was equally distributed with vertebrae C3, C4, C5 at around 12.7% of the anterior height, and around 15.3% of posterior height of the part C2–C5. The trend of increasing anterior and posterior C3, C4 and C5 body distribution was observed from group I to group III, while percentages of anterior and posterior C2 body height, as well as anterior and posterior height of all the intervertebral spaces, were lower (Table 5). Overall values of anterior and posterior body height were more presented in the total height of the spine in females, but statistical significances were found in anterior C4 and C5 body height. The values of all anterior and posterior intervertebral spaces were more present in the total height of the spine in males, but statistical significances were found in anterior C2–C3 and C4–C5 intervertebral spaces.

The percentage of anterior and posterior C2, C3, C4 and C5 body height sum compared to total C2–C5 height showed the trend of increasing from group I to group III and the percentage was greater in females from all groups. Statistical significance was found in most parameters of anterior part of the spine (Table 6).

In order to lower the margin of error, repeated measurements were taken during one week, by a single observer

(E.L.), on 20 randomly selected radiograms. Inter-observer reliability was measured with inter-class correlation coefficient. The coefficient was high ($ICC = 0.986$; $p < 0.001$), which suggested high precision of measurements and low error.

DISCUSSION

Incompletely clarified link between craniofacial and cervical structures and common questions about the reliability of skeletal maturity estimations using cervical morphology changes makes the cervical region still a current field of research. Considering the visibility of C1–C5 vertebrae in lateral cephalograms, this study described the morphology of the stated cervical segment and cervical lordosis (OPT/CVT). Some previous studies analyzed the upper and middle (OPT, CVT) segment [4, 7, 21], and lower (EVT) segment of the cervical column and it was found that morphology changes in upper and middle segments were affected by facial development [6].

Age and sex play important roles in cervical lordosis change during growth as studies conducted by Hellsing et al. [3] and Nik and Aciyabar [7] have shown, so our study included three age groups of patients in different stages of development in order to notice the differences in values of OPT/CVT angle. Our results indicated a trend of increased angle in females with age, while the angle decreased after 12 and 13 years of age in male patients. Lower angle was found in males, which indicates straighter spine.

The positive correlation was found between cervical lordosis, and age and sex (Table 3). These results are in agreement with previous studies of differences in spinal curvature between sexes [3, 6, 7], not confirmed by Tecco and Festa [22]. Dos Santos et al. [1] included Brazilian six- to 16-year-old patients and analyzed angular inclination of cervical vertebrae (C1–C5) along the sagittal plane. They found opposite angular tendency of vertebrae C2, C3 and C4 during growth. The spine has a tendency for flexion in females, but extension in males. These findings match with the results of our study, but as a consequence of differences in age groups it was not possible to determine the magnitude of variations between them.

Dimensions of cervical vertebrae and intervertebral spaces change during growth [1, 2, 12, 23, 24]. Generally, in our study, the values of the vertebrae body heights got higher with age, while the spaces between them became smaller (Table 4). Anterior and posterior C2 body height, posterior C3, C4 and C5 body heights, anterior and posterior C2–C3, C3–C4 and C4–C5 intervertebral space heights were greater in males, while the values of the anterior C3, C4 and C5 body heights were greater in females. At the age of eight, the values of C2, C3, C4 and C5 anterior and posterior body heights and posterior intervertebral space C2–C3 were greater in females that entered puberty earlier. At the ages of 12 and 13, the values of anterior and posterior C3 and C4 body heights, anterior C5 body height, and posterior intervertebral space C3–C4 and C4–C5 were greater in females, while at the ages of 17 and 18, all linear parameters became greater in

males (they reached females). The values of anterior and posterior C3, C4, and C5 body heights showed a positive correlation between cervical lordosis, while the values of anterior C4–C5 and posterior C2–C3, C3–C4, C4–C5 intervertebral spaces showed negative correlation (Table 3). The tendency of greater cervical dimensions in males and

the fact that males have a longer spine than females was noted in several studies [5, 8]. On the other hand, Baydas et al. [23] study included 13- to 15-year-old patients and found similar results in most parameters for both sexes. Dos Santos et al. [1] study showed that anterior body height of the vertebra C2, anterior and posterior body

Table 4. Changes of cervical linear parameters according to age and gender

Variable (mm)		Gender ^b	Age groups ^a				
			Overall	I	vs	II	vs III
C2	ABH	Total	31.94±3.97	28.31±2.58	***	31.97±2.57	***
		Male	32.44±4.76	27.28±2.28	***	32.38±2.75	***
		Female	31.60±3.31†	28.92±2.60†	**	31.63±2.42	***
	PBH	Total	28.76±3.37	25.92±2.35	***	28.79±2.23	***
		Male	29.31±4.14	25.13±2.39	***	29.07±2.60	***
		Female	28.39±2.68†	26.40±2.23	**	28.55±1.90	**
C3	ABH	Total	9.57±3.04	6.45±0.90	***	9.18±1.63	***
		Male	9.56±3.27	6.20±0.77	***	8.68±1.16	***
		Female	9.57±2.89	6.60±0.94	***	9.58±1.87	***
	PBH	Total	10.63±2.51	8.03±0.86	***	10.47±1.47	***
		Male	10.86±2.81	7.87±0.65	***	10.41±1.32	***
		Female	10.48±2.31	8.13±0.97	***	10.53±1.62	***
C4	ABH	Total	9.26±2.79	6.46±0.78	***	8.76±1.50	***
		Male	9.11±2.91	6.17±0.36	***	8.22±1.00	***
		Female	9.35±2.72	6.64±0.91	***	9.21±1.71†	***
	PBH	Total	10.55±2.59	7.87±0.94	***	10.32±1.33	***
		Male	10.82±2.91	7.60±0.74	***	10.46±1.42	***
		Female	10.36±2.35	8.02±1.03	***	10.20±1.28	***
C5	ABH	Total	9.27±2.73	6.76±0.83	***	8.63±1.42	***
		Male	9.17±2.91	6.20±0.41	***	8.33±1.08	***
		Female	9.35±2.62	6.76±0.74†	***	9.07±1.56	***
	PBH	Total	10.49±2.58	7.84±0.89	***	10.19±1.23	***
		Male	10.71±2.94	7.53±0.86	***	10.23±1.28	***
		Female	10.34±2.31	8.03±0.87	***	10.15±1.22	***
C2–C3	AIS	Total	4.18±1.39	4.95±1.05		4.58±1.22	***
		Male	4.64±1.30	5.16±1.12		5.16±0.88	***
		Female	3.87±1.37	4.82±1.01		4.10±1.27†	***
	PIS	Total	2.84±0.96	3.33±0.86	**	2.80±0.95	
		Male	2.94±0.96	3.19±0.74		2.93±1.17	
		Female	2.77±0.96	3.41±0.92	**	2.68±0.74	
C3–C4	AIS	Total	4.29±1.42	5.18±1.06		4.69±1.16	***
		Male	4.70±1.35	5.49±0.67		5.11±1.19	***
		Female	4.00±1.41	4.98±1.21		4.35±1.05†	***
	PIS	Total	2.48±0.96	3.06±0.85	**	2.26±0.87	
		Male	2.67±1.10	3.43±0.79	**	2.26±1.06	
		Female	2.35±0.85†	2.83±0.84†	*	2.27±0.71	
C4–C5	AIS	Total	3.88±1.23	4.48±0.96		4.27±1.04	***
		Male	4.40±1.11	4.89±0.90		4.87±0.67	***
		Female	3.51±1.18	4.24±0.92†		3.78±1.05†	***
	PIS	Total	2.44±0.92	3.03±0.78	***	2.20±0.83	
		Male	2.51±1.02	3.23±0.93	**	2.16±0.81	
		Female	2.39±0.85	2.92±0.67	**	2.23±0.86	
C2–C5	AH	Total	72.44±9.80	62.58±4.63	***	72.07±5.27	***
		Male	74.08±11.34	61.60±4.62	***	72.63±5.11	***
		Female	71.30±8.49	63.17±4.64	***	71.62±5.47	***
	PH	Total	68.19±9.51	59.08±3.81	***	67.01±4.84	***
		Male	69.81±11.27	57.97±3.35	***	67.51±4.87	***
		Female	67.07±7.97	59.74±3.98	***	66.60±4.89	***

^a ANOVA; ^b Student's t-test;

Significant gender difference † p<0.05; Significance level at * p<0.05, ** p<0.01, *** p<0.001

For a description of the variables, refer to Table 1.

Table 5. Percentage of anterior and posterior cervical vertebrae body height and intervertebral space compared to total anterior and posterior height of C2–C5 part

Variable (%)		Gender ^b	Age groups ^a					
			Overall	I	vs	II	vs	III
C2	ABH	Total	44.21±2.09	45.21±1.95		44.37±1.88	**	43.04±1.88
		Male	43.88±1.99	44.30±1.98		44.57±1.73	*	42.71±1.83
		Female	44.43±2.14	45.76±1.75†	*	44.20±2.01		43.27±1.92
	PBH	Total	42.35±2.35	43.84±1.92		42.97±1.72	***	40.26±1.73
		Male	42.15±2.27	43.28±2.18		43.03±1.58	***	40.10±1.55
		Female	42.50±2.41	44.17±1.71		42.92±1.87	***	40.37±1.87
C3	ABH	Total	12.94±2.67	10.32±1.28	***	12.69±1.79	***	15.81±1.17
		Male	12.58±2.55	10.07±1.01	***	11.93±1.11	***	15.68±1.18
		Female	13.19±2.75	10.47±1.42	***	13.32±2.01†	***	15.90±1.19
	PBH	Total	15.42±1.91	13.61±1.25	***	15.59±1.53	***	17.07±1.02
		Male	15.35±1.82	13.59±1.12	***	15.39±1.35	**	16.96±1.24
		Female	15.47±1.98	13.62±1.34	***	15.75±1.67	**	17.15±0.86
C4	ABH	Total	12.55±2.41	10.34±1.19	***	12.12±1.58	***	15.20±1.20
		Male	12.05±2.21	10.04±0.59	**	11.30±0.97	***	14.78±1.25
		Female	12.90±2.49†	10.53±1.14	***	12.79±1.68†	***	15.47±1.11
	PBH	Total	15.28±1.98	13.30±1.25	***	15.37±1.40	***	17.16±0.88
		Male	15.27±2.04	13.13±1.27	***	15.47±1.51	**	17.06±1.07
		Female	15.28±1.95	13.41±1.25	***	15.29±1.33	***	17.23±0.75
C5	ABH	Total	12.65±2.24	10.81±1.15	***	11.94±1.46	***	15.19±1.13
		Male	12.16±2.20	10.41±0.95		11.29±1.29	***	14.76±1.23
		Female	12.98±2.22†	11.05±1.21	***	12.47±1.40†	***	15.47±0.98
	PBH	Total	15.19±1.96	13.28±1.33	***	15.18±1.27	***	17.13±0.89
		Male	15.11±2.08	13.01±1.59	***	15.12±1.31	***	17.06±1.07
		Female	15.25±1.89	13.44±1.15	***	15.22±1.26	***	17.18±0.77
C2–C3	AIS	Total	5.97±2.32	7.89±1.50	***	6.39±1.81	***	3.64±1.19
		Male	6.52±2.26	8.35±1.53		7.15±1.38	***	4.09±1.40
		Female	5.60±2.30†	7.61±1.44	***	5.77±1.90†	***	3.34±0.95
	PIS	Total	4.29±1.67	5.64±1.36	***	4.21±1.46	***	3.04±1.03
		Male	4.37±1.68	5.51±1.28		4.39±1.77		3.27±1.13
		Female	4.24±1.68	5.71±1.42	***	4.05±1.17	**	2.29±0.96
C3–C4	AIS	Total	6.14±2.39	8.26±1.54	***	6.54±1.62	***	3.63±1.13
		Male	6.62±2.34	8.91±0.72	***	7.04±1.52	***	4.01±1.33
		Female	5.81±2.39	7.87±1.77†	***	6.12±1.61	***	3.38±0.92
	PIS	Total	3.76±1.70	5.20±1.53	***	3.40±1.37		2.68±1.07
		Male	3.99±1.93	5.91±1.35	***	3.38±1.67		2.68±1.21
		Female	3.60±1.51	4.77±1.50	**	3.42±1.10		2.65±0.96
C4–C5	AIS	Total	5.54±2.06	7.17±1.49	***	5.96±1.51	***	3.48±1.12
		Male	6.19±2.00	7.92±1.34	*	6.73±0.93	***	3.97±1.25
		Female	5.08±1.99†	6.71±1.40†	**	5.34±1.61†	***	3.16±0.91†
	PIS	Total	3.69±1.60	5.14±1.30	***	3.28±1.26		2.66±1.06
		Male	3.76±1.80	5.56±1.57	***	3.21±1.22		2.68±1.21
		Female	3.65±1.46	4.88±1.07	***	3.34±1.31		2.65±0.96

^a ANOVA; ^b Student's t-test;Significant gender difference † p<0.05; Significance level at * p<0.05, ** p<0.01, *** p<0.001
For a description of the variables, refer to Table 1.**Table 6.** Percentage of anterior and posterior C2, C3, C4, C5 body heights sum compared to total anterior and posterior height of C2–C5 part

Variable		%ΣABH C/AH C2–C5					%ΣPBH C/PH C2–C5				
		Age groups ^a									
		I	vs	II	vs	III	I	vs	II	vs	III
Gender ^b	Total	76.68±3.55	**	81.11±4.31	**	89.24±3.13	84.03±3.20	**	89.11±3.33	**	91.62±2.46
	Male	74.82±2.40	**	79.08±2.62	**	87.93±3.68	83.02±3.48	**	89.01±3.82		91.16±3.25
	Female	77.81±3.68*	**	82.78±4.75*	**	90.12±2.41*	84.63±2.92	**	89.19±2.95	**	91.92±1.78

^a ANOVA; ^b Student's t-test

* p<0.05; ** p<0.01

For a description of the variables, refer to Table 1.

height C3 and posterior height C5, anterior intervertebral space C3–C4 and posterior C4–C5 were greater in females, but without statistical significance, in the beginning of pubertal growth, while anterior body height C3 was greater in females with accelerated growth only. The results of the Altan et al. [2] longitudinal study, which included Turkish girls aged eight to 17 years, showed that the growth of the vertebrae had its peak at around 13.5 years of age, immediately before the s4 stage of cervical maturity. The slowing of the process started at around 15.5 years of age, but anterior vertebrae growth stopped at around the age of 16.5 (s6). Mito et al. [25] analyzed vertebrae growth in Japanese eight- to 14-year-old girls, and concluded that in girls, accelerated growth of the anterior and posterior body height existed between the ages of 10 and 13. In our study, greater linear growth was present mostly between the group of 12- and 13-year-olds and the group of 17- and 18-year-olds.

Due to possible differences in the patients' body constitution, as well as individual variations during growth, we wanted to show in our study the percentual presence of vertebrae and intervertebral spaces in addition to linear measures and how their relationship changed in different age periods. The study showed that body growth of the vertebra C2 is different than that of vertebrae C3, C4 and C5. It was determined that the biggest part of the cervical spine is the vertebra C2. The rest was equally distributed with vertebrae C3, C4 and C5 (Table 5). With age, percentage of anterior and posterior body height of the vertebra C2 was decreased in total length, while anterior and posterior body heights of the vertebrae C3, C4 and C5 was increased. The percentage of intervertebral spaces was decreased as well. Higher percentage of vertebra C2 was found in females, except at the ages of 12 and 13. Anterior and posterior C3, C4 and C5 body heights occupied more space in females, except for posterior body height of the vertebra C4 at the ages of 12 and 13. With age, their anterior and posterior side occupied greater percent and posterior side was greater than the anterior in all three age groups (Table 5). It was noted that anterior and posterior intervertebral space height decreased with greater values in males, except for the posterior intervertebral space C2–C3 height at the age of eight, and for the anterior intervertebral space C3–C4 and C4–C5 height at the ages of 12 and 13. This study demonstrated that the vertebra C2 was the biggest, but grew slowly, and that intervertebral spaces were reduced due to growth of vertebral bodies. Females showed a greater presence of anterior and posterior body height of all vertebrae in total length, while intervertebral spaces were smaller. This means that females had higher percentage of vertebral body presence, while males had more intervertebral spaces.

Percentage-wise, the total sum of anterior and posterior C2, C3, C4 and C5 body heights increased in growth and took up more space in C2–C5 height regardless of sex. At the age of eight, anterior height of all vertebrae (C2–C5) occupied about 75% in total length, while the posterior one occupied around 85%. At the ages of 12 and 13, the anterior height was about 80% and the posterior one was

90%. At the ages of 17 and 18, anterior height occupied about 90%, the same as posterior. Thus, the sum of all anterior body heights increased around 15%, while the sum of the posterior heights increased about 5% (Table 6). The percentage of anterior and posterior body height sum compared to total C2–C5 height showed positive correlation between cervical lordosis, while the percentage of anterior and posterior intervertebral spaces height sum compared to total C2–C5 height showed negative correlation (Table 3). Accordingly, these changes were monitored more easily if the sum of all anterior heights was taken into account. Larger changes of anterior vertebral dimensions indicate the possibility for easier growth curve detection (the puberty onset, growth spurt, maximum growth and decrease of the growth intensity).

Some of the studies consider that CVM method is subjective and should be used in combination with some other parameter that estimates skeletal maturity [1, 2, 13–16]. Our research offers the percentage of anterior body heights of vertebrae C2, C3, C4 and C5 sum compared to total anterior C2–C5 part of the spine, as possible skeletal maturity estimation.

Our study is designed as a cross-sectional study, which might have its limitations. To accurately determine the changes in cervical lordosis and cervicovertebral morphology at different age and the possibility of estimating skeletal maturity, it is necessary to perform longitudinal studies, or obtain the values for every year of patient's life. Further growth researches are necessary to determine the growth curve and exact percentage ratio of the cervical vertebral bodies to the total length of the measured spine. Limitations in inclusion criteria, necessity of repeated radiographic examinations and potential loss of subjects for follow-up make such studies difficult to perform.

CONCLUSION

Cervical lordosis alters during growth and is more curved in females. The connection was observed between cervical lordosis and the values of C3, C4, and C5 body heights and intervertebral spaces.

Anterior and posterior vertebrae body height increase, and intervertebral spaces decrease in older age groups, and they are larger in 17- to 18-year-old males compared to females of the same age.

Vertebral body height and spaces between them change their percentage ratio with growth. The percentual presence of vertebra C2 body height and intervertebral spaces decrease and the percentual presence of vertebrae C3, C4, and C5 increase in older age groups. Vertebral bodies occupy more space of the spine in females, while intervertebral spaces occupy more of this space in males.

It might be expected that skeletal maturity can be estimated by determining percentage distribution of anterior C2, C3, C4 and C5 body height sum compared to the total anterior C2–C5 spine part. This percentage ratio should be used with some other parameters in estimation of skeletal maturity.

REFERENCES

- dos Santos MFH, de Lima RL, De-Ary-Pires B, Pires-Neto MA, de Ary-Pires R. Developmental steps of the human cervical spine: parameters for evaluation of skeletal maturation stages. *Anat Sci Int.* 2010; 85(2):105-14. [DOI: 10.1007/s12565-009-0065-7] [PMID: 19943131]
- Altan M, Dalci ON, Iseri H. Growth of the cervical vertebrae in girls from 8 to 17 years. A longitudinal study. *Eur J Orthod.* 2012; 34(3):327-34. [DOI: 10.1093/ejo/cjr013] [PMID: 21511819]
- Hellsing E, McWilliam J, Reigo T, Spangfort E. The relationship between craniofacial morphology, head posture and spinal curvature in 8, 11 and 15-year-old children. *Eur J Orthod.* 1987; 9(4):254-64. [DOI: 10.1093/ejo/9.4.254] [PMID: 3480226]
- Solow B, Tallgren A. Head posture and craniofacial morphology. *Am J Phys Anthropol.* 1976; 44(3):417-35. [PMID: 937521]
- Cooke MS, Wei SHY. Intersex differences in craniocervical morphology and posture in southern Chinese and British Caucasians. *Am J Phys Anthropol.* 1988; 77(1):43-51. [PMID: 3189522]
- D'Attilio M, Caputi S, Epifania E, Festa F, Tecco S. Evaluation of cervical posture of children in skeletal class I, II, and III. *Cranio.* 2005; 23(3):219-28. [DOI: 10.1179/crn.2005.031] [PMID: 16128357]
- Nik TH, Aciyabar PJ. The relationship between cervical column curvature and sagittal position of the jaws: using a new method for evaluating curvature. *Iran J Radiol.* 2011; 8(3):161-6. [DOI: 10.5812/kmp.iranjradiol.17351065.3379] [PMID: 23329934]
- Grave B, Brown T, Townsend G. Comparison of cervicovertebral dimensions in Australian Aborigines and Caucasians. *Eur J Orthod.* 1999; 21(2):127-35. [PMID: 10327736]
- Watanabe M, Yamaguchi T, Maki K. Cervical vertebra morphology in different skeletal classes: a three-dimensional computed tomography evaluation. *Angle Orthod.* 2010; 80(4):719-24. [DOI: 10.2319/100609-557.1] [PMID: 20482359]
- Lamparski DG. Skeletal age assessment utilizing cervical vertebrae [thesis]. Pittsburgh: University of Pittsburgh; 1972.
- Hassel B, Farman AG. Skeletal maturation evaluation using cervical vertebrae. *Am J Orthod Dentofac Orthop.* 1995; 107(1):58-66. [PMID: 7817962]
- Baccetti T, Franchi L, McNamara Jr JA. The Cervical Vertebral Maturation (CVM) method for the assessment of optimal treatment timing in dentofacial orthopedics. *Seminars in Orthodontics.* 2005; 11(3):119-29.
- Gabriel DB, Southard KA, Qian F, Marshall SD, Franciscus RG, Southard TE. Cervical vertebrae maturation method: poor reproducibility. *Am J Orthod Dentofac Orthop.* 2009; 136(4):478.e1-478.e7. [DOI: 10.1016/j.jajodo.2007.08.028] [PMID: 19815136]
- Fudalej P, Bollen AM. Effectiveness of the cervical vertebral maturation method to predict postpeak circumpubertal growth of craniofacial structures. *Am J Orthod Dentofac Orthop.* 2010; 137(1):59-65. [DOI: 10.1016/j.jajodo.2008.01.018] [PMID: 20122432]
- Nestman TS, Marshall SD, Qian F, Holton N, Franciscus RG, Southard TE. Cervical vertebrae maturation method morphologic criteria: poor reproducibility. *Am J Orthod Dentofac Orthop.* 2011; 140(2):182-8. [DOI: 10.1016/j.jajodo.2011.04.013] [PMID: 21803255]
- Zhao XG, Lin JX, Jiang JH, Wang QZ, Ng SH. Validity and reliability of a method for assessment of cervical vertebral maturation. *Angle Orthod.* 2012; 82(2):229-34. [DOI: 10.2319/051511-333.1] [PMID: 21875315]
- Baccetti T, Franchi L, McNamara JA. Reproducibility of the CVM method: a reply. *Am J Orthod Dentofac Orthop.* 2010; 137(4):446-7. [DOI: 10.1016/j.jajodo.2010.02.010] [PMID: 20362890]
- Santiago RC, Costa LFD, Vitral RWF, Fraga MR, Bolognese AM, Maia LC. Cervical vertebral maturation as a biologic indicator of skeletal maturity – a systematic review. *Angle Orthod.* 2012; 82(6):1123-31. [DOI: 10.2319/103111-673.1] [PMID: 22417653]
- Nguyen, Ngoc-Lam M, Baluch, Daniel A, Patel, Alpesh A. Cervical sagittal balance: a review. *Contemporary Spine Surgery.* 2014; 15(1):1-8.
- Solow B, Tallgren A. Natural head position in standing subjects. *Acta Odontol Scand.* 1971; 29:591-607. [PMID: 5290983]
- Pachi F, Turla R, Checchi AP. Head posture and lower arch dental crowding. *Angle Orthod.* 2009; 79(5):873-9. [DOI: 10.2319/060708-595.1] [PMID: 19705927]
- Tecco S, Festa F. Cervical spine curvature and craniofacial morphology in an adult Caucasian group: a multiple regression analysis. *Eur J Orthod.* 2007; 29(2):204-9. [DOI: 10.1093/ejo/cjl061] [PMID: 17218718]
- Baydas B, Yavuz I, Durna N, Ceylan I. An investigation of cervicovertebral morphology in different sagittal skeletal growth patterns. *Eur J Orthod.* 2004; 26(1):43-9. [DOI: 10.1093/ejo/26.1.43] [PMID: 14994881]
- Chen LL, Xu TM, Jiang JH, Zhang XZ, Lin JX. Quantitative cervical vertebral maturation assessment in adolescents with normal occlusion: a mixed longitudinal study. *Am J Orthod Dentofac Orthop.* 2008; 134(6):720.e1-720.e7. [DOI: 10.1016/j.jajodo.2008.03.014] [PMID: 19061795]
- Mito T, Sato K, Mitani H. Cervical vertebral bone age in girls. *Am J Orthod Dentofac Orthop.* 2002; 122(4):380-5. [DOI: 10.1067/mod.2002.126896] [PMID: 12411883]

Промене кривине вратне кичме и морфологије цервикалних пршљенова у различитим узрастима и могућност процене скелетне зрелости

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КРАТАК САДРЖАЈ

Увод Током раста пропорције краниофацијалних и цервикоквертебралних структура се мењају. Ове структуре су морфолошки и функционално повезане, али је њихов међусобни утицај и даље непознат.

Циљ рада Циљ ове студије је био да се уоче промене кривине вратне кичме и морфологије вратних пршљенова у различитим узрастима групама, као и могућност процене скелетне зрелости засноване на процентуалној заступљености збира предњих висина вратних пршљенова Ц2, Ц3, Ц4 и Ц5 у укупној дужини предње висине кичме од Ц2 до Ц5.

Методе рада Студија је обухватила 120 испитаника оба пола који су сврстани у три старосне групе: 8, 12–13 и 17–18 година. Пет кранијалних и 15 цервикалних параметара је мерено и анализирано.

Резултати Резултати су показали статистички значајну корелацију између закривљености вратне кичме и година, пола, предње и задње висине тела пршљена Ц2, Ц3, Ц4, предњег Ц4–Ц5 и задњег Ц2–Ц3, Ц3–Ц4, Ц4–Ц5 међупршљенског простора. Просечне вредности висине тела вратних пршљенова процентуално су биле чешће код испитаница, а сви међупршљенски простори код особа мушког пола. Проценат збира предње и задње висине пршљена Ц2, Ц3, Ц4 и Ц5 повећавао се са годинама.

Закључак Кривина вратне кичме постаје закривљенија и тела пршљенова заузимају више простора код жена, а међупршљенски простор више код мушкараца. Процена скелетне зрелости би могла да се прати на основу процентуалне заступљености висине тела пршљена у укупној дужини предњег дела кичме (Ц2–Ц5).

Кључне речи: кичмена кривина; лордоза; раст; сазревање

Evaluation of Surfactant Replacement Therapy Effects – A New Potential Role of Lung Ultrasound

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SUMMARY

Introduction Previous studies suggested that effects of the surfactant administration in preterm infants with respiratory distress syndrome cannot be followed by lung ultrasound (L-US).

Objective The aim of the paper is to evaluate the surfactant replacement therapy effects using a new, proposed grading system for L-US findings.

Methods We report the series of 12 preterm infants with clinical and radiographic signs of respiratory distress syndrome, in whom L-US examinations were performed prior to, and within the first 24 hours after surfactant administration. To evaluate the surfactant replacement therapy effects, we proposed a new grading system (1 to 6) for L-US findings at each examined lung area, based on the presence of normal finding, the amount of B-lines and subpleural consolidations.

Results All preterm infants had an improvement of L-US findings from one to four grades observed within the first 24 hours after surfactant administration, which has not been previously reported. The improvement of L-US findings was most commonly observed in anterior lung areas.

Conclusion L-US might enable an early detection of the surfactant replacement therapy effects. Further prospective studies are necessary to define the role of L-US in this field.

Keywords: respiratory distress syndrome; premature; ultrasound; lung; surfactant

INTRODUCTION

Of the many complications of prematurity (intracranial hemorrhage, necrotizing enterocolitis, sepsis, and retinopathy), lung diseases remain the most common cause of neonatal morbidity. Respiratory distress syndrome (RDS) is one of them, and presents the clinical expression of surfactant deficiency in neonates [1].

Administration of exogenous surfactant after delivery improves oxygenation, decreases the need for mechanical ventilation, and reduces mortality in neonates with RDS. The effects of surfactant replacement therapy are commonly followed up using chest X-rays (CXR) [1].

Although lung ultrasound (L-US) in children has already been recognized as a potentially useful diagnostic modality, it is not, at present, frequently used in detection and follow-up of neonatal respiratory diseases [2-10]. There have been just a few studies dealing with application of L-US in this field [11-19].

OBJECTIVE

The aim of this study was to evaluate surfactant replacement therapy effects using a new, proposed grading system for L-US findings.

METHODS

A prospective study was carried out in association with the Neonatal Intensive Care Unit (NICU) and the Radiology Department. The inclusion criteria were both clinical and radiographic signs of RDS, gestational age (GA) under 37 weeks, and administration of surfactant performed in our NICU.

The study included 12 preterm infants (six males and females). GA was ranging from 29 to 36 weeks of gestation. The average GA of patients was 32.83 weeks of gestation (SD=2.84). The birth weight of patients ranged between 1,190 g and 3,280 g (mean value 2,216.7 g, SD=875.9).

Out of 12 premature infants four received prenatal corticosteroids. Four infants were born vaginally, while eight were delivered by C-section. Porcine exogenous surfactant (Curosurf, Chiesi Pharmaceutical, Parma, Italy) was endotracheally administered in all patients at the average time of 8.1 hours (SD 3.53 hours). Mechanical ventilation was required in each preterm infant, with mean duration of mechanical ventilation being 4.17 days (SD 2.04 days).

The Ethical Committee approved the research and informed consent was obtained from the parents of each examined preterm infant.

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L-US was performed in all infants just before and within the first hour after surfactant administration, as well as within the first 20 to 24 hours of surfactant application. All the L-US examinations were performed by one experienced pediatric radiologist (J.L.) in supine, as well as in right and left lateral decubitus positions, using a 7.5 MHz linear probe (Sonoline Adara, Siemens, Erlangen, Germany). Due to their clinical conditions, all the preterm infants were examined in incubators. The radiologist was blinded to the CXR and clinical findings of each preterm infant. CXRs were reported by other experienced pediatric radiologists of the department, apart from J.L. The clinical condition of each infant was estimated by an experienced neonatologist (A.D.). The double lung point sign, characteristic of transient tachypnea of the newborn, was ultrasonographically excluded in each patient as a possible cause of respiratory distress [15].

L-US examinations were performed using both trans-thoracic and trans-abdominal approach. The trans-thoracic US approach included examination of the anterior (between the sternum and the anterior axillary line), lateral (between the anterior and posterior axillary lines) and posterior (between the posterior axillary line and the spine) lung areas in caudocranial direction. Anterior and lateral lung areas were evaluated in supine position, while posterior lung areas were examined in lateral decubitus positions. The trans-abdominal US included the trans-hepatic and trans-splenic approach to examine both lung bases in supine position of the patient.

These two US techniques provided division of each hemithorax into four lung areas, i.e. eight lung areas per patient. The right lung base was examined by trans-hepatic approach, while right anterior, lateral, and posterior lung areas were examined by trans-thoracic approach. The left lung base was examined by trans-splenic approach, and trans-thoracic approach was used to examine left anterior, lateral

and posterior lung areas. Longitudinal and transverse (intercostal) sections were used in the trans-thoracic examinations of each lung area. Oblique transverse sections were mostly used for the trans-hepatic approach, whereas oblique longitudinal sections were used for the trans-splenic approach.

Normal L-US findings

The pleura is trans-thoracically visualized as a smooth, echogenic line, whose thickness is normally up to 0.5 mm [16]. The evaluation of the pleura also includes the “lung sliding” sign, which represents the sliding of the visceral pleura over the parietal pleura [9].

Underneath the pleura are the lungs, filled with air, which disables the visualization of the lung parenchyma. However, horizontal artifacts resulting from the high acoustic impedance between the visceral pleura and the lung parenchyma are seen, and are called A-lines – the parallel echogenic lines below the pleural line, equally distanced from one another (Figure 1) [20, 21]. If the US examination of the lung bases is performed using the trans-abdominal approach, with the liver or spleen forming the acoustic window, it is normally based on the acoustic phenomenon of “mirror image,” which is a supra-diaphragmatic projection of the liver or spleen [11, 22].

Pathological L-US findings

When the parenchymal disease propagates to the pleura, an acoustic window is formed and this creates a transmission of an ultrasound beam, enabling the evaluation of lung tissue. The absence of alveolar air in the lung periphery is visualized as a hypoechoic area, representing the subpleural consolidation (Figure 2) [10].

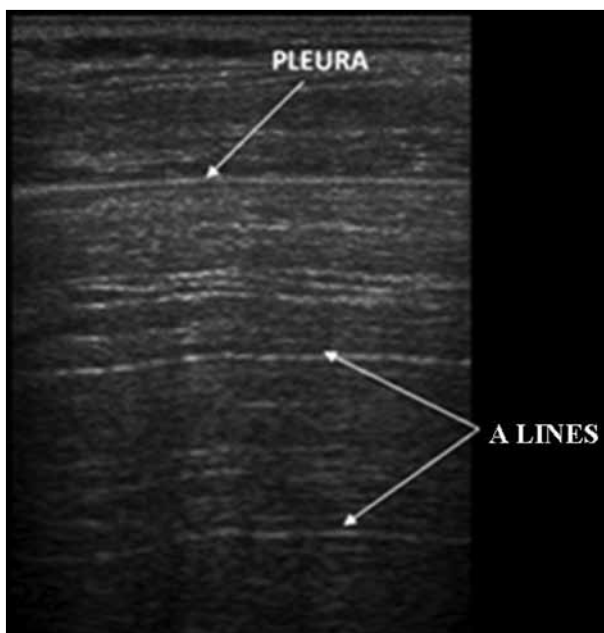


Figure 1. Normal lung ultrasound finding using the trans-thoracic approach in a transverse (intercostal) section



Figure 2. Subpleural consolidation (marked with asterisks) using the trans-thoracic approach

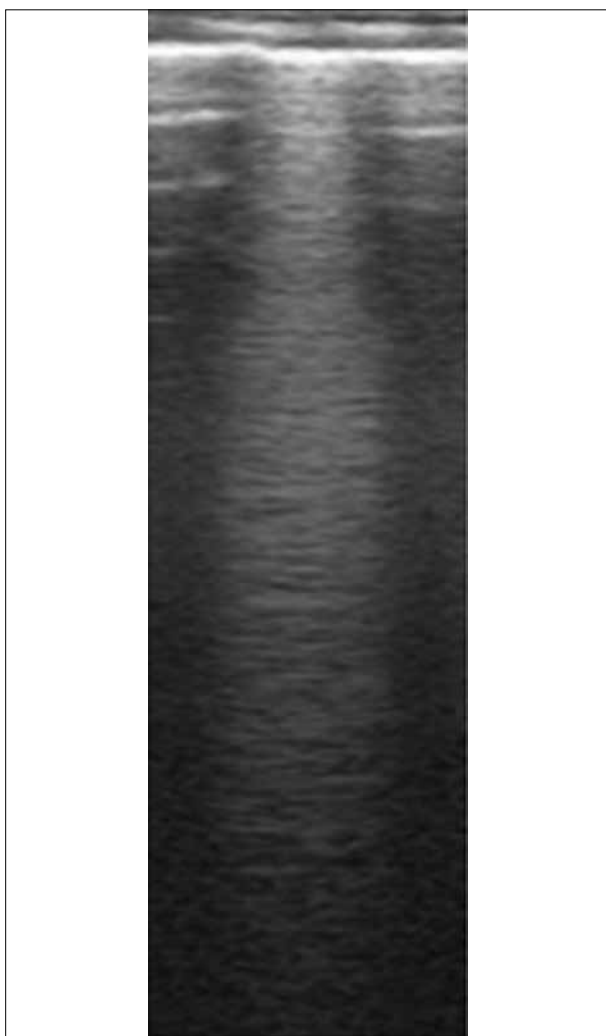


Figure 3. B-line

The presence of the vertically oriented “comet tail” artifacts in the lungs, called B-lines, is a result of the accumulation of fluid in the subpleural interlobular septa surrounded by air [23]. B-lines extend from the pleural line to the bottom of the screen. They are hyperechoic, sharply defined, erase the A-lines, and move with “lung sliding” (Figure 3). Depending on the amount of B-lines, the interstitial edema (B-lines combined with “spared” areas of normal L-US finding) and alveolar-interstitial edema (compact pattern of B-lines) can be recognized [23].

Grading system of L-US findings

In order to provide more precise and adequate evaluation and classification of L-US findings, the following grading system has been applied for each examined lung area, using the longitudinal section in the trans-thoracic approach, and oblique transverse and oblique longitudinal sections in the trans-abdominal approach. Grade 1 stands for a normal finding (Figure 4). Grade 2 stands for a distribution of B-lines in less than 50% of the visualized lung area (Figure 5). Grade 3 stands for a distribution of B-lines within the

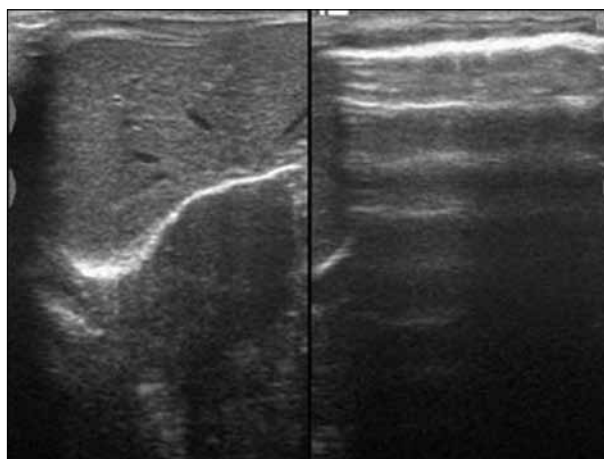


Figure 4. Normal lung ultrasound finding trans-hepatically (“mirror image” phenomenon, left image), and trans-thoracically (right image), on longitudinal section

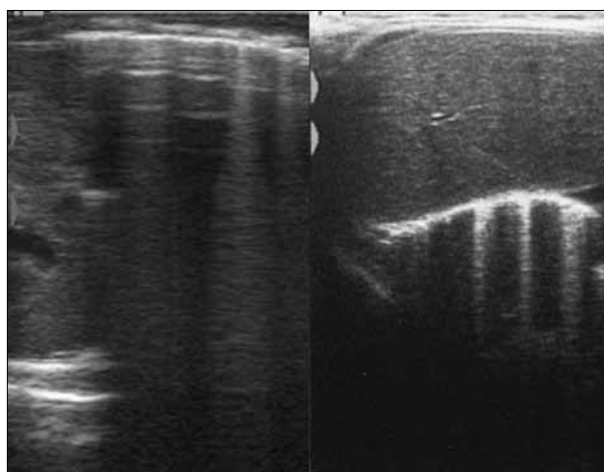


Figure 5. Grade 2, using the trans-thoracic (left image) and the trans-hepatic approach (right image)

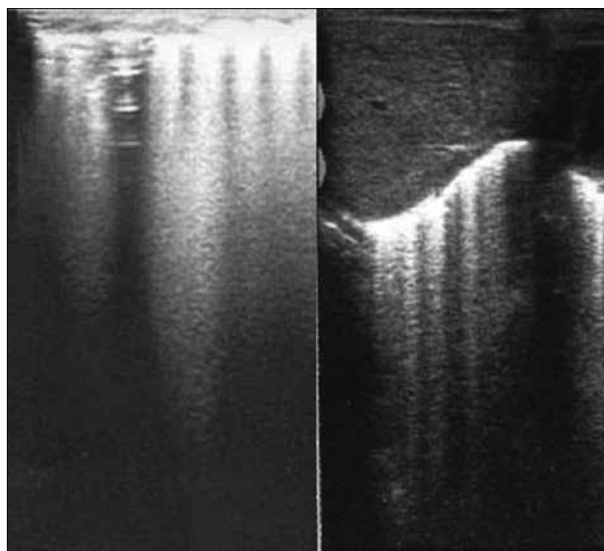


Figure 6. Grade 4, using the trans-thoracic (left image) and the trans-hepatic approach (right image)

half of the lung area, whereas their distribution over 50% corresponds with grade 4 (Figure 6). Grade 5 stands for a compact pattern of B-lines which extend through the whole lung area (Figure 7). The worst finding, graded 6,

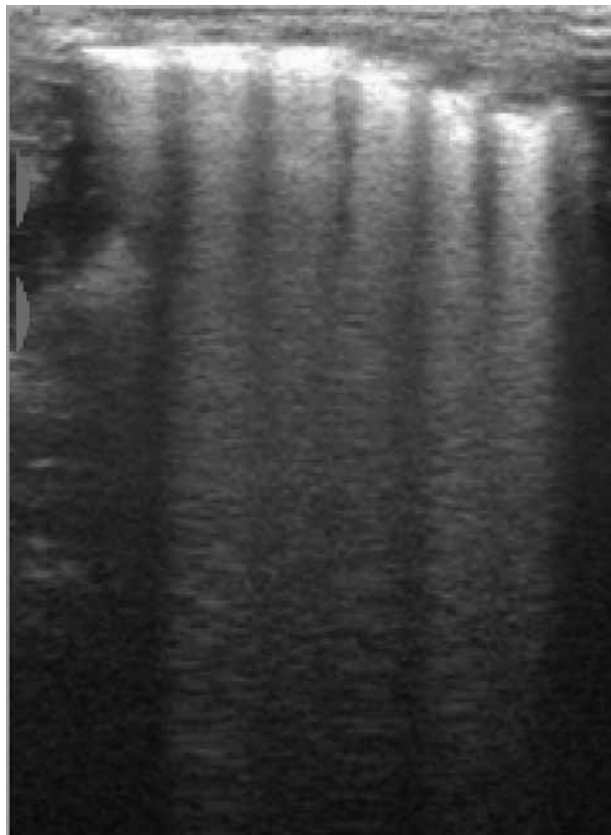


Figure 7. Grade 5, using the trans-thoracic approach

presents with subpleural consolidation in the lung area, regardless of the relation between A- and B-lines.

Based on the proposed L-US grading system, L-US findings in all infants were compared before surfactant administration, and within the first hour and 20–24 hours after surfactant administration at each examined lung area. In preterm infants with CXRs performed before and within 24 hours after surfactant application, the comparison between L-US and CXR findings was made. In each infant the number of lung areas with regression of L-US finding was recorded, and the lung areas with the highest frequency of improvement of L-US finding were detected.

RESULTS

During the first hour after surfactant administration, in eight out of 12 patients the regression of L-US findings in at least one lung area was detected, showing an improvement of one to two grades. An improvement of up to four grades, in relation to initial examination prior to surfactant administration, occurred in all infants between 20 and 24 hours after surfactant application at one or more lung areas. In preterm infants with CXRs performed before and within 24 hours after surfactant application, the improvement of L-US findings was consistent with improvement of the CXR findings (Figures 8, 9 and 10).

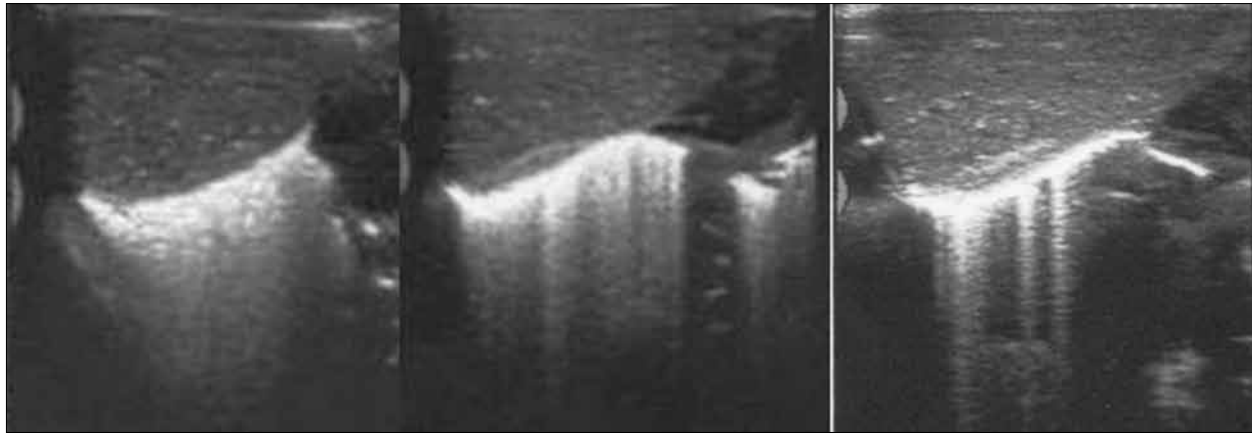


Figure 8. Change of the US finding at the right lung base, using trans-hepatic approach, from a grade 6 (prior to surfactant administration, left image), over a grade 4 (0.5 hours after surfactant administration, image in the middle), to a grade 2 (22 hours after surfactant application, image to the right)

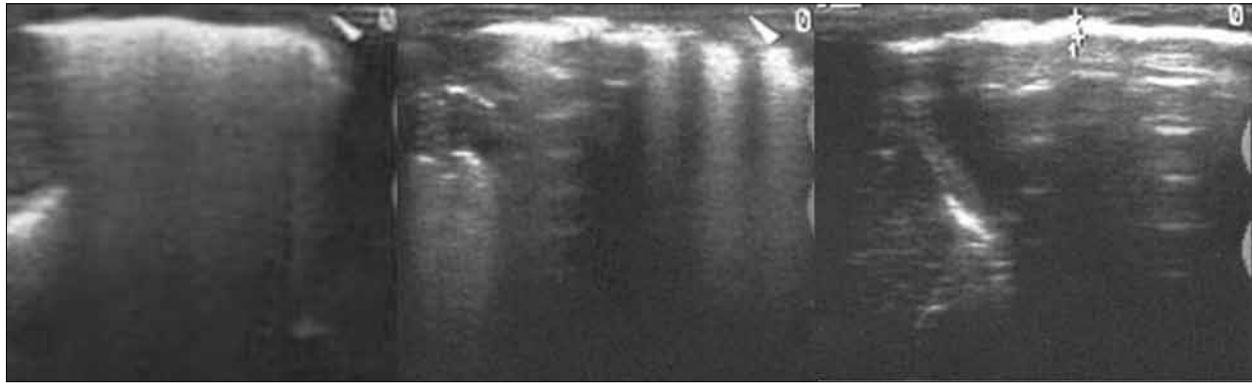


Figure 9. Change of the US finding at the anterior left lung area (trans-thoracic approach) from a grade 5 (prior to surfactant administration, left image), over a grade 3 (0.5 hours after surfactant administration, image in the middle), to a grade 1 (22 hours after surfactant application, image to the right)

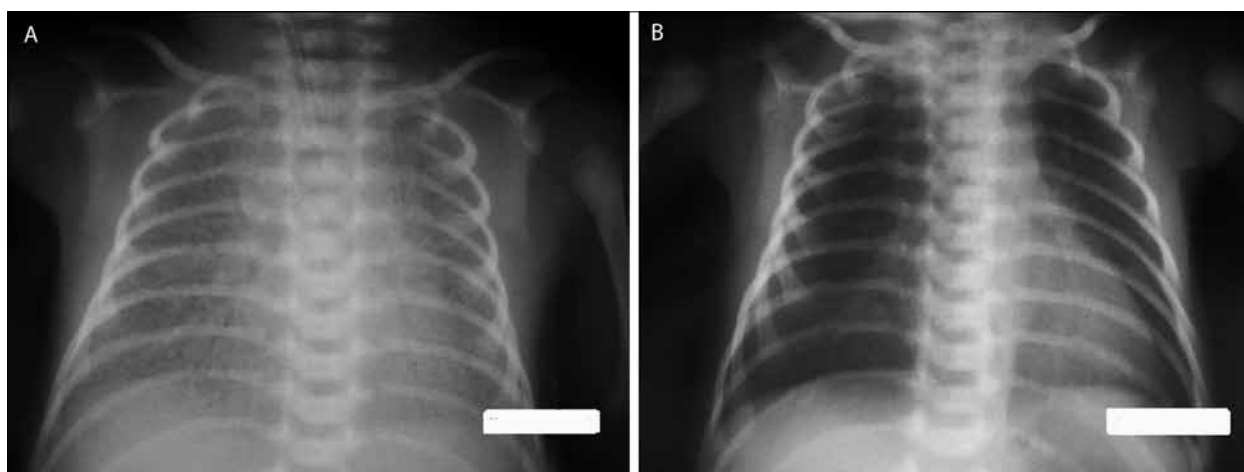


Figure 10. Chest X-ray findings in the same child as in the Figures 7 and 8 just before (A) and 22 hours after (B) surfactant application. A – respiratory distress syndrome (RDS), B – significant regression of RDS signs

Table 1. The number of preterm infants with an improvement of lung ultrasound finding at examined lung areas within the first 24 hours after surfactant administration

Lung area	H	Ar	Lr	Pr	S	Al	LI	PI
Preterm infants	4	10	4	6	2	6	8	6

H – trans-hepatic approach to the right lung base; S – trans-splenic approach to the left lung base; trans-thoracic approach to the: Ar – anterior right, Al – anterior left, Lr – lateral right, LI – lateral left, Pr – posterior right, PI – posterior left lung areas

In four preterm infants an improvement of the L-US findings was observed in one lung area within the first 24 hours after surfactant application, whereas the regression of L-US findings visualized at three, four, six and all eight lung areas was equally distributed throughout the remaining eight infants (two per each).

The improvement of L-US findings was most commonly observed in anterior lung areas (right and left) – 16 times, followed by lateral and posterior lung areas – 12 times both (Table 1).

DISCUSSION

The application of L-US in preterm infants with RDS has so far been evaluated only in a small number of studies [11, 13, 16, 17, 18]. In some of these studies the trans-abdominal approach was used exclusively [11, 13], but the major step forward seems to be the introduction of the trans-thoracic approach in newborns with transient tachypnea in the Copetti and Cattarossi's [15] study. It allowed evaluation of all the lung areas, and not only the bases, and was later applied for the first time in the diagnosis of RDS by Copetti et al. [16]. This study showed no significant changes of L-US findings in preterm infants before and after the administration of surfactant in the first 48 hours of life [16]. These results were further confirmed by animal experiments [17]. In one study L-US examinations were performed using the combination of the trans-thoracic and trans-abdominal approach [18].

Our everyday experience showed that although the lung bases could be in most cases adequately visualized

using the trans-thoracic approach, with a certain number of patients the US findings on the lung bases were clearer and more precise when using the trans-abdominal approach. Therefore, we performed each L-US examination using a combined US technique, i.e. using both the trans-thoracic and trans-abdominal approach. The need to grade US findings in each lung area emerged. Up to now, the US findings in the lungs were distinguished as normal, interstitial edema, alveolar-interstitial edema and subpleural consolidation, or divided into the three types, as in the study of Raimondi et al. [16, 19, 23]. In order to establish an easily applicable and more precisely defined grading of L-US findings, we proposed the new grading system ranging from 1 to 6, where grade 1 presented a normal finding and grade 6 the subpleural consolidation. The grades from 2 to 5 depended on the ratio between the B-lines and the “spare areas” of normal L-US finding defined by the horizontal A-lines.

Even though previous studies suggested that the administration of surfactant in preterm infants with RDS does not affect the interstitial compartment and lung water clearance [16, 17], we showed the improvement of L-US findings in each of the 12 preterm infants within the first 24 hours after application of the same type of exogenous surfactant (Curosurf) as in the study by Copetti et al. [16]. In four preterm infants, this improvement was observed in only one lung area, but in the rest of the infants it was detected in three and more lung areas, in two patients even in all eight of them. The most common was an improvement of L-US findings in anterior lung areas (right and left).

We can only hypothesize about the reasons of regression of L-US findings. Sometimes an improvement was very subtle, especially within the first hour after surfactant administration. We think that the proposed grading system gives the ultrasonographer an opportunity to observe even some discreet changes, which may easily go undetected. The most frequent improvement of L-US findings in anterior lung areas might be the result of mostly supine position of preterm infants in incubators, which might enable the fastest interstitial fluid clearance due to the force of gravity, opposed to the reduced ventilation in the pos-

terior lung areas. Also, our results might indicate the need to reconsider the standpoint that surfactant administration in preterm infants affects only the alveolar space, and not the interstitial compartment [16, 17]. The use of L-US in monitoring surfactant replacement therapy effects might also have a potential to reduce the number of CXRs in NICUs, and decrease the dose of ionizing radiation preterm infants are exposed to.

Our study has certain limitations. Even though blinded for the CXR and clinical findings prior to each US examination, a single experienced pediatric radiologist performed and evaluated all L-US examinations. However, the issue of inter- and intra-observer variability in the interpretation of L-US findings is reported to be significantly less relevant compared to the CXR findings [16, 24]. On the other hand, it is reasonable to hypothesize that similar results might not be immediately achieved by less experienced operators.

REFERENCES

1. Agrons GA, Courtney SE, Stocker JT, Markowitz RI. Lung disease in premature neonates: radiologic – pathologic correlation. *Radiographics*. 2005; 25:1047-73.
2. Glasier CM, Leithiser RE, Williamson SL, Seibert JJ. Extracardiac chest ultrasonography in infants and children: radiographic and clinical implications. *J Pediatr*. 1989; 114:540-4.
3. Haller JO, Schneider M, Kassner EG, Friedman AP, Waldroup LD. Sonographic evaluation of the chest in infants and children. *Am J Roentgenol*. 1980; 134:1019-27.
4. Hirsch JH, Rogers JV, Mack LA. Real-time sonography of pleural opacities. *Am J Roentgenol*. 1981; 136:297-301.
5. Hirsch JH, Carter SJ, Chikos PM, Colacurcio C. Ultrasonic evaluation of radiographic opacities of the chest. *Am J Roentgenol*. 1978; 130:1153-6.
6. Miller JH, Reid BS, Kemberling CR. Water-path ultrasound of chest disease in childhood. *Radiology*. 1984; 152:401-8.
7. Rosenberg HK. The complementary roles of ultrasound and plain film radiography in differentiating pediatric chest abnormalities. *Radiographics*. 1986; 6:427-45.
8. Ben-Ami TE, O'Donovan JC, Yousefzadeh DK. Sonography of the chest in children. *Radiol Clin North Am*. 1993; 31:517-31.
9. Mathis G. Thoraxsonography. I. Chest wall and pleura. *Ultrasound Med Biol*. 1997; 23:1131-9.
10. Mathis G. Thoraxsonography. II. Peripheral pulmonary consolidation. *Ultrasound Med Biol*. 1997; 23:1141-53.
11. Avni EV, Braude P, Pardou A, Matos C. Hyaline membrane disease in the newborn: diagnosis by ultrasound. *Pediatr Radiol*. 1990; 20:143-6.
12. Avni EF, Cassart M, de Maertelaer V, Rypens F, Vermeylen D, Gevenois PA. Sonographic prediction of chronic lung disease in the premature undergoing mechanical ventilation. *Pediatr Radiol*. 1996; 26:463-9.
13. Bober K, Swietliński J. Diagnostic utility of ultrasonography for respiratory distress syndrome in neonates. *Med Sci Monit*. 2006; 12:440-6.
14. Pieper CH, Smith J, Brand EJ. The value of ultrasound examination of the lungs in predicting bronchopulmonary dysplasia. *Pediatr Radiol*. 2004; 34:227-31.
15. Copetti R, Cattarossi L. The 'Double lung point': an ultrasound sign diagnostic of transient tachypnea of the newborn. *Neonatology*. 2007; 91:203-9.
16. Copetti R, Cattarossi L, Macagno F, Violino M, Furlan R. Lung ultrasound in respiratory distress syndrome: a useful tool for early diagnosis. *Neonatology*. 2008; 94:52-9.
17. Cattarossi L, Copetti R, Poskurica B, Misericocchi G. Surfactant administration for neonatal respiratory distress does not improve lung interstitial fluid clearance: echographic and experimental evidence. *J Perinat Med*. 2010; 38(5):557-63.
18. Lovrenski J. Lung ultrasonography of pulmonary complications in preterm infants with respiratory distress syndrome. *Ups J Med Sci*. 2012; 117:10-7.
19. Raimondi F, Migliaro F, Sodano A, Umbaldo A, Romano A, Vallone G, et al. Can neonatal lung ultrasound monitor fluid clearance and predict the need of respiratory support? *Critical Care*. 2012; 16:R220.
20. Lichtenstein D, Mezière G, Biderman P, Gepner A. The comet-tail artifact: an ultrasound sign ruling out pneumothorax. *Intensive Care Med*. 1999; 25:383-8.
21. Lichtenstein DA, Lascols N, Mezière G, Gepner A. Ultrasound diagnosis of alveolar consolidation in the critically ill. *Intensive Care Med*. 2004; 30:276-81.
22. Cosgrove DO, Garbutt P, Hill CR. Echos across the diaphragm. *Ultrasound in Med Biol*. 1978; 3:385-92.
23. Lichtenstein D, Mezière G, Biderman P, Gepner A, Barre O. The comet-tail artifact. An ultrasound sign of alveolar-interstitial syndrome. *Am J Respir Crit Care Med*. 1997; 156:1640-6.
24. Bedetti G, Gargani L, Corbisiero A, Frassi F, Poggianti E, Mottola G. Evaluation of ultrasound lung comets by hand-held echocardiography. *Cardiovasc Ultrasound*. 2006; 4:34.

CONCLUSION

This study revealed the potential of ultrasound in monitoring the effects of surfactant replacement therapy, which has not been reported so far. Further, more extensive, prospective studies are necessary to define the role of L-US in this field.

Процена ефекта терапије сурфактантом – нова потенцијална улога ултразвука плућа

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КРАТАК САДРЖАЈ

Увод Претходно објављене студије су показале да се ефекти терапије сурфактантом код претерминске новорођенчади с респираторним дистрес синдромом (РДС) не могу пратити помоћу ултразвука плућа (УЗП).

Циљ рада Циљ рада је био да се процене ефекти лечења сурфактантом код недоношчади са РДС користећи нови предложени систем степеновања налаза УЗП.

Методе рада Студија је обухватила 12 новорођенчади рођене пре термина с клиничким и радиографским знацима РДС код којих је УЗП био начињен пре и у прва 24 часа након примене сурфактанта. Да бисмо оценили ефекте терапије сурфактантом, предложили смо нови систем степеновања (1–6) за налазе УЗП у свакој прегледаној плућној зони који

је заснован на постојању нормалног налаза, субплеуралних консолидација и заступљености Б линија.

Резултати Код све претерминске новорођенчади уочено је побољшање налаза УЗП од једног до четири степена током прва 24 часа од примене сурфактанта, што досад није објављено. Побољшање налаза УЗП је најчешће било видљиво у предњим регијама плућа.

Закључак УЗП може да омогући рано откривање ефекта терапије сурфактантом. Неопходно је урадити нове проспективне студије које би јасно дефинисале улогу УЗП у овој области.

Кључне речи: синдром респираторног дистреса; прематур; ултразвук; плућа; сурфактант

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The Burden of Gastroesophageal Reflux Disease on Patients' Daily Lives: A Cross-Sectional Study Conducted in a Primary Care Setting in Serbia

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SUMMARY

Introduction Recent data from the studies conducted in the Western countries have proved that patients with gastroesophageal reflux disease have significantly impaired health-related quality of life compared to general population.

Objective The study is aimed at evaluating the burden of reflux symptoms on patients' health-related quality of life.

Methods The study involved 1,593 patients with diagnosed gastroesophageal reflux disease. The Serbian version of a generic self-administered Centers for Disease Control and Prevention questionnaire was used. Statistical analyses included descriptive statistics, Pearson chi-square test and a multiple regression model.

Results Among all participants, 43.9% reported fair or poor health. Mean value of unhealthy days during the past 30 days was 10.4 days, physically unhealthy days 6.4 days, mentally unhealthy days 5.3 days and activity limitation days 4.3 days. Furthermore, 24.8% participants reported having ≥ 14 unhealthy days, 14.9% had ≥ 14 physically unhealthy days, 11.8% reported ≥ 14 mentally unhealthy days, and 9.4% had ≥ 14 activity limitation days.

Conclusion This study addressed complex relationships between reflux symptoms and patients' impaired everyday lives.

Keywords: gastroesophageal reflux disease; burden; health-related quality of life

INTRODUCTION

The population based studies have revealed that gastroesophageal reflux disease (GERD) represents a common chronic disease with a prevalence of 10–20% in Western Europe and North America [1]. Recent data from studies conducted in the Western countries have proved that patients with GERD have a significantly impaired health-related quality of life (HRQoL) compared to the general population [2, 3].

Even in cases with mild reflux symptoms, a clinically meaningful reduction of well-being was demonstrated [4]. The burden associated with GERD encompassed a meaningful reduction of physical activity, psychological well-being, daily functioning, as well as reduced vitality and disturbed sleep [5, 6, 7]. The burden of reflux symptoms also included reduced work productivity [8]. A study conducted in Germany estimated the loss of gross domestic product of €688 million per year due to GERD related work inability [9]. In some domains of HRQoL, GERD brings with it similar or higher burden than that observed in patients with diabetes, hypertension or angina pectoris [2, 10].

Data about GERD related HRQoL in Eastern European countries have been scarce. GERD

was often considered a minor public health problem compared to other chronic non-transmittable diseases and its potential severity was not fully recognized by the general public, patients, the healthcare system, and in some cases healthcare providers [11].

OBJECTIVE

The study was aimed at evaluating the burden of GERD on HRQoL in patients living in urban and rural areas, treated in Serbian primary healthcare settings.

METHODS

The current sample was derived from a large cross-sectional survey conducted in Serbian primary healthcare during January–December 2011 period, regarding HRQoL patients with chronic non-transmittable diseases from urban and rural areas.

Using the Montreal definition of GERD for population-based studies, GERD was diagnosed by primary care physicians (PCPs), and general internists based upon the presence of

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mild symptoms of heartburn and/or regurgitation occurring at least two days per week, or moderate/severe symptoms of heartburn and/or regurgitation occurring at least one day per week [12].

These criteria ensured that only patients suffering from chronic reflux disease could be eligible for study participation. The disease classification was also done by PCPs and general internists according to the International Classification of Diseases, Tenth Revision (ICD-10). The exclusion criteria included other significant upper gastrointestinal disorders, including complications of the reflux disease in which upper flexible endoscopy was mandatory. A written informed consent was obtained from all participants before the study enrolment. The participants completed the questionnaire in the office of their PCPs.

In the current survey, the Serbian version of the generic self-administered Centers for Disease Control and Prevention questionnaire (CDC-HRQOL-4) was used. The CDC-HRQOL-4 questionnaire was developed as a survey to assess patients' subjective sense of well-being. The questions despite their brevity had reasonably good criterion validity as predictors of mortality and global disability [13, 14, 15]. In this respect, this questionnaire has advantages over other HRQoL instruments which have been described as difficult to interpret and had limited practical value [16, 17].

Data collection and statistical analysis

The descriptive statistics, including numbers and percentages of categorical variables or mean and standard deviation of numerical data, were used to characterize the study sample. Univariate association between sociodemographic characteristics and self-rated healthy and unhealthy days (≥ 14) during the previous 30 days were evaluated using the Pearson chi-square test. Multivariate analyses were performed using multiple logistic regression with self-rated health and ≥ 14 unhealthy days during the previous 30 days as dependent variables, and sociodemographic variables as independent variables. The level of significance was set at $\alpha=0.05$. All statistical analyses were performed using SPSS 20.

RESULTS

The response rate of participants was 93.4%, and 1,593 patients with GERD were suitable for analysis. Overall, this survey included 810 males and 783 females, all Caucasians; 1,427 (89.6%) participants were economically active population. All participants were distributed into two groups based on the International Standard Classification of Education. Among all participants, 55.2% had a lower education level, which included no education or primary education level, 44.8% had a higher education level, which included secondary education, tertiary and post-tertiary education levels. Among all GERD participants, 43.9% reported fair or poor health. During the previous 30 days,

10.4 was the mean value of the number of unhealthy days, 6.4 was the mean value of physically unhealthy days, 5.3 of mentally unhealthy days, and 4.3 of activity limitation days. Furthermore, 24.8% participants reported having ≥ 14 unhealthy days, 14.9% had ≥ 14 physically unhealthy days, 11.6% reported ≥ 14 mentally unhealthy days, and 9.4% had ≥ 14 activity limitation days (Table 1).

Overall, the participants with GERD reported significantly increased physically unhealthy days, mentally unhealthy days and activity limitation days compared to the general population.

Impaired HRQoL of GERD participants was particularly evident when analyzing the duration of symptoms for the past 30 days (Table 2). The mean value of pain limitation days was 5.1 days. The participants with GERD experienced an average 5.9 days with depression, 6.8 days with anxiety, 7.2 days with poor sleep and 12.7 days of good health, during the previous 30 days. Overall, 8.9% of the participants had ≥ 14 pain limitation days, 10.4% felt depressed ≥ 14 days, 11.4% felt anxious ≥ 14 days and 12.9% had difficulty sleeping ≥ 14 days, as opposed to 29.6% who felt healthy ≥ 14 days during the previous 30 days.

As shown in Table 3, 3.33% GERD participants were without prescribed therapy, 7.78% self-administered over-

Table 1. Self-rated health and number of unhealthy days of the study group

Characteristics		Number
Self-rated health	Excellent, very good, good	878 (55.1%)
	Fair, poor	700 (43.9%)
Number of unhealthy days	≥ 14 unhealthy days	395 (24.8%)
	Unhealthy days (mean $\pm$ SD)	10.4 $\pm$ 10.6
	≥ 14 physically unhealthy days	237 (14.9%)
	Physically unhealthy days (mean $\pm$ SD)	6.4 $\pm$ 7.4
	≥ 14 mentally unhealthy days	185 (11.6%)
	Mentally unhealthy days (mean $\pm$ SD)	5.3 $\pm$ 7.3
	≥ 14 activity limitation days	149 (9.4%)
	Activity limitation days (mean $\pm$ SD)	4.3 $\pm$ 6.7

Table 2. Duration of symptoms during the previous 30 days

Symptoms	Number
≥ 14 days limited by pain	141 (8.9%)
Pain limitation days (mean $\pm$ SD)	5.1 $\pm$ 6.4
≥ 14 days felt depressed	165 (10.4%)
Days with depression (mean $\pm$ SD)	5.9 $\pm$ 7.7
≥ 14 days felt anxious	181 (11.4%)
Days with anxiety (mean $\pm$ SD)	6.8 $\pm$ 7.5
≥ 14 days had difficulty with sleep	206 (12.9%)
Days with poor sleep (mean $\pm$ SD)	7.2 $\pm$ 7.6
≥ 14 days felt healthy	471 (29.6%)
Days with good health (mean $\pm$ SD)	12.7 $\pm$ 10

Table 3. Therapy administration

Therapy administration	Number
No	53 (3.33%)
Yes, self-administered OTC drugs	124 (7.78%)
Yes, PPIs prescribed by PCPs	441 (27.7%)
Yes, PPIs prescribed by a specialist	974 (61.14%)
In total	1,593 (100%)

Table 4. Odds ratio (OR) from multiple logistic regression model

OR (95% CI)		Independent variables		
		Sex	Age	Education
Dependent variables	Fair or poor self-rated health	1.19 (0.97–1.49)	2.53 (2.04–3.14)	0.39 (0.31–0.48)
	≥14 physically unhealthy days	1.28 (0.97–1.70)	1.48 (1.10–1.98)	0.46 (0.33–0.62)
	≥ 14 mentally unhealthy days	1.65 (1.21–2.26)	1.03 (0.79–1.51)	0.48 (0.34–0.67)
	≥ 14 unhealthy days	1.30 (1.03–1.63)	1.41 (1.11–1.78)	0.65 (0.51–0.83)
	≥14 activity limitation days	1.31 (0.93–1.85)	1.71 (1.19–2.47)	0.44 (0.29–0.65)
	≥14 pain limitation days	1.60 (1.12–2.28)	1.58 (1.09–2.30)	0.46 (0.31–0.69)
	≥14 days felt depressed	1.51 (1.09–2.10)	1.20 (0.86–1.68)	0.44 (0.30–0.63)
	≥14 days felt anxious	1.51 (1.10–2.07)	1.31 (0.95–1.82)	0.48 (0.34–0.68)
	≥14 days had poor sleep	1.41 (1.05–1.90)	1.01 (0.75–1.37)	0.62 (0.45–0.84)
	≥14 days felt healthy	0.95 (0.76–1.19)	0.35 (0.28–0.45)	1.52 (1.21–1.94)

the-counter (OTC) medications. In total, 88.84% were on proton pump inhibitors (PPIs) therapy prescribed either by PCPs or a specialist.

After adjustment for age, sex and education level in the multiple logistic regression model (Table 4), GERD participants over 50 years of age (odds ratio – OR=1.19; 95% confidence interval – CI=0.97–1.48) with lower education level (OR=0.39; 95%, CI=0.31–0.48), had a significantly higher prevalence of poor or fair health, without gender differences. Furthermore, GERD participants over 50 years of age (OR=1.48; 95%, CI=1.10–1.98) with lower education level (OR=0.46; 95%, CI=0.33–0.62) had a higher prevalence of physically unhealthy days (≥14), without gender differences.

Regarding ≥14 mentally unhealthy days, female GERD participants (OR=1.65; 95% CI=1.21–2.26) with lower education level (OR=0.48; 95%, CI=0.34–0.67) had a higher prevalence of mental problems, without age difference. Significant predictors for ≥14 unhealthy days were gender, age and education level. Female GERD participants (OR=1.30; 95%, CI=1.03–1.63) aged over 50 years (OR=1.41; 95%, CI=1.11–1.78), and of lower education level (OR=0.65; 95%, CI=0.51–0.83) reported ≥14 unhealthy days. Furthermore, significant predictors for limited activities were age and education level, without gender differences.

For pain limitation days, sex, age and education level were significant predictors. Overall, female GERD participants (OR=1.60; 95%, CI=1.12–2.28) aged over 50 years (OR=1.58; 95%, CI=1.09–2.30) with lower education level (OR=0.46; 95%, CI=0.31–0.69) had a significantly higher prevalence of pain limitation days (≥14). Analyzing healthy days, the GERD participants under 50 years of age (OR=0.35; 95%, CI=0.28–0.45) with a higher education level (OR=1.52; 95%, CI=1.21–1.91), had ≥14 healthy days during the previous 30 days.

DISCUSSION

The current study, to the best of our knowledge, was the first population-based study regarding HRQoL in GERD patients ever conducted in Serbian primary healthcare settings. The validation of the study was achieved using adequate survey methodology and the certified generic self-

administered CDC-HRQOL-4 questionnaire. Its validity and reliability are comparable to other patients' reported outcomes instruments, including SF-36 form, which has been accepted as the "golden standard" in HRQoL measures [18].

The term "GERD iceberg" has been introduced recently in the clinical practice to provide better perception of GERD patients distribution among physicians [19].

In this survey, the analysis of therapy administration revealed that up to 3.33% of participants were without therapy. Furthermore, 7.78% of participants used self-administered over-the-counter medications. Only 27.7% of participants were treated at primary healthcare level institutions with empirical PPIs therapy, as opposed to 61.14% of patients who were treated with PPIs therapy at secondary and tertiary healthcare levels by a gastroenterologist or digestive surgeon specialist. These results were in high discrepancy with currently valid treatment protocols which stated that majority of GERD patients should be diagnosed and treated at the primary care setting [12]. Indeed, the empirical PPIs therapy has been well documented and widely accepted in the management of uncomplicated GERD. The "GERD iceberg" concept has underscored the need for public education and awareness about GERD among PCPs, as well as the empowerment of patients regarding the expression of symptoms, worry and impairment of overall wellbeing [20].

Among all the participants in this survey, 43.9% self-rated their health status as fair or poor. These results highly correlated with the fact that not a negligible number of participants were without therapy or on self-administered over-the-counter medications, although up to 88.84% of the participants were treated with therapy prescribed by PCPs. However, several explanations are possible. The proportion of treated patients was higher than that observed in other studies [11, 21]. A large proportion of treated patients could be addressed to the inclusion criteria that involved patients treated with routine clinical care. Furthermore, insufficient data were obtained regarding therapy regimes (on demand or regular visits of PCPs), and no comparison of the efficacy between different types of PPIs could be made. Moreover, the participants' medication compliance could not be evaluated. All these questions should be addressed in future studies.

The mean value of unhealthy days was 10.4 during the previous 30 days. The obtained results were in high correlation with results obtained from other studies [22, 23]. The feedback relation between reflux symptoms and impaired emotional status was also demonstrated, with mean values of days with depression and anxiety of 5.9 days and 6.8 days, respectively, during the previous 30 days. Pacini et al. [24] demonstrated the presence of reflux symptoms in a large proportion of patients with deteriorated mental health. The nocturnal reflux was shown to be associated with extra-esophageal manifestations, GERD complications and a variety of sleep disturbances [25]. In this survey, the mean value of the number of past days with poor sleep was 7.2 during 30 days. Mody et al. [5] demonstrated that patients with nighttime reflux symptoms are more likely to experience sleep difficulties.

The number of unhealthy days as predictors of disability proved that GERD impacts patients' everyday lives with a higher burden than that observed in other chronic non-transmittable diseases [26].

Ford et al. [27] demonstrated that 10.4% of coronary heart disease patients reported having ≥ 14 physically unhealthy days, 10.3% had ≥ 14 mentally unhealthy days, 6.6% had ≥ 14 activity limitation days compared to our results, which demonstrated that 14.9% of GERD patients reported having ≥ 14 physically unhealthy days, 11.6% had ≥ 14 mentally unhealthy days and 9.4% had ≥ 14 activity limitation days. Similar results were obtained comparing the impact of GERD and metabolic syndrome on patients' HRQoL. Ford et al. [28] demonstrated that 41% of participants with metabolic syndrome reported fair or poor health, 11.5% had ≥ 14 physically unhealthy days, 11.1% had ≥ 14 mentally unhealthy days, while 3.9% had ≥ 14 activity limitation days, as opposed to our results.

The results of this survey demonstrated that predicament of HRQoL in GERD patients in a large proportion depended on variables such as age, gender and education level. GERD patients above 50 years of age and with a lower education level, without gender differences, were more likely to express impaired health status including fair or poor health. Elderly patients in large percentage usually had one or more co-

morbidities, which were not the subject of this survey, while the lower education level usually led to a lower income status and could explain difficulties in understanding disease severity and could affect patients' therapy compliance. Similar results were obtained in all CDC-HRQoL-4 core module questions with the exception of mental health questions in which females above 50 years of age and a lower education level were more likely to manifest depression, anxiety and sleep difficulties. These differences could be attributed to a higher prevalence of mood disorders in female population while several studies addressed a complex relationship between night reflux and sleep disturbances [5, 29].

Moreover, all displayed diversities in the multiple logistic regression model could be attributed to employment and income status, marital status and cultural differences, which could not be examined in this survey. According to this hypothesis and based on our results we could conclude that GERD patients of both genders, under 50 years of age and with a high education level were presumably of better disease understanding and therapy compliance, which led to a lower impairment of HRQoL.

Limitations of the study included inability to determine which particular reflux symptom participants deemed troublesome. Other limitations also included PPIs therapy regime, therapy compliance and cultural differences. Further work is obviously needed to assess these characteristics and the severity of their impact on HRQoL of GERD patients in Serbia.

CONCLUSION

This study has addressed the complex relationships between GERD and patients' HRQoL. The obtained results demonstrate that GERD impairs patients' everyday lives in large proportion. However, worldwide, GERD is still an underestimated health problem according to patients, as well as a substantial number of PCPs.

A better understanding of the relationships between GERD and impaired HRQoL may allow healthcare providers to manage these patients more effectively in the future.

REFERENCES

1. Stanghellini V. Relationship between upper gastrointestinal symptoms and lifestyle, psychosocial factors and comorbidity in the general population: results from the Domestic/International Gastroenterology Surveillance Study (DIGEST). *Scand J Gastroenterol Suppl.* 1999; 231:29-37.
2. Revicki DA, Sorensen S, Maton PN, Orlando RC. Health-related quality of life outcomes of omeprazole versus ranitidine in poorly responsive symptomatic gastroesophageal reflux disease. *Dig Dis.* 1998; 16:284-91.
3. Kulig M, Leodolter A, Vieth M, Schulte E, Jaspersen D, Labenz J, et al. Quality of life in relation to symptoms in patients with gastroesophageal reflux disease – an analysis based on the ProGERD initiative. *Aliment Pharmacol Ther.* 2003; 18:767-76.
4. Wiklund I. Review of the quality of life and burden of illness in gastroesophageal reflux disease. *Dig Dis.* 2004; 22:108-14.
5. Mody R, Bolge SC, Kannan H, Fass R. Effects of gastroesophageal reflux disease on sleep and outcomes. *Clin Gastroenterol Hepatol.* 2009; 7:953-9.
6. Ronkainen J, Aro P, Storskrubb T, Lind T, Bolling-Sternevald E, Junghard O, et al. Gastro-oesophageal reflux symptoms and health-related quality of life in the adult general population – the Kalixanda study. *Aliment Pharmacol Ther.* 2006; 23:1725-33.
7. Dubois RW, Aguilar D, Fass R, Orr WC, Elfant AB, Dean BB, et al. Consequences of frequent nocturnal gastro-oesophageal reflux disease among employed adults: symptom severity, quality of life and work productivity. *Aliment Pharmacol Ther.* 2007; 25:487-500.
8. Wahlqvist P, Carlsson J, Stalhammar NO, Wiklund I. Validity of a Work Productivity and Activity Impairment questionnaire for patients with symptoms of gastro-esophageal reflux disease (WPAI-GERD) – results from a cross-sectional study. *Value Health.* 2002; 5:106-13.
9. Leodolter A, Nocon M, Kulig M, Willich SN, Malferteiner P, Labenz J. Gastro esophageal reflux disease is associated with absence from work: results from a prospective cohort study. *World J Gastroenterol.* 2005; 11:7148-51.

10. Dimenas E, Glise H, Hallerback B, Hernqvist H, Svedlund J, Wiklund I. Quality of life in patients with upper gastrointestinal symptoms. An improved evaluation of treatment regimens? *Scand J Gastroenterol.* 1993; 28:681-7.
11. Jones R, Armstrong D, Malfertheiner P, Ducrotte P. Does the treatment of gastroesophageal reflux disease (GERD) meet patients' needs? A survey-based study. *Curr Med Res Opin.* 2006; 22:657-62.
12. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus G. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol.* 2006; 101:1900-20; quiz 43.
13. Zullig KJ. Creating and using the CDC HRQOL healthy days index with fixed option survey responses. *Qual Life Res.* 2010; 19:413-24.
14. Zahran HS, Kobau R, Moriarty DG, Zack MM, Holt J, Donehoo R. Health-related quality of life surveillance – United States, 1993–2002. *MMWR Surveill Summ.* 2005; 54:1-35.
15. Moriarty DG, Kobau R, Zack MM, Zahran HS. Tracking Healthy Days – a window on the health of older adults. *Prev Chronic Dis.* 2005; 2:A16.
16. Frank L, Kleinman L, Rentz A, Ciesla G, Kim JJ, Zacker C. Health-related quality of life associated with irritable bowel syndrome: comparison with other chronic diseases. *Clin Ther.* 2002; 24:675-89; discussion 74.
17. Bijkerk CJ, de Wit NJ, Muris JW, Jones RH, Knottnerus JA, Hoes AW. Outcome measures in irritable bowel syndrome: comparison of psychometric and methodological characteristics. *Am J Gastroenterol.* 2003; 98:122-7.
18. Andresen EM, Fouts BS, Romeis JC, Brownson CA. Performance of health-related quality-of-life instruments in a spinal cord injured population. *Arch Phys Med Rehabil.* 1999; 80:877-84.
19. Castell D. Clinical spectrum of GERD. *Practical Gastroenterology.* 2004; 14-6.
20. Castell DO, Murray JA, Tutuian R, Orlando RC, Arnold R. Review article: the pathophysiology of gastro-oesophageal reflux disease – oesophageal manifestations. *Aliment Pharmacol Ther.* 2004; 20(Suppl 9):14-25.
21. Rey E, Moreno Elola-Olaso C, Rodriguez Artalejo F, Diaz-Rubio M. Impact of gastroesophageal reflux symptoms on health resource usage and work absenteeism in Spain. *Rev Esp Enferm Dig.* 2006; 98:518-26.
22. Lee SW, Chang CM, Chang CS, Kao AW, Chou MC. Comparison of presentation and impact on quality of life of gastroesophageal reflux disease between young and old adults in a Chinese population. *World J Gastroenterol.* 2011; 17:4614-8.
23. Fedorak RN, Wong K, Bridges R. Canadian Digestive Health Foundation Public Impact Series. Inflammatory bowel disease in Canada: Incidence, prevalence, and direct and indirect economic impact. *Can J Gastroenterol.* 2010; 24:651-5.
24. Pacini F, Calabrese C, Cipolletta L, Valva MD, Russo A, Savarino V, et al. Burden of illness in Italian patients with gastro-oesophageal reflux disease. *Curr Med Res Opin.* 2005; 21:495-502.
25. Shaker R, Castell DO, Schoenfeld PS, Spechler SJ. Nighttime heartburn is an under-appreciated clinical problem that impacts sleep and daytime function: the results of a Gallup survey conducted on behalf of the American Gastroenterological Association. *Am J Gastroenterol.* 2003; 98:1487-93.
26. Revicki DA, Wood M, Maton PN, Sorensen S. The impact of gastroesophageal reflux disease on health-related quality of life. *Am J Med.* 1998; 104:252-8.
27. Ford ES, Mokdad AH, Li C, McGuire LC, Strine TW, Okoro CA, et al. Gender differences in coronary heart disease and health-related quality of life: findings from 10 states from the 2004 behavioral risk factor surveillance system. *J Womens Health (Larchmt).* 2008; 17:757-68.
28. Ford ES, Li C. Metabolic syndrome and health-related quality of life among U.S. adults. *Ann Epidemiol.* 2008; 18:165-71.
29. Williams L, Jacka F, Pasco J, Henry M, Dodd S, Nicholson G, et al. The prevalence of mood and anxiety disorders in Australian women. *Australas Psychiatry.* 2010; 18:250-5.

Утицај гастроезофагеалне рефлуксне болести на свакодневни живот болесника: резултати студије пресека спроведене у установама примарне здравствене заштите у Србији

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КРАТАК САДРЖАЈ

Увод Недавни резултати студија урађених у земљама западне Европе доказали су да је код болесника са дијагностикованом гастроезофагеалном рефлуксном болешћу (ГЕРБ) знатно нижи квалитет живота повезан са здрављем у односу на општу популацију.

Циљ рада Циљ истраживања је био да покаже у којој мери рефлуксне тегобе утичу на квалитет живота повезан са здрављем код болесника са дијагностикованом ГЕРБ.

Методе рада Истраживањем су обухваћена укупно 1.593 болесника са дијагностикованом ГЕРБ. Током истраживања анализирани су резултати добијени помоћу српске верзије општег упитника за процену квалитета живота повезаног са здрављем Центара за контролу и превенцију болести у Атланти. У обради добијених налаза коришћене су следеће статистичке методе: методе дескриптивне статистике, Пирсонов χ^2 -тест и мултипли регресиони модел.

Резултати Од укупног броја болесника са ГЕРБ, 43,9% је оценило своје тренутно здравствено стање као озбиљно на-

рушено или лоше. Средња вредност броја дана нарушеног здравственог стања у последњих 30 дана била је 10,4 дана, дана нарушеног физичког здравља 6,4 дана, дана нарушеног менталног здравља 5,3 дана и 4,3 дана с немогућношћу обављања свакодневних активности. Даљом анализом добијени су следећи резултати: 24,8% болесника са ГЕРБ је пријавило ≥ 14 дана са нарушеним здравственим стањем у протеклих 30 дана, 14,9% болесника је пријавило ≥ 14 дана нарушеног физичког здравља, 11,8% болесника је пријавило ≥ 14 дана нарушеног металног здравља и 9,4% је пријавило ≥ 14 дана с немогућношћу обављања свакодневних активности.

Закључак Резултати овог истраживања показали су сложен однос између рефлуксних тегоба и смањеног квалитета живота повезаног са здрављем у групи болесника са дијагностикованом ГЕРБ.

Кључне речи: гастроезофагеална рефлуксна болест; рефлуксне тегобе; квалитет живота повезан са здрављем

Scoring System Development and Validation for Prediction Choledocholithiasis before Open Cholecystectomy

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SUMMARY

Introduction Accurate precholecystectomy detection of concurrent asymptomatic common bile duct stones (CBDS) is key in the clinical decision-making process. The standard preoperative methods used to diagnose these patients are often not accurate enough.

Objective The aim of the study was to develop a scoring model that would predict CBDS before open cholecystectomy.

Methods We retrospectively collected preoperative (demographic, biochemical, ultrasonographic) and intraoperative (intraoperative cholangiography) data for 313 patients at the department of General Surgery at Gornji Milanovac from 2004 to 2007. The patients were divided into a derivation (213) and a validation set (100). Univariate and multivariate regression analysis was used to determine independent predictors of CBDS. These predictors were used to develop scoring model. Various measures for the assessment of risk prediction models were determined, such as predictive ability, accuracy, the area under the receiver operating characteristic curve (AUC), calibration and clinical utility using decision curve analysis.

Results In a univariate analysis, seven risk factors displayed significant correlation with CBDS. Total bilirubin, alkaline phosphatase and bile duct dilation were identified as independent predictors of choledocholithiasis. The resultant total possible score in the derivation set ranged from 7.6 to 27.9. Scoring model shows good discriminatory ability in the derivation and validation set (AUC 94.3 and 89.9%, respectively), excellent accuracy (95.5%), satisfactory calibration in the derivation set, similar Brier scores and clinical utility in decision curve analysis.

Conclusion Developed scoring model might successfully estimate the presence of choledocholithiasis in patients planned for elective open cholecystectomy.

Keywords: scoring system; choledocholithiasis; open cholecystectomy

INTRODUCTION

Gallstone disease is one of the most common problems in Europe and North America [1]. Surgical cholecystectomy (laparoscopic or open) is the usual method of treatment of patients with symptomatic gallstones. However, the risk that a patient has asymptomatic concurrent common bile duct stones (CBDS) is the key factor in determining diagnostic and treatment strategies [2]. CBDS can cause serious morbidity or mortality, and evidence for them should be sought in all patients with symptomatic gallstones undergoing cholecystectomy. However, preoperative identification of asymptomatic CBDS is a challenge for all surgeons in order to decrease operative risks and health care costs.

The standard preoperative methods used to diagnose patients with gallstones (liver function tests and abdominal ultrasound [US]) are often not accurate enough to establish a firm diagnosis of CBDS [3]. Risk factors for CBDS include abnormal liver chemistry jaundice, and abdominal ultrasound evidence of bile duct dilation (BDD). Also, several different diagnostic studies have been proposed to

make the diagnosis including magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography (ERCP), spiral computed tomography cholangiography, before any therapeutic intervention and intraoperative cholangiography (IOC), endoscopic ultrasound and laparoscopic common bile duct exploration at the time of surgery. Despite their good results, these imaging modalities cannot be anticipated as routine due to high costs, limited availability and technical difficulties in performing laparoscopic exploration of the common bile duct.

Several recent studies have demonstrated that multivariate models are more accurate than most informative single predictors. Consequently, clinical prediction has evolved from physician judgment alone to risk group stratification, to prediction models (predictive scores) based on multivariate regression [2, 4, 5, 6] or discriminant functions [7], to artificial neural network in predicting CBDS or the need for therapeutic ERCP in patients with suspected choledocholithiasis [8, 9]. Many of these scoring systems were validated and were able to predict CBDS in 80–100% of the patients in both the training and test sets [2, 5, 8, 9]. However,

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discriminative ability is not sufficient for a model to be clinically useful, and not all authors demonstrated their clinical usefulness [10]. Furthermore, unfortunately, such models do not always perform well for patients other than those from whose data the models were derived.

Based on these considerations, the objective of the study was to assess whether pre-treatment clinical and biochemical parameters expressed in our scoring system could improve the prediction of choledocholithiasis in patients scheduled for open cholecystectomy because of symptomatic cholelithiasis.

OBJECTIVE

Based on these considerations, the objective of the study was to assess whether pre-treatment clinical and biochemical parameters expressed in our scoring system could improve the prediction of choledocholithiasis in patients scheduled for open cholecystectomy because of symptomatic cholelithiasis.

METHODS

We retrospectively collected preoperative and intraoperative data of consecutive patients considered for open cholecystectomy for symptomatic gallstones at the department of General Surgery at General Hospital in Gornji Milanovac, Serbia, in the course of five years, from January 2003 through August 2007. The study was approved by the local committee on human research, and all patients gave written informed consent.

For each patient, comprehensive clinical, current biochemical tests, and abdominal US findings (General ELECTRIC® Logiq 3 Pro, USA) were collected as regards precholecystectomy assessment. The clinical data included the patients' sex and age, the presence of acute biliary colic and history of previous acute biliary pancreatitis or jaundice. The biochemical data included preoperative liver function tests (serum total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, amylase, γ -glutamyl transpeptidase and white blood cell count. Each ultrasound finding included a description of the common bile duct (CBD) appearance (for stones and BDD in millimeters), and number and dimension of gallstones. Gallstones were classified as dangerous or not dangerous as described previously [4]. Briefly, multiple gallstones were classified as dangerous when they were micro (<3 mm), small (3–5 mm), or heterogeneous in size; multiple gallstones were considered not dangerous when they were medium (5–10 mm) or large (>10 mm) sized; and a single stone, irrespective of dimension.

The patients were operated on using technique of open cholecystectomy, under general endotracheal anesthesia. Biliary tree anatomy and the presence of stones in the common bile duct were checked by using IOC. Suspicion of choledocholithiasis was based upon the following: (i) deranged liver function tests (past or present); (ii) history

of jaundice (past or present) or acute pancreatitis; (iii) a dilated CBD or demonstration of CBDS on imaging; or (iv) a combination of these factors [11]. In situations when cholangiogram was positive, choledochotomy with extraction of calculi was performed. Complete clearance was finally checked using proximal and distal fluoroscopic cholangiography. In all patients T-tube insertion was left. T-tube removal after check cholangiography was performed after a minimum of two weeks. Demonstrable CBDS was considered the "gold standard" for the presence of CBDS. It was defined as CBDS visually and was extracted, during surgery or ERCP. After hospital discharge, patients were checked after a week, then once a month as the outpatients, and after a year using the telephone calls checking whether they had pain under the right rib cage, which would resemble those before operations, whether they had to consult their general practitioner or surgeon due to jaundice or other symptoms from the digestive system.

Derivation and validation sets

The patients were randomized into a derivation set (two-thirds of the patients) and a validation set (one-third of the patients) by random sampling. The validation set was not used until after the multiple logistic regressions model and the scoring system had been created.

Statistical analyses

Univariate and multivariate LR was used to identify and quantify the independent predictors of CBDS. The results of regressions were expressed in odds ratios with 95% confidence intervals. The resultant beta coefficients for each variable were reported and used to develop an integer based weighted point system for CBDS. The B coefficient for each variable was divided by nine. Individual scores were assigned to each patient discharge record by summing the individual risk factor points. The Hosmer–Lemeshow goodness-of-fit test was performed. Non-significant p-values on this test imply good fit.

For scoring system in the testing and validation sets we calculated the area under the receiver operating characteristic curve (AUC) analysis, sensitivity, specificity, positive (PPV), negative predictive value (NPV), accuracy, calibration plots, Hosmer–Lemeshow statistic, and the Brier score. In order to examine the generality of the constructed models, data of an independent cohort of 100 patients were used for validation.

Clinical usefulness was assessed by using decision curve analyses [12]. These analyses estimate a "net benefit" for prediction models by summing the benefits (true positives) and subtracting the harms (false positives). Assumption is made that the suspicion of CBDS would lead to diagnosis with IOC. Net benefit is plotted against threshold probabilities compared with 'NC for all' and 'NC for none' strategy. The interpretation of a decision curve is that the model with the highest net benefit at a particular threshold

probability should be chosen. Calculations and graphic net benefit were performed in Microsoft Excel using the recommended formula from true- and false-positive count of patients [12]. All other analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

RESULTS

Patients' characteristics

The study included 313 patients, the mean $\pm$ standard deviation (range) patient age at the time of open cholecystectomy was 55.9 ± 13.4 (21–85) years and 225 (71.9%)

patients were female. Of all the patients, in 249 (79.6%) the IOCs were successfully performed. Twenty-two of 249 (8.8%) IOCs were positive for bile duct stones that subsequently underwent open choledochotomy with stone extraction. Retained CBDS were detected in two patients during follow-up evaluation and were treated with ERCP. The patients were divided into the derivation (213) and the validation set (100). Baseline clinical characteristics of the patients in the derivation and validation sets are shown in Table 1. There were no significant differences in these sets (Table 1) except in the presence of acute or chronic cholecystitis.

In a univariate analysis, seven risk factors displayed significant correlation with CBDS (Table 2). During multivariable analysis, three of them sustained their prognostic

Table 1. Baseline patients' characteristics in the derivation and the validation set

Characteristics			Derivation set (n=213)	Validation set (n=100)	p-value
Demographic factor	Age (years)	Mean (SD)	55.8±13.3	56.1±13.5	0.820
	Sex (%)	Female	71.8	72.0	0.975
		Male	18.2	28.0	
Laboratory data, median (IQR)		Total bilirubin	16 (13.5)	16 (10)	0.590
		ALT	20 (18)	19 (12.5)	0.550
		AST	18 (11)	18 (10)	0.293
		ALP	76 (35)	70.5 (31)	0.290
		Amylase	51 (19)	52 (24)	0.206
		GGT	24 (19.5)	21 (17)	0.086
		WBC count (×10 ⁹ /L)	8 (4)	7 (4)	0.188
Bile duct diameter (mm)			7 (2)	7 (2)	0.498
Types of biliary calculus (%)		1	17.4	15.0	0.865
		2	68.5	70.0	
		3	14.1	15.0	
"Dangerous" stones (%)		No	31.1	32.9	0.808
		Yes	68.9	67.1	
Clinical finding	Acute/chronic cholecystitis (%)	No	39.9	25.3	0.007
		Yes	60.1	74.7	
	Biliary colic (%)	No	32.4	31.8	1.000
		Yes	67.6	68.2	
	Pancreatitis (%)	No	46.7	31.2	0.257
		Yes	53.3	68.8	
CBDS (%)		No	91.5	94.0	0.504
		Yes	8.5	6.0	
IOC (%)		No	17.8	26.0	0.100
		Yes	82.2	74.0	

All values are reported as mean $\pm$ SD or median $\pm$ IQR, and percentage of group.

SD – standard deviation; IQR – interquartile range; ALT – alanine aminotransferase; AST – aspartate aminotransferase; ALP – alkaline phosphatase;

GGT – γ -glutamyl transpeptidase; WBC – white blood cells; 1/2/3 – bilirubin/cholesterol/ mixed stones; CBDS – common bile duct stones;

IOC – intraoperative cholangiography

Table 2. The analysis of possible and independent predictors for choledocholithiasis in the derivation set and point value

Factor	Univariate analysis		Multivariable analysis			Point value
	OR (95% CI)	p-value	OR (95% CI)	p-value	B	
Total bilirubin	1.041 (1.020–1.062)	0.000	1.027 (1.008–1.046)	0.005	0.027	0.003
ALT	1.008 (1.004–1.012)	0.000				
ALP	1.015 (1.007–1.022)	0.000	1.018 (1.002–1.034)	0.028	0.018	0.002
GGT	1.007 (1.003–1.011)	0.000				
Bile duct diameter	2.881 (1.941–4.276)	0.000	2.669 (1.739–4.098)	0.000	0.982	0.110
"Dangerous" stones	3.536 (1.124–11.124)	0.031				
Acute/chronic cholecystitis	0.165 (0.037–0.738)	0.018				

OR – odds ratio; CI – confidence interval; B – coefficient

Table 3. Efficacy measure from model both in the test and the validation set

Efficacy measure	Test set	p-value	Validation set	p-value
AUC (95% CI)	94.3 (90.2–96.9)	<0.001	89.9 (82.2–95)	<0.001
Sensitivity (95% CI)	61.1 (35.7–82.7)		66.7 (22.3–95.7)	
Specificity (95% CI)	98.5 (95.6–99.7)		95.7 (89.3–98.8)	
PPV (95% CI)	78.6 (49.2–95.3)		50.0 (15.7–84.3)	
NPV (95% CI)	96.5 (92.9–98.6)		97.8 (92.3–99.7)	
Accuracy (95% CI)	95.3 (91.5–97.7)		93.9 (87.3–97.7)	
HL test χ^2	2.682	0.953	16.705	0.019
Brier score	0.0357		0.052	

AUC – area under the receiver operating characteristic curve; PPV – positive predictive value; NPV – negative predictive value; HL – Hosmer–Lemeshow; χ^2 – chi-square

significance (Table 2). The analysis demonstrated that total bilirubin, alkaline phosphatase and bile duct diameter have strong prognostic value for CBDS (Table 2). Critical values of the independent variables were as follows (the limits of normal range are in parentheses): total bilirubin >29 $\mu\text{mol/L}$ (5–21 $\mu\text{mol/L}$), alkaline phosphatase >108 U/L (34–104 U/L) and bile duct diameter >8 mm. Also, the resultant beta coefficients and point value for each variable were reported (Table 2). Next, a total score was calculated by summing the points from each variable for each patient. The resultant total possible score in derivation set ranged from 7.6 to 27.9. In the test set in patients with or without CBDS the median (IQR) scoring values were 16.9 (7.6) and 9.8 (2.4), respectively.

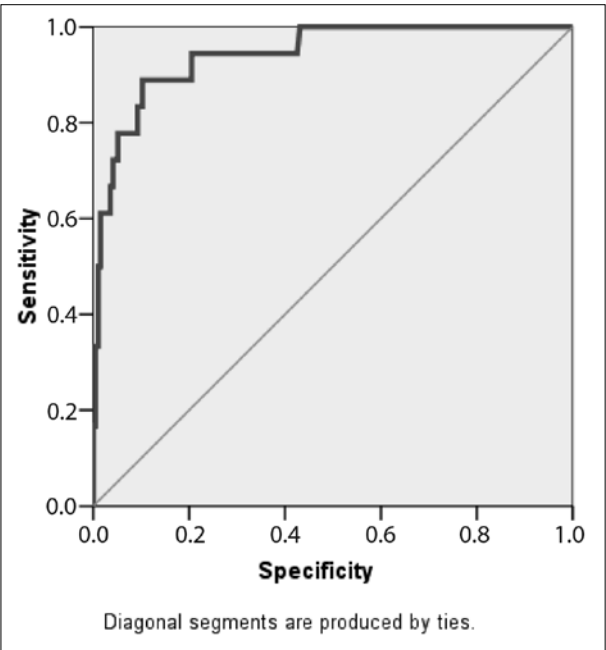
AUC for the scoring system was 94.3 (95% CI, 90.2–96.9), showing the scoring system to have good discriminatory ability (Graph 1). The scoring model retained the performance characteristics (AUC) in the validation set (Graph 2). The estimated AUC, sensitivity, specificity, PPV, NPV, accuracy, Hosmer–Lemeshow tests and Brier scores of the scoring models in the derivation and validation sets are summarized in Table 3. The scoring model was well

calibrated in the derivation set but did not show satisfactory calibration in the validation set (Table 3). The patients with a score between 15 and 20 have a probability of the presence of CBDS in about 50% of cases, whereas the patients with score over 20 have a probability of the presence of CBDS in about 80% of cases. Results of the Brier score showed to be informative in both the derivation and the validation set (Table 3).

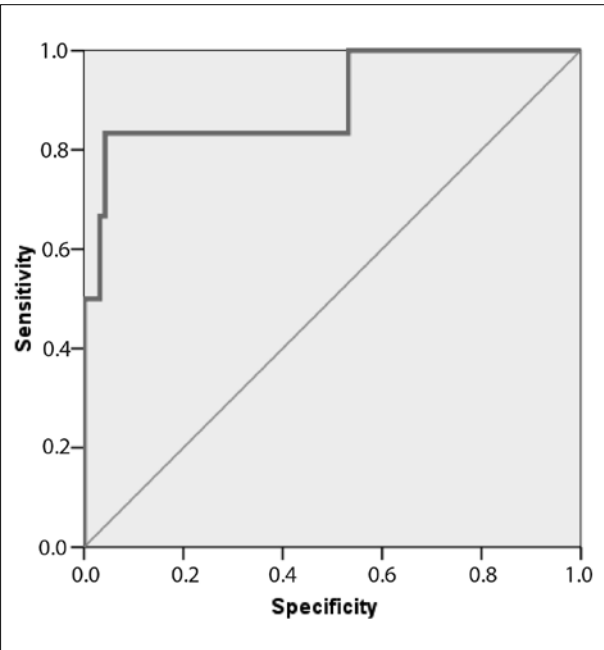
In the decision curve analysis (Graph 3), scoring model provided net benefit throughout the entire range of threshold probabilities as compared to the strategy of treating all patients with IOC, or, alternatively, treating no one.

DISCUSSION

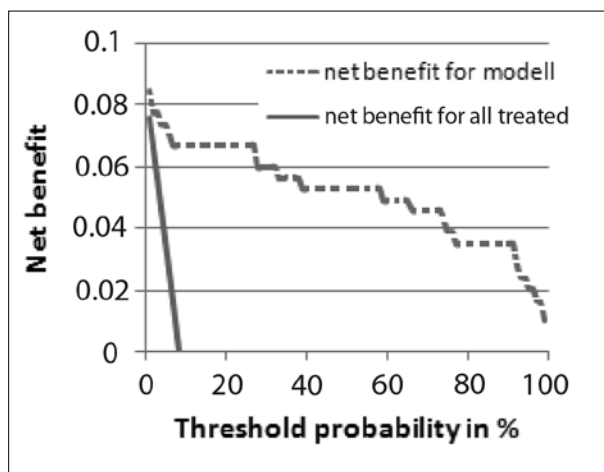
Pretreatment identification of patients undergoing elective cholecystectomy with asymptomatic concurrent CBDS is key in the clinical decision-making process. In the current study, we have taken a unique approach for prediction of choledocholithiasis using clinical and laboratory parameters before open cholecystectomy. The essential



Graph 1. Receiver operating characteristic (ROC) curves analyses in the derivation set



Graph 2. ROC curves analyses in the validation set



Graph 3. Decision curve analyses

results of this study indicated that the prediction models expressed in our scoring system were able to achieve an accuracy of 95.3%. The most useful traits of precystectomy assessment of CBDS were the rise in alkaline phosphatase, elevated total bilirubin and BDD on ultrasonography. The tool showed satisfactory discrimination, calibration, and clinical usefulness in the internal validation.

Standard methods used to diagnose choledocholithiasis in all patients with symptomatic gallstones are often not perfect [3]. On the other hand, routine use of more sophisticated methods is not cost-effective. Several prognostic models have been developed which basically use scoring system, including independent prognostic predictors obtained by multivariate regression analysis [4, 5, 6, 10, 13]. In previous literature numerous predictors have been identified that related with higher risk of CBDS: age [1, 2, 5, 10], sex [5], history of biliary colic [2, 4, 14], jaundice [1, 5], ascending cholangitis [5], acute cholecystitis [2, 14], acute biliary pancreatitis [14], total bilirubin [1, 6, 10, 15-17], γ -glutamyl transferase [1, 15], alkaline phosphatase [1, 3, 4, 6, 10, 15, 16, 18], aspartate aminotransferase [1, 10], alanine aminotransferase [1, 18], number and size of gallbladder stones [2, 4, 6], CBD diameter on ultrasonography [1-6, 17, 19]. In line with previous studies, several of these predictors have reached statistical significance in the univariate or multivariate analysis in our study. However, many of these parameters did not sustain their independent value. Nevertheless, we found that elevated alkaline phosphatase and total bilirubin were strong independent predictors of CBDS. However, levels of alkaline phosphatase and bilirubin may be deranged by mechanisms that are not related to CBDS (sphincter of Oddi dysfunction, microlithiasis and sludge in the CBD, numerous medical conditions or syndromes) [16, 20]. It was established that alanine aminotransferase and γ -glutamyl transpeptidase, increase progressively with the duration and severity of biliary obstruction [15]. The best agreement between elevated liver function values and presence of CBDS was seen in patients without acute pancreatitis or cholecystitis and operated electively [16] as were our patients. The previous authors suggested that serum total bilirubin on hospital Day 2 best predicts persisting

CBDS in gallstone pancreatitis [21]. Our study also supports findings of previous investigations that dilated CBD at US, or evidence of CBDS is the most powerful preoperative attribute of precystectomy assessment of CBDS [1-6, 13, 17, 19, 22]. Although there is controversy about the cutoff of dilated CBD diameter, our findings are in agreement with others which reported that cystic duct leaks may be considered when dilation of the CBD greater than 8 mm is present on US or computed tomography [14, 23]. Possibility of CBD stones increases in an approximately linear fashion with an increasing CBD diameter [9]). Practical implication of our results that patients with symptomatic gallstones but normal liver function test and US are considered to be at low risk for choledocholithiasis. On the other hand, patients with score from 15 to 20 points, expressed through our scoring system, should be considered to be at intermediate risk of choledocholithiasis and should be further evaluated with preoperative imaging, while a patient with score above 20 points should be considered to be at high risk of CBDS. Similar recommendations can be found in the proposed guideline [24].

It was found that the accuracy of the present models was higher than the accuracy of many earlier models. Incorporating identified factors in our scoring model resulted in an AUC of 94.3%, which is statistically better than many other models (79–88.4%) [9, 10]. Also, the specificity and NPV were similar to other reports (82–100%), but sensitivity and PPV was somewhat worse (61.1% and 78.6%, respectively) [2, 4, 5, 6, 13, 16]. However, it should be emphasized that we included a non-selective population of patients with no clear predictors for synchronous CBDS, unlike other studies, whose proposed scoring systems were effective in identifying symptomatic CBDS. In summary, our model was more able to exclude outcome of interest than confirm it.

However, metrics of accuracy do not address the clinical value of a model. The second advantage of decision curve analysis is that it can be used to compare several different models [12]. In our decision curve analysis we identified almost a whole range of threshold probabilities in which our scoring model was of value. Nevertheless, in the group of CBDS patients there are many unresolved issues regarding the IOC and thus the threshold probability of clinical implementation remains an open question. The primary methods for assessing the CBD for stones during cholecystectomy are IOC and intraoperative US. However, the issue of routine versus selective cholangiography has been long debated. Furthermore, in patients with symptomatic or suspected choledocholithiasis the treatment remains a complex and controversial issue depending on numerous factors (patients' characteristics, surgeon preference, laparoscopic expertise, availability of equipment). Although the era of open cholecystectomy ended in recent years, and the traditional approach to CBD exploration has been supplemented by newer, less-invasive procedures, (open) surgical exploration remains an important treatment option and is still the simple and straight-forward solution for management of choledocholithiasis with an excellent stone-clearance rate, as recommended by the

guideline [25, 26]. Several limitations also need to be addressed. First, enrolled patients were retrospectively collected in a single center. Second, we included only those variables that we believed might be related to the outcome of interest. Furthermore, a reference standard for diagnosing CBDS, such as IOC, is not always described. In addition, the results of the current study are limited by the short follow-up time that may have resulted in an underestimation of the true positive predictive value. Also, CBDS are encountered in our study in only approximately 8% of unselected population undergoing cholecystectomy, and therefore a very large number of patients is required to achieve a power sufficient to assess the ability of the model to predict CBDS. Finally, there is a so-called data barrier, beyond which mathematical models fail to make reliable predictions in biological systems, which is more of a consequence of the (un)availability of the information in data than a consequence of the imperfection of a particular model. Nevertheless, we have proposed a scoring system that, using noninvasive investigative methods, enables simple screening and identification of patients at low risk for asymptomatic CBDS, and patients at higher risk, who should undergo further common bile duct assessment, and which could allow a significant reduction of the total number of preoperative examinations. Our findings provide a

prognostic tool that relies on information that is regularly or simply collected in clinical practice, should be readily obtainable and may be used as a tool for subsequent choice of diagnostic or therapeutic procedures.

CONCLUSION

The proposed scoring system that uses preoperative total bilirubin, alkaline phosphatase and common bile duct diameter can successfully estimate presence of choledocholithiasis in patients planned for elective cholecystectomy. Developed scoring model may be used as a tool for risk stratification and subsequent choice of diagnostic or therapeutic procedures. However, before recommending its use in clinical practice, a controlled prospective study is required to verify our results.

ACKNOWLEDGMENT

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REFERENCES

- Prat F, Meduri B, Chiche BDR, Salimbeni-bartolini R, Pelletier G. Prediction of common bile duct stones by noninvasive tests. *Ann Surg.* 1999; 229(3):362-8. [DOI: 10.1097/0000658-199903000-00009] [PMID: 1007748]
- Khalfallah M, Dougaz W, Bedoui R, Bouasker I, Chaker Y, Nouira R, et al. Validation of the Lacaine-Huguier predictive score for choledocholithiasis: prospective study of 380 patients. *J Visc Surg.* 2012; 149(1):66-72. [DOI: 10.1016/j.jvisc.2011.11.001] [PMID: 22310294]
- Al-Jiffry BO, Elfateh A, Chundrigar T, Othman B, Almalki O, Rayza F, et al. Non-invasive assessment of choledocholithiasis in patients with gallstones and abnormal liver function. *World J Gastroenterol.* 2013; 19(35):5877-82. [DOI: 10.3748/wjg.v19.i35.5877] [PMID: 24124333]
- Sarli L, Costi R, Gobbi S, Iusco D, Sgobba G, Roncoroni L. Scoring system to predict asymptomatic choledocholithiasis before laparoscopic cholecystectomy. A matched case-control study. *Surg Endosc.* 2003; 17(9):1396-403. [DOI: 10.1007/s00464-002-9200-4] [PMID: 12802652]
- Menezes N, Marson LP, deBeaux AC, Muir IM, Auld CD. Prospective analysis of a scoring system to predict choledocholithiasis. *Br J Surg.* 2000; 87(9):1176-81. [DOI: 10.1046/j.1365-2168.2000.01511.x] [PMID: 10971424]
- Grande M, Torquati A, Tucci G, Rulli F, Adorisio O, Farinon AM. Preoperative risk factors for common bile duct stones: defining the patient at high risk in the laparoscopic cholecystectomy era. *J Laparoendosc Adv Surg Tech A.* 2004; 14(5):281-6. [DOI: 10.1089/lap.2004.14.281] [PMID: 15630944]
- Trondsen E, Edwin B, Reierstsen O, Faerden AE, Fagertun H, Rosseland AR. Prediction of common bile duct stone prior to cholecystectomy. A prospective validation of a discriminant analysis function. *Arch Surg.* 1998; 133:162-6. [DOI: 10.1001/archsurg.133.2.162] [PMID: 9484728]
- Golub R, Cantu R J, Tan M. The prediction of common bile duct stones using a neural network. *J Am Coll Surg.* 1998; 187(6):584-90. [DOI: 10.1016/S1072-7515(98)00241-5] [PMID: 9849730]
- Jovanovic P, Salkic NN, Zerem E. Artificial neural network predicts the need for therapeutic ERCP in patients with suspected choledocholithiasis. *Gastrointest Endosc.* 2014; 80(2):260-8. [DOI: 10.1016/j.gie.2014.01.023] [PMID: 2459347]
- Topal B, Fieuws S, Tomczyk K, Aerts R, Van Steenberghe W, Verslype C, et al. Clinical models are inaccurate in predicting bile duct stones in situ for patients with gallbladder. *Surg Endosc.* 2009; 23(1):38-44. [DOI: 10.1007/s00464-008-9868-1] [PMID: 18389316]
- Horwood J, Akbar F, Davis K, Morgan R. Prospective evaluation of a selective approach to cholangiography for suspected common bile duct stones. *Ann R Coll Surg Engl.* 2010; 92(3):206-10. [DOI: 10.1308/003588410X12628812458] [PMID: 20223077]
- Vickers JA, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making.* 2006; 26(6):565-74. [DOI: 10.1177/0272989X06295361] [PMID: 17099194]
- Sarli L, Costi R, Gobbi S, Sansebastiano G, Roncoroni L. Asymptomatic bile duct stones: selection criteria for intravenous cholangiography and/or endoscopic retrograde cholangiography prior to laparoscopic cholecystectomy. *Eur J Gastroenterol Hepatol.* 2000; 12(11):1175-80. [DOI: 10.1097/00042737-200012110-00002] [PMID: 11111772]
- Bueno Lledó J, Ibáñez Cirión JL, Torregrosa Gallud A, López Andújar R. Design of a preoperative predictive score for choledocholithiasis. *Gastroenterol Hepatol.* 2014; 37(9):511-8. [DOI: 10.1016/j.gastrohep.2014.04.001] [PMID: 24948445]
- Yang MH, Chen TH, Wang SE, Tsai YF, Su CH, Wu CW, et al. Biochemical predictors for absence of common bile duct stones in patients undergoing laparoscopic cholecystectomy. *Surg Endosc.* 2008; 22:1620-4. [DOI: 10.1007/s00464-007-9665-2] [PMID: 18000708]
- Videhult P, Sandblom G, Rudberg C, Rasmussen IC. Are liver function tests, pancreatitis and cholecystitis predictors of common bile duct stones? Results of a prospective, population-based, cohort study of 1171 patients undergoing cholecystectomy. *HPB (Oxford).* 2011; 13(8):519-27. [DOI: 10.1111/j.1477-2574.2011.00317.x] [PMID: 21762294]
- Song SH, Kwon CI, Jin SM, Park HJ, Chung CW, Kwon SW, et al. Clinical characteristics of acute cholecystitis with elevated liver enzymes not associated with choledocholithiasis. *Eur J Gastroenterol Hepatol.* 2014; 26(4):452-7. [DOI: 10.1097/MEG.000000000000053] [PMID: 24518492]
- Isherwood J, Garcea G, Williams R, Metcalfe M, Dennison AR. Serology and ultrasound for diagnosis of choledocholithiasis. *Ann R Coll Surg Engl.* 2014; 96(3):224-8. [DOI: 10.1308/0035884X13814021678033] [PMID: 24780789]

19. Tabone LE, Sarker S, Fisichella PM, Conlon M, Fernando E, Yi S, et al. To 'gram or not'? Indications for intraoperative cholangiogram. *Surgery*. 2011; 150(4):810-9. [DOI: 10.1016/j.surg.2011.07.062] [PMID: 22000195]
20. Shipman KE, Holt AD, Gama R. Interpreting an isolated raised serum alkaline phosphatase level in an asymptomatic patient. *BMJ*. 2013; 346:f976. [DOI: 10.1136/bmj.f976] [PMID: 23553977]
21. Chan T, Yaghoobian A, Rosing D, Lee E, Lewis RJ, Stabile BE, et al. Total bilirubin is a useful predictor of persisting common bile duct stone in gallstone pancreatitis. *Am Surg*. 2008; 74(10):77-80. [PMID: 18942626]
22. Abboud PA, Malet PF, Berlin JA, Staroscik R, Cabana MD, Clarke JR, et al. Predictors of common bile duct stones prior to cholecystectomy: a metaanalysis. *Gastrointest Endosc*. 1996; 44(4):450-5. [DOI: 10.1016/S0016-5107(96)70098-6] [PMID: 8905367]
23. LeBedis AC, Luna A, Soto AJ. Use of magnetic resonance imaging contrast agents in the liver and biliary tract. *Magn Reson Imaging Clin N Am*. 2012; 20(4):715-37. [DOI: 10.1016/j.mric.2012.07.006] [PMID: 23088947]
24. Maple JT, Ben-Menachem T, Anderson MA, Appalaneni V, Banerjee S, Cash BD, et al. The role of endoscopy in the evaluation of suspected choledocholithiasis. *Gastrointest Endosc*. 2010; 71:1-9. [DOI: 10.1016/j.gie.2009.09.041] [PMID: 20105473]
25. Lien HH, Huang CC, Huang CS, Shi MY, Chen DF, Wang NY, et al. Laparoscopic common bile duct exploration with T-tube choledochotomy for the management of choledocholithiasis. *J Laparoendosc Adv Surg Tech A*. 2005; 15(3):298-302. [DOI: 10.1089/lap.2005.15.298] [PMID: 15954833]
26. Williams EJ, Green J, Beckingham I, Parks R, Martin D, Lombard M. Guidelines on the management of common bile duct stones (CBDs). *Gut*. 2008; 57(7):1004-21. [DOI: 10.1136/gut.2007.121657] [PMID: 18321943]

Развој и провера система бодовања за предвиђање холедохолитијазе пре отворене холецистектомије

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КРАТАК САДРЖАЈ

Увод Тачна процена постојања придружене асимптоматске калкулозе заједничког жучног вода пре извођења отворене холецистектомије основа је клиничке одлуке. Стандардне преоперационе методе које се користе у ту сврху често нису довољне.

Циљ рада Циљ ове студије је био да развије модел бодовања који би могао предвидети постојање конкремената у заједничком жучном воду пре извођења отворене холецистектомије.

Методе рада Ретроспективно су прикупљени и анализирани преоперациони (демографски, биохемијски, ултразвучни) и интраоперациони (интраоперациона холангиографија) подаци о 313 болесника оперисаних од 2004. до 2007. године на Хируршком одељењу Опште болнице у Горњем Милановцу. Болесници су сврстани у тзв. деривациони (213) и валидациони сет (100). За одређивање независних предиктора холедохолитијазе коришћене су једноваријантна и мултиваријантна регресиона анализа. Овако добијени предиктори коришћени су за развијање система бодовања.

Ефикасност овог модела процењивана је на основу: предиктивних вредности, прецизности, површине испод ROC криве (AUC), калибрације и клиничке корисности модела коришћењем криве одлучивања.

Резултати Једноваријантна анализа је показала да је седам фактора ризика у корелацији с калкулозом заједничког жучног вода. Као независни предиктори холедохолитијазе означени су укупни билирубин, алкална фосфатаза и ширина холедохуса. Вредности скор у деривационом сету биле су од 7,6 до 27,9. Прогностички модел показује добру дискриминаторну способност и у деривационом и у валидационом сету (AUC 94,3% и 89,9%), одличну прецизност (95,5%), задовољавајућу калибрацију у деривационом сету, као и сличан Бријеров (Brier) скор и клиничку корист одређену кривом одлучивања.

Закључак Приказаним моделом бодовања може се успешно проценити постојање конкремената у холедохусу код болесника планираних за елективну отворену холецистектомију.

Кључне речи: скоринг систем; холедохолитијаза; отворена холецистектомија

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Assessment of the Reliability of the Serbian Version of the Sickness Impact Profile Questionnaire in Patients with Chronic Viral Hepatitis

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SUMMARY

Introduction Health-related quality of life (HRQL) of chronic patients has been researched as the ultimate goal of modern treatment of chronic diseases to improve patients' quality of life.

Objective The objective was to assess the reliability of the Serbian version of the Sickness Impact Profile (SIP) questionnaire on the sample of patients with chronic viral hepatitis.

Methods The research covered 102 patients with chronic hepatitis (47 type B and 55 type C). The assessment of the reliability of the SIP questionnaire was performed by testing the internal consistency of the questions by calculating the Cronbach's alpha coefficient. The factor analysis was used to assess whether the grouping of the questions within dimensions matches the distribution of the questions in the original English version of the questionnaire administered to U.S. patient population.

Results The Cronbach's alpha coefficient for the entire questionnaire is 0.925, 0.869 for the physical dimension, and 0.857 for the psychosocial dimension. After running a factor analysis of the psychosocial dimension, "emotional instability" was extracted as the key factor, confirming the results of previous research. Compared with the English version of the questionnaire, the Cronbach's alpha coefficient of the Serbian version does not diverge significantly, whereas the factor analysis confirms the classification of the questionnaire into two dimensions.

Conclusion Our study has shown that the Serbian version of the SIP questionnaire is a reliable tool for assessing the HRQL of patients with chronic hepatitis B and C before starting treatment.

Keywords: Sickness Impact Profile (SIP); questionnaire reliability; chronic viral hepatitis

INTRODUCTION

The health-related quality of life (HRQL) of patients suffering from chronic diseases has often been studied, as improved quality of life is the ultimate goal of modern treatments of such diseases. HRQL refers to the degree to which health condition or treatment impacts the usual or expected individual's physical, emotional and social wellbeing [1].

More often than not, diagnosed by chance, and frequently associated with liver cirrhosis and hepatocellular carcinoma, chronic hepatitis B and C are accompanied by a patient's fear of helping spread the infection, which is an additional burden on the patient. Previous studies indicate that the quality of life of patients suffering from chronic hepatitis B and C is lower compared to the healthy population [2-7].

The findings of most studies comparing the quality of life of the two cohorts indicate that patients with chronic viral hepatitis C have a lower quality of life [3, 8].

The Sickness Impact Profile (SIP) is one of the most frequently used generic questionnaires for HRQL assessment [9]. The SIP has

been designed to record subjective perceptions of the impacts of the disease on physical, psychological and social functioning of respondents, assessing how illness leads to changes in behaviour and everyday activities [10]. The original 1976 version was developed by Bergner et al. [11]. The revised version (1981) had 136 question, i.e. defined activities, which can be responded to affirmatively only if the activity in question fully describes the subject's condition resulting from the disease [11]. The HRQL examination by using the generic SIP questionnaire on patients diagnosed with two types of chronic viral hepatitis makes it possible to identify the domain, dimensions of, and degree to which the adverse effects of the disease are recordable. The assessments of the reliability of the SIP questionnaire on the population of chronic hepatitis patients have not yet been conducted in our country.

OBJECTIVE

The objective of this paper was to assess the reliability of the Serbian version of the SIP

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questionnaire on the sample of patients diagnosed with chronic viral hepatitis.

METHODS

The study was conducted in the form of a prospective study at the Clinic for Infectious Diseases of the Clinical Centre of Kragujevac. It covered all patients whose diagnosis of chronic hepatitis B and C has been confirmed serologically and virologically (using the polymerase chain reaction technique), and who made appointments at the hepatology outpatient ward for regular check-ups or were admitted to hospital for treatment between December 2013 and August 2014. The hospitalised patients were interviewed before the commencement of therapy. The sample comprises 102 patients, 47 diagnosed with chronic hepatitis B, and 55 with chronic hepatitis C.

The criteria for including patients in the study were the following: a hepatitis B or C diagnosis, older than 18 years, both sexes and voluntary participation. The exclusion criteria were the following: older than 65 years, people with hepatocellular carcinoma, people with decompensated cirrhosis, and those who refused to participate. All the patients signed a consent stating their voluntary participation. The study was approved by the Board of Ethics of the Clinical Centre of Kragujevac (01-39 of January 3, 2013).

The consent for the SIP questionnaire was obtained from the Mapi Research Trust on December 17, 2013.

The SIP examines quality of life across 12 domains. Physical dimensions are described by the following domains: ambulation (A) – 12 questions, mobility (M) – 10, and body care and movement (BCM) – 23 questions. Psychosocial dimensions are assessed through the following: emotional behaviour (EB) – 9 questions, social interaction (SI) – 20, alertness behaviour (AB) – 10, and communication (C) – 9. Independent categories (domains) are as follows: home management (HM) – 10 questions, recreation and pastimes (RP) – 8, work (W) – 9, sleep and rest (SR) – 7, and eating (E) – 9. The result of the questionnaire can be calculated for each domain, as a total score for physical and psychosocial dimensions and for the entire questionnaire. Higher scores indicate a lower quality of life. The questionnaires were filled out using 30-minute interviews.

Statistical data processing

First, a correlation matrix was established for all the questions. Then, Cronbach's alpha was calculated and values higher than 0.7 were considered significant. The former and the latter were done for both dimensions and for each domain. After that, a factor analysis was conducted on both the entire questionnaire and on its dimensions and individual domains, taking into consideration the factors with an inherent value (eigenvalue) higher than 1, if they were above the breaking point on the scree plot. Varimax rotation was used to extract factors.

RESULTS

The study encompassed 102 patients. Table 1 provides the respondents' sociodemographic characteristics. All the respondents reported that there had been no comprehensive limitations in performing everyday activities within certain domains (Table 2).

Table 1. Demographic characteristics of the respondents

Characteristic	N (%)
Age (years)	18–29
	16 (15.7)
	30–39
	31 (30.4)
	40–49
Sex	26 (25.5)
	50–59
	23 (22.5)
	≥60
	6 (6.9)
Marital status	Male
	66 (64.7)
Education	Female
	36 (35.3)
	Primary
	14 (13.7)
Employment status	Secondary
	66 (64.7)
	College/University
	22 (21.6)
Etiology	Married
	63 (61.8)
	Unmarried
	31 (30.4)
Etology	Divorced
	6 (5.9)
	Widow/er
Employment status	2 (2.0)
	Employed
	45 (44.2)
Etology	Unemployed
	49 (48.0)
	Retired
Etology	8 (7.8)
	Hepatitis B
Etology	47 (46.1)
	Hepatitis C
Etology	55 (53.9)

Table 2. Domains and questions to which all the patients responded negatively

Domain	Questions
BCM	I do not move into or out of bed or chair by myself...
	I move my hands or fingers with some limitation...
	I stand up only with someone's help
	I hold on to something to move myself...
	I do not bathe myself at all, ...
	I use bedpan with assistance
	I do not have control of my bladder
	I do not fasten my clothing, ...
	I do not have control of my bowels
	I get dressed only with someone's help
A	I get around in a wheelchair
	I do not walk at all
	I walk only with help
	I get around only by using a walker, ...
M	I go to places with restrooms nearby
C	I communicate mostly by gestures, ...
	I am understood with difficulty
E	I feed myself only by using specially prepared food or utensils
	I eat no food at all but am taking fluids
	I feed myself with help
	I do not feed myself at all, but must be fed
	I am eating no food at all (tubes or intravenous fluids)
HM	I am not doing any of the clothes washing that I would usually do

BCM – body care and movement; A – ambulation; M – mobility; C – communication; E – eating; HM – home management

Table 3. The reliability of the domains and dimensions of the generic Sickness Impact Profile (SIP) questionnaire in chronic viral hepatitis B and C patients

Domain	Min	Max	Mean	SD	Variance	Cronbach's alpha	Cronbach's alpha*
BCM	0.0	40.0	2.13	5.66	32.08	0.884	0.908
A	0.0	46.4	5.64	8.16	66.54	0.683	
M	0.0	75.5	7.49	13.82	190.94	0.806	0.813
EB	0.0	81.3	14.23	15.27	233.29	0.619	0.626
AB	0.0	100.0	13.82	18.16	329.73	0.731	
SI	0.0	74.0	17.43	16.69	278.62	0.819	
C	0.0	22.5	2.35	5.89	34.80	0.354	0.503
SR	0.0	83.2	17.27	18.68	348.89	0.522	0.590
E	0.0	24.8	4.81	5.64	31.85	0.570	
HM	0.0	70.1	9.89	14.52	210.77	0.710	
W	0.0	70.1	18.39	27.66	764.94	0.557	
RP	0.0	100.0	19.17	19.06	363.17	0.655	0.646
Physical dimensions	0.0	27.2	4.04	5.89	34.78	0.869	0.894
Psychosocial dimensions	0.0	58.4	13.05	11.26	126.80	0.857	0.865
SIP	0.52	38.25	9.80	8.01	64.10	0.925	0.929

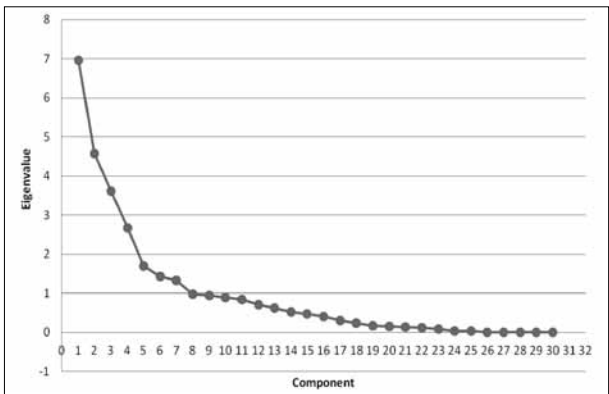
* a calculated value after eliminating the questions which correlated negatively to the overall score of a domain, dimension or the entire questionnaire

BCM – body care and movement; A – ambulation; M – mobility; EB – emotional behaviour; AB – alertness behaviour; SI – social interaction; C – communication; SR – sleep and rest; E – eating; HM – home management; W – work; RP – recreation and pastimes; Min – minimum value; Max – maximum value; SD – standard deviation

The average value of the overall SIP score was 9.80, varying between 0.52 and 38.25. The questionnaire reliability was checked by calculating the Cronbach's alpha coefficient in the following manner: 0.925 for the entire questionnaire, 0.869 for the physical dimension, 0.857 for the psychosocial dimension. The reliability over 0.70 was recorded in the five domains. In certain domains the reliability (Cronbach's alpha) increased significantly after eliminating the questions in reverse relation to the overall domain score (Table 3).

Seven factors with an inherent value (eigenvalue) above 1 were extracted in the factor analysis of the answers under the physical dimension. Of these factors, the first two are the most important (Table 4).

The first and most important factor accounts for 23.178% of variance and comprises the following questions: 'I make difficult moves with help...', 'I stand only for a short time', 'I do not maintain balance', 'I kneel... only by holding onto something', 'I am very clumsy...', 'I get in and out of bed or chairs by grasping something for support...', 'I require assistance with bathing' and 'I dress myself slowly', which are an integral part of the BCM domain in the original questionnaire (Graph 1).



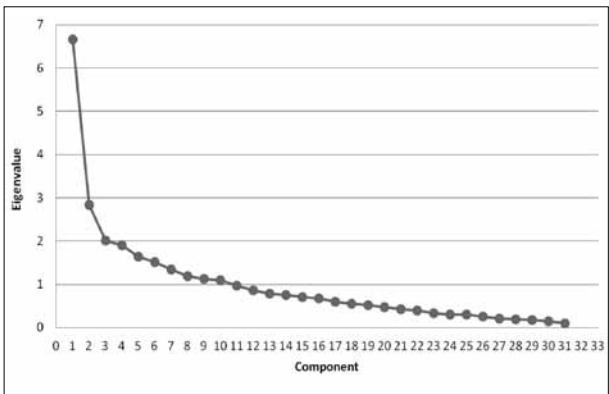
Graph 1. Scree plot for the physical dimension after varimax rotation

The other extracted factor (15.227% of overall variability) spans the following questions: 'I do not walk up or down hills', 'I use stairs only with mechanical support...', 'I walk up or down stairs only with assistance', 'I walk by myself but with some difficulty...', which imply one's ability to move, with the question concerning the ability to put one's shoes on.

Table 5 gives the break-up of the factor analysis results obtained from the questions under the psychosocial dimension. This analysis yielded two most important factors, altogether accounting for 30.638% of variability.

In the first factor (21.503 % of variability) there are four important and interlinked questions, from the SI domain in the original version of the questionnaire ('I show less affection', 'I am avoiding social visits from others', 'I act disagreeable to family members...' and 'I have frequent outbursts of anger at family members...') and question 'I laugh or cry suddenly.' These questions show the degree of 'emotional instability,' which is the name of the first factor (Graph 2).

In the second factor (9.135% of variability), there are three questions which originally referred to the AB do-



Graph 2. Scree Plot for the psychological dimension after varimax rotation

Table 4. Factor analysis of the physical dimension

Questions	Factors						
	1	2	3	4	5	6	7
	Ability to take care of oneself	Ability to move	Physical mobility	Physical activity	Isolation due to physical difficulties	Physical fitness / stamina	Orientation in space
Difficulty in moving	0.974	-0.012	-0.039	0.027	0.075	-0.072	-0.036
Difficulty in standing	0.536	0.203	0.193	0.323	-0.041	0.223	-0.483
Inability to maintain balance	0.594	0.498	-0.028	-0.092	0.403	0.065	0.188
Difficulty in kneeling, stooping and bending down	0.538	0.519	-0.035	-0.079	0.107	0.078	0.069
Restricted position	0.481	-0.064	-0.036	0.514	0.357	-0.042	-0.169
Clumsiness in body movements	0.761	-0.050	0.318	0.170	-0.158	0.012	0.470
Support needed when sitting and getting up	0.974	-0.012	-0.039	0.027	0.075	-0.072	-0.036
Lying down most of the time during the day	-0.062	0.013	0.309	0.836	0.019	0.014	0.020
Frequent changes of position	0.294	0.179	0.395	0.545	-0.102	0.142	-0.188
Assistance needed when bathing	0.974	-0.012	-0.039	0.027	0.075	-0.072	-0.036
Trouble getting shoes on	0.544	0.694	0.006	-0.007	-0.021	0.140	-0.107
Most of the time spent partly undressed	-0.056	0.028	0.334	0.835	-0.031	0.039	0.008
Getting dressed slowly	0.594	0.498	-0.028	-0.092	0.403	0.065	0.188
Getting around only within one building	0.001	-0.035	0.848	0.109	-0.088	-0.057	0.234
Time spent within one room	0.097	-0.058	0.487	0.212	-0.297	0.089	0.697
Lying in bed	0.001	-0.104	0.844	0.139	0.080	0.054	-0.017
Most of the time spent in bed	-0.004	-0.099	0.874	0.152	0.144	0.006	0.001
Public transport not used	-0.042	0.287	0.678	0.072	0.197	0.002	0.181
Most of the time spent at home	0.101	0.007	0.219	0.137	0.733	0.194	-0.114
No visits to town	0.297	-0.135	0.140	0.490	0.168	0.084	0.266
Only brief periods of time spent away from home	0.181	0.025	0.065	0.179	0.764	0.290	-0.027
Inability to get around in the dark without someone's help	0.046	0.547	0.354	0.076	0.032	0.076	0.706
I walk shorter distances or stop to rest often	-0.039	0.022	-0.039	0.116	0.291	0.776	0.002
I do not walk up or down hills	-0.030	0.404	-0.065	0.023	-0.089	0.386	-0.036
Using stairs only with mechanical support	-0.059	0.625	-0.063	0.101	-0.230	0.090	-0.089
Assistance needed when using stairs	-0.032	0.827	0.010	-0.105	0.342	0.017	0.296
Difficulty in walking	0.011	0.863	0.047	-0.019	0.033	0.114	-0.043
Going up and down stairs more slowly	0.025	0.209	0.022	-0.083	0.114	0.745	-0.139
I do not use stairs at all	-0.065	-0.053	-0.267	0.670	0.282	-0.001	0.135
I walk more slowly	-0.048	0.069	0.073	0.074	0.073	0.758	0.197
The percentage of variability	23.178	15.227	12.061	8.912	5.688	4.803	4.424

main ('I forget things...', 'I make more mistakes than usual' and 'I have difficulty doing activities involving concentration and thinking') and another question from the C domain ('I often lose control of my voice...'). This factor was named "attention and focus."

DISCUSSION

The SIP is a generic questionnaire, which uses 136 questions to describe changes in an individual's behaviour which have occurred as a result of the impact of illness, and which is evident at the time of filling in the questionnaire. The respondents are asked to confirm the presence of only those changes in performing everyday activities for which the respondents are sure to be characteristic of them at the time of conducting research, and which can be ascribed to the impact of their illness. Low SIP score values correlate with a better quality of life, and vice versa.

The questionnaire has been used in studies involving populations with a wide range of illnesses, mostly chronic ones [10]. However, the reliability of the SIP questionnaire on the population of chronic hepatitis patients has not been assessed in our country.

The content of the statements which were denied by all the respondents, and which were consequently excluded from the analysis, goes to show that this illness does not lead to absolute limitations in domains of taking care of oneself, mobility, ambulation, communication, nutrition and home management.

The questions negatively correlating to the overall score in separate domains or the entire questionnaire should be eliminated from the Serbian version when used for HRQL assessment in chronic hepatitis patients. Those question are the following: 'I am lying down most of the time' and 'I spend most of the time partly undressed or in pajamas' in the BCM domain, which were answered affirmatively only by the patients (9.08%) who were hospitalised for treatment at the

Table 5. Factor analysis of the psychosocial dimension

Questions	Factors						
	1	2	3	4	5	6	7
	Emotional instability	Ability to maintain attention and concentration	Somatic manifestations of emotional reaction	Social interaction	Frustration tolerance threshold	Basic insecurity	Mental functions efficiency
I say how bad or useless I am	0.119	0.085	0.016	0.158	0.081	0.069	-0.024
I laugh or cry suddenly	0.352	0.217	0.342	-0.208	0.338	-0.118	0.047
I often moan and groan in pain	0.079	0.041	0.858	0.128	0.056	0.067	0.018
I act nervous	-0.001	0.050	-0.019	0.085	0.760	0.105	0.047
I keep rubbing or holding areas of my body that hurt	0.241	0.241	0.772	0.098	-0.124	0.127	0.029
I act irritable with myself	0.253	-0.105	-0.058	0.161	0.607	0.002	0.212
I talk about the future without hope	0.095	-0.033	0.259	-0.119	-0.059	0.621	0.019
I am visiting people less	0.015	0.104	0.104	0.788	0.206	-0.024	0.013
I act irritable toward those around me	0.435	0.155	-0.251	0.032	0.447	0.004	0.048
I show less affection	0.570	-0.265	0.161	0.306	0.234	-0.250	0.218
I am doing less social activities	0.279	-0.005	-0.131	0.592	-0.174	-0.244	0.050
I am cutting down the length of visits	0.171	0.140	0.104	0.626	0.123	0.041	0.106
I am avoiding visits from others	0.481	-0.114	0.293	0.432	0.087	0.075	-0.058
My sexual activity is decreased	-0.060	0.063	0.052	0.192	0.098	0.038	0.016
I often express concern over my health	0.267	0.333	0.079	0.130	0.393	-0.305	-0.045
I talk less with those around me	0.255	0.144	0.374	0.462	0.431	0.017	0.001
I stay alone most of the time	0.108	0.111	0.141	0.080	0.035	-0.055	0.033
I act disagreeable to family members	0.727	0.130	0.165	0.240	0.255	0.135	0.026
I have frequent outbursts of anger at family members	0.793	0.238	0.174	0.065	0.014	0.040	0.126
I isolate myself from the rest of the family	0.183	0.258	0.267	0.276	0.463	0.181	-0.007
I refuse contact with family members	-0.094	0.165	0.405	0.045	0.206	0.192	0.107
I am not joking with family members	0.133	0.685	-0.018	0.129	0.166	0.032	0.018
I start several actions at a time	0.313	0.037	-0.057	0.052	0.138	0.059	0.688
I have more minor accidents	0.043	0.341	-0.139	0.080	0.071	0.346	0.521
I react slowly	-0.408	-0.035	0.285	-0.020	0.006	-0.099	0.661
I do not finish things I start	0.138	0.080	0.144	0.065	0.021	0.178	0.519
I forget a lot	0.393	0.497	-0.047	-0.019	-0.041	0.067	0.409
I make more mistakes than usual	0.020	0.675	0.330	0.152	0.063	0.293	0.099
I have difficulty doing activities involving concentration and thinking	-0.038	0.787	0.073	0.005	-0.080	-0.107	0.091
I often lose control of my voice	0.217	0.631	0.348	-0.004	0.121	0.380	-0.030
I do not speak clearly when I am under stress	-0.010	0.180	0.019	0.016	0.166	0.829	0.166
The percentage of variability	21.503	9.135	6.471	6.144	5.281	4.874	4.341

time of filling in the questionnaire. Statement, 'I stay away from home only for brief periods of time' in the M domain, with which almost one-fifth of all the respondents agreed (19.61%), might be interpreted as the impact of the disease on a patient's psychological health, and not on the physical condition which the question should be treating. Also, in the EB domain, the question on attempted suicide was answered affirmatively by the patients (1.96%) whose way of contracting the disease is linked with the intravenous use of narcotics; 'I get sudden frights' was stated by one-fifth of the respondents (19.61%). In the C domain the following questions should be eliminated: 'I often lose control of my voice when I talk...' (2.94%); 'I don't write except to sign my name' (1.96%); 'I carry on a conversation only when very close to the other person...' (0.98%) and 'I do not speak clearly when I am under stress' (5.88%). Given that hepatitis diseases are not normally accompanied by communication problems, their random presence within the given population leads to

a conclusion that such findings might be the effect of co-morbidity. In the SR domain, the question which should be eliminated is, 'I sit around half-asleep' (12.74%), while in the RP domain the following should be left out: 'I am not doing any of my usual inactive recreation and pastimes...'

The results obtained through the SIP questionnaire confirm the existing results of the studies into this population. The SIP questionnaire contains specific problems which these patients have to deal with, as well as everyday activities affected by the problems.

Using the SIP questionnaire, Davis et al. [12] assessed the impact of illnesses and treatments on HRQL of patients with chronic hepatitis C. The results of this study suggest that this questionnaire could be a valid and reliable instrument for describing the impact of chronic hepatitis C on one's quality of life, but that it is not the best instrument for the assessment of the impact of the interferon treatment on this population [12].

Blasiole et al. [13] have used the SIP questionnaire to investigate the impact of social support on physical and psychological symptoms in the population of patients with chronic hepatitis C. The findings of this study indicate that a patient's quality of life is directly linked to the amount of social support patients get. Comparing the average domain scores of the abovementioned study and the findings of our study, higher scores were recorded in domains within physical and psychosocial dimensions, i.e. a lower quality of life of the patients in the study by Blasiole et al. [13] than is the case with the patients in our study. This can be attributed to the fact that the patients participating in our study had not started with their interferon treatment, while those from the study by Blasiole et al. [13] did so before, during and after the treatment.

The factor analysis of the psychosocial dimension has yielded two key factors. The first one covers questions by which it is possible to determine the degree of 'emotional instability'. The results of the research conducted by Janke et al. [14] in a population of patients with chronic hepatitis C point specifically to emotional instability, which ranges from irritability to outbursts of anger, which has a significant influence on patients' self-confidence and their interrelation with people in their surroundings, and is frequently at the heart of social exclusion.

The questions on 'the ability to maintain attention and focus,' with the items such as 'I frequently lose control of my voice' (found in a mere 2.94% of the subjects) and 'I don't joke with family members' (stated by 11.8% of the subjects), are grouped around the second factor. The grouping of the responses makes sense even though the abovementioned questions seem to be unrelated. Confronting the problems caused by an illness is likely to lead to changes in the behaviour of an individual, especially within a family, because of the uncertainty of the outcome on the one hand, and the chances of passing on the disease

on the other. The positive responses to these questions are probably the consequences of a patient's difficulty with maintaining attention and focus, but they can also be attributed to one's coming to terms with the disease. Monaco et al. [15] stated that more than a half of the patients with chronic hepatitis C stress problems with concentration and poor memory regardless of the stage of the disease.

The factor analysis of the physical dimension has yielded two key factors which group the responses to the questions assessing the ability to take care of oneself and move, as it was done in the original version. Although there are no absolute limitations in these domains, it is evident that due to the disease or its accompanying extrahepatic manifestations (arthralgia) some difficulty in performing everyday activities was recorded by the SIP questionnaire. The results conform with the existing studies into the population of patients with chronic hepatitis B and chronic hepatitis C, which stress that mental and physical health are the domains affected by this disease [7, 16].

CONCLUSION

Our study has shown that the Serbian version of the SIP questionnaire is a reliable tool for measuring the HRQL in patients with chronic viral hepatitis before starting treatment. The factor analysis confirms the separated dimensions of questionnaire. Although two factors were extracted for the psychosocial dimension, the first one, which relates to emotional instability, is the most characteristic of that dimension, which was further confirmed in the studies using the original version. Further research of the Serbian version of this questionnaire should assess its reliability on patients with hepatitis B and C who receive biological treatment.

REFERENCES

1. Cella D, Nowinski CJ. Measuring quality of life in chronic illness: the functional assessment of chronic illness therapy measurement system. *Arch Phys Med Rehabil.* 2002; 83(2):S10-7. [DOI: 10.1053/apmr.2002.36959] [PMID: 12474167]
2. Pojoga C, Dumitraşcu DL, Pascu O, Grigorescu M, Radu C, Damian D. Impaired health-related quality of life in Romanian patients with chronic viral hepatitis before antiviral therapy. *Eur J Gastroenterol Hepatol.* 2004;16(1):27-31. [DOI: 10.1097/00042737-200401000-00005] [PMID: 15095849]
3. Pavić S, Delić D, Simonović J, Švrtlih N. Quality of life in patients with chronic hepatitis C. *Srp Arh Celok Lek.* 2011; 139(3-4):165-9. [DOI: 10.2298/SARH1104165P] [PMID: 21626762]
4. Lam ETP, Lam CLK, Lai CL, Yuen MF, Fong DYT, So TMK. Health-related quality of life of Southern Chinese with chronic hepatitis B infection. *Health Qual Life Outcomes.* 2009; 7:52. [DOI: 10.1186/1477-7525-7-52] [PMID: 19500349]
5. Zhuang G, Zhang M, Liu Y, Guo Y, Wu Q, Zhou K, et al. Significant impairment of health-related quality of life in mainland Chinese patients with chronic hepatitis B: a cross-sectional survey with pair-matched healthy controls. *Health Qual Life Outcomes.* 2014; 12:101. [DOI: 10.1186/1477-7525-12-101] [PMID: 24928466]
6. Liu GG, DiBonaventura MD, Yuan Y, Wagner JS, L'Italien GJ, Langley P, et al. The burden of illness for patients with viral hepatitis C: evidence from a national survey in Japan. *Value Health.* 2012; 15(1 Suppl):S65-71. [DOI: 10.1016/j.jval.2011.11.012] [PMID: 22265070]
7. Švrtlih N, Pavić S, Terzić D, Delić D, Simonović D, Gvozdenović E, et al. Reduced quality of life in patients with chronic viral liver disease as assessed by SF12 questionnaire. *J Gastrointest Liver Dis.* 2008; 17(4):405-9. [PMID: 19104701]
8. Abdo AA. Health-related quality of life of Saudi hepatitis B and C patients. *Ann Saudi Med.* 2012; 32(4):397-403. [DOI: 10.5144/0256-4947.2012.397] [PMID: 22705611]
9. Gutteling JJ, de Man RA, Busschbach JJ, Darlington AS. Overview of research on health-related quality of life in patients with chronic liver disease. *Neth J Med.* 2007; 65(7):227-34. [PMID: 17656809]
10. De Bruin A, De Witte LP, Stevens F, Diederiks JP. Sickness Impact Profile: The state of the art of a generic functional status measure. *Soc Sci Med.* 1992; 35(8):1003-14. [DOI: 10.1016/0277-9536(92)90240-Q] [PMID: 1411695]
11. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. *Med Care.* 1981; 19:787-805. [PMID: 7278416]
12. Davis GL, Balart LA, Schiff ER, Lindsay K, Bodenheimer HC Jr, Perrillo RP, et al. Assessing health-related quality of life in chronic hepatitis C using the Sickness Impact Profile. *Clin Ther.* 1994; 16(2):334-43. [PMID: 8062327]
13. Blasiole JA, Shinkunas L, LaBrecque DR, Arnold RM, Zickmund SL. Mental and physical symptoms associated with lower social support for patients with hepatitis C. *World J Gastroenterol.* 2006; 12(29):4665-72. [PMID: 16937437]

14. Janke EA, McGraw S, Fraenkel L, Garcia-Tsao G. Psychosocial correlates of hepatitis C: interaction and impact on quality of life. *Psychosomatics*. 2008; 49(6):494-501. [DOI: 10.1176/appi.psy.49.6.494]
15. Monaco S, Ferrari S, Gajofatto A, Zanusso G, Mariotto S. HCV-related nervous system disorders. *Clin Dev Immunol*. 2012; 2012:236148. [DOI: 10.1155/2012/236148] [PMID: 22899946]
16. Pavić S, Švrtlih N, Simonović J, Delić D. Influence of depression on the quality of life in patients with chronic hepatitis C. *Srp Arh Celok Lek*. 2011; 139(9-10):645-50. [DOI: 10.2298/SARH1110645P] [PMID: 22070000]

Процена поузданости српске верзије упитника *Sickness Impact Profile* код болесника с хроничним вирусним хепатитисом

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КРАТАК САДРЖАЈ

Увод Квалитет живота у вези са здрављем (*HRQL*) особа с хроничним обољењима често је истраживан, јер је побољшање квалитета живота болесника крајњи циљ савремених процедура у лечењу од ових болести.

Циљ рада Циљ рада је био да се испита поузданост српске верзије упитника *Sickness Impact Profile* (*SIP*) на узорку испитаника оболелих од хроничног вирусног хепатитиса.

Методе рада Истраживање је обухватило 102 болесника с хроничним хепатитисом: 47 с хепатитисом Б и 55 с хепатитисом Ц. Поузданост генеричког упитника *SIP* процењена је кроз испитивање интерне конзистентности питања помоћу израчунавања Кронбаховог (*Cronbach*) коефицијента алфа. Факторском анализом је процењивано да ли груписање питања унутар димензија одговара дистрибуцији питања у оригиналној енглеској верзији упитника испитаној на популацији болесника из Сједињених Америчких Држава.

Резултати Вредност Кронбаховог коефицијента алфа за цео упитник била је 0,925, за физичку димензију 0,869, док је за психосоцијалну димензију била 0,857. Факторском анализом психосоцијалне димензије је као кључни фактор издвојена „емоционална нестабилност“, што потврђује резултате досадашњих истраживања у овој популацији. У односу на енглеску верзију упитника, Кронбахов коефицијент алфа српске верзије се не разликује значајно, а факторска анализа потврђује издвојене димензије упитника.

Закључак Наша студија је показала да је српска верзија упитника *SIP* поуздан инструмент за процену квалитета живота у вези са здрављем код особа оболелих од хроничног хепатитиса Б и Ц који још нису започели лечење.

Кључне речи: *Sickness Impact Profile* (*SIP*); поузданост упитника; хронични вирусни хепатитис

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Analysis of Macronutrients Intake and Body Mass Index in Preschool Children in the Western Region of the Republic of Srpska

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SUMMARY

Introduction Childhood obesity is currently considered to be one of the most prevailing and challenging public health issues in industrialized countries and some developing countries, including the Republic of Srpska.

Objective Our objective was to determine macronutrients intake in collective diet of preschool children and to estimate the rate of obesity in this population.

Methods Samples of food intended for preschool children diet were collected in a preschool facility in the western region of the Republic of Srpska. In daily portions, the content of proteins, fats, carbohydrates, water and mineral matter were determined using standard methods. The body mass index was determined on the basis of anthropometric measurements.

Results An average daily meal contained 17.5 g of fats, 19.1 g of proteins and 101.5 g of carbohydrates. The energy value was 676 Kcal. The analysis of the data from the menu showed that the number of consumed servings of fruits, vegetables, legumes, milk and dairy products was less than one portion per day. However, the amount of consumed meat and meat products exceeded one portion per day. Out of the total number of children, 10.0% were undernourished, 16.7% were overweight and 13.3% were obese.

Conclusion Daily portions in the preschool facility are not in accordance with the recommended dietary allowance for energy and carbohydrates intake, and the composition of meals is inadequate. Parents and caregivers should be encouraged to expose young children to a wide variety of fruit and vegetables, whole grains, low-fat dairy products, and to balance food intake with the requirements.

Keywords: nutrition; preschool children; food; body mass index; obesity

INTRODUCTION

Many diseases are caused by poor or improper diet. Inadequate diet results in occasional improper intake (either excessive or insufficient) of certain foodstuffs, thus causing the imbalance in intake of essential nutrients. The etiology of obesity, as well as the majority of biological functions, is multifactorial and, as commonly believed, is caused by energy imbalance [1]. World Health Organization reported that there were over 1.5 billion overweight adults in the world, while approximately four million of them were classified as clinically obese [2]. It is estimated that in Europe 20–30% of children and adolescents are obese [3, 4], while in the Mediterranean region the prevalence of childhood obesity is as much as 20–40% [3]. Out of the total number of diseases in Europe, 4.6% were associated with poor diet. The percentage of years of life lost due to obesity was 7–8% [5].

The Centers for Disease Control and Prevention in the United States reported tripling of the number of obese people in the last 20 years. Researches in the United States indicate that 16% of children and adolescents between the ages of six and 19 are overweight [6,7, 8] and that among preschool children (between the ages of two and five) the total energy intake in

2009–2010 period is significantly higher than in the period from 1989 to 1991 [9].

There is an assessment that in Northern Africa one in six preschool-aged children is either overweight or obese. This obesity rate is the highest in the world and three times higher than that recorded in 1990. However, numbers vary from country to country: approximately 20% of Egypt's preschoolers in 2008 were overweight or obese, compared to 5% in Sudan. In sub-Saharan Africa, though, overweight and obesity rates among preschoolers can still be expressed at a single-digit level: roughly 9% in Central Africa, 6% in Western Africa, 7% in Eastern Africa, and 8% in Southern Africa [10]. However, for most parts of this region, the rates doubled or tripled, compared to the results of two decades ago; only Southern Africa had a slight rate drop since 1990.

There are only a few research studies on the nutritional status of children and adolescents in the Republic of Srpska. A research on school-children in the city of Banjaluka during 2003 indicated that 21.4% of children had increased body mass, out of which 8.3% were obese. It was deduced that excessive body weight and obesity were more prevalent in boys. Higher obesity rates were observed in both sexes in the group of seven-year-olds. More specifically, obesity

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was observed in cases of 24.4% of boys and 15.2% of girls [11]. The second research was conducted in 2007 in four primary schools in the Banjaluka area, involving 405 participants. It revealed that 19.8% of the total sample were overweight, and 11.6% were obese [12]. The research on nutritional status of children under the age of five during 2006 reported that almost one quarter of children at that age in the Republic of Srpska has increased body mass [13].

OBJECTIVE

Nutrition and nutritional status follow-up in children and adolescents is especially important since the period of their growth acceleration and development makes children a particularly sensitive category of population, at the same time being a reliable nutritional status indicator in their local communities.

There is no published data on nutritional status in preschool children between the ages of five and six in the Republic of Srpska. Due to the facts stated above, the objective of our study was to assess the quality of nutrition in preschool children in kindergartens, i.e. to estimate macronutrients intake and the rate of obesity increase in this population.

METHODS

This research investigated the diet of preschool children between the ages of five and six who were included in a collective diet program. Samples of food intended for children's diet were collected in the Radost kindergarten in Prijedor.

Children stay up to 10 hours per day in the preschool facility and their diet is composed of the following three meals: breakfast, snack and lunch.

A collection of 20 samples was taken over the period of 20 working days. The sampling was made by taking meal portions served for the consumer (by spot check method). The portions collected during the day were combined and homogenized to make a unique working sample (hereinafter: a daily meal, which comprises breakfast, lunch and snack). The samples were delivered to an accredited laboratory for foodstuffs, where the collected daily meals were homogenized. This was followed by a chemical analysis of freshly homogenized samples of daily portions, in order to evaluate the fat, proteins, ash and moisture content, whereas the content of carbohydrates and the total energy level of daily portions were mathematically calculated from the results obtained. All evaluations were made in duplicate in the accredited laboratory. All reagents applied were of analytical purity grade.

Considering that the sampled daily meal was composed of only 75% of dietary intake in this population, the results obtained were modified by multiplying them by factor 1/0.75.

To evaluate the nutritional status, we used anthropometric measurements of 60 children (28 girls and 32 boys), which included body height and weight measurements.

The height and weight were measured with height rod and digital scales. Based on the anthropometric measurements, body mass index (BMI) was calculated in accordance with the following formula: BMI = body weight (kg) / body height (m²).

The calculation of BMI was followed by the calculation of BMI percentile and comparison of BMI with typical values for other children of the same age. The BMI percentile was used to identify the children's weight status either as underweight (<5%), normal (5–85%), at risk of being overweight (85–95%), or overweight (>95%) [14].

In the statistical analysis we used the Pearson's common linear correlation coefficient and Student's t-test for comparison of calculated average values for various nutrients intake and their recommended daily allowance [15]. Statistical hypotheses were tested with 95% certainty. The data was statistically processed using statistical software package SPSS 15.

RESULTS

Analysis of the data from the menu showed the prevalence of certain foods (Table 1). The number of fruit portions was extremely inadequate (only 0.45 portions per day). The number of portions of milk and dairy products was also inadequate (0.9 portions per day). The number of portions of leguminous and green vegetables was extremely small. Only the number of meat and meat products portions was above one portion per day.

The results of calculation of the contents of fat, proteins and carbohydrates and energy in daily meals are shown in Table 2. The minimum and maximum values of daily meals amounted to 520 and 844 Kcal and the average energy intake was 676 Kcal. Considering that the sampled daily portions comprised of only 75% of dietary intake for this population, for the purpose of calculation of daily intake, we multiplied mean levels of macronutrients by the coefficient 1/0.75.

The proportion of proteins, fats and carbohydrates in the total energy intake was approximately 12% from proteins, 63% from carbohydrates and 25% from fats, which is shown in Table 3. The participation of protein and carbohydrates in energy intake was in accordance with the recommendations, whereas the percentage of fat was slightly smaller than recommended.

Table 1. Proportion of different foodstuffs in the daily diet of preschool children during 20 consecutive days

Foodstuffs and food groups	Number of portions
Milk and dairy products	18
Legumes	5
Meat and meat products	21
Fish	0
Eggs	4
Green leafy vegetables	5
Fruit	8
Grains	2
Potato	6

Table 2. The contents of fat, proteins, carbohydrates and energy in a daily meal (n=20)

Parameters	Fats (g/daily meal)	Proteins (g/daily meal)	Carbohydrates (g/daily meal)	Energy (kcal/daily meal)
Minimum value	8.2	13.4	69.9	520
Maximum value	23.0	26.2	139.6	844
Average level	17.5	19.1	101.5	676
Estimated level*	23.3	25.4	135.3	901
RDA	-	19	130	1,632**
Standard deviation	4.6	4.2	19.5	381.8

* Estimated daily intake was calculated by multiplying mean level by 1/0.75; ** The average value for both sexes, FAO/WHO recommendations in Prentice et al., 2004; British Nutrition Foundation, Available from: <http://www.nutrition.org.uk/>

RDA – recommended daily allowance

Table 3. Distribution of energy from macronutrients in a diet

Proportion in energy intake (%)	Macronutrient		
	Fat	Proteins	Carbohydrates
Average±SD	24.6±6.7	12.0±1.7	63.3±6.0
Minimum limit	9.9	9.5	52.8
Maximum limit	33.7	15.6	72.4
Recommendation [16]	25–35	10–30	45–65

Table 4. The results obtained in this research and the results calculated using tables of the chemical composition of foods

Macronutrient (g)	USDA [21]	Finelli [22]	The experimental results
Carbohydrates	113.2	96.8	101.5
Proteins	34.8	29.1	19.1
Fat	30.7	34.5	17.5

Table 5. Age and sex structure of study participants

Age (years)	Female		Male		Total	
	N	%	N	%	N	%
5.0–5.24	6	21.4	6	18.7	12	20.0
5.25–5.49	8	28.6	14	43.8	22	36.7
5.5–5.74	7	25.0	6	18.7	13	21.6
5.75–6.0	7	25.0	6	18.8	13	21.7
Total	28	100.0	32	100.0	60	100.0

Table 6. Height, weight and BMI percentile

Parameter		Sex	
		Female	Male
Height (cm)	Min	114	109
	Max	128	124
	Average	119.7	118.8
Weight (kg)	Min	18	17
	Max	36.3	27.8
	Average	24.2	23.7
BMI (percentile)	<5 th	4	2
	5 th –85 th	16	20
	85 th –95 th	4	6
	>95 th	4	4

BMI – body mass index; Min – minimum value; Max – maximum value

Table 7. SD score of height for chronological age

Age (years)	SSD			
	<-3	-3 to -2	-2 to 2	>3
5–5.24	0	0	14	2
5.25–5.49	0	0	12	2
5.50–5.74	0	0	14	0
5.75–6.0	0	0	16	0
Total	0	0	56	4

SD – standard deviation; SSD – score standard deviation

The comparison of results obtained in this research for macronutrients content, together with data obtained in the calculation using different food composition tables (source) is reported in Table 4. Our results for the content of carbohydrates mainly coincide with the calculated results, whereas for proteins and fats content significant deviations were observed.

Data about age and sex structure of children which were included in this research are shown in Table 5. The average age of children was 66.0 months, 66.1 months for girls and 65.9 months for boys.

Results of anthropologic measurements of the study participants are reported in Tables 6 and 7. What is interesting is that girls had a higher maximum value, as well as weight and height. It is shown that there are no children who lag in growth.

In terms of BMI, out of the total number of children, 10.0% were undernourished, 16.7% were overweight and 13.3% were obese (BMI > 95 percentiles); 14.3% of girls and 18.7% of boys were overweight, and obesity was detected in 14.3% of girls and in 12.5% of boys. The rate of undernourished girls (14.3%) was significantly higher than that of boys (6.3%). Minimal BMI for girls and for boys was one percentile, and maximum BMI for both sexes was 99 percentile.

Table 8 shows the value of BMI percentile for chronological age. It is noted that the number of obese children is constant throughout the age groups.

DISCUSSION

In this study, data on the composition of meals shows that consumed meat was mostly chicken and beef. It was noticed that veal, pork and fish were not present in meals during the test period. This data may suggest a possible deficiency of micronutrients in the diet. The research results

Table 8. BMI percentiles for chronological age

Age (years)	BMI percentiles			
	<5 th	5 th –85 th	85 th –95 th	>95 th
5–5.24	0	8	2	2
5.25–5.49	2	8	4	2
5.50–5.74	2	12	0	2
5.75–6.0	2	8	4	2
Total	6	36	10	8

BMI – body mass index

confirm non-compliance of the diet with the principles of rational nutrition.

In Belgium, Flemish preschoolers have the intake of fruit of 109.9 g/day, their intake of milk is 439.9 g/day and the intake of meat and meat products is 90.3 g/day, which is significantly higher than what the results of our research show [16]. Fox et al. [17] state that, in the case of US children at the ages of two and three, the level of fruit and vegetables consumption represents roughly one third and one half of recommended intakes of vegetables and fruit, respectively.

The Donald Study shows increased intake of bread and grain products in two- to 18-year-olds in Germany, which corresponds to our findings. Further research could examine the use of different types of grain. Traditionally, in the Dortmund region, wheat is used more often than other grains [18].

Research in the Republic of Serbia indicated insufficient energy value of daily meals of preschool children in 1990 and 1993 (938 Kcal and 876 Kcal) [19]. Moreover, data obtained in this study showed inadequacy of dietary energy intake. The average energy value of a daily meal in the kindergarten in the Republic of Srpska comprised only two thirds of the recommended value [20]. The meal schedule prescribes the following eating times: breakfast at 8:00 a.m., lunch at 12:00 noon and snack at 2:00 p.m. This meal schedule and the lack of energy and nutritional value of meals are probably the reason why children meet most of their nutritional needs at home. Diet at home was beyond our control, therefore we had no information about it. However, the results of anthropological measurements indicate that the amount and/or composition of the food were inadequate. The most popular and cheapest types of food are high in calories, fat, carbohydrates and salt and are low in micronutrients. These facts, combined with the present global trend of reduced physical activity resulted in the rapid increase of obesity rate.

The results obtained in this research concerning fat and protein content differ significantly from the results derived using tables of the chemical composition of foods (Fineli and USDA), which suggests that it is necessary to create tables of nutritional composition of foods that will represent the Republic of Srpska region [21, 22].

In our study, the proportions of proteins, fats and carbohydrates in energy intake were 12%, 25% and 63%, respectively, which does not differ significantly from the recommendations. The research conducted in Serbia reported that the proportion of proteins, fats and carbohydrates in energy intake is 15.7%, 35.6% and 48.6%, respectively [17]. In their study of preschool children diet in Bahrain, Gharib et al. [23] reported that the proportions of proteins and fats in energy value are slightly higher, whereas the percentage of carbohydrates is lower, compared to the results obtained in this study. Other authors showed that fats and proteins have higher proportions in energy value and that the proportion of carbohydrates is lower, compared to our study [16, 18].

In our study, 13.3% of children were obese, and 16.7% of children were overweight.

The obtained results are comparable with the data on children in Poland and the Tuscany region in Italy [24, 25].

Also, the research conducted in the Republic of Srpska by the Ministry of Health and Social Welfare in collaboration with UNICEF showed a similar number of overweight children under five years of age and lower prevalence of childhood obesity [26]. In a study conducted in Bosnia and Herzegovina, 20.2% of children were obese and 1.9% were underweight [13]. Research data outside the European continent was somewhat different. The research of Mushtaq et al. [27] in Pakistan showed a higher number of underweight children (19%) and less children who were overweight and obese (8%).

Data about correlation of energy intake and obesity in children is inconsistent. Several cross-sectional studies have shown positive correlation between fat intake and a degree of obesity in children [28, 29, 30], while others have not [30]. There are only a small number of published studies which have been dealing specifically with intake of fats, proteins and carbohydrates in relation to BMI in children [31]. These studies provide an obvious proof that the role of dietary composition in the development of childhood obesity is yet to be clarified. Researchers are now investigating the correlation between diet composition and obesity in children [28]. Several studies have investigated the correlation between BMI and energy intake and it is assumed that dietary composition with respect to macronutrients (proteins, carbohydrates, fat) can play an important role in the development of childhood obesity as is the case with adults [15, 32]. The research shown in this paper, which aimed to investigate the possible correlation between BMI and macronutrients intake, did not find statistically significant difference in relation to the recommendations. When considering the proportion of certain macronutrients in the total energy intake, with 95% certainty, i.e. within the certainty interval (Student's t-test), the situation is quite clear in case of proteins, which do not exceed the recommended range, while in the case of fats and sugar we obtained cut points. The obtained results also show that, statistically, the intake of fats and carbohydrates was not significantly different compared to recommended daily allowance, while the protein intake was above the recommendations.

Thus the occurrence of a certain number of obese study participants could be explained by means of consumption of meals outside the kindergarten. In the same manner, the study on correlation of BMI and the food intake outside the home, conducted on approximately 14,000 adolescents in America, showed that BMI increases with the increase of the number of meals outside the home, which is associated with a higher intake of total energy, fizzy drinks, trans-fatty acids and low intake of low-fat foods, fruit and vegetables [33]. The proportions of nutrients are extremely important for normal metabolism and prevention of certain conditions and diseases caused by imbalance of nutrients intake in the body [34].

Efforts to foster healthy eating habits need to begin early in life. In a longitudinal analysis of food preferences among young children, Skinner et al. [35] showed that the number of preferred foods did not change significantly between the ages of two or three, and eight.

The general prevalence of obesity in the child population in the Šumadija region of Serbia is 10.7%, which is lower than the number of obese children in our population (13.3%) [36]. The average height of the study participants was between 114 cm and 128 cm for girls and between 109 cm and 124 cm for boys [36]. Our findings are opposite to those obtained in the study conducted by Pokos et al. [37], whose results show that the average height for boys was between 116 cm and 117.6 cm, whereas the girls were somewhat shorter (113.9–115.9 cm). The research conducted by Pavlović et al. [19] on anthropometric indicators and the quality of collective and family nutrition in children, suggests the necessity to adapt an adequate nutrition practice and thus prevent nutrition and health disorders in preschooler population. This conclusion was also supported by the results of our research.

REFERENCES

- Doak CM, Visscher TLS, Renders CM, Seidell JC. The prevention of overweight and obesity in children and adolescents: a review of interventions and programmes. *Obes Rev.* 2006; 7:111-36.
- WHO Technical Report Series No 894. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation. Geneva: World Health Organization; 2000.
- Lobstein T, Frelut M. Prevalence of overweight among children in Europe. *Obes Rev.* 2003; 4:195-20
- Banićević M, Zdravković D. Sprečimo gojaznost. Beograd: Cicero; 2008.
- World Health Organization. World Report on Disability. Geneva (Switzerland): WHO Press; 2011.
- Ogden CL, Carroll MD, Flegal KM. High body mass index for age among US children and adolescents, 2003-2006. *JAMA.* 2008; 299(20):2401-5.
- Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. *JAMA.* 2004; 291(23):2847-50.
- Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. Inter-relationships among childhood BMI, childhood height, and adult obesity: the Bogalusa Heart Study. *Int J Obes Relat Metab Disord.* 2004; 28:10-6.
- Slining MM, Mathias KC, Popkin BM. Trends in food and beverage sources among US children and adolescents: 1989-2010. *J Acad Nutr Diet.* 2013; 113(12):1683-94.
- de Onis M, Blossner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. *Am J Clin Nutr.* 2010; 92:1257-64.
- Ministarstvo zdravlja i socijalne zaštite Republike Srpske. Zdravstveno stanje, zdravstvene potrebe i korišćenje zdravstvene zaštite stanovništva u Republici Srpskoj. Izveštaj o rezultatima istraživanja i prijedlog za razvoj budućih istraživanja. Banja Luka: Ministarstvo zdravlja i socijalne zaštite Republike Srpske; 2003.
- Institut za zaštitu zdravlja Republike Srpske. Publikacija o zdravstvenom stanju stanovništva za 2007. godinu. Banja Luka: Institut za zaštitu zdravlja Republike Srpske; 2008.
- Istraživanje višestrukih pokazatelja (MICS 3) 2006. Izveštaj o rezultatima. Bosna i Hercegovina: Direkcija za ekonomsko planiranje Bosne i Hercegovine, Ministarstvo zdravlja i socijalne zaštite Republike Srpske, Ministarstvo zdravstva Federacije Bosne i Hercegovine, UNICEF, Dječiji fond Ujedinjenih nacija; 2007.
- Centers for Disease Control and Prevention. Body mass index – for age percentiles. Available from: http://www.cdc.gov/growthcharts/cdc_charts.htm.
- Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington (DC): The National Academies Press; 2006.
- De Keyser W, Lin Y, Vereecken C, Maes L, Van Oyen H, Vanhauwaert E, et al. Dietary sources of energy and macronutrient intakes among Flemish preschoolers. *Arch Public Health.* 2011; 69(1):5.
- Fox MK, Condon E, Briefel RR, Reidy KC, Deming DM. Food consumption patterns of young preschoolers: are they starting off on the right path? *J Am Diet Assoc.* 2010; 110(12 Suppl):S52-9.
- Alexy U, Sichert-Hellert W, Kersting M. Fifteen-year time trends in energy and macronutrient intake in German children and adolescents: results of the DONALD study. *Br J Nutr.* 2002; 87:595-604.
- Pavlović M. Ishrana dece predškolskog uzrasta. Subotica: Zavod za zaštitu zdravlja; 1997.
- Stoisavljević D, Stanivuk Lj, Lolić A, Lolić B, Bojanić J, Vulin V. Smjernice za ishranu dojenčadi i djece predškolskog uzrasta. Banja Luka: Ministarstvo porodice omladine i sporta; 2013.
- National Nutrient Database for Standard Reference Release 28. Available from: <http://ndb.nal.usda.gov/ndb/foods>.
- Finnish Food Composition Database. Available from: <http://www.fineli.fi/foodbasket.php?lang=en>.
- Gharib N, Rasheed P. Energy and macronutrient intake and dietary pattern among school children in Bahrain: a cross-sectional study. *Nutr J.* 2011; 10:62.
- Weker H, Barańska M, Dyląg H, Riahi A, Więch M, Strucińska M, et al. Analysis of nutrition of children aged 13-36 months in Poland: a nation-wide study. *Med Wieku Rozwoj.* 2011; 15(3):224-31.
- Lazzeri G, Pammolli A, Simi R, Pilato V, Giacchi MV. BMI from nutritional surveillance of 8-9 year old children in Tuscany (Italy). *J Prev Med Hyg.* 2011; 52(4):181-5.
- Istraživanje višestrukih pokazatelja 2011-2012. godina. Izveštaj o rezultatima. Banja Luka: Ministarstvo zdravlja i socijalne zaštite Republike Srpske, UNICEF Kancelarija dječijeg fonda Ujedinjenih nacija; 2012.
- Mushtaq MU, Gull S, Abdullah HM, Shahid U, Shad MA, Akram J. Prevalence and socioeconomic correlates of overweight and obesity among Pakistani primary school children. *BMC Public Health.* 2011; 11: 724.
- Scaglioni S, Agostoni C, De Notaris R, Radaelli G, Radice N, Valenti M, et al. Early macronutrient intake and overweight at five years of age. *Int J Obes Relat Metab Disord.* 2000; 24(6):777-81.
- Margarey AM, Daniels LA, Boulton TJ. Prevalence of overweight and obesity in Australian children and adolescents: reassessment of 1985 and 1995 data against new standard international definitions. *Med J Aust.* 2001; 174:561-4.
- Maillard G, Charles MA, Lafay L, Thibault N, Vray M, Borys JM, et al. Macronutrient energy intake and adiposity in non-obese prepubertal children aged 5-11 y (the Fleurbaix Laventie Ville Santé Study). *Int J Obes Relat Metab Disord.* 2000; 24(12):1608-17.
- Trichopoulou A, Gnardellis C, Benetou V, Lagiou P, Bamia C, Trichopoulou D. Lipid, protein, and carbohydrate intake in relation to body mass index. *Eur J Clinical Nutr.* 2002; 56(1):37-43.
- Gillis LJ, Kennedy LC, Gillis AM, Bar-Or O. Relationship between juvenile obesity, dietary energy and fat intake and physical activity. *Int J Obes Relat Metab Disord.* 2002; 26(4):458-63.

CONCLUSION

The results of this research indicate an alarming situation related to children nutrition in preschool facilities in the Republic of Srpska and suggest the need for its regular monitoring. Daily portions in the preschool facility are not in accordance with the recommended dietary allowance for energy and carbohydrates intake and the composition of meals is inadequate. Data showing that 10% of preschool children were undernourished, and that 16.7% of them were overweight, as well as that 13.3% of them were obese, suggest that parents and caregivers should be encouraged to expose young children to a wide variety of fruit and vegetables, whole grains, low-fat dairy products, and to balance the food intake with the requirements.

33. Taveras EM, Berkey CS, Rifas-Shiman SL, Ludwig DS, Rockett HR, Field AE, et al. Association of consumption of fried food away from home with body mass index and diet quality in older children and adolescents. *Pediatrics*. 2005; 116(4):e518-24.
34. Kaić-Rak A, Kralj V, Antić-Degac K, Petrović Z. Prehrambene navike i kardiovaskularne bolesti. Knjiga sažetaka 1. hrvatskog kongresa preventivne medicine s međunarodnim sudjelovanjem; 2003, Nov 26-29 Zagreb. Zagreb: Zavod za javno zdravstvo Zagreba; 2003. p.126.
35. Skinner J, Carruth BR, Bounds W, Ziegler P. Children's food preferences: a longitudinal analysis. *J Am Diet Assoc*. 2002; 102:1638-47.
36. Marković S, Igrutinović Z, Kostić G, Vuletić B. Stanje uhranjenosti i mogući činioci etiopatogeneze gojaznosti kod školske dece. *Medicinski časopis*. 2008; 42(1):7-14.
37. Pokos H, Lauš D, Badrov T. Razvoj stanja uhranjenosti petogodišnjih djevojčica i dječaka od 2008. do 2012. godine. *Sestrinski glasnik*. 2014; 19(1):17-21.

Анализа уноса макронутријената и индекса телесне масе код деце предшколског узраста у регији западне Републике Српске

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КРАТАК САДРЖАЈ

Увод Гојазност у дечјој доби је данас један од важнијих проблема здравства, како у индустријским, тако и у земљама у развоју, укључујући и Републику Српску.

Циљ рада Циљ истраживања је био да се одреди унос макронутријената у колективној исхрани деце предшколског узраста и процени учесталост гојазности у овој популацији.

Методе рада Узорци хране намењени исхрани деце прикупљани су у предшколској установи у западном делу Републике Српске. У дневним оброцима садржаји масти, беланчевина, угљених хидрата, воде и минералних материја одређени су стандардним методама. Индекс телесне масе (BMI) је утврђен на основу антропометријских мерења.

Резултати Просечан садржај масти у дневном obroку био је 17,5 g, беланчевина 19,1 g, а угљених хидрата 101,5 g, док

је енергетска вредност била 676 Kcal. Анализа података из јеловника показала је да је број порција воћа, поврћа, млека и млечних производа мањи од једне порције на дан. Само је број порција меса и месних производа био већи од једне порције дневно. Од укупног броја деце потхрањено је било 10,0%, с прекомерном телесном тежином 16,7%, док је 13,3% деце било гојазно.

Закључак Дневни оброци у предшколској установи нису у складу с препорученим уносом за енергију и угљене хидрате, а састав obroка је неодговарајући. Родитељи и васпитачи би требало да подстакну децу да једу различите врсте воћа и поврћа, житарица од целог зрна и немасних млечних производа, те да се избалансира унос хране с препорукама.

Кључне речи: исхрана; деца предшколског узраста; храна; индекс телесне масе; гојазност

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Parental Factors Associated with Intrauterine Growth Restriction

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SUMMARY

Introduction Linear growth failure is caused by multiple factors including parental factors.

Objective The aim of this study was to evaluate parental risk factors for intrauterine growth restriction (IUGR) on a population of Romanian newborn infants in a tertiary level maternity facility for a period of 2.5 years.

Methods A retrospective matched case-control study was conducted in the Emergency County Hospital of Cluj-Napoca, a university hospital in North-Western Romania. The sample was selected from 4,790 infants admitted to the Neonatal Ward at 1st Gynecology Clinic between January 2012 and June 2014.

Results The age of mothers was significantly lower in the IUGR group compared to controls ($p=0.041$). A significantly higher percentage of mothers had hypertension in the IUGR group compared to those in the control group ($p<0.05$). No other significant differences were identified with regard to the investigated characteristics of mothers between IUGR infants compared to controls ($p>0.13$). The age of fathers of infants with IUGR proved significantly lower compared to controls ($p=0.0278$). The analysis of infants' comorbidities revealed no significant difference between groups for respiratory distress, hyperbilirubinemia, hypocalcaemia, and heart failure ($p>0.27$). Intracranial hemorrhage, necrotizing enterocolitis and hypoglycemia were significantly higher in the IUGR group compared to controls. The logistic regression identified hypertension as a significant risk factor for IUGR (OR=2.4, 95% CI [1.3–4.5]).

Conclusion Although the age of the mothers and fathers proved significantly lower in the IUGR group compared to controls, only hypertension in the mothers proved significant risk factors for IUGR.

Keywords: intrauterine growth restriction; parental characteristics; risk factor

INTRODUCTION

Infants with intrauterine growth restriction (IUGR) are defined as those with birth weight below the 10th percentile for its gestational age and it is a consequence of several factors [1]. Genetic and environmental factors influence the development throughout the growth period. Linear growth failure is largely confined to the intrauterine period and the first few years of life, and it is caused by multiple factors like inadequate diets, infections, maternal chronic diseases [2, 3]. Few studies have examined the effect of parental factors on postnatal growth of infants with IUGR. Short stature of the mother and poor maternal nutrition stores are associated with an increased risk of intrauterine growth retardation [4]. Maternal weight was found to be a stronger predictor of offspring birth weight than maternal height [5, 6]. Geographical differences in newborn phenotype showed to be related to the differences in maternal size and body composition [4]. The same study suggests that the mother's skeletal size and soft tissue mass have independent effects on birth weight. Maternal birth weight proved to be one of the strongest pre-

dictors of neonatal size and is associated with offspring birth length, head circumference and mid-upper arm circumference as well as with infant birth weight [4]. A positive association between increasing maternal age and increasing risk for IUGR was also demonstrated with an odd ratio of 3.2 (95% CI [1.9–5.4]) for maternal age ≥ 40 years [7]. Another study identified that advanced maternal age (≥ 35 years old) is an independent risk factor for IUGR [6]. A different factor that has been shown to influence the fetal development is maternal smoking behavior due to epigenetic change on human placental genes observed on mothers who smoked [8]. In a pregnancy with hypertension and preeclampsia the risk for IUGR is higher, and the risk increases with the severity of preeclampsia [9, 10].

The fathers of infants with IUGR showed more likely to be insulin resistant (log insulin resistance: OR=5.99, 95% CI [2.25–15.91]), hypertensive (OR=1.09, 95% CI [1.02–1.16], $p=0.006$ for diastolic blood pressure; OR=1.08, 95% CI [1.02–1.14], $p=0.007$ for systolic blood pressure), and to smoke cigarettes (OR=3.09, 95% CI [1.10–8.22], $p=0.01$) compared with fathers of normally grown offspring [11].

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OBJECTIVE

The main objective of our study was to identify and to quantify parental risk factors for IUGR of a Romanian population in a tertiary level maternity facility for a period of 2.5 years and to compare them to newborns without IUGR.

METHODS

A matched case-control study was conducted in the Emergency County Hospital of Cluj-Napoca, a university hospital in North-Western Romania. The hospital serves as a referral center for the Cluj, Sălaj, Bistrița-Năsăud, and Maramureș counties. Subjects for this study were selected from 4,790 infants admitted to the Neonatal Ward at 1st Gynecology Clinic, Emergency County Hospital Cluj-Napoca, and discharged in the period from January 2012 to June 2014. The inclusion criteria for the IUGR group were as follows: IUGR diagnosis (defined as birth weight below the 10th percentile), and availability of the following data on medical records [12]:

- Infant sex (F/M) and gestational age (weeks);
- Infant anthropometric measurements: weight (kg), height (cm), head circumference (cm);
- Infant co-morbidities (yes/no): birth injuries, respiratory distress, hyperbilirubinemia, hypoglycemia, hypocalcaemia, necrotizing enterocolitis, heart-failure, intracranial hemorrhage;
- Maternal data: maternal age, ethnicity, number of pregnancies, number of deliveries, medical history (especially hypertension).

Whenever possible, data related to age, ethnicity and health history of father were also collected.

A matched control in terms of gender and gestational age was chosen in a 1:1 ratio for each IUGR infant. A total number of 150 infants with IUGR were admitted to the Neonatal Ward at 1st Gynecology Clinic during the study period, and 142 of them met the eligibility requirements. A total of 140 matched controls were identified, resulting in an investigated sample of 280 subjects (140 with IUGR and 140 controls).

Ethical approval was obtained from the Iuliu Hațieganu University of Medicine and Pharmacy Ethics Committee.

Statistical analysis

Neonatal ponderal index (NPI), a derivate index calculated based on collected data, was computed for each infant included in the study using the following formula [13, 14]: $NPI = 100 \times \text{weight (g)} / \text{height (cm}^3\text{)}$.

Variables were analyzed as collected and/or as derived variables:

- Infants with the number of weeks of gestation smaller than 37 were considered preterm, while infants with 37 to 41 weeks of gestation were considered term.
- Birth weight (classification regardless of the gestational age – according to International Classification of Diseases version 10 [15]): LBW = low birth weight, defined as birth weight < 2.5kg (ICD-10: P07.1); VLBW = very low birth weight, defined as birth weight < 1.5kg (ICD-10: P07.1); and ELBW = extremely low birth weight, defined as birth weight < 1.0kg (ICD-10: P07.0).

- Maternal age: 15–19 years old, 20–34 years old, ≥35 years old.

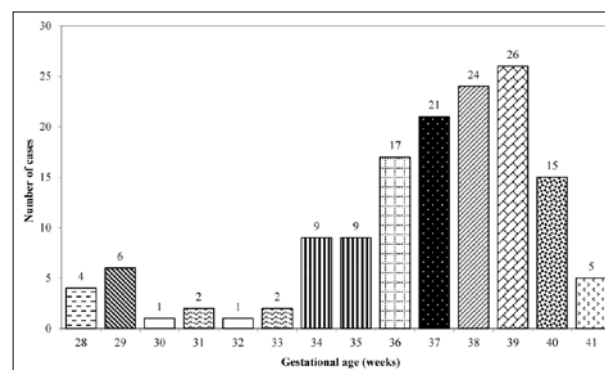
Descriptive statistical analysis of data as percentages and associated 95% confidence interval (values presented in square brackets throughout the manuscript, calculated with an exact formula) were used for qualitative variables and mean $\pm$ standard deviation for normally distributed data or median and 1st and 3rd quartiles (values provided in round brackets) [16, 17]. Cross tabulations with cases in rows and controls in columns were used to assess the association between the groups. The McNemar's test was used in cross tabulations, while paired Student's t-test for quantitative normally distributed data and the Wilcoxon test for not-normally distributed quantitative variables were applied to compare the groups. Uni- and multivariate logistic regression was used to investigate the association of parental factors with intrauterine growth restriction. Parental variables with a p-value lower than or equal to 0.25 in the univariate analysis were the input data for the multivariate logistic regression. Statistical analysis was done with Statistica (v. 8.1) at a significance level of 5%.

RESULTS

Infants with and without IUGR were similar regarding birth as preterm vs. term, with a 1:1 ratio. The majority of infants included in the study were female (62.9%) [54.9–70.7], their percentage being significantly higher compared to male ($p < 0.0001$). No significant difference in terms of living place defined as rural or urban was identified between IUGR group and control group (IUGR 64.8% from urban vs. controls 70.4%; $p = 0.3107$).

The gestational age of most infants included in the study was from 36 to 40 weeks (Graph 1).

The infants with IUGR proved to have significantly lower anthropometric characteristics compared to controls (Table 1). Median for weight recovery was of eight days (interquartile range [5–12]) for IUGR group and of



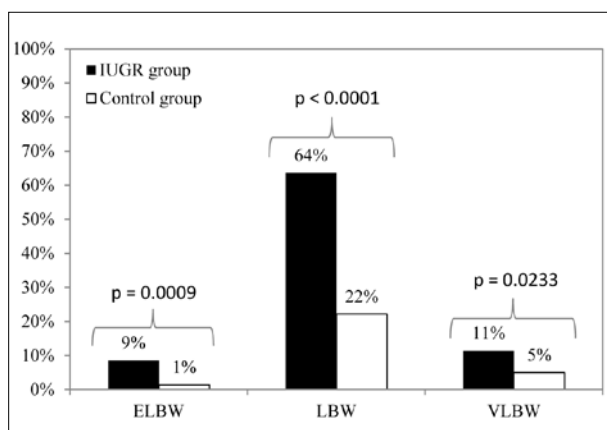
Graph 1. Distribution of gestational age

Table 1. Anthropometric characteristics of infants

Characteristic	IUGR	Control	p-value
Birth weight (kg)	2.2 (1.7–2.5)	2.9 (2.5–3.3)	<0.0001
Height (cm)	48 (44–50)	51 (48–53)	<0.0001
Neonatal ponderal index (g/cm ³)	2.0 (1.8–2.2)	2.1 (2.0–2.4)	<0.0001
Head circumference (cm)	31 (29–33)	33 (32–34)	<0.0001

The values are median and Q1–Q3, where Q1 = 1st quartile (25th percentile) and Q3 = 3rd quartile (75th percentile).

IUGR – intrauterine growth restriction

**Graph 2.** Differences on classes of birth weight according to group

ELBW – extremely low birth weight; LBW – low birth weight;
VLBW – very low birth weight

12 days (interquartile range [7–13]) for controls, the difference being significant ($p=0.0010$).

The percentage of infants with LBW, VLBW, or ELBW proved significantly higher compared to controls (Graph 2), the groups being identified as significantly different by the McNemar's test ($p=0.0376$).

Birth injuries, necrotizing enterocolitis, and hypoglycemia co-morbidities proved significantly different between groups. A higher percentage of trauma in the control group and higher percentage for necrotizing enterocolitis and hypoglycemia in the IUGR group (Table 2).

Distribution of maternal age on classes was homogeneous between groups (three mothers younger than 20 years, 107 with an age between 20 and 34 years, and 30 with an age of 35 years or older). The summary and comparison of parental characteristics are presented in Table 3.

In the IUGR group, 37 mothers were hypertensive (26.4%) [CI 19–34] while in the control group just 19 mothers had hypertension (13.6%) [8.6–20.0]. In the majority of cases, mother's hypertension was diagnosed during pregnancy (IUGR group: 91.9% [78.5–97.2] vs. control group: 84.2% [58.2–94.5]). A significantly higher percentage of mothers with hypertension in the IUGR group was diagnosed during pregnancy ($p=0.0082$).

The logistic regression analysis was conducted to identify significant parental factors related to IUGR. Hypertension in mothers proved a significant factor for IUGR (Table 4).

The power of the study calculated for a sample size of 140 and a significance level of 5%, taking into consider-

Table 2. Co-morbidities (summary and comparison)

Characteristic	IUGR		Control		p-value
	N (%)	95% CI	N (%)	95% CI	
Intracranial hemorrhage	9 (6.4)	2.9–12.1	3 (2.1)	0.7–6.4	0.0518
Birth injuries	20 (14.3)	8.6–21.4	52 (37.1)	29.3–45.7	<0.0001
Respiratory distress	21 (15.0)	9.3–22.1	22 (15.7)	10.0–22.9	0.9062
Hyperbilirubinemia	99 (70.7)	62.2–77.9	91 (65.0)	56.4–72.9	0.2790
Necrotizing enterocolitis	3 (2.1)	0.7–6.4	0 (0.0)		<0.0001
Hypoglycemia	39 (27.9)	20.7–35.7	6 (4.3)	1.4–9.3	<0.0001
Hypocalcaemia	9 (6.4)	2.9–12.1	5 (3.6)	1.4–7.9	0.3123
Heart failure	6 (4.3)	1.4–9.3	3 (2.1)	0.7–6.4	0.4047

N – number of subjects; 95% CI – 95% confidence interval; IUGR – intrauterine growth restriction

Table 3. Parental characteristics by groups: summary and comparisons

Characteristic		IUGR	Control	p-value
Mother	Age (years) ^a	29.2±5.2	30.5±5.3	0.0415
	Romanian ^b	137 (97.9)	133 (95.0)	0.1336
	Number of children ^b	85 (60.7)	79 (56.4)	0.5048
	Positive medical history ^b	29 (20.7)	26 (18.6)	0.6811
	Hypertension ^b	37 (26.4)	19 (13.6)	0.0119
	Double test positive (n=51) ^b	1 (0.7)	0 (0.0)	n.a.
	Triple test positive (n=53) ^b	2 (1.4)	1 (0.7)	0.7728
	Torch Rubella (n=65) ^b	1 (0.7)	0 (0.0)	n.a.
	Torch CMV (n=65) ^c	1 (0.7)	1 (0.7)	0.7237
Father	Age (years) ^c	32 (28–35)	33 (30–36)	0.0278
	Romanian ^b	135 (96.4)	131 (93.6)	0.2684
	Positive medical history ^b	3 (2.1)	4 (2.9)	0.8501

a: mean value ± standard deviation; paired t-test

b: number (%); McNemar's test

c: median (Q1–Q3), where Q1 = 1st quartile (25th percentile), Q3 = 3rd quartile (75th percentile); Wilcoxon test

n – number of subjects; CMV – cytomegalovirus; n.a. – not available

Table 4. Results of logistic regression on paternal factors

Characteristic	OR	95%CI	Coefficient±SE	p-value
Mother age (years)	0.96	0.90–1.02	-0.04±0.03	0.1885
Father age (years)	0.98	0.91–1.04	-0.02±0.03	0.4901
Mother hypertension	2.48	1.2–4.52	0.88±0.32	0.0060
Mother ethnicity	0.42	0.10–1.73	-0.87±0.73	0.2280
Constant			1.85±0.86	0.0319

SE – standard error

ation a percentage of 13.6 of hypertension in mothers of infants without IUGR for our matched case-control design, is equal to 0.98.

DISCUSSION

The investigated sample of newborns proved homogeneous in terms of number of preterm and term infants in both IUGR and control groups. A significant proportion of newborns were female, reflecting the distribution of gender in the Romanian newborn population during the investigated period.

The gestational age of the investigated sample varied from 28 weeks to 41 weeks, with the majority of cases between 36 and 40 weeks. In our sample, most of the newborns were born at term, which explains why incidence of respiratory distress was equal in the two groups.

IUGR is a frequent complication in preterm infants and is the cause of most elective late-preterm (birth between 34 weeks and 36 6/7 weeks of gestation) deliveries [18]. In our sample we had 35 late-preterm infants, which represents 70% of preterm infants and is similar to the previously published data (63–70% of all preterm births [19, 20]).

The analysis of the anthropometric characteristics (birth weight, height, NPI and head circumference) proved significantly lower in the IUGR infants compared to controls (see Table 1). The number of days needed to recover the weight proved significantly lower in the IUGR group compared to controls (IUGR group = eight days, control group = 12 days, $p < 0.05$) since parenteral nutrition support associated with enteral nutrition was required in the first days.

As expected, the majority of infants in the control group had normal weight at birth. The number of infants with low, very low, and extremely low birth weight proved significantly higher in the IUGR group compared to controls (Graph 2), with the highest proportion of LBW in infants with IUGR (64%).

Infants with IUGR and prematurity had risk for hypoglycemia, intraventricular hemorrhage, prolonged hospital stay and increased need for neonatal intensive care unit treatment when compared to appropriate for gestation age infants, thus demonstrating the severity of these cases [20, 21].

The analysis of co-morbidities as presented in Table 2 revealed several findings.

No significant difference in respiratory distress, hyperbilirubinemia, hypocalcaemia and heart failure ($p > 0.27$) was obtained between groups.

Intracranial hemorrhage was more frequent in the IUGR group compared to the control group (Table 2).

Identification of a significantly higher proportion of hemorrhage in the IUGR group compared to controls is expected if a larger sample size is investigated.

Compared to controls, a significantly lower proportion of IUGR infants had birth injuries ($p < 0.0001$). This result could be explained by the type of delivery, most of the infants in the IUGR group being delivered through caesarean section [22].

Necrotizing enterocolitis was observed in the IUGR group only, as necrotizing enterocolitis is morbidity characteristic to the infants with IUGR that have intestinal ischemia, and is significantly more frequent in comparison with the appropriate age for gestation in the population [20].

A significantly higher percentage of infants in the IUGR group had hypoglycemia, compared to controls ($p < 0.0001$). It is known that hypoglycemia is significantly more frequent in newborns with IUGR in comparison with the appropriate age for gestation in the population [23, 24].

The analysis of parental characteristics on the investigated sample revealed the following (Table 3):

- The age of the mothers proved significantly lower in the IUGR group compared to controls ($p = 0.041$), but was not identified as a risk factor for IUGR. Other studies showed that maternal age equal to or greater than 35–40 years is a risk factor for IUGR [5, 6].
- A significantly higher percentage of the mothers had hypertension in the IUGR group compared to controls ($p < 0.05$).
- No other significant differences were identified with regard to the investigated mothers' characteristics between the IUGR infants and those in the control group ($p > 0.13$).
- Similar with maternal age, the age of the fathers of infants with IUGR proved significantly lower compared to controls ($p = 0.0278$).

Multivariate logistic regression analysis was conducted using those predictors that showed in univariate analysis p -values equal to or greater than 0.25. The following four predictors accomplished the criterion and were included in multivariate logistic regression: maternal and paternal age, presence of hypertension in mother and mother's ethnicity. The logistic regression conducted on our sample identified neither maternal nor the paternal age as risk factors for IUGR (Table 4). Just one predictor, namely mother's hypertension, proved a significant risk factor for IUGR (OR=2.41, 95% CI [1.29–4.52]).

Preeclampsia, gestational hypertension and unexplained intrauterine growth restriction may have similar determinants and consequences [25]. Hypertensive disorders in pregnancy determine vascular abnormalities of the placenta, fetal hypoxia, malnutrition and IUGR [26]. In our study, the presence of hypertension in the mother in the IUGR group especially diagnosed during pregnancy has been identified. Hypertension in the mother has been identified in the majority of the cases during pregnancy (IUGR group: 91.9% [78.5–97.2] vs. control group: 84.2% [58.2–94.5]). A significantly higher proportion of mothers with hypertension in the IUGR group was proved when

hypertension diagnosed during pregnancy was considered. Furthermore, the single significant risk factor for IUGR identified by logistic regression analysis was also hypertension in mothers.

The power of our study (0.98) sustains that the results obtained in it are true for the North-Western Romanian population. Despite reasonable power of the study, several limitations could be listed. The first one is related to the absence of an appropriate growth reference chart – growth charts adapted from Fenton were used in this study as recommended by the Nutrition Guide for preterm infants from Romania [27, 28]. The second limitation of the study is determined by the restricted access to other parental characteristics (such as mother's weight and height, father's weight and height, maternal pre-pregnancy weight, maternal diet, lifestyle) due to retrospective collection of data.

REFERENCES

- Gluckman PD, Pinal CS. Regulation of fetal growth by the somatotrophic axis. *J Nutr*. 2003; 133(5 Suppl 2):1741S-1746S. [PMID: 12730493]
- Shrimpton R, Victora CG, de Onis M, Lima RC, Blossner M, Clugston G. Worldwide timing of growth faltering: implications for nutritional interventions. *Pediatrics*. 2001; 107:E75. [DOI: 10.1542/peds.107.5.e75] [PMID: 11331725]
- Xue F, Willett WC, Rosner BA, Forman MR, Michels KB. Parental characteristics as predictors of birthweight. *Hum Reprod*. 2008; 23(1):168-77. [DOI: 10.1093/humrep/dem316] [PMID: 17934185]
- Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet*. 2008; 371(9608):243-60. [DOI: 10.1016/S0140-6736(07)61690-0] [PMID: 18207566]
- Leary S, Fall C, Osmond C, Lovel H, Campbell D, Eriksson J, et al. Geographical variation in relationships between parental body size and offspring phenotype at birth. *Acta Obstet Gynecol Scand*. 2006; 85(9):1066-79. [DOI: 10.1080/00016340600697306] [PMID: 16929411]
- World Health Organisation. Maternal anthropometry and pregnancy outcomes. A WHO Collaborative Study. *Bull World Health Organ*. 1995; 73(Suppl):1-98. [PMID: 8529277]
- Odibo AO, Nelson D, Stamilio DM, Sehdev HM, Macones GA. Advanced maternal age is an independent risk factor for intrauterine growth restriction. *Am J Perinatol*. 2006; 23(5):325-8. [DOI: 10.1055/s-2006-947164] [PMID: 16799913]
- Suter M, Abramovici A, Showalter L, Hu M, Shope CD, Varner M, et al. In utero tobacco exposure epigenetically modifies placental CYP1A1 expression. *Metabolism*. 2010; 59(10):1481-90. [DOI: 10.1016/j.metabol.2010.01.013] [PMID: 20462615]
- Rasmussen S, Irgens LM. The effects of smoking and hypertensive disorders on fetal growth. *BMC Pregnancy Childbirth*. 2006; 6:16. [DOI: 10.1186/1471-2393-6-16] [PMID: 16630351]
- Rasmussen S, Irgens LM. History of fetal growth restriction is more strongly associated with severe rather than milder pregnancy-induced hypertension. *Hypertension*. 2008; 51(4):1231-8. [DOI: 10.1161/HYPERTENSIONAHA.107.096248] [PMID: 18259045]
- Hillman S, Peebles DM, Williams DJ. Paternal metabolic and cardiovascular risk factors for fetal growth restriction: a case-control study. *Diabetes Care*. 2013; 36(6):1675-80. [DOI: 10.2337/dc12-1280] [PMID: 23315598]
- Wollmann HA. Intrauterine growth restriction: definition and etiology. *Horm Res*. 1998; 49(Suppl 2):1-6. [DOI: 10.1159/000053079] [PMID: 9730664]
- Waterlow JC, Buzina R, Keller W, Lane JM, Nichaman MZ, Tanner JM. The presentation and use of height and weight data for comparing the nutritional status of groups of children under the age of 10 years. *Bull World Health Organ*. 1977; 55:489-98. [PMID: 304391]
- Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser*. 1995; 854:1-452. [PMID: 8594834]
- International Statistical Classification of Diseases and Related Health Problems 10th Revision [online] 2010 [accessed March 21, 2014]. Available from: <http://apps.who.int/classifications/icd10/browse/2010/en>.
- Jäntschi L, Bolboacă SD. Exact probabilities and confidence limits for binomial samples: applied to the difference between two proportions. *ScientificWorldJournal*. 2010; 10:865-78. [DOI: 10.1100/tsw.2010.75] [PMID: 20495766]
- Bolboacă SD, Jäntschi L. Optimized confidence intervals for binomial distributed samples. *Int J Pure Applied Math*. 2008; 47(1):1-8.
- Engle WA. A recommendation for the definition of "late preterm" (near-term) and the birth weight-gestational age classification system. *Semin Perinatol*. 2006; 30(1):2-7. [DOI: 10.1053/j.semperi.2006.01.007] [PMID: 16549206]
- Tan JH, Poon WB, Lian WB, Ho SK. A comparison of the short-term morbidity and mortality between late preterm and term newborns. *Ann Acad Med Singapore*. 2014; 43(7):346-54. [PMID: 25142470]
- March of Dimes Perinatal Data Center. Late preterm birth: every week matters. 2005. National Center for Health Statistics, final natality data, January 2008. Available from: <http://www.marchofdimes.com/peristats/>.
- Engineer N, Kumar S. Perinatal variables and neonatal outcomes in severely growth restricted preterm fetuses. *Acta Obstet Gynecol Scand*. 2010; 89(9):1174-81. [DOI: 10.3109/00016349.2010.501370] [PMID: 20804344]
- Hasmasanu MG, Bolboacă SD, Baizat MI, Drugan TC, Zaharie GC. Neonatal short-term outcomes in infants with intrauterine growth restriction. *Saudi Med J*. 2015; 36(8):947-53. [DOI: 10.15537/smj.2015.8.11533] [PMID: 26219445]
- Flamant C, Gascoin G. Short-term outcome and small for gestational age newborn management. *J Gynecol Obstet Biol Reprod (Paris)*. 2013; 42(8):985-95. [DOI: 10.1016/j.jgyn.2013.09.020] [PMID: 24210715]
- Rocha CO, Bittar RE, Zugaib M. Neonatal outcomes of late-preterm birth associated or not with intrauterine growth restriction. *Obstet Gynecol Int*. 2010; 2010:231842. [DOI: 10.1155/2010/231842] [PMID: 20339531]
- Villar J, Carroli G, Wojdyla D, Abalos E, Giordano D, Ba'aqeel H, et al. World Health Organization Antenatal Care Trial Research Group. Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? *Am J Obstet Gynecol*. 2006; 194(4):921-31. [DOI: 10.1016/j.ajog.2005.10.813] [PMID: 16580277]
- Szostak-Wegierek D. Intrauterine nutrition: long-term consequences for vascular health. *Int J Womens Health*. 2014; 6:647-56. [DOI: 10.2147/IJWH.S48751] [PMID: 25050077]
- Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr*. 2013; 13:59. [DOI: 10.1186/1471-2431-13-59] [PMID: 23601190]
- Ognean ML. Alimentația enterală a nou-născutului prematur. Colecția Ghiduri clinice pentru neonatologie. Ghidul 15/revizia 1. [2010] online [accessed September 15, 2014]. Available from: http://www.ms.ro/documente/15%20alimentatia%20enterala%20a%20prematurlui_9180_7494.pdf.

CONCLUSION

The maternal and paternal age was significantly lower in the IUGR group compared to controls. Despite this fact, neither was identified as a risk factor for IUGR. A significantly higher percentage of mothers in the IUGR group had hypertension, compared to the control group, while logistic regression analysis identified the mother hypertension as a significant risk factor for IUGR.

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Карактеристике родитеља повезане с интраутерусним заостајањем у расту

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КРАТАК САДРЖАЈ

Увод Недостатак линеарног раста узрокује неколико чинилаца, укључујући карактеристике родитеља.

Циљ рада Циљ ове студије била је процена карактеристика родитеља као фактора ризика за интраутерусно заостајање у расту (ИУЗР) новорођенчади у румунској гинеколошко-акушерској здравственој установи терцијарног нивоа током две и по године.

Методе рада Ретроспективна анамнестичка студија упарених случајева изведена је у Ургентној окружној болници у Клужу, универзитетској болници на северозападу Румуније. Узорак је одабран међу 4.790 новорођенчади примљених на Неонатално одељење Прве гинеколошке клинике између јануара 2012. и јуна 2014. године.

Резултати Мајке чија су деца заостјала у расту (ИУЗР група) биле су статистички значајно млађе од мајки деце контролне групе ($p=0,041$). Хипертензија је утврђена у значајно већем проценту код мајки у ИУЗР групи него код мајки у

контролној групи ($p<0,05$). Нису установљене друге значајне разлике у погледу истраживаних карактеристика новорођенчади из ИУЗР групе наспрам оних из контролне групе ($p>0,13$). Очеви новорођенчади са ИУЗР били су такође статистички значајно млађи у поређењу с очевима деце из контролне групе ($p=0,0278$). Анализа коморбидитета новорођенчади није показала значајне разлике између група у погледу дисајних сметњи, хипербилирубинемije, хипокалцемије и слабости срца ($p>0,27$). Интракранијална крварења, некротизирајући ентероколитис и хипогликемија значајно су били чешћи у ИУЗР него у контролној групи. Логистичка регресија је препознала хипертензију као значајан фактор ризика за ИУЗР ($OR=2,4$; $95\%CI=1,3-4,5$).

Закључак Иако се старосна доб мајки и очева показала знатно нижом у ИУЗР него у контролној групи, само се хипертензија мајки показала значајним фактором ризика за ИУЗР.

Кључне речи: интраутерусно заостајање у расту; карактеристике родитеља; фактори ризика

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Epidemiological Surveillance of Leishmaniasis in Montenegro, 1992–2013

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SUMMARY

Introduction The diseases caused by *Leishmania* are spread worldwide and represent a significant public health problem.

Objective The aim of this study was to present the results of epidemiological surveillance of leishmaniasis in humans in Montenegro in the period from 1992 to 2013.

Methods The study was planned and realized as a descriptive epidemiological study. The sample included patients of leishmaniasis in Montenegro in the period from 1992 to 2013. The health and demographic data were collected from medical records. The disease was microbiologically proven in the patients. For statistical analysis the χ^2 -test was used, which examined the significance of the incidence rate.

Results During this period, 66 cases of leishmaniasis were identified (40 men and 26 women) aged 0 to 62 (mean 15.61 ± 16.76 years). A visceral form of the disease was diagnosed in 65 (98%) patients, and one patient was diagnosed with cutaneous leishmaniasis. The average incidence rate for the abovementioned period is 0.48 per 100,000 inhabitants. The highest average incidence rate was identified in patients up to seven years of age (3.50 per 100,000 inhabitants). The highest average incidence rates of leishmaniasis were identified in the coastal region of Montenegro, while seasonal distribution indicates that the disease occurs throughout the year with predominance in late spring and summer.

Conclusion The research has shown that Montenegro is among the countries with low incidence of leishmaniasis. Nevertheless, because of leishmaniasis re-emergence in the entire Mediterranean Basin, a comprehensive research of ecological and epidemiological characteristics of leishmaniasis, including better monitoring and notification system, is required.

Keywords: leishmaniasis; incidence; Montenegro

INTRODUCTION

Leishmaniasis is defined as a spectrum of diseases caused by protozoan parasites of the genus *Leishmania*. It is a parasite that causes clinical manifestations from localized ulceration of the skin and mucous membranes, to systemic changes. Clinically, it can be described as cutaneous, mucocutaneous or visceral leishmaniasis. The disease is transmitted to animals and from animals to humans by phlebotomine sandflies of the genus *Lutzomyia* and it is more common in warmer climates [1].

The diseases caused by leishmanii are registered in 98 countries worldwide and represent a significant public health problem. An estimated incidence of visceral leishmaniasis is between 0.2 and 0.4 million cases and of cutaneous leishmaniasis from 0.7 to 1.2 million cases worldwide annually [2]. Epidemiological studies show that leishmaniasis is spread worldwide, in tropical zones of South and Central America and Africa, as well as in temperate regions of South America, Southern Europe and Asia. [3]. More frequent human migrations represent a risk for the occurrence of leish-

maniasis in Europe, together with the spreading of the disease from endemic regions, such as the Mediterranean, to the neighboring areas where there are no vectors of the disease, and the re-emergence of the disease in the Mediterranean Region because of a larger number of immunosuppressed people [4]. The incidence of visceral leishmaniasis in the Mediterranean Region is 1,200–2,000 cases annually while on a global basis it is 202,200–389,100 cases annually [2].

This disease, caused by *Leishmania infantum*, is endemic in almost all countries of the Mediterranean Basin. In former Yugoslavia, endemic areas of visceral leishmaniasis were Macedonia, southern Serbia, southern Hercegovina, Dalmatia and the coastal part of Montenegro. According to the epidemiological data, in the territory of Serbia and Montenegro, 39 cases were reported in the period from 1991 to 2000. [5]. In Montenegro, as well as in the surrounding region, the visceral form of leishmaniasis is dominant. The first case of the disease was detected in the area of the town of Bar, which is also the endemic focus of visceral leishmaniasis [6]. The increase in the number

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of individuals infected by leishmaniasis pathogens occurs due to the disturbance of the ecosystem, increasing density of vectors and reservoirs of infection. Since 2005, one to three cases have been registered per year [7].

In March 2010 the World Health Organization convened a leishmaniasis expert panel, which emphasized the need for updating the epidemiological data base of this disease in order to plan appropriate control of leishmaniasis [8].

OBJECTIVE

The aim of this study was to present results of epidemiological surveillance of leishmaniasis in humans in Montenegro in the period from 1992 to 2013.

METHODS

The study was planned and conducted as a descriptive epidemiological study. The sample included patients of leishmaniasis in Montenegro in the period from 1992 to 2013.

Pursuant to General Law on Prevention and Suppression of Contagious Diseases [9, 10], Law on Protection of Population against Communicable Diseases [11], and Rule Book on Reporting Communicable Diseases and Hospital Infections [12], leishmaniasis is included in the list of diseases which must be reported (report cards). The database on occurrence of communicable diseases is kept by the Centre for Control and Prevention of Diseases within the Institute for Public Health of Montenegro. For the period from 1945 to 1994 there are written reports on occurrence of communicable diseases and since 1995 to present day an electronic database has been used.

In our research, the source of data on the patients with leishmaniasis in Montenegro from 1992 until 2013 were the report cards from the database of the Centre for Control and Prevention of Diseases within the Institute for Public Health of Montenegro, and the medical documentation of the patients (gender, age, municipality and date of birth).

Data on parasitological diagnosis were collected from the Centre of Microbiology, the Institute for Public Health of Montenegro. In this center, microbiological confirmation of the disease, i.e. presence of parasites, was made using microscopy techniques while the ELISA and indirect Hemagglutination Assays were used to prove antibodies against the pathogen.

The survey instrument was the incidence rate per 100,000 inhabitants, based on the census of Montenegro for 1991, 2003 and 2011 [13].

The χ^2 -test was used to test the frequency of respondents of different gender and age in the observed group of patients. Material for the study was processed in the computer program SPSS v.13.0 (SPSS Inc.) and Microsoft Office 2003.

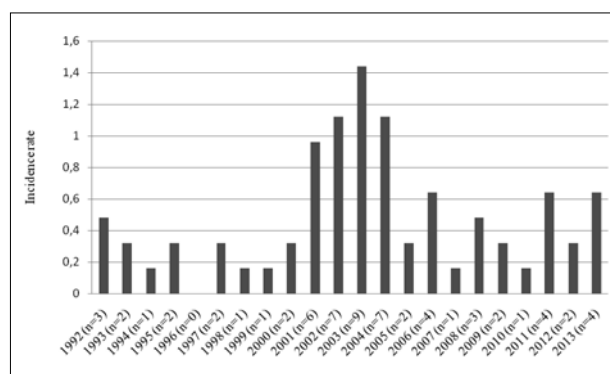
RESULTS

In the period from 1992 to 2013, 66 people were affected by leishmaniasis in Montenegro, out of which 65 (98%) patients were diagnosed with visceral form of the disease, and one patient had cutaneous leishmaniasis (infected in 1999, female, aged 36 years).

The average morbidity incidence rate for the above-mentioned period was 0.48 per 100,000 inhabitants (range: 0 to 1.44). Slightly higher rates of incidence of the disease were registered in the four-year period from 2001 to 2004 (0.96, 1.12, 1.44 and 1.12 per 100,000 inhabitants, respectively) (Graph 1).

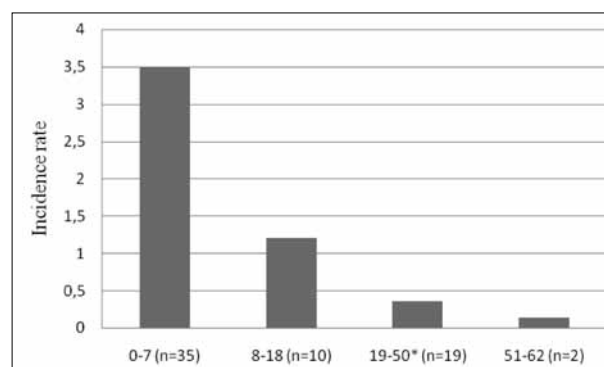
The distribution of patients according to gender indicates that 40 (61%) men and 26 (39%) women ($p < 0.05$) were affected. The average incidence rate was 0.30 per 100,000 for men and 0.20 per 100,000 for women. The average age was 15.61 ± 16.76 (range 0–62 years). The highest average incidence rate was in the age group of zero to seven years (3.50 per 100,000 population) and was statistically significantly higher than in all other age groups ($p < 0.001$ for all comparisons) (Graph 2).

The geographical distribution of patients with leishmaniasis in Montenegro indicates that they are registered in 11 out of total of 21 municipalities. The average inci-



Graph 1. Incidence rate of leishmaniasis per 100,000 population, Montenegro, 1992–2013 (n=66)

n – number of leishmaniasis cases



Graph 2. Average incidence rate of visceral leishmaniasis per 100,000 population depending on the age, Montenegro, 1992–2013 (n=66)

n – number of leishmaniasis cases

* one case of cutaneous leishmaniasis

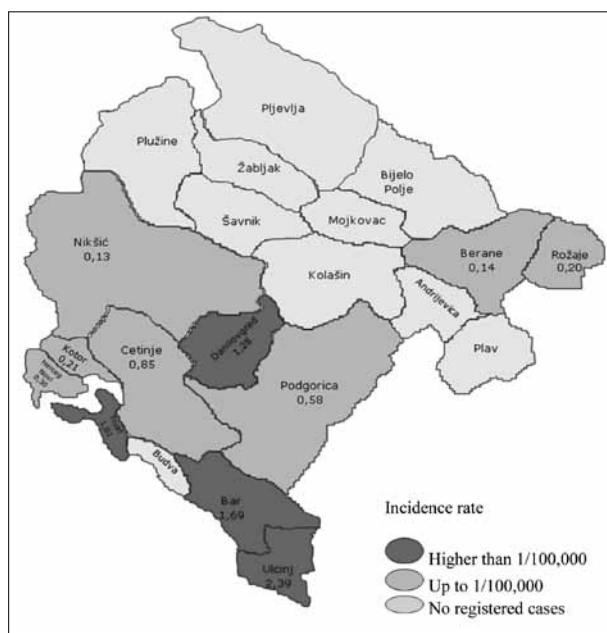
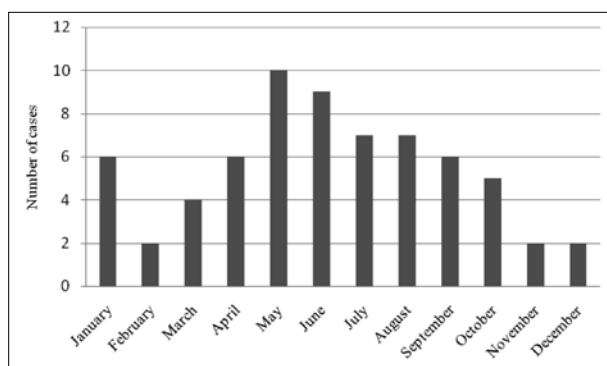


Figure 1. Average incidence rate of leishmaniasis per 100,000 population in municipalities, Montenegro, 1992–2013



Graph 3. Seasonal distribution of leishmaniasis to the number of patients, Montenegro, 1992–2013

dence rate of leishmaniasis is the highest in the coastal region of Montenegro, with 2.39 per 100,000 inhabitants in Ulcinj, and 1.69 per 100,000 inhabitants in Bar (Figure 1).

The number of new cases of leishmaniasis in relation to the reporting period within the year is shown in Graph 3. Seasonal distribution of leishmaniasis indicates that the disease occurs throughout the year with predominance in late spring and summer. In the period from April to October, the number of patients is 50, which represents 76% of all registered cases.

DISCUSSION

This study presents the results of epidemiological surveillance of leishmaniasis in humans in the Republic of Montenegro in the period from 1992 to 2013. A total of 66 persons were registered in the database of the Centre for Control and Prevention of Diseases within the Institute for Public Health of Montenegro. During this period, the vis-

ceral form of leishmaniasis was dominant and was present in 65 (98%) patients, while one patient was diagnosed with cutaneous leishmaniasis. Considering the fact that vectors are the same for the both forms, it is unlikely that in the former period only one person was affected by cutaneous leishmaniasis. It is more probable that a lighter form of the disease was in question and that these patients did not contact a doctor, or, if they had contacted the Department for Skin Disease, these patients were not registered. The average incidence rate for the abovementioned period was 0.48 per 100,000 inhabitants. This is in accordance with the low incidence rate of the disease that is characteristic for the southern European countries, ranging from 0.02 to 0.49 per 100,000 inhabitants [14]. Low values of incidence were also found in other countries in the region such as Greece 0.36, Algeria 0.45, Spain 0.23 and France 0.24 [15, 16, 17].

Our study shows that a larger number of patients and a higher rate of incidence (0.96 to 1.44 per 100,000 inhabitants), were recorded in the four-year period from 2001 to 2004. Similarly, in neighboring Italy, in the period ranging from 2000 to 2004, the annual number of cases reached its peak and then began to decline. Similar results were reported in Bulgaria, although the incidence rate of visceral leishmaniasis was low (0.06 per 100,000 inhabitants) compared to other countries in the region [18, 19].

When it comes to the age of patients, the disease was present in all age groups. The largest number of cases of visceral leishmaniasis was recorded in children up to seven years old (35 affected in total), with the highest average incidence rate (3.5 per 100,000 inhabitants). The results were similar in Bulgaria, Spain, Turkey and Malta [19–22]. The results of our study show that children are the most vulnerable segment of the population due to a weaker immune response. Contrary to our results, in Greece the largest number of patients were over 14, and in Italy over 17 years of age [15, 18].

By analyzing the gender structure of the patients, higher morbidity was recorded in men (61%) than in women (39%). A similar percentage ratio between the sexes was obtained in Greece and Spain [15, 20]. Greater susceptibility of men compared to women is due to men involvement in different activities such as fishing, agriculture and physical activities. However, other studies of this disease show no difference in occurrence among men and women within equal exposure [23, 24].

Our study shows that the highest average incidence rates of visceral leishmaniasis for the reporting period were in the municipalities of Ulcinj and Bar. In addition to these two municipalities, patients were registered in nine other out of 21 municipalities in Montenegro. In the paper by Dakić et al. [5] it is shown that a great number of patients affected by visceral leishmaniasis in Serbia in the period from 2001 to 2007 had been previously on vacation on the Montenegrin coast.

A seasonal variation of registered cases in Montenegro in the period from 1992 to 2013 was associated with the change of seasons. The disease occurs throughout the year, but in the period from April to October, 76% of cases were

registered. In Bulgaria, the majority were indigenous cases infected in warmer months (June–October), and the first clinical symptoms were recorded from October to January [19]. In our study, the largest number of cases were registered in May and June. Considering the fact that the incubation period lasts from two to 12 months, in Montenegro the disease has either minimal or maximal incubation. As the activity of vector is highest in the warm months, infection is possible either in early spring, in the case of shorter incubation, or at the end of the warm season the previous year, if the incubation is the longest.

CONCLUSION

The research has shown that Montenegro is among the countries with a low incidence rate of visceral leishmaniasis. This form of leishmaniasis is more frequent on the Montenegrin coast (municipalities of Bar and Ulcinj), in men and pre-school children.

Nevertheless, because of leishmaniasis re-emergence in the entire Mediterranean Basin, a comprehensive research of ecological and epidemiological characteristics of leishmaniasis, including better monitoring and notification system, is required.

REFERENCES

- Herwaldt BL. Leishmaniasis. *Lancet*. 1999; 354(9185):1191-9. [DOI: 10.1016/S0140-6736(98)10178-2] [PMID: 10513726]
- Alvar J, Velez ID, Bern C, Herrero M, Desjeux P, Cano J, et al. Leishmaniasis worldwide and global estimates of its incidence. *PLOS ONE*. 2012; 7(5):e35671. [DOI: 10.1371/journal.pone.0035671] [PMID: 22693548]
- Dawit G, Girma Z, Simenew K. A review on biology, epidemiology and public health significance of leishmaniasis. *J Bacteriol Parasitol*. 2013; 4(2):166. [DOI: 10.4172/2155-9597.1000166]
- Ready PD. Leishmaniasis emergence in Europe. *Euro Surveill*. 2010; 15(10):19505. [PMID: 20403308]
- Dakic ZD, Pelemis MR, Stevanovic GD, Poluga JL, Lavadinovic LS, Milosevic IS, et al. Epidemiology and diagnostics of visceral leishmaniasis in Serbia. *Clin Microbiol Infect*. 2009; 15(12):1173-6. [DOI: 10.1111/j.1469-0691.2009.02768.x] [PMID: 19392902]
- Ivović V, Ivović M, Mišević Z. Sandflies (Diptera: Psychodidae) in the Bar area of Montenegro (Yugoslavia). *Ann Trop Med and Parasit*. 2003; 97:193-7. [DOI: 10.1179/000349804225003352] [PMID: 12803875]
- Andric B, Mijovic G, Terzic D, Dupanovic B. Vector borne transmissible zoonoses in Montenegro. *Journal of IMAB*. 2012; 18(1):220-5. [DOI: 10.5272/jimab.2012181.220]
- World Health Organization (WHO). Library Cataloguing-in-Publication Data: Control of the leishmaniasis: report of a meeting of the WHO Expert Committee on the Control of Leishmaniasis. Geneva, 22-26 March 2010. Available from: http://whqlibdoc.who.int/trs/WHO_TRS_949_eng.pdf.
- Zakon o sprečavanju i suzbijanju zaraznih bolesti. Službeni list FNRJ, br. 37/48.
- Zakon o sprečavanju i suzbijanju zaraznih bolesti. Službeni list SFRJ, br. 17/64.
- Zakon o zaštiti stanovništva od zaraznih bolesti. Službeni list RCG, Podgorica, br. 51/84, 63/90, 45/92, 46/96, 32/2005, 14/2010, 40/2011 i 30/12.
- Pravilnik o prijavljivanju zaraznih bolesti i bolničkih infekcija. Službeni list RCG, Podgorica, br. 45/07.
- Statistički godišnjak Crne Gore 2011. Podgorica: Zavod za statistiku Crne Gore; 2011.
- Dujardin JC, Campino L, Canavate C, Dedet JP, Gradoni L, Soteriadou K, et al. Spread of vector-borne diseases and neglect of leishmaniasis, Europa. *Emerg Infect Dis*. 2008; 14(7):1013-8. [DOI: 10.3201/eid1407.071589] [PMID: 18598618]
- Gkolfinopoulou K, Bitsolas N, Patrinos S, Veneti L, Marka A, Douglas G, et al. Epidemiology of human leishmaniasis in Greece, 1981–2011. *Euro Surveill*. 2013; 18(29):20532. [DOI: 10.2807/1560-7917.ES2013.18.29.20532] [PMID: 23929118]
- Adel A, Boughoufalah A, Saegerman C, Deken RD, Bouchene Z, Soukehal A, et al. Epidemiology of visceral leishmaniasis in Algeria: an update. *PLOS ONE*. 2014; 9(6):e99207. [DOI: 10.1371/journal.pone.0099207] [PMID: 24949958]
- World Health Organization (WHO). Centralized Information System for Infectious Diseases. Geneva: WHO; 2012.
- Gramiccia M, Scalone A, Di Muccio T, Orsini S, Fiorentino E, Gradoni L. The burden of visceral leishmaniasis in Italy from 1982 to 2012: a retrospective analysis of the multi-annual epidemic that occurred from 1989 to 2009. *Euro Surveill*. 2013; 18(29):20535. [DOI: 10.2807/1560-7917.ES2013.18.29.20535] [PMID: 23929120]
- Harizanov R, Rainova I, Tzvetkova N, Kaftandjiev I, Bikov I, Mikov O. Geographical distribution and epidemiological characteristics of visceral leishmaniasis in Bulgaria, 1988 to 2012. *Euro Surveill*. 2013; 18(29):20531. [PMID: 23929117]
- Arce A, Estirado A, Ordobas M, Sevilla S, García N, Moratilla L, et al. Re-emergence of leishmaniasis in Spain: community outbreak in Madrid, Spain, 2009 to 2012. *Euro Surveill*. 2013; 18(30):20546. [DOI: 10.2807/1560-7917.ES2013.18.30.20546] [PMID: 23929177]
- Fenech FF. Leishmaniasis in Malta and the Mediterranean basin. *Ann Trop Med Parasitol*. 1997; 91(7):747-53. [DOI: 10.1080/00034989760491] [PMID: 9625930]
- Ok UZ, Balcioglu IC, Taylan Ozkan A, Ozensoy S, Ozbei Y. Leishmaniasis in Turkey. *Acta Trop*. 2002; 84(1):43-8. [DOI: 10.1016/S0001-706X(02)00134-1] [PMID: 12387909]
- Desjeux P. (1996) Leishmaniasis. Public health aspects and control. *Clin Dermatol*. 1996; 14:417-23. [DOI: 10.1016/0738-081X(96)00057-0] [PMID: 8889319]
- Desjeux P. Leishmaniasis: current situation and new perspectives. *Comp Immunol Microbiol Infect Dis*. 2004; 27:305-18. [DOI: 10.1016/j.cimid.2004.03.004] [PMID: 15225981]

Епидемиолошко истраживање лајшманијазе у Црној Гори 1992–2013. године

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КРАТАК САДРЖАЈ

Увод Обољења изазвана лајшманијама су распрострањена широм света и значајан су здравствени проблем.

Циљ рада Циљ рада је био да се представе резултати епидемиолошког истраживања лајшманијазе код људи на подручју Црне Горе у периоду 1992–2013. године.

Методе рада Истраживање је планирано и реализовано као дескриптивна епидемиолошка студија. Узорак истраживања су чинили оболели од лајшманијазе у Црној Гори од 1992. до 2013. године. Здравствени и демографски подаци прикупљени су из медицинске документације. Код свих оболелих болест је микробиолошки доказана. За статистичку анализу резултата коришћен је χ^2 -тест, којим је испитана значајност стопа инциденције.

Резултати У наведеном периоду од лајшманијазе је оболело 66 особа (40 мушкараца и 26 жена) старих до 62 године (просечно $15,61 \pm 16,76$ година). Код 65 (98%) болесни-

ка дијагностикован је висцерални облик обољења, а код једног болесника кожни тип лајшманијазе. Просечна стопа инциденције била је 0,48 оболелих на 100.000 становника. Највиша просечна стопа инциденције била је у узрасту до седам година (3,50 на 100.000 становника). Просечне стопе инциденције лајшманијазе с највишом вредности биле су у приобаљу Црне Горе, док сезонска дистрибуција указује на то да се болест јавља током целе године с преминацијом с краја пролећа и на лето.

Закључак Наше истраживање је показало да је Црна Гора међу државама с ниском стопом инциденције оболевања од лајшманијазе. Ипак, због поновног појављивања ове болести у Медитеранском басену и значаја за народно здравље, потребно је свеобухватно истраживање еколошких и епидемиолошких одлика лајшманијазе, укључујући бољи мониторинг и систем регистрације.

Кључне речи: лајшманијаза; инциденција; Црна Гора

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Long-Term Treatment with Olanzapine in Hospital Conditions: Prevalence and Predictors of the Metabolic Syndrome

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SUMMARY

Introduction The risk of metabolic abnormalities is greatly increased in schizophrenic patients started on an atypical antipsychotic medication. Patients with psychiatric disorders exceed mortality ranges resulting from, among others, increased risk of cardiovascular events. Other factors contributing to the development of metabolic syndrome include prolonged duration of illness, increasing age, female sex and lifestyle factors.

Objective This cross-sectional study was taken up to assess the prevalence of the metabolic syndrome (MetS) in schizophrenic patients receiving olanzapine monotherapy for at least six months and to determine the most important risk factors associated with metabolic syndrome presence in these patients.

Methods A total of 93 long term hospitalized schizophrenic patients (71 men, 22 women), had a screening of the following: case-history data, psychiatric scales, anthropometric measures, blood (fasting glucose, lipid status, C-reactive protein – CRP) and urine samples (microalbuminuria).

Results Prevalence of MetS according to International Diabetes Federation criteria in our study was 34.4%. The multivariate analysis distinguished the following significant predictors of MetS presence (in order of appearance): data about diabetes mellitus in family history ($p=0.002$), body mass index $>25 \text{ kg/m}^2$ ($p=0.002$), hyperlipidemia in family history ($p=0.008$), and elevated CRP value ($p=0.042$).

Conclusion High rate of MetS in patients treated with olanzapine in this study exceeds MetS prevalence in general population. Among observed parameters, our study pointed to several “high risk” predictors associated with MetS presence. Regular monitoring of cardiometabolic risk factors is highly recommended. Positive heredity distress mentioned above may direct a psychiatrist to prescribe some other drug than olanzapine in the long term treatment of schizophrenia.

Keywords: metabolic syndrome; schizophrenia; olanzapine

INTRODUCTION

Schizophrenia is a chronic and debilitating psychiatric illness with a worldwide prevalence of approximately 1% [1]. It is characterized by positive, negative and affective symptoms. Since the introduction of chlorpromazine in 1952, antipsychotic drugs are the mainstay of the pharmacologic treatment of psychosis and schizophrenia [2]. By blocking dopaminergic neurotransmission in subcortical areas, antipsychotics are capable of producing extrapyramidal side-effects. This propensity is more pronounced with the first-generation antipsychotics (FGA), than with the second-generation antipsychotics (SGA). Thus, during the past two decades, SGA replaced FGA as the standard treatments for schizophrenia [3]. SGAs antagonism to histamine H_1 and serotonin $5HT_{2c}$ receptors, associated with weight gain and metabolic deregulation, enhance the prevalence of the metabolic syndrome (MetS) in patients taking this kind of medication [4]. Factors that also contribute to the development of MetS are long-term duration of illness, old age, female sex, lifestyle factors related to psy-

chotic disorder [5]. Patients suffering from psychiatric disorders have significantly increased morbidity and mortality ranges – increased risk of cardiovascular events and premature death is estimated to 10 to 25 years earlier than in general population [6]. Data in literature indicate that treatment-induced metabolic abnormalities, such as raised lipids and glucose blood levels, eventually result in abdominal obesity, may contribute to the development of diabetes mellitus type 2 and arterial hypertension, and may account for up to 60% of premature deaths of persons with serious mental illness [7].

International Diabetes Federation (IDF) criteria are the most widely used in European studies (Table 1). Definition of MetS includes an assembly of disorders such as the abdominal obesity, hypercholesterolemia, hyperlipidemia, arterial hypertension and raised blood glucose levels [8].

In comparison to general population, the prevalence of MetS is increased in patients taking psychotropic agents [9, 10]. This applies not only to antipsychotics, but also to mood stabilizers and antidepressants [11, 12]. Apart from that, subjects with schizophrenia or bi-

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Table 1. IDF metabolic syndrome worldwide definition*

Parameter		Ethnicity specific – Europids
Waist circumference		Male ≥ 94 cm Female ≥ 80 cm
..plus any two of the following	Raised triglycerides	≥ 1.7 mmol/L (150 mg/dl) or specific treatment for this lipid abnormality
	Raised blood pressure	systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg or treatment of previously diagnosed arterial hypertension
	Reduced HDL cholesterol	< 1.03 mmol/L (40 mg/dL) in males < 1.29 mmol/L (50 mg/dL) in females
	Raised plasma glucose	fasting plasma glucose ≥ 5.6 mmol/L (100 mg/dl) or previously diagnosed diabetes mellitus type 2

* Consensus Statement from the International Diabetes Federation (IDF) [8]

polar disorder may be prone to metabolic deregulation regardless of any specific drug treatment, which correlates with genetic factors [13]. Furthermore, origination of metabolic disturbances via enhanced food intake, insulin resistance, further diabetes mellitus type 2 development, as well as elevated serum lipids fractions, implies a timeframe of at least three months [14]. Consequently, the authors of this cross-sectional study set the six months of previous olanzapine monotherapy treatment as time long enough to declare with high probability that MetS is caused by the actual antipsychotic consumption, considering that long term hospitalization conditions control other confounders (nutrition, concomitant therapy, physical activity).

Olanzapine is an antipsychotic agent displaying nanomolar affinity at dopamine D_1 – D_4 , serotonergic ($5\text{-HT}_{2,3,6}$), muscarinic ($M_{1,5}$), adrenergic (α_1), and histaminergic (H_1) binding sites [15]. The pharmacology may further include a glutamatergic mechanism [16]. Such profile distinguishes olanzapine from other, conventional antipsychotic agents. However, olanzapine causes MetS in 19–50% of schizophrenic patients on long-term therapy [17, 18].

OBJECTIVE

The objectives of the present cross-sectional study were as follows:

1) To assess the prevalence of the metabolic syndrome (according to the IDF criteria) and its constituting components in long-term olanzapine treated patients;

2) To determine potential cardiometabolic risk factors in a subgroup of patients with diagnosed MetS, related to:

- social-demographic parameters (age, sex, schizophrenia type according to International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) classification, heredity of diabetes or hyperlipidemia in family history, number of previous hospitalizations, smoking habit, duration of the illness, duration of the antipsychotic treatment, average olanzapine daily doses);
- anthropometric parameters (waist circumference, body mass index [BMI], blood pressure);

- laboratory parameters (fasting glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, total triglycerides, microalbuminuria);
- psychiatric clinical state evaluated by Positive and Negative Syndrome Scale (PANSS) for schizophrenia [19] and Brief Psychiatric Rating Scale (BPRS) [20].

METHODS

The present study was designed as a cross-sectional, case-control study, undertaken during the year 2012, among patients hospitalized at Specialized Psychiatric Hospital Gornja Toponica, Niš, Serbia, after receiving approval from the Institutional Human Ethics Committee. It included 93 long-term hospitalized patients (71 men, 22 women), diagnosed with Schizophrenia group (F20–F29), according to diagnostic criteria from the ICD-10 [21]. Those who were receiving a single SGA agent olanzapine for a period of six months or more were enrolled in the study after obtaining written informed consent. Additional administration of benzodiazepines and/or hypnotics was allowed in therapeutic doses, but no other psychotropic drugs. Concomitant somatic medication was allowed, if necessary (antihypertensives, antidiabetics). Nutrition in hospital conditions was up to standard dietary protocols, without changes of physical activity during the study.

The IDF criteria were used to distinguish presence/absence of MetS (Table 1). According to MetS presence, patients were divided into two subgroups – those with diagnosed MetS (observed as “cases” in the study), and those without diagnosed MetS (observed as “controls” in the study).

The clinical psychiatric state of the patients was measured by PANSS for schizophrenia, and the BPRS. The following demographic characteristics were obtained using a questionnaire: age and sex, duration of illness, details of medication, duration of medical treatment, case-history of co-morbid conditions (arterial hypertension and/or diabetes mellitus type 2), as well as diabetes mellitus type 2 and hyperlipidemia in family history. The patients were fasting (overnight fast of 12–14 hours) for the purpose of blood collection for lipid blood tests and measurement of blood glucose. Venous puncture was performed for all subjects between eight and nine a.m. after a 12-hour overnight fast. Immediately after collecting blood samples, serum concentrations of total cholesterol, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), total triglycerides and fasting glucose were determined using enzyme methods and commercial kits (Olympus Diagnostic, GmbH, Hamburg, Germany) on Olympus AU 600 automated analyzer. C-reactive protein (CRP) serum levels were determined using immunoturbidimetric method. The cut-off point for CRP elevation was set at 5 mg/L. Microalbuminuria was detected by standard spot urine albumin sample (referent value 30–300 mg/L). BMI was calculated after measuring patients' weight and height (kg/m^2). Waist as a major marker (central adiposity) was measured in the midpoint of distance between

Table 2. Patient sample's structure (according to gender)

Parameter	Total (n=93)	Men (n=71)	Women (n=22)	p*
Age (years)	48.13±8.78	48.14±8.94	48.09±8.41	0.981
Antipsychotic treatment (years)	4.15±2.62	4.39±2.77	3.36±1.91	0.107
Olanzapine treatment (months)	8.39±2.15	8.51±2.23	8.00±1.82	0.288
Olanzapine dose (mg pro die)	13.96±2.15	13.90±4.26	14.14±4.45	0.824
Number of previous hospitalizations	5.62±4.94	4.96±3.66	7.77±7.47	0.019
Illness length (years)	13.53±5.05	13.41±5.15	13.91±4.78	0.687
Smoking habit	90 (96.8)	68 (95.8)	22 (100.0)	0.933 ^b
MetS presence	32 (34.4)	21 (29.6)	12 (54.5)	0.078 ^b
F20.0**	46 (49.5)	38 (53.5)	8 (36.4)	0.161 ^b
F20.1**	20 (21.5)	14 (19.7)	6 (27.3)	0.553 ^a
F20.5**	12 (12.9)	10 (14.1)	2 (9.1)	0.724 ^a
F25**	5 (5.4)	3 (4.2)	2 (9.1)	0.588 ^a
F22**	10 (10.8)	6 (8.5)	4 (18.2)	0.239 ^a

Data are presented as mean value ± standard deviation, or as the number of patients (frequency) with percentage.

* p – Student's t-test value (p<0.05 bolded if significant)

^a Fisher's exact p; ^b Pearson's χ^2 p

** Diagnosis according to ICD-10 classification: F20.0 – paranoid schizophrenia; F20.1 – hebephrenic schizophrenia; F20.5 – residual schizophrenia; F25 – schizoaffective disorder; F22 – persistent delusional psychosis

the costal arc and iliac crest when the patient was standing up and at mid-expiration. Blood pressure was measured with an aneroid sphygmomanometer in an office setting. Average daily dose of olanzapine was calculated for each patient for the complete previous period of administration (mg pro die).

Excluded from the study were patients who had shown symptoms of chronic or acute infection, allergies, or any other condition known to affect the immune system for at least two weeks before the study. They were also free of using other concomitant drugs known to alter immune function.

Statistical analyses

Simple descriptive statistics (means, standard deviations and 95% confidence interval) were generated for all continuous variables. For discrete variables number of patients and percentages are given. The difference between the two group means was analyzed by Student's t-test. The difference between the two group proportions was analyzed by Pearson's chi-squared test, and Fisher's test where appropriate. The significance level was set at p<0.05. Multivariate logistic regression was used to access predictors of MetS. Analyses were performed using SPSS for Windows, Version 18.0.

RESULTS

The average age of the patients was 48.13±8.78 years. For the majority of patients (49.5%) clinical diagnosis (ICD-10) was the paranoid form of schizophrenia, followed by the hebephrenic form (21.5%). Permanent antipsychotic treatment with olanzapine lasted for 8.39±2.15 months, with average doses of 13.96±4.28 mg pro die, which is middle to high therapeutic range. Average duration of illness of 13.53±5.05 years and number of previous hos-

pitalizations of 5.62±4.94 suggest that this patient sample can be considered to consist of schizophrenic patients. In this regard, the fact that the vast majority of patients were smokers (over 96%) was expected. As it is shown in Table 2, there was no significant difference by sex according to the data, except for the number of previous hospitalizations, in favor of women.

The prevalence of MetS in our study group was 34.4%, women insignificantly higher than men (54.5% and 29.6%, respectively) (Table 2).

In Table 3 data were compared according to MetS presence (IDF criteria). We found statistically significant difference in favor of the subgroup with present MetS among these observed parameters: age (p=0.039), waist circumference (p<0.001), both the systolic (p=0.001) and diastolic (p<0.001) blood pressure, heredity data about diabetes mellitus type 2 (p=0.001) and hyperlipidemia (p<0.001). BMI was also significantly different in the subgroup with diagnosed MetS (p<0.001), where patients were overweight (average BMI of 27.82±4.34). Subgroup of patients without MetS was in the normal weight range of BMI (average 24.21±3.81). Presence microalbuminuria in our patient sample was also significantly higher in the subgroup with diagnosed MetS. Smoking habit, average daily dose of olanzapine, duration of olanzapine administration, as well as the illness length, did not show statistical difference regarding MetS presence.

Clinical state of patients evaluated by PANSS for schizophrenia showed average total PANSS score of 85.73±26.13. Also, none of the PANSS subscales significantly differed according to MetS presence. The similar ratio is present for BPRS scores – average total score of 39.69±10.26, no statistically significant difference regarding the presence of MetS among patients (Table 4).

On the contrary, the laboratory tests results (Table 5) revealed significant differences. In comparison to patients without MetS, subjects with a diagnosis of MetS had significantly higher the following measured parameters: fast-

Table 3. Metabolic syndrome presence related to anamnestic, anthropometric data and microalbuminuria spot urine test

Parameter	MetS present (n=32)	Without MetS (n=61)	p*
Age (years)	50.72±7.82	46.77±9.00	0.039
Smoking habit	32 (100.0)	57 (93.4)	0.139 ^b
Olanzapine dose (mg/pd)	14.12±4.26	13.88±4.34	0.800
Olanzapine treatment (months)	8.31±2.07	8.43±2.20	0.810
Illness length (years)	14.72±5.31	12.90±4.84	0.099
Waist circumference (cm)	99.06±12.34	86.84±11.16	<0.001
BMI (kg/m ²)	27.82±4.34	24.21±3.81	<0.001
Systolic blood pressure (mmHg)	132.03±15.34	118.79±19.80	0.001
Diastolic blood pressure (mmHg)	81.41±8.25	74.75±8.08	<0.001
Diabetes mellitus type 2 heredity data	12 (37.5)	5 (8.2)	0.001^b
Hyperlipidemia heredity data	10 (31.3)	1 (1.6)	<0.001^a
Microalbuminuria (>300 mg/L)	5 (15.6)	0 (0.0)	0.002^a

Data are presented as mean value ± standard deviation, or as number of patients (frequency) with percentage.

* p – Student's t-test value (p<0.05 bolded if significant)

^a Fisher's exact p; ^b Pearson's χ^2 p

MetS – metabolic syndrome (diagnosed by IDF criteria); BMI – body mass index

Table 4. Psychiatric scales scores and presence of the metabolic syndrome

Parameter	Total (n=93)	MetS present (n=32)	Without MetS (n=61)	p*
PANSS total score	85.73±26.13	91.81±27.98	82.54±24.75	0.104
PANSS positive score	18.71±8.21	20.59±10.30	17.72±6.77	0.110
PANSS negative score	26.53±9.57	28.72±8.78	25.38±9.85	0.110
PANSS general psychopathology score	41.20±12.00	42.66±12.10	40.44±11.98	0.401
BPRS total score	39.69±10.26	40.22±12.59	39.41±8.90	0.720

Data are presented as mean value ± standard deviation.

* p – Student's t test value (p<0.05 bolded if significant)

Table 5. Metabolic syndrome in relation to laboratory test results

Parameter	Total (n=93)	MetS present (n=32)	Without MetS (n=61)	p*
Fasting glucose (mmol/l)	4.97±1.20	5.39±1.29	4.75±1.09	0.014
Triglycerides (mmol/l)	2.00±1.10	2.47±1.25	1.76±0.93	0.003
HDL-cholesterol (mmol/l)	1.27±0.25	1.14±0.26	1.33±0.22	<0.001
CRP (mg/L)	6.31±3.92	7.13±4.79	5.89±3.33	0.147
LDL-cholesterol (mmol/L)	3.06±0.77	3.14±0.78	3.02±0.78	0.488
Cholesterol (mmol/L)	5.27±0.98	5.43±1.06	5.18±0.94	0.265

Data are presented as mean value ± standard deviation.

* p – Student's t-test value (**p<0.05 bolded if significant**)

Table 6. Multivariate analysis of metabolic syndrome risk factors

Risk factor	OR	95% CI		p*
		Lower limit	Upper limit	
Age (years)	1.095	0.998	1.202	0.056
Enhanced CRP value (>5 mg/L)	4.555	1.057	19.627	0.042
BMI (kg/m ²)	1.328	1.105	1.597	0.002
DM type 2 heredity data	14.134	2.724	73.348	0.002
Microalbuminuria (>300 mg/L)	1.208	0.000	0.000	0.999
Hyperlipidemia heredity data	53.134	2.768	1019.916	0.008

Hosmer–Lemeshow goodness-of-fit test $\chi^2=5.847$; df=8; p=0.664; p<0.05 significance bolded; DM – diabetes mellitus

ing glucose (p=0.014), total triglycerides (p=0.003) and significantly lower HDL-c levels (p<0.001). Interestingly, CRP plasma levels did not differ significantly according to MetS presence, while all the ranges were above the cutoff point of 5 mg/L: total average of 6.31±3.92, subgroup with

MetS 7.13±4.79, subgroup without MetS 5.89±3.33. In addition, the LDL-c ranges as well as total cholesterol ranges did not show statistically significant difference in regard to the presence of MetS.

The multivariate logistic regression was done with the aim to reveal factors associated with MetS (in addition to its constituting variables by the IDF criteria) in our sample of patients (Table 6). We chose risk factors which are easy to handle in everyday clinical work. Among them, we found several statistically significant parameters, marked as strong predictors in this patient sample, in order of appearance: case history data about diabetes mellitus type 2 in family history (p=0.002); BMI (p=0.002); case history data about hyperlipidemia in family history (p=0.008); enhanced CRP levels (over the cutoff point of 5 mg/L) (p=0.042).

The age of the patients was close to being a significant predictor (p=0.056), while microalbuminuria did not present itself as a significant risk factor in our study (p=0.999).

DISCUSSION

According to data provided by meta-analysis, the overall rate of MetS in schizophrenia and related disorders is 32.5% [22]. A European study showed prevalence of the metabolic syndrome in patients with schizophrenia treated with antipsychotics to be 36% (IDF criteria) [9]. In our study group treated with olanzapine prevalence of MetS was similar (34.4%). Such high prevalence of MetS in this population reaches as much as twice the prevalence of general population: in European countries it varies from 5.9% in men and 2.1% in women in France [23], to 15.7% in men and 14.2% in women in Finland [24]. Kagal et al. [25] described comparable results in 2012 on a sample of 80 patients with a diagnosis of schizophrenia and treated with a single SGA for three months, where prevalence of MetS was found to be 35%. In the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study, the authors identified 88% of patients with dyslipidemia, 62% of patients with arterial hypertension and 38% of patients with diabetes who were not properly diagnosed and had received no treatment for their physical disorders [26].

Despite the fact that our results didn't find statistical variance associated with MetS presence in parameters such as olanzapine treatment duration, daily dose of olanzapine, smoking habit, length of illness, Park et al. [27] noticed life-style factors that correlate with MetS – smoking habit, illness length and antipsychotic administration length. Otherwise, significantly marked variables associated with MetS were older age, waist circumference, overweight (BMI>25) and elevated blood pressure. Straker et al. [28], on a similar patient sample size receiving different SGA agents, also reported abdominal obesity with the highest sensitivity for MetS presence. Combining abdominal obesity and elevated fasting blood glucose they found 100% sensitivity, calculated with positive predictive value test. Frequent screening of waist circumference and blood pressure in patients receiving SGAs, like olanzapine, is an inexpensive as well as a sensitive method. Variations in these values during SGA treatment should further alert us to collect blood samples for lipid profile and fasting glucose levels.

In our study, patients with diagnosed MetS were overweight (average BMI of 27.82 ± 4.34), in comparison with the subgroup without MetS, which were in normal weight range (average BMI of 24.21 ± 3.81). Baptista and Kin [14] have also found high correlation of BMI and metabolic disturbances during the SGA treatment. In a cross sectional study of Mackin et al. [17], the relationship between obesity and elevated glucose levels was statistically more significant with SGA than with FGA treated subjects. Our results showed significant difference of waist circumference among the subgroups with/without MetS, but both subgroups of patients had values above those set by the IDF criteria.

Our data about fasting glucose levels, although significantly higher in favor of the subgroup with MetS, didn't show elevated values over the cutoff point of 5.6 mmol/L. In literature there is evidence that olanzapine has greater potency for glucose disturbances than other SGA agents

[29]. A recent systematic review and meta-analysis concluded that all SGAs (excluding aripiprazole, ziprasidone and amisulpride, for which there were insufficient data to be included in the analysis) were associated with a 30% increased risk of diabetes as compared to FGAs in people with schizophrenia [30].

Also, HDL-c levels were within the normal range despite the statistical significance in favor of MetS presence. Triglyceride levels were above the cutoff point of 1.7 mmol/L, with the average total of 2.00 ± 1.10 , for the subgroup with MetS the average was 2.47 ± 1.25 , and for the subgroup without MetS the average was 1.76 ± 0.93 , with high statistical significance ($p=0.003$). Atmaca et al. [31] found significant rise of plasma triglycerides after six weeks of olanzapine treatment. LDL-c and cholesterol ranges were on the upper limit of normal ranges, with no statistical difference among observed subgroups.

Absence of the positive correlation between the symptom severity and metabolic disturbances, especially weight gain, in our study could be discussed in relation to long time antipsychotic treatment and persistence of chronic schizophrenic symptoms, illustrated by PANSS and BPRS scores (average total PANSS 85.73 ± 26.13 , average BPRS 39.69 ± 10.26). In literature, there is clear evidence in short term monitoring (between two and four months), that weight gain is strongly related to significant decrease of psychiatric scales scores [32].

Using multivariate logistic regression analysis, where the presence of MetS was a dependent variable, we found significant odds ratios for positive data about diabetes mellitus type 2 and hyperlipidemia in family history, as well as for the BMI. De Leon et al. [13] marked genetic factors that are competent for direct lipid abnormalities associated with SGA administration.

CRP values over the cutoff point of 5 mg/L were a significant predictor in our study group. Inflammation of the visceral adipose tissue in the pathophysiology of MetS is well established in literature [33]. Both subgroups of our patient sample (with/without MetS – 7.13 ± 4.79 vs. 5.89 ± 3.33 , respectively), as well as the average total ranges of CRP (6.31 ± 3.92), were above the cutoff point of 5 mg/L.

CONCLUSION

High rate of MetS in patients treated with olanzapine that we found in this study (34.4%) significantly exceeds MetS prevalence in general population. Among observed parameters, our study pointed to several cardiometabolic "high risk" predictors associated with MetS presence: heredity of diabetes and hyperlipidemia in family history, overweight, and enhanced CRP ranges. Since the risk of various cardiovascular events significantly increases in patients with MetS, regular monitoring of cardiometabolic risk factors in patients on long-term olanzapine treatment is highly recommended. Positive heredity distress mentioned above may direct a psychiatrist to prescribe some other drug than olanzapine in the long-term treatment of schizophrenia.

REFERENCES

- Hennenkens CH, Hennenkens AR, Hollar D. Schizophrenia and increased risk of cardiovascular disease. *Am Heart J*. 2005; 150(6):1115-21.
- Miyake N, Miyamoto S, Jarskog LF. New serotonin-dopamine antagonists for the treatment of schizophrenia. *Clin Schizophr Relat Psychoses*. 2012; 6:122-3.
- Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009; 373:31-41.
- Nasrallah HA, Newcomer JW. Atypical antipsychotics and metabolic dysregulation: evaluating the risk/benefit equation and improving the standard of care. *J Clin Psychopharmacol*. 2004; 24:S7-S14.
- De Hert M, Schreurs V, Vancampfort D. Metabolic syndrome in people with schizophrenia: a review. *World Psychiatry*. 2009; 8(1):15-22.
- Correll CU, Frederickson AM, Kane JM, Manu P. Metabolic syndrome and the risk of coronary heart disease in 367 patients treated with second-generation antipsychotic drugs. *J Clin Psychiatry*. 2006; 67:575-83.
- Parks J, Svendsen D, Singer P, Foti M. Morbidity and Mortality in People with Serious Mental Illness. Washington, DC: National Association of State Mental Health Program Directors (NASMHPD) Medical Directors Council; 2006.
- Alberti KG, Zimmet P, Shaw J. Metabolic syndrome – a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med*. 2006; 23:469-80.
- De Hert M, van Winkel R, Van Eyck D. Prevalence of the metabolic syndrome in patients with schizophrenia treated with antipsychotic medication. *Schizophr Res*. 2006; 83:87-93.
- Kozumplik O, Uzun S, Jakovljević M. Metabolic syndrome in patients with psychotic disorders: diagnostic issues, comorbidity and side effects of antipsychotics. *Psychiatr Danub*. 2010; 22:69-74.
- Teixeira PJ, Rocha FL. The prevalence of metabolic syndrome among psychiatric inpatients in Brazil. *Rev Bras Psiquiatr*. 2007; 29:330-6.
- McIntyre RS, Park KY, Law CW. The association between conventional antidepressants and the metabolic syndrome: a review of the evidence and clinical implications. *CNS Drugs*. 2010; 24:741-53.
- de Leon J, Correa JC, Ruano G, Windemuth A, Arranz MJ, Diaz FJ. Exploring genetic variations that may be associated with the direct effects of some antipsychotics on lipid levels. *Schizophr Res*. 2008; 98:40-6.
- Baptista T, Kin NM. Obesity and related metabolic abnormalities during antipsychotic drug administration: mechanisms, management and research perspectives. *Pharmacopsychiatry*. 2002; 35:205-19.
- Bymaster FP, Calligaro DO, Falcone JF. Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology*. 1996; 14:87-96.
- Corbett R, Camacho F, Woods AT. Antipsychotic agents antagonize non-competitive N-methyl-D-aspartate antagonist-induced behaviors. *Psychopharmacology (Berl)*. 1995; 120:67-74.
- Mackin P, Watkinson HM, Young AH. Prevalence of obesity, glucose homeostasis disorders and metabolic syndrome in psychiatric patients taking typical or atypical antipsychotic drugs: a cross-sectional study. *Diabetologia*. 2005; 48(2):215-21.
- Kerna V, Nosalova G, Ondrejka I. Metabolic risk in selected second-generation antipsychotics. *Bratisl Lek Listy*. 2010; 111(12):640-3.
- Kay SR, Opler LA, Fiszbein A. Positive and Negative Syndrome Scale (PANSS) Manual. North Tonawanda, NY: Multi-Health Systems; 1986.
- Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep*. 1962; 10:799-812.
- International Statistical Classification of Diseases and Related Health Problems ICD-10. Geneva, Switzerland: WHO; 1992.
- Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders – a systematic review and meta-analysis. *Schizophr Bull*. 2013; 39(2):306-18.
- Maumus S, Marie B, Siest G, Visvikis-Siest S. A prospective study on the prevalence of metabolic syndrome among healthy french families: two cardiovascular risk factors (HDL cholesterol and tumor necrosis factor-alpha) are revealed in the offspring of parents with metabolic syndrome. *Diabetes Care*. 2005; 28:675-82.
- Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyörälä K. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. *Arch Intern Med*. 2004; 164:1066-76.
- Kagal UA, Torgal SS, Patil NM, Malleshappa A. Prevalence of the metabolic syndrome in schizophrenic patients receiving second-generation antipsychotic agents – a cross-sectional study. *J Pharm Practice*. 2012; 25(3):368-73.
- McEvoy JP, Meyer JM, Goff DC. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res*. 2005; 80:19-32.
- Park HS, Oh SW, Cho SI, Choi WH, Kim YS. The metabolic syndrome and associated lifestyle factors among South Korean adults. *Int J Epidemiol*. 2004; 33:328-36.
- Straker D, Correll CU, Kramer-Ginsberg E. Cost-effective screening for the metabolic syndrome in patients treated with second-generation antipsychotic medications. *Am J Psychiatry*. 2005; 162:1217-21.
- Gianfrancesco FD, Grogg AL, Mabmoud RA. Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan data base. *J Clin Psychiatry*. 2002; 63:920-30.
- Smith M, Hopkins D, Peveler RC. First vs. second generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry*. 2008; 192(6):406-11.
- Atmaca M, Kuloglu M, Tezcan E, Ustundag B. Serum leptin and triglyceride levels in patients on treatment with atypical antipsychotics. *J Clin Psychiatry*. 2003; 64:598-604.
- Ascher-Svanum H, Stensland M, Zhongyun ZZ, Kinon BJ. Acute weight gain, gender, and therapeutic response to antipsychotics in the treatment of patients with schizophrenia. *BMC Psychiatry*. 2005; 5:3-18.
- Akanji AO, Ohaeri JU, Al-Shammri S, Fatania HR. Association of blood levels of C-reactive protein with clinical phenotypes in Arab schizophrenic patients. *Psychiatry Research*. 2009; 169:56-61.

Дугорочно лечење оланзапином у болничким условима: преваленција и предиктори метаболичког синдрома

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КРАТАК САДРЖАЈ

Увод Ризик од метаболичких поремећаја знатно је већи код особа оболелих од шизофренија који се лече нетипичним антипсихотикима. Код ових болесника генерално је већа стопа смртности у односу на општу популацију, што укључује и повећану смртност од кардиоваскуларних обољења. Други фактори који доприносе развоју метаболичког синдрома (МетС) су: трајање болести, старост, женски пол и лоше животне навике.

Циљ рада Ова студија је урађена ради утврђивања преваленције МетС код шизофреничних болесника који дуго бораве у болници и лече се оланзапином дуже од шест месеци (монотерапија), као и факторе – предикторе који су у позитивној корелацији са постојањем МетС према критеријумима Међународне федерације за дијабетес (IDF).

Методе рада Укупно 93 испитаника (71 мушкарац и 22 жене) оболела од шизофреније, који су дуже време били хоспитализовани у Специјалној болници за психијатријске болести „Горња Топоница“ код Ниша и који су били на монотерапији оланзапином најмање шест месеци без престанка, подвргнуто је основном прегледу који је укључивао: про-

цену према психијатријским скалама, антропометријска мерења, социодемографску анкету и лабораторијске анализе.

Резултати Преваленција МетС на посматраном узорку испитаника, мерено критеријумима IDF, била је 34,4%. Фактори ризика који су се у нашем истраживању мултиваријантном анализом издвојили као значајни предиктори МетС су (по реду значајности): позитивна анамнеза о дијабетесу тип 2 у ужој породици ($p=0,002$), индекс телесне масе већи од 25 kg/m^2 ($p=0,002$), позитивна анамнеза о хиперлипидемији у ужој породици ($p=0,008$) и повишени нивои С-реактивног протеина ($p=0,042$).

Закључак Преваленција МетС у нашем истраживању значајно превазилази преваленцију овог поремећаја у општој популацији. Међу посматраним варијаблама ова студија издваја неколико предиктора „високог ризика“ удружених с постојањем МетС код болесника на дугорочном лечењу оланзапином. Код постојања генетског оптерећења за дијабетес мелитус тип 2, односно хиперлипидемију, боље је одлучити се за други антипсихотик безбеднијег метаболичког профила.

Кључне речи: метаболички синдром; шизофренија; оланзапин

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Prevalence of Internet Addiction among Schoolchildren in Novi Sad

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SUMMARY

Introduction Internet use has increased rapidly all over the world. Excessive Internet use tends to lead to the creation of a non-chemical addiction, most commonly known as "Internet addiction."

Objective The aim of this study was an assessment of the prevalence of Internet use and Internet addiction among school children aged 14–18 years in the Municipality of Novi Sad, Serbia, and influence of sociodemographic variables on Internet use.

Methods A cross-sectional study was conducted in Novi Sad among final-year students from elementary and first- and second-year students from high schools. The prevalence of Internet addiction was assessed by using Young's Diagnostic Questionnaire.

Results Out of 553 participants, 62.7% were females, and the average age was 15.6 years. The sample consisted of 153 elementary school students and 400 high school students. Majority of respondents had a computer in their household. Our study showed widespread Internet use among adolescents. Facebook and YouTube were among most visited web-sites. The main purpose of Internet use was entertainment. Estimated prevalence of Internet addiction was high (18.7%), mostly among younger adolescents ($p=0.013$).

Conclusion Internet addiction was found in every fifth adolescent. Accessibility and availability of Internet use is constantly growing and therefore it is necessary to define more sensitive diagnostic tools for the assessment of Internet addiction and its underlying causes, in order to implement effective preventive programs.

Keywords: Internet addiction; schoolchildren; prevalence

INTRODUCTION

Internet use has increased rapidly and it is estimated that the number of global Internet users has reached 2.3 billion in 2011 [1]. According to the Internet World Stats in March 2014, 40.7% of global population used the Internet [2]. The first assessment of Internet use in Serbia was conducted in 1999, when it was reported that 10% of households possessed a personal computer, while 5% had Internet connection [3]. Thirteen years later an increase in Internet use in Serbia was observed, and computer possession was found in 55.2% of households, while Internet connection was available in 47.5% of the households [4].

Excessive Internet use tends to lead to the creation of a non-chemical addiction, most commonly known as "Internet addiction." This phenomenon is also referred to as "excessive Internet use," "problematic Internet use," "Internet dependency" or "pathological Internet use" (PIU) [5], and it is obvious that there is no consistency in usage of terms and definitions. According to Young [6], Internet addiction is "maladaptive pattern of Internet use leading to clinically significant impairment or distress." Although there is no generally accepted definition of Internet addiction, an addictive behavior can be recognized because it leads to behavioral changes, sleep disorders, social isolation, and decrease of work performance, impaired self-esteem and family problems [7].

Adolescents are a population at risk for developing Internet addiction because of the fact that their cognitive control and boundary setting skills are low, while the peer influence is high [8]. This population group faces many challenges and pressures due to growing expectations of society on the one hand, and great emotional changes associated with maturation on the other. This is the period of life when habits are being developed and they usually define future lifestyle of an individual [9].

Tsitsika et al. [10] reviewed literature on the topic and presented various prevalence rates of Internet addiction among adolescents, with the restriction that the studies were conducted in a different period. They also discussed whether the underlying cause of variability in the observed prevalence rates of Internet addiction among adolescents might be partly attributed to inconsistency in defining Internet addiction, as well as the fact that its assessment tools have not been uniquely established. They found prevalence ranged between 1.0% and 18.3% in European countries, and between 13.7% and 18.4% in Asian countries.

OBJECTIVE

The objective of this study was assessment of the prevalence of Internet use and Internet addiction among schoolchildren aged between 14

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and 18 years in the Municipality of Novi Sad, Serbia, as well as assessment of influence of sociodemographic variables on Internet use.

METHODS

Study design and participants

A cross-sectional study was conducted in the Municipality of Novi Sad, with 341,625 inhabitants, according to 2011 Census of Population, Households and Dwellings in the Republic of Serbia [11]. There are 37 elementary schools and 16 high schools in the municipality, with about 26,000 and 18,000 students, respectively.

A stratified cluster random sampling was applied to choose participants. Students attend elementary schools according to their home address, so the sample of elementary schools was designed proportionally to overall number of children aged 7–15 years in urban, peri-urban and rural area of the Municipality of Novi Sad. Applying that criterion, four schools in the urban area, two in peri-urban and one school in the rural area were selected randomly. The participants from chosen elementary schools were selected randomly.

The participants from high schools were selected according to the type of the high school, since majority of high schools are located in the urban area of the Municipality of Novi Sad. In Serbia, high schools are classified into the following types: vocational schools (that can have only four-year education sections or both three- and four-year sections) and gymnasiums (gymnasiums have better teaching resources, such as school facilities and equipment, than those present in vocational schools). Proportionally, from each type, high schools were selected randomly: three gymnasiums, four regular secondary vocational schools (four-year) and two vocational schools with both three- and four-year sections. From each school one class from the first and one class from the second year were randomly selected.

School approvals were obtained before participation in the study. Investigators visited schools, explained the purpose of the study to school principals and teachers and informed them of the objectives of the study, of the guarantee of confidentiality, and provided a contact telephone number of the prime investigator for any questions and concerns. All students in the selected classes were asked to participate in the study and anonymously fill out the self-administered questionnaire. The researchers explained the procedures and requirements. The questionnaires were collected immediately after they were completed. The entire procedure took 10–15 minutes to complete.

Instrument

The instrument was a questionnaire divided into the following four sections: a) sociodemographic data; b) data on Internet use; c) assessment of Internet addiction and d)

health education aspect and students' perception of having school class or discussion with parent about Internet use.

Internet addiction was assessed by using translated and culturally adapted Young's Diagnostic Questionnaire for Internet Addiction, which was adapted from DSM-IV criteria for pathological gambling. This questionnaire consists of eight dichotomous questions. One point was given to each "yes" answer, while "no" answer was given 0 points. Scores ranged 0–8, and the cut-off point was set up at 4/5 [6]. We applied original Young's criteria.

Data analysis

All statistical analyses were conducted using SPSS version 18.0. Descriptive analysis was used to describe the students' demographic characteristics, patterns of Internet use and the prevalence of Internet addiction. Chi-square, Mann–Whitney and Kruskal–Wallis tests were used to examine the differences with a statistical significance criterion of $p < 0.05$.

RESULTS

Socio demographic characteristics

A total of 600 questionnaires was distributed, but 553 of them were eligible to be included in the study (92.2%).

Of the 553 participants, 62.7% were females, and the average age was 15.6 years ($SD = 0.96$, $Min = 14$, $Max = 18$). The sample consisted of 153 elementary and 400 high school students. More than half of them (54.1%) had high academic achievement in the previous school year (Table 1).

Majority of respondents had computer in their household (97.7%), with no statistically significant differences between boys and girls, or in terms of either age or academic achievement in the previous school year. Internet use was common for majority of respondents (96.4%),

Table 1. Sociodemographic characteristics of the sample

Variables	Responses	N	%
Gender	Male	207	37.3
	Female	346	62.7
Age (years)	14	75	13.5
	15	157	28.5
	16	217	36.2
	17	98	17.7
	18	6	1.1
School	Elementary	153	27.5
	Secondary three-year	53	9.5
	Secondary four-year	175	31.8
	Gymnasium	172	31.3
Average grade in the previous school year	Middle low	15	2.7
	Middle	74	13.4
	Middle high	151	27.3
	High	299	54.1
	No answers	14	2.5

N – number of subjects

mostly among students with better academic achievement ($p=0.000$). The other socio-economic variables didn't have statistically significant impact on distribution of Internet use. More than 80% of respondents used Internet outside their households, more often elementary school students ($p=0.018$). Every fifth respondent used Internet less than an hour per day; there were no differences among gender, but significantly more time on the Internet was spent by elementary school students ($p=0.006$), students with poorer academic achievement ($p=0.013$) and younger respondents ($p=0.044$) (Table 2).

The most commonly visited web-sites were Facebook (75.9%) and YouTube (17.6%). Girls more frequently visited Facebook, while boys preferred YouTube and online games ($p=0.000$). Other sociodemographic variables didn't have significant impact (Table 2).

The most common purpose of Internet use was entertainment (59.9%) – secondary school students used Internet for entertainment more often ($p=0.016$), every fourth respondent used it because of a need, for every tenth it was a way of acquiring knowledge and 6.6% of the respondents used the Internet for communicative reasons. Academic achievement also had significant impact on perception of Internet use – students with better academic achievement used Internet for entertainment more than other students, students with middle level of academic achievement because of a need and students with poorer academic achievement perceived Internet use as a way for communication ($p=0.030$) (Table 2).

Analyzing all items in Diagnostic Questionnaire we saw that more than 28% of respondents felt preoccupied with the Internet, significantly more often students with poorer

academic achievement ($p<0.000$); more than three fourths of respondents replied that they feel the need to use the Internet with increasing amount of time in order to achieve satisfaction, significantly more often boys ($p=0.028$); almost every fourth adolescent had repeatedly made unsuccessful efforts to control, cut back or stop Internet use; every tenth respondent reported to feel restless, moody, depressed or irritable when attempting to cut down or stop Internet use; almost 68% of them stayed online longer than originally intended; more than two fifths of students considered they jeopardized or risked the loss of a significant relationship or educational opportunity because of the Internet; more than one fourth confirmed that they lied to family members or others to conceal the extent of involvement with the Internet; 26.1% of the adolescents used the Internet as a way of escaping from problems or of relieving a dysphoric mood (Table 3).

Using Young's criteria for addiction, 18.7% of students had score 5 or more. There were no statistically significant differences between boys and girls, schools, or students with different academic achievement. However, it was observed that Internet dependence was more frequent among younger age group (14–15 years) compared to their older peers ($p=0.013$) (Table 4). The mean score of Internet addiction was 3.03 ($SD=1.75$, $Min=1$, $Max=8$).

The final questionnaire section included two items regarding the students' perception of health education lessons about Internet use. One fifth of the students (19.5%) stated they had school lessons about safe Internet use, significantly more so students aged 14–15 years ($p<0.000$), elementary school students ($p<0.000$), and lower graded students ($p=0.017$), while gender didn't have a significant

Table 2. Internet use in adolescents

Parameter		Total (%)	Gender		Age		School		Average grade in the previous school year			
			Boys	Girls	14–15	16–18	Elementary	Secondary	Middle low	Middle	Middle high	High
Having a computer in the household		97.7	98.0	97.7	97.8	97.5	98.0	97.7	93.3	95.9	98.0	98.3
p			0.276		0.067		0.855		0.402			
Internet users		96.4	96.1	96.5	97.9	95.3	98.0	95.7	93.3	86.5	96.0	99.3
p			0.796		0.115		0.201		0.000			
Use of Internet outside home		80.8	81.5	80.2	83.0	79.1	87.2	78.1	100.0	86.3	77.3	79.5
p			0.724		0.243		0.018		0.057			
Time spent on the Internet daily	<1 hour	20.9	16.9	23.3	16.0	24.5	13.7	23.9	26.7	14.5	17.8	23.5
	1–2 hours	41.2	39.5	41.9	42.2	40.6	39.0	41.8	26.7	33.3	41.8	44.7
	>2 hours	37.9	43.6	34.8	41.8	34.8	47.3	34.3	46.7	52.2	40.4	31.7
	p		0.079		0.044		0.006		0.013			
Most frequently visited web-sites	Facebook	75.9	64.0		74.4		73.6	76.7	73.3	72.6	79.2	75.3
	YouTube	17.6	23.6		19.4		20.3	16.5	6.7	19.2	14.8	19.0
	Online games	2.4	5.9		2.6		2.7	2.3	0.0	1.4	2.0	2.4
	Other	4.1	6.4		3.5		3.4	4.6	0.0	6.8	4.0	3.4
	p		0.000		0.746		0.691		0.275			
Purpose of Internet use	Entertainment	59.9	53.7		53.7		49.3		53.3	48.6	54.3	67.0
	Need	23.0	27.8		26.2		31.1		20.0	29.2	31.3	16.5
	Communication	6.6	6.8		7.9		8.1		13.3	6.9	7.9	5.4
	Acquiring knowledge	10.6	11.7		12.2		11.5		13.3	15.3	6.6	11.1
	p		0.114		0.107		0.016		0.030			

Table 3. Young's Diagnostic Questionnaire items by sociodemographic variables*

	Total (%)	Gender		Age		School		Average grade in the previous school year			
		Boys	Girls	14–15	16–18	Elementary	Secondary	Middle low	Middle	Middle high	High
Do you feel preoccupied with the Internet (think about previous online activity or anticipate next online session)?	28.2	28.4	27.8	29.4	30.8	28.3	27.5	45.5	44.3	33.3	19.0
p		0.879		0.159		0.862		0.000			
Do you feel the need to use the Internet with increasing amount of time in order to achieve satisfaction?	77.4	83.0	73.8	80.9	74.6	80.5	75.5	81.8	78.6	80.5	75.1
p		0.028		0.126		0.283		0.689			
Have you repeatedly made unsuccessful efforts to control, cut back or stop Internet use?	24.1	20.9	25.5	33.3	17.5	34.1	20.2	16.7	33.3	25.0	22.3
p		0.254		0.000		0.001		0.292			
Do you feel restless, moody, depressed, or irritable when attempting to cut down or stop Internet use?	10.1	8.2	11.2	12.4	8.1	12.8	9.1	7.1	23.8	10.5	6.3
p		0.295		0.115		0.230		0.000			
Do you stay online longer than originally intended?	67.9	62.2	71.0	70.5	66.1	68.0	67.8	86.7	66.7	66.4	69.0
p		0.055		0.310		0.975		0.444			
Have you jeopardized or risked the loss of significant relationship, job, educational or career opportunity because of the Internet?	41.2	45.1	39.1	48.6	35.6	50.0	38.1	40.0	53.3	48.3	34.0
p		0.217		0.006		0.024		0.010			
Have you lied to family members, therapist or others to conceal the extent of involvement with the Internet?	27.8	28.1	27.7	35.1	22.5	35.6	24.9	13.3	28.4	32.0	27.4
p		0.933		0.001		0.014		0.427			
Do you use the Internet as a way of escaping from problems or of relieving a dysphoric mood (e.g. feelings of helplessness, guilt, anxiety or depression)?	26.1	20.9	28.9	30.3	23.3	32.0	23.8	30.0	33.3	30.5	21.9
p		0.056		0.083		0.069		0.136			

* Percentages of positive answers are listed

Table 4. Internet addiction by sociodemographic variables

Variable	Gender		Age		School		Average grade in previous school year			
	Boys	Girls	14–15	16–18	Elementary	Secondary	Middle low	Middle		High
%	15.1	20.6	23.7	14.7	24.0	16.6	6.7	27.7	20.8	15.8
p	0.141		0.013		0.067		0.085			

impact. Almost half of the respondents (47.2%) discussed Internet use with their parents.

DISCUSSION

Internet users are defined as people with access to the worldwide network. New technology innovations, mass production and availability of personal computers resulted in global expansion of Internet use in the last decade. Over the years, the Internet has become more accessible

in homes, schools, libraries and Internet cafes, mostly due to increasing affordability of home computers and high-speed connections. With easy access to various information, the Internet provides tremendous educational, entertainment and interpersonal communication benefits [12]. Our results indicate that the vast majority of respondents (97.7%) had computer in their households and also use the Internet. This proportion is higher than reported in other studies conducted three to five years earlier; thus, 85.1% of adolescents aged 15–16 in Iași County, Romania, had a computer at home, and 94.8% used the Internet [13].

Among junior high school students in Taiwan, 86% of boys and 82% of girls self-reported to have a computer at home [14].

According to the World Bank estimates, the number of Internet users in Serbia is on the increase in recent years. In 2009 Internet use rate was 38.1%, while in 2012 the rate was 48.1%. This trend seems to comply with global trends in Internet use [15]. There is lack of evidence about prevalence of Internet use among Serbian adolescents, but our findings suggest higher prevalence among adolescents compared to general population, which is similar to a limited case study of Internet addiction in the City of Niš among student population aged 19–23 who had the prevalence of Internet use of 100% [16]. Guan and Subrahmanyam [5] referred to the 2008 World Internet Project, a survey of 13 countries, which showed that the prevalence of Internet use among adolescents aged 12–14 was 88% in the United States, 100% in the United Kingdom, 98% in Israel, 95% in Canada and over 70% in Singapore. Among seventh- and tenth-graders from suburban California public schools, occasional or regular Internet use was reported by 91% of the students [17]. Some studies showed significant gender differences in Internet use in favor of boys [5], while our study showed that academic achievement was positively related to Internet use ($p < 0.000$). It was also observed that older students saw Internet use as an entertainment, in contrast to their younger peers, who perceived it as a need. Differences were also found regarding the academic achievement – students with higher grades perceived Internet use as entertainment, while for students with lower grades it was a communication tool.

Excessive Internet use can cause negative outcomes such as poor school performance, social isolation, and might interfere with psychosocial development of adolescents. It has been observed that Internet use becomes pathological when it interferes with one or more major areas of life, such as creation of significant relationships, occupation, school or health [18]. Though our study design does not allow for making case-effect inferences, the results are similar to the situation in Singapore, where significantly more adolescents who used the Internet excessively felt that grades and schoolwork almost always suffered because of being online [12].

In our study students most frequently visited Facebook (75.9%), which complies with the study findings among Irish teenagers aged 11–16, where 72% frequently use social networks, mainly Facebook [19]. Regarding gender patterns, we found that girls visited Facebook significantly more frequently than boys, and boys were more involved in online games and YouTube. Gross [17] showed similar gender patterns in Internet use, where boys spent more time playing video games, and girls were more likely to spend time online in social interactions. Similar patterns can be found in some other studies [14, 20].

We found that the main purpose of Internet use was entertainment (59.9%). Among 1,380 high school students in the city of Isparta, Turkey, the main purposes of Internet use were communication (39.2%) and obtaining information (29.7%) [21].

Population-based studies showed that prevalence of Internet use varies and that it is lower in adult population than in adolescents. The large study in all 50 states of the USA showed that 68.9% of telephone interviewed adults were regular Internet users, and 13.7% showed some features of problematic Internet use [22]. Norwegian study on 3,399 adults showed prevalence of Internet use to be 87%, Internet addiction 1% and “at risk” Internet use 5.2% (according to Young’s Diagnostic Questionnaire criteria) [23].

Since adolescents are more likely to adopt new technologies and are more susceptible to development of addictive behavior, prevalence rates among adolescents were more in focus of researchers. Chang and Hung [24] reviewed epidemiological data from several studies and presented that problematic Internet use can be found in 1–18% of adolescents in both Western and Eastern societies. Our findings showed that 18.7% of adolescents were Internet addicted according to Young’s criteria. The same approach was used in several other studies. Thus, prevalence of Internet addiction was assessed to be 6.7% among Hong Kong adolescents aged 15–19, while a randomized controlled trial evaluating interventions for risk behaviors among adolescents in Austria, Estonia, France, Germany, Hungary, Ireland, Israel, Italy, Romania, Slovenia and Spain demonstrated that prevalence of pathological Internet use was 4.4% [25, 26].

Cao and Su [27] used the same diagnostic tool, but modified by Beard and Wolf [28] and, according to this rigid modification, found the prevalence of Internet addiction among high school students in Changcha City in China to be 2.4%. Zhang et al. [29] showed 9.5% of adolescents aged 12–17 in four Chinese provinces to be pathological Internet users, by using Adolescent Pathological Internet Use Scale (APIUS), 38-item simplified Chinese scale for measuring PIU.

The proportion of Internet addiction in our study was significantly more frequent among younger age groups, with no influence of gender, type of school or academic achievement. Fu et al. [25] also did not find gender differences among the addicted to the Internet, in contrast to Al-hantoushi and Al-abdullateef [18], who revealed that among secondary school students with Internet addiction in Riyadh City, Saudi Arabia, boys and those with lower degree of school performance were significantly more represented [18]. In an Adolescent Health Unit in Athens, Greece, a correlation between Internet addiction and poor academic performance was also demonstrated [10]. Cao and Su [27] revealed male-to-female ratio of 4.8:1 among those with Internet addiction.

According to the published data, there have not been large population studies about prevalence of PIU in Serbia, but Hinić [30] performed clinical study among 50 subjects who asked for professional help due to the symptoms of the excessive Internet use. Hinić used diagnostic criteria for Internet behavior disorder proposed by the American Psychology Association as inclusion criteria. His results have shown that the population with Internet addiction symptoms equally included males and females, mostly adolescents, younger population and university students.

CONCLUSION

Our study showed that almost all adolescents use the Internet, which is more frequent among students with better academic achievement. On the other hand, elementary school students and students with poorer academic achievement spent greater amount of time daily on the Internet. Most frequently visited web site is Facebook, and the dominant purpose of Internet use was entertainment. Prevalence of

Internet addiction was high (18.7%), mostly among younger students. The results of this study posed a recommendation for more specific research and inclusion of more sensitive diagnostic tools on a larger population sample, as well as inclusion of wider scale of sociodemographic variables. Furthermore, some additional factors should be explored, such as the impact on personal development, family relations and functioning, socialization, academic achievement and other aspects of the quality of life.

REFERENCES

1. ICT Facts and Figures, the World in 2013. www.itu.int [homepage on the Internet]. Geneva: International Telecommunication Union [cited 2014 December 29]. Available from: <http://www.itu.int/en/ITU-D/Statistics/Documents/facts/ICTFactsFigures2013-e.pdf>.
2. www.internetworldstats.com [homepage on the Internet]. Bogota: Internet World Stats [cited 2015 January 3]. Available from: <http://www.internetworldstats.com/stats.htm>.
3. Mandić S. Kompiuterizacija i istoriografija 1995-2005. Beograd: Istorijski arhiv Beograda; 2008.
4. Information Technologies, Chapter 17. www.stat.gov.rs [homepage on the internet]. Statistical Yearbook of the Republic of Serbia 2013 Information technologies. Statistical Office of the Republic of Serbia [cited on 2014 December 30]. Available from: http://webzrzs.stat.gov.rs/WebSite/repository/documents/00/01/17/66/17_Informacione_tehnologije.pdf.
5. Guan SS, Subrahmanyam K. Youth Internet use: risk and opportunities. *Curr Opin Psychiatry*. 2009; 22(4):351-6. [DOI: 10.1097/YCO.0b013e32832bd7e0] [PMID:19387347]
6. Lee S. Problematic Internet Use among College Students: An Exploratory Survey Research Study [dissertation]. Austin (TX): The University of Texas; 2009.
7. Van Rooij AJ, Prause N. A critical review of "Internet addiction" criteria with suggestions for the future. *J Behav Addict*. 2014; 3(4):203-13. [DOI: 10.1556/JBA.3.2014.4.1] [PMID: 25592305]
8. Kuss DJ, van Rooij AJ, Shorter GW, Griffiths MD, van de Mheen D. Internet addiction in adolescents: prevalence and risk factors. *Computers in Human Behavior*. 2013; 29(5):1987-96. [DOI: 10.1016/j.chb.2013.04.002]
9. Currie C et al., editors. Social Determinants of Health and Well-being among Young People. Health Behavior in School-aged Children (HBSC) Study: International Report from the 2009/2010 Survey. Copenhagen: WHO Regional Office for Europe; 2012.
10. Tsitsika A, Critselis E, Louizou A, Janikian M, Freskou A, Marangou E, et al. Determinants of Internet addiction among adolescents: a case-control study. *ScientificWorldJournal*. 2011; 11:866-74. [DOI: 10.1100/tsw.2011.85] [PMID: 21516283]
11. Census of Population, Households and Dwellings in the Republic of Serbia (2011). Population. Age and Sex. Data by Settlements. www.stat.gov.rs [homepage on the internet]. Belgrade: Statistical Office of the Republic of Serbia [cited on 2014 December 30]. Available from: <http://pod2.stat.gov.rs/ObjavljenjePublikacije/Popis2011/Starost%20i%20pol-Age%20and%20sex.pdf>.
12. Mythily S, Qiu S, Winslow M. Prevalence and correlates of excessive Internet use among youth in Singapore. *Ann Acad Med Singapore*. 2008; 37(1):9-14. [PMID: 18265891]
13. Makarie GF, Stefanescu C, Tebeanu AV, Chele GE. Characteristics of computer and Internet use among adolescents in Iasi County. *Procedia – Social and Behavioral Sciences*. 2012; 3:835-9. [DOI: 10.1016/j.sbspro.2012.01.239]
14. Tsai MJ, Tsai CC. Junior high school students' Internet usage and self-efficacy: a re-examination of the gender gap. *Computers & Education*. 2010; 54:1182-92. [DOI: 10.1016/j.compedu.2009.11.004]
15. Internet Users (per 100 people). www.worldbank.org [homepage on the internet]. International Telecommunication Union, World Telecommunication/ICT Development Report and database, and World Bank estimates. Catalog Sources World Development Indicators [cited on 2014 December 21]. Available from: <http://data.worldbank.org/indicator/IT.NET.USER.P2>.
16. Živković S, Stojković N. Cyberspace – addiction or not: a limited case study of the Internet addiction among student population. *AJIS*. 2013; 2(11):150-9. [DOI: 10.5901/ajis.2013.v2n11p150]
17. Gross EF. Adolescent Internet use: What we expect, what teens report. *J Appl Dev Psychol*. 2004; 25:633-49. [DOI: 10.1016/j.appdev.2004.09.005]
18. Al-hantoushi MN, Al-abdullateef SH. Internet addiction among secondary school students in Riyadh city, its prevalence, correlates and relation to depression: a questionnaire survey. A questionnaire survey. *Int J Med Sci Public Health*. 2014; 3(1):10-5. [DOI: 10.5455/ijmsph.2013.130920131]
19. Machold C, Judge G, Mavrinac A, Elliott J, Murphy AM, Roche E. Social networking patterns/hazards among teenagers. *Ir Med J*. 2012; 105(5):151-2. [PMID: 22803496]
20. Holstein B, Pedersen TP, Bendtsen P, Madsen KR, Meilstrup CR, Nielsen L, et al. Perceived problems with computer gaming and internet use among adolescents: measurement tool for non-clinical survey studies. *BMC Public Health*. 2014; 14:361. [DOI: 10.1186/1471-2458-14-361] [PMID: 24731270]
21. Gencer SL, Koc M. Internet abuse among teenagers and its relations to internet usage patterns and demographics. *Educational Technology & Society*. 2012; 15(2):25-36.
22. Aboujaoude E. Problematic Internet use: an overview. *World Psychiatry*. 2010; 9:85-90. [DOI: 10.1002/j.2051-5545.2010.tb00278.x] [PMID: 20671890]
23. Bakken IJ, Wenzel HG, Götestam KG, Johansson A, Oren A. Internet addiction among Norwegian adults: a stratified probability sample study. *Scand J Psychol*. 2009; 50:121-7. [DOI: 10.1111/j.1467-9450.2008.00685.x] [PMID: 18826420]
24. Chang JP-C, Hung C-C. Problematic Internet Use. In: Rey JM, editor. IACAPAP e-Textbook of Child and Adolescent Mental Health. Geneva: International Association for Child and Adolescent Psychiatry and Allied Professions; 2012.
25. Fu KW, Chan WSC, Wong PWC, Yip PSF. Internet addiction: prevalence, discriminant validity and correlates among adolescents in Hong Kong. *Br J Psychiatry*. 2010; 196:486-92. [DOI: 10.1192/bjp.bp.109.075002] [PMID:20513862]
26. Durkee T, Kaess M, Carli V, Parzer P, Wasserman C, Floderus B, et al. Prevalence of pathological internet use among adolescents in Europe: demographic and social factors. *Addiction*. 2012; 107(12):2210-22. [DOI: 10.1111/j.1360-0443.2012.03946.x] [PMID:22621402]
27. Cao F, Su L. Internet addiction among Chinese adolescents: prevalence and psychological features. *Child Care Health Dev*. 2006; 33(3):275-81. [DOI: 10.1111/j.1365-2214.2006.00715.x] [PMID: 17439441]
28. Beard KW, Wolf EM. Modification in the proposed diagnostic criteria for Internet addiction. *Cyberpsychol Behav*. 2001; 4(3):377-83. [PMID: 11710263]
29. Zhang Y, Yang Z, Duan W, Tang X, Gan F, Wang F, et al. A preliminary investigation on the relationship between virtues and pathological internet use among Chinese adolescents. *Child Adolesc Psychiatry Ment Health*. 2014; 8(1):8. [DOI: 10.1186/1753-2000-8-8] [PMID: 24594317]
30. Hinić D. Korisnički profili internet zavisnika u Srbiji. *Psihologija*. 2008; 41(4):435-53. [DOI: 10.2298/PSI0804435H]

Преваленција зависности од интернета међу децом школског узраста у Новом Саду

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КРАТАК САДРЖАЈ

Увод Употреба интернета се незаустављиво повећава свуда у свету. Његова прекомерна употреба може довести до нехемијске зависности познате као „зависност од интернета“.

Циљ рада Циљ овог истраживања био је да се утврди преваленција употребе интернета и зависности од интернета међу ученицима узраста 14–18 година који живе на територији града Новог Сада, као и утицај социодемографских варијабли на коришћење интернета.

Методе рада Изведена је студија пресека у Новом Саду међу ученицима завршних разреда основних школа и ученицима прва два разреда средњих школа. Зависност је процењивана на основу дијагностичких критеријума по Јанговој (Young).

Резултати Од укупно 553 испитаника, 62,7% је било женског пола, а просечан узраст испитаника био је 15,6 година. У узорку је било 153 ученика основних школа и 400 учени-

ка средњих школа. Већина испитаника имала је рачунар у свом домаћинству. Испитаници су најчешће посећивали веб-сајтове *Facebook* и *Youtube*, а основни и најчешћи разлог коришћења интернета била је разонода. Истраживање је показало широку употребу интернета међу адолесцентима, с високом преваленцијом зависности од интернета (18,7%) статистички значајно чешће међу млађим ученицима ($p=0,013$).

Закључак Код сваког петог адолесцента утврђена је зависност од интернета. Доступност и приступачност коришћења интернета је у непрестаном порасту, те постоји потреба за креирањем осетљивијих инструмената за процену зависности од интернета, као и за утврђивањем узрока настанка те зависности, како би се могли применити одговарајући превентивно-промотивни програми.

Кључне речи: зависност од интернета; деца школског узраста; преваленција

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The First Telephone Line for the Psychological Support to Oncological Patients and Their Family Members in Serbia

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SUMMARY

Introduction In October of 2010, Serbian Association for Psycho-Oncology, in collaboration with the Ministry of Health of Serbia and the National Health Insurance has launched the first national telephone line for free psychological counseling and support for oncology patients and their families.

Objective The aim of this study was to present results of the first national telephone helpline for psychological support for oncological patients and their families.

Methods The telephone line for the psychological help and support was available from 10 a.m. to 10 p.m., seven days a week and on holidays. A total of 12 previously educated psychologists were involved, with two on duty in the mornings and two in the afternoons. The basic work principles of the Line were anonymity for users (if they wished), free of charge service available to patients from all of Serbia, careful listening, emphatic reflection on anything communicated by users and adequate counselling.

Results Since the beginning of the project (October 2010 up to April 2011) we received a total of 2,748 calls from across Serbia. Almost half of these calls were repeated calls, as patients asked for continuous psychological counselling. Larger percent (63.9%) of women called, when compared to men (35.4%) who used the Line. Most (52.4%) conversations were categorized as "psychological support and counseling," and as continual psychological counseling work (21.1%).

Conclusion The large number of calls suggests that this kind of public, free service for psychosocial and psychological support to cancer patients is necessary in Serbia.

Keywords: psychosocial support; psychosocial aspects; oncology

INTRODUCTION

Since the cancer experience is a negative life event that requires an enormous amount of effort from patients and their families in order to adapt to the multiple challenges posed by the disease, it is important to understand the psychosocial aspects of cancer and its treatment, and the needs of patients and their families to successfully deal with such a challenge [1]. The holistic approach to cancer treatment includes the participation of psychologists during all phases of the disease [2].

Although the psychosocial dimensions of cancer have been explored in the literature since 1958, it is only over the past 50 years that this area has developed into a specific discipline, known as psycho-oncology [3]. This small but emerging field of care deals with the psychological aspects of care, the training of staff in these areas, and provides expertise in psychological, social, and behavioral quality of life [4]. Psycho-oncology has two dimensions: the first one is the study of the psychological reaction of patients at all stages of the disease, as well as that of family members and oncology staff, and the second one is exploring the psychological, social, and behavioral factors that impact cancer risk and survival [5].

However, psychosocial care and support for patients and their families is not yet standard

care in many cancer treatment centers in the developed world, and is even less available in the developing countries, including Serbia. The fact is that in Serbia psycho-oncology has not been developed to the necessary extent, primarily as a scientific discipline, and therefore there is no systematic, organized, professional and easily "available" psychological support and psychotherapy to help patients who suffer from various forms of malignant disease in all stages of treatment, as well as their family members.

As the very first step in providing the patients and their family members the psychological support, we organized the first national SOS phone line in October of 2010. In this report, we present the first results of this project.

OBJECTIVE

The overall objective of launching an SOS phone line was providing professional psychological support and assistance to cancer patients in all stages of the disease and treatment, as well as to their family members.

Launching the first national psycho-social program of providing organized and professional psychological support and assistance to patients suffering from various malignant diseases through helpline represents the pro-

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motion and provision of a specialized services for cancer patients, as the phone calls are free and available to patients from all over Serbia [6].

Specific objectives of the psychological helpline for oncology patients were as follows:

- Organizing easily accessible, highly professional and specialized psychological support and help for people suffering from malignant diseases, as well as for their families;
- Launching of the first line of psychological support for cancer patients and their families also represents the first psychological helpline in oncology and humane approach in dealing with the psychological, social, spiritual and practical problems of cancer patients, in the manner it has been organized in the developed countries of Europe and the world for decades;
- Launching the first helpline for psychological support is a way of overcoming the problem related to the fact that in Serbia there are few employed psychology experts in everyday oncology practice [6].

METHODS

The SOS phone line for psychological support of cancer patients and their families was based on several basic principles: it was free, anonymous and easily accessible. The broader public was informed of the existence of the phone line through press conferences, guest appearances on popular shows on national television, guest appearances on specialised shows, TV advertisements, articles in daily newspapers and weekly magazines. As promotion material, posters, flyers and brochures were printed and delivered to the general public [6, 7, 8].

The telephone line for the psychological help and support was available from 10 a.m. to 10 p.m., seven days a week and on holidays. Two counseling psychologists were appointed in the morning and two in the afternoon. They were specifically educated on various aspects of malignant diseases, including medical, psychological, social and spiritual consequences of the disease, and also trained on communication skills related to careful listening, emphatic reflection on anything communicated by users, and counselling callers according to their needs. At group meetings held once a week, we provided supervision and discussed what happened during the week (who called, why they called, which problems were the most complex ones and how we could solve them).

According to the Ministry of Health, there are about 50 oncology departments in Serbia, both in large oncology centers and in general hospitals. Only a few, mostly pediatric oncology departments, hire psychologists (majority of them), while departments for adult oncology patients employ neither psychologists nor psychiatrists. In the two comprehensive oncology centers (Institute for Oncology and Radiology of Serbia, Belgrade, and Institute for Oncology of Vojvodina, Sremska Kamenica) there are two psychologists for all the patients, while in other centers consultations with psychiatrists and psychologists are per-

formed only for the most urgent cases, or “when patients make a problem,” which means that the psychosocial support is not easily accessible, and is not a part of the daily oncology practice, as the world and European standards require.

Call logs and data processing

For purposes of the Line, a database was created with a record of each call, as well as the information on the number of calls, first or repeated call, who was making a call (patient, family member, friend, colleague, medical staff), sociodemographic data (gender, age, diagnosis, stage of treatment, place, i.e. area of residence), the description of the problem for which the patient called, check types of psychological, social, spiritual and existential problems as reasons of calling, the types of psychological interventions provided.

Statistical analysis

The data were statistically analyzed using nonparametric statistical procedures (frequencies, percentages).

RESULTS

Out of total number of calls ($n=2,748$), about two thirds were female users and one third were male.

The average age of Line users was 55 (the youngest one was a six-year-old child, and the oldest one was an 88-year-old patient). Most calls were made by persons from Belgrade (63.9%); all other regions were represented in a much lesser extent. Analysis of calls per region demonstrated that there were significantly more calls from some regions (63.9% from Belgrade, 17.8% from Southern Serbia and 11.7% from Central Serbia) than from others (6.2% from Eastern and 7% from Western Serbia), while the least number of calls came from the Republic of Srpska and Kosovo and Metohija (0.1% each).

Significant percentage of callers (28.8%) did not give the information regarding the tumor site, while breast cancer patients (19.7%) and patients with urological malignancies (16.3%) were significantly represented. Majority of callers were oncological patients (66.4%) (1,826 calls in total), followed by their spouses as the so-called “first-line support” (7.7%), and their children (7.3%) (Table 1).

There were also calls we categorized as non-oncological patients (6.1%) (drug addiction, alcohol abuse, suicidal persons, persons with different serious somatic diseases such as hepatitis, AIDS, multiple sclerosis, psychiatric patients, disabled persons, as well as calls regarding family violence and various individual and multiple family psychological problems).

Most (52.4%) conversations were categorized as “psychological support and counseling,” and as continual psychological counseling work (21.1%). Needs for medical in-

Table 1. Demographic and clinical characteristics of Line users (N=2,748)

Characteristics		N (%)
Patient's age (years)	Mean (SD)	55.64 (12.39)*
	Median (range)	58 (6-88)*
Gender of the caller	Female	1755 (63.9)
	Male	993 (36.1)
Geographic area	Belgrade	692 (63.9)
	Republic of Srpska	3 (0.1)
	Central Serbia	321 (11.7)
	Eastern Serbia	171 (6.2)
	Southern Serbia	489 (17.8)
	Western Serbia	192 (7.0)
	Kosovo and Metohija	3 (0.1)
	Vojvodina	538 (19.6)
	Unknown	339 (12.3)
Tumor site	Breast	541 (19.7)
	Gynecological	194 (7.1)
	Lung	152 (5.5)
	ORL	82 (3.0)
	Genitourinary male	453 (16.5)
	Skin and soft tissue	28 (1.0)
	Melanoma	36 (1.3)
	Thyroid	48 (1.7)
	Digestive tract	167 (6.1)
	Maxillofacial	24 (0.9)
	CNS	36 (1.3)
	Hematological	187 (6.8)
	Bone	8 (0.3)
	Unknown	792 (28.8)
Relationship with the patient	Patient/himself/herself	1826 (66.4)
	Partner	212 (7.7)
	Daughter	140 (5.1)
	Son	60 (2.2)
	Brother	11 (0.4)
	Sister	55 (2.0)
	Colleague	1 (0)
	Neighbor	4 (0.1)
	Doctor	2 (0.1)
	Nurse	1 (0)
	Non-oncological patients	168 (6.1)
	Friend	45 (1.6)
	Cousin	78 (2.8)
	Parents	70 (2.5)
	Other	2 (0.1)
	Unknown	71 (2.6)

* Data are presented as mean value with standard deviation, and median with range.

formation and advice was required by 12.9% of the callers (information regarding the diet while on chemotherapy, information on the skin care following a combined oncological treatment, information on public health services that treat cancer pain, information on blood test results and other diagnostic procedures, information on where mammography can be done, etc.) (Table 2).

Line users mostly called due to the following psychological problems: feeling sad, desperate, helpless, hopeless, feelings of meaninglessness; depressive reaction and demoralization about the positive outcome of the disease;

Table 2. Psychological needs and type of intervention (N=2,748)

Characteristics		N (%)
Repeated call	Yes	1137 (41.4)
	No	1611 (58.6)
	Total	2748 (100.0)
Type of conversation	Psychological counseling	1440 (52.4)
	Medical information	354 (12.9)
	Consultation	18 (0.7)
	Continuous psychological counseling	581 (21.1)
	Provocative indecent calls	35 (1.3)
	Complaint	29 (1.1)
	Recommendation	18 (0.7)
	Rehabilitative and educational	221 (8.0)
	Unknown	52 (1.9)

suicidal thoughts; fears (of being ruined, of pain, disease deterioration, loneliness and being left to themselves); anxiety (feeling worried, uneasy, tense, nervous); mood swings and irritability; family problems (lack of understanding, conflicts, poor communication and relations); feeling rejected in the social and work environment; and the need to be better informed, both quantitatively and qualitatively, on the disease, treatment, adverse side effects of a combined oncological treatment, disease prognosis and treatment outcome.

DISCUSSION

Since an impressive number of calls was noted (2,748 calls over a six-month period), it is obvious that a public, free service for psychology support to cancer patients is needed in Serbia, a country in which psycho-oncology is an underdeveloped area, compared with more developed countries [6, 7]. The largest number of calls was from Belgrade, indicating that the majority of patients from the capital have the availability of information and the awareness of the need for psychological support in situations of crisis and stress, which is the case with the treatment of malignant diseases [8].

The highest percentage of calls was made by patients with breast cancer (19.7%) and patients with urological (16.5%) and digestive system (6.1%) malignancies. We believe that this is the result of the National Campaign against Cancer, which had been conducted in previous years, primarily dedicated to the fight against breast and colon cancer. National Campaign conducted by the Ministry of Health, together with non-governmental associations of patients with breast and colon cancer, resulted in a raised level of awareness of patients in general, as well as in the reduction of stigma and shame to seek psychosocial support.

The majority of callers were cancer patients in various stages of the disease indicating that they find this easily accessible and free service to be needed and useful. Numerous calls by the patients' family members (spouses, children, siblings) indicates that they also suffer due to their family member's illness, since in Serbia there still exists a tradition of family care for the sick member. The

family offers special care in terminal stages of the disease when the patient is literally left to the next of kin, as appropriate units or departments for comprehensive palliative care are not yet sufficiently developed according to existing needs in Serbia.

Unfortunately, further operation of phone lines dedicated to psychological support to cancer patients and their families was not supported by the relevant authorities, who lack any good will to find an acceptable way to continue the work of the first useful service of this kind designed for cancer patients in Serbia.

CONCLUSION

Recognizing the physical, psychological, social, spiritual and existential needs of cancer patients and their families is an important step in the implementation of various psychosocial services for oncology patients during all phases of treatment.

Sensitivity to a variety of psychological problems, which, from the moment of diagnosis of a malignant disease, and then during all phases of an uncertain, long-term oncologic treatment cancer patients and their family members are facing, is a prerequisite to any kind of psychosocial interventions implemented in oncology practice. Without this prerequisite, the basic postulates (bio-psycho-social model, holistic approach and empathic attitude toward the most difficult patients) are neglected, thus undermining the basis of modern oncological approach. The overall

objective of launching free of charge SOS telephone line was providing professional psychological support and assistance to cancer patients in all stages of the disease and treatment, as well as to their family members, keeping in mind several important facts: firstly, a malignant disease has a specific "background" and brings with it special psychological weight; secondly, a malignant disease of a family member is a powerful source of stress and crisis for the entire family; and thirdly, in Serbia, cancer patients from all over the country and in all cancer centers usually do not have the opportunity to receive face-to-face professional counseling and support if they need it during different phases of oncology treatment. Providing psychological support by telephone is a useful and necessary free of charge service for cancer patients and their families in Serbia.

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NOTE

The preliminary findings of this paper were presented at the 13th World Congress of Psycho-Oncology, Antalya, Turkey, in 2011 (references 6 and 8).

REFERENCES

1. Young P. Caring for the whole patient: the Institute of Medicine proposes a new standard of care. *Commun Oncol*. 2007; 4:748-51.
2. Adler N, Page A, editors. *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs*. Washington, DC: Institute of Medicine, The National Academies; 2007.
3. Holland JC. History of psycho-oncology: overcoming attitudinal and conceptual barriers. *Psychosom Med*. 2002; 64:206-21. [PMID: 11914437]
4. Holland JC, editor. *Psycho-oncology*. New York: Oxford University Press; 1998.
5. Holland JC. American Cancer Society Award lecture. Psychological care of patients: psycho-oncology's contribution. *J Clin Oncol*. 2003; 21(23 Suppl):253s-265s. [PMID: 14645405]
6. Klikovac T. National telephone for the psychological support to oncological patients and their family members. *Journal of the Psychological, Social and Behavioral Dimensions of Cancer*. 2011; 20:209. [DOI: 10.1002/pon.2078]
7. Arnabold P, Lupo F, Santor L, Rubio L, Tenore A, Solinas I, et al. A psychosocial cancer phone center staffed by professional psychologists as an integral part of the standard process of care: It's utility during the course of illness. *Palliat Support Care*. 2010; 8:305-12. [DOI: 10.1017/S1478951510000106] [PMID: 20875174]
8. Klikovac T, Stavrić I, Blagojević S. Media promotion of the project: National Telephone for the Psychological Support to Oncological Patients and their Family Members. *Journal of the Psychological, Social and Behavioral Dimensions of Cancer*. 2011; 20:210. [DOI: 10.1002/pon.2078]

Прва телефонска линија за пружање психолошке подршке онколошким болесницима и њиховим породицама у Србији

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КРАТАК САДРЖАЈ

Увод У октобру 2010. године Српска асоцијација за психоонкологију, у сарадњи са Министарством здравља Републике Србије и Републичким заводом за здравствено осигурање, покренула је први Национални телефон за бесплатну психолошку помоћ и подршку онколошким болесницима и њиховим породицама.

Циљ рада Циљ овог рада био је да се прикажу резултати рада првог националног телефона за психолошку подршку особама с онколошким обољењима и члановима њихових породица.

Методе рада Телефон за пружање психолошке помоћи и подршке био је доступан свих седам дана у недељи и празницима од 10 сати ујутру до 10 сати увече. Било је едуковано 12 психолога, по два саветника-психолога била су ангажована пре подне и после подне. Једном недељно смо на групним састанцима размењивали информације о свему што се током недеље дешавало (ко се јавља, зашто се јавља, који су проблеми најсложенији и како их превазићи). Основ-

ни принципи рада Линије су: анонимност за кориснике (ако то желе), бесплатна услуга, доступност корисницима из целе Србије, пажљиво слушање, емпатично рефлектовање свих садржаја које корисници износе и адекватно саветовање.

Резултати Од почетка до краја пројекта (октобар 2010 – април 2011) било је укупно 2.748 позива из целе Србије. Више од половине позива били су поновљени позиви, јер су пацијенти имали потребу за континуираним психолошким саветовањем. Већином су се јављале жене (63,9%) у поређењу с мушкарцима (35,4%) који су користили Линију. Већина разговора је категорисана као „психолошка подршка и саветовање“ (52,4%) и као континуиран психолошки саветодавни рад (21,1%).

Закључак Велики број позива указује на то да је овакав начин јавног, бесплатног сервиса потребан за пружање психосоцијалне помоћи и психолошке подршке онколошким болесницима.

Кључне речи: психосоцијална подршка; психосоцијални аспекти; онкологија

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Giant Vertebrobasilar Fusiform Aneurysm as a Cerebellopontine Angle Mass

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SUMMARY

Introduction According to the literature, a fusiform aneurysm located in the cerebellopontine angle (CPA) is an extremely rare condition.

Case Outline We report a case of a 59-year-old patient with initial dizziness and left-sided sensorineural hearing loss that had gradually developed over six months. Vertebrobasilar fusiform aneurysm, with intraluminal thrombus, which was displaced to the right cerebellopontine angle, creating mass effect, was diagnosed using brain magnetic resonance imaging and magnetic resonance angiography.

Conclusion Atherosclerosis may be the essential factor in the pathogenesis of a fusiform aneurysm of the basilar artery, especially in elderly patients. The best treatment option is yet to be determined, but in spite of numerous previous large studies, personalized approach is probably the best.

Keywords: fusiform vertebrobasilar aneurysm; basilar artery; cerebellopontine angle

INTRODUCTION

The predominant lesions in cerebellopontine angle (CPA) are different benign tumors, and schwannoma are the commonest [1, 2]. Vascular lesions are not so frequent, and vertebrobasilar fusiform aneurysm, with estimated incidence of 0.06–5.8%, are rarely located in the CPA [3]. Unruptured intracranial aneurysms usually present with symptoms of raised intracranial pressure, such as headaches, nausea, vomiting and blurring of vision, or with cranial nerve deficits, embolic ischemia and mass effects. Otological symptoms are extremely rare and include pulsatile tinnitus, vertigo, and progressive and sudden sensorineural hearing loss [4]. Treatment of fusiform aneurysms is divided into conservative and surgical approach. We report a case of a patient with unruptured giant vertebrobasilar fusiform right-sided aneurysm with intraluminal thrombus, diagnosed using brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), which raises several questions related to the pathogenesis of recurrent ischemic events and medical management. Written informed consent was obtained from the patient who participated in this case.

CASE REPORT

The patient was a 59-year-old man with past medical history of treated hypertension. He was suffering from chronic headache and occasional dizziness. Two months before hospital admission, the patient had right side facial hypoesthesia and difficulties with eating.

On admission, the patient's blood pressure was 130/70 mmHg with a sinus heart rhythm. Neurological tests revealed evidence of left-sided nystagmus, truncal ataxia, vertigo, dysarthria and dysphagia. He also presented right-sided facial hypoesthesia, absent right corneal reflex, loss of taste sensation and hearing loss in the left ear. Caloric testing with ice water revealed a normal response in the right ear, but no response in the left one. Cerebellar tests were positive and there was right deviation of uvula.

Brain MRI (1.5 TE Siemens, Avanto, Erlingen, Germany) confirmed the presence of an elongated, tubular, tortuous, hyperdense, fusiform, extra-axial, 35 mm long mass lesion, which compressed the porus of the left internal auditory canal and extended into the CPA causing compression of the left cerebellar hemisphere, rotation of the brainstem to the right and minimal compression of the fourth ventricle (Figures 1 and 2). MRA (1.5 TE Siemens, Avanto, Erlingen, Germany) showed an ectatic basilar artery markedly displaced to the left (Figures 3 and 4), which coincided with the lesion in the left CPA. The patient was diagnosed with having a fusiform vertebrobasilar aneurysm with thrombus formation. There was a double lumen and recent hemosiderin deposition. We decided to treat the patient with anticoagulation therapy.

DISCUSSION

Interest in studying fusiform aneurysms has increased recently because little is known about their pathogenesis and the best way of their management. The fusiform type is the rarest

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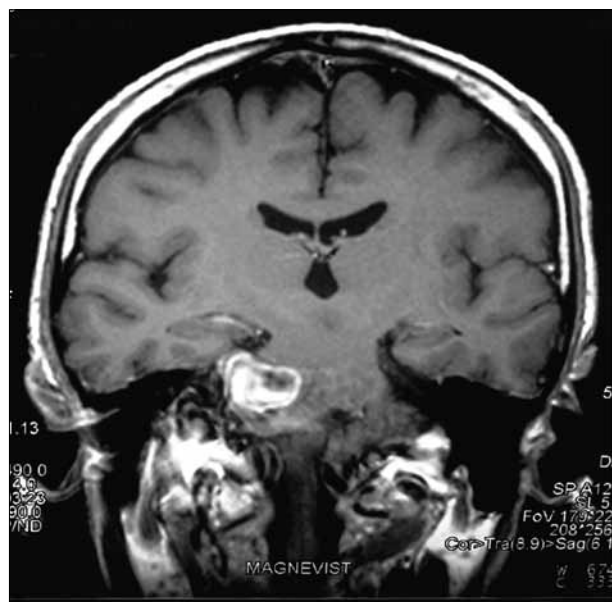


Figure 1. Coronal brain MRI showing a giant hyperdense tubular extra-axial lesion in the right CPA with significant compression

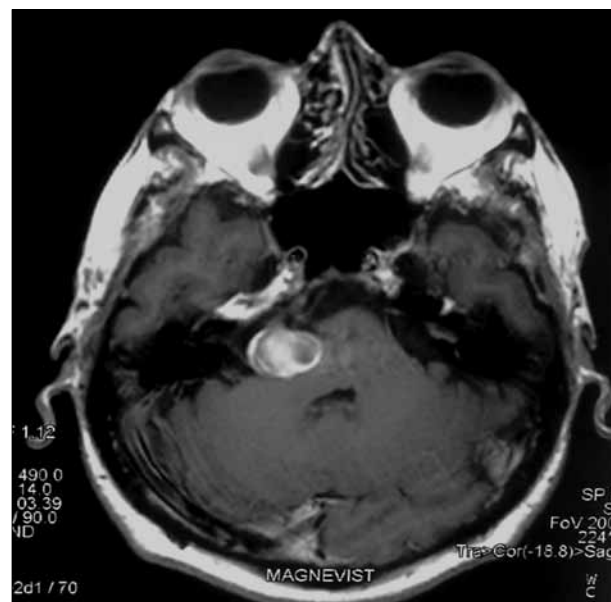


Figure 2. Axial MR images with gadolinium show a partial thrombosed fusiform aneurysm of the basilar artery and a double lumen of the fusiform basilar dissection. The external wall of thrombosed aneurysm is with recent hemosiderin deposition.

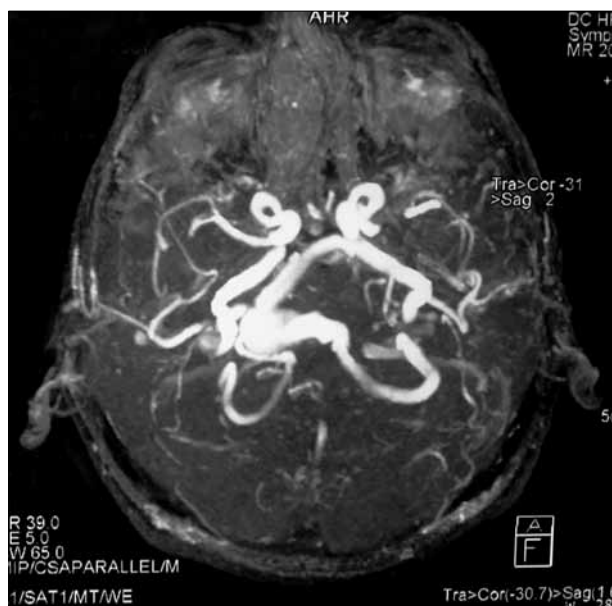


Figure 3. MRA showing an ectatic basilar artery markedly displaced to the right



Figure 4. Digital subtraction angiography image

form of vertebrobasilar aneurysm, characterized by dilatation and elongation of an artery [5]. The origin of fusiform aneurysms is unclear and several hypotheses exist. They are most common in elderly patients with advanced atherosclerosis and hypertension, and are believed to be the result of a degenerative process of the arterial wall [6]. Contrary, other authors stated that out of 120 patients with giant fusiform aneurysms, who underwent surgical treatment, atherosclerosis was found in only six of them. A congenital anomaly, mechanical injury by post-stenotic turbulence, intimal disruption from arterial dissection and severe reticular fiber deficiency in the muscle layer have been proposed as alternative explanations for the formation of fusiform aneurysms [7]. It was speculated that initial event in the formation of

a fusiform aneurysm is lipid deposition in and beneath the intima that disrupts the internal elastic lamina and infiltrates the muscular wall. The resultant atrophy of the elastic substance and the musculature then leads to tortuosity of the vessel due to high intravascular pressure causing the ectatic vessel to expand in diameter and length. Our patient was a 59-year-old man with past medical history of treated hypertension. He had no history of mechanical trauma or congenital coronary illness in his family.

The natural tendency for a fusiform aneurysm is to slow down the circulation, because of this increased luminal diameter, and to expand and produce mass effects on nearby structures. Repeated thrombosis near the wall also makes the vessel stiff and thick. The expanding fusiform aneurysm

can distort vascular branches, reducing distal flow, or can even serve as a nidus for clot formation and distant embolization. This clinical evolution was also seen in our patient.

Otological symptoms are rarely seen but our patient initially had a unilateral hearing loss, as well as a characteristic form of nystagmus called Bruns nystagmus, caused by lateral brainstem compression. Right-sided hypoesthesia could be explained by the aneurysm's compressive effect, which displaced the brainstem contralaterally. This characteristic form of nystagmus is a combination of low-frequency, horizontal nystagmus on looking ipsilaterally and high-frequency, small amplitude on looking contralaterally, but it is observed in patients with large tumors located in the CPA [8].

Two types of fusiform cerebral aneurysms are reported: acute type, presented as subarachnoidal hemorrhage or stroke, and chronic type that rarely bleeds [9]. Basilar aneurysms can be graded according to their diameter into small (<12 mm), large (12–25 mm) and giant (>25 mm). Considering that our patient had a long history of treated hypertension, headaches, and dizziness, we presume that he had a small intracranial aneurysm with slow progression to a giant aneurysm of 35 mm. According to the literature, this is also one of the biggest fusiform aneurysms in this region.

Treatment of fusiform aneurysms is divided into conservative and surgical approach, but there is no general agreement regarding the treatment, nor have consistently successful results been reported in the literature. Small advantage is given to conservative therapy, since surgery and endovascular embolization are very risky. Antithrombotic medication is as effective as anticoagulation in stroke prophylaxis in the setting of fusiform aneurysm. Median survival rate of patients with intracranial fusiform aneurysms who were treated conservatively was 7.8 years and death was most commonly caused by ischemia [10]. Considering the abovementioned data, we chose conservative therapy for our patient, with anticoagulants and a policy of vigilant follow-up.

We emphasize the need to think of a giant fusiform aneurysm as differential diagnosis when mass in the CPA is presented, diagnosed using brain MRI and MRA. We speculate that a fusiform aneurysm was the final outcome of dynamic pathological process of the arterial wall. Hypertension and atherosclerosis may be the essential factors in the pathogenesis of a fusiform aneurysm of the basilar artery, especially in elderly patients. More prospective, randomized studies are needed to find the best treatment for this pathological vascular change.

REFERENCES

- Boeri R, Passerini A. The megadolichobasilar anomaly. *J Neurol Sci.* 1964; 1:476-84.
- Buttner U, Ott M, Helmchen C, Yousry T. Bilateral loss of eight nerve function as the only clinical sign of vertebrobasilar dolichoectasia. *J Vest Res.* 1955; 5:47-51.
- Chihara Y, Iwasaki S, Ushio M, Sugawara K, Murofushi T. Fusiform aneurysm of the basilar artery presenting as a cerebellopontine angle mass. *Eur Arch Otorhinolaryngol.* 2009; 266:151-2.
- Kalavagunta S, Karkanevatos A, Swift AC. Giant vertebra-basilar aneurysm: an unusual cerebello-pontine angle lesion. *J Laryngol Otol.* 2006; 120:e8.
- Cappellari M, Tomelleri G, Piovan E, Bovi P, Moretto G, Gulli G. Chronic fusiform aneurysm evolving into giant aneurysm in basilar artery. *Neurol Sci.* 2012; 33:111-5.
- Martinez Velilla N, Idoate Saralegui F, Gomez Herrero H, Alonso Renedo J, Casas Herrero A, Iraizoz Apeztequia I. Gait impairment and dysphagia due to a giant basilar aneurysm in a nonagenarian. *Rev Esp Geriatr Gerontol.* 2009; 44:159-61.
- Drake CG, Peerless SJ. Giant fusiform intracranial aneurysms: review of 120 patients treated surgically from 1965 to 1992. *J Neurosurg.* 1997; 87:141-62.
- Venkateswaran R, Gupta R, Swaminathan RP. Bruns nystagmus in cerebellopontine angle tumor. *JAMA Neurol.* 2013; 70:646-7.
- Sarica FB, Cekinmez M, Tufan K, Sen O, Erdogan B, Altinors MN. A non-bleeding complex intracerebral giant aneurysm case: case report. *Turk Neurosurg.* 2008; 18:236-40.
- Flemming KD, Wiebers DO, Brown RD Jr, Link MJ, Huston J 3rd, McClelland RL, et al. The natural history of radiographically defined vertebrobasilar nonsaccular intracranial aneurysms. *Cerebrovasc Dis.* 2005; 20:270-9.

Џиновска вертебробазиларна фузиформна анеуризма као маса у понтоцеребеларном углу

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КРАТАК САДРЖАЈ

Увод Према подацима из литературе, фузиформна анеуризма која се налази у понтоцеребеларном углу је изузетно ретко стање.

Приказ болесника Приказујемо 59-годишњег болесника с почетним вртоглавицама и губитком слуха на лево уво који су се постепено развили током шест месеци. Вертебробазиларна фузиформна анеуризма с интралуминалним тромбом, који је расељен у десни понтоцеребеларни угао, стварајући мас-ефекат, дијагностикован је применом магнетне

резонанције мозга и магнетнорезонантне ангиографије. Атеросклероза може бити суштински фактор у патогенези фузиформне анеуризме на базиларној артерији, посебно код болесника старијег животног доба.

Закључак Најбоља опција лечења тек треба да се утврди, али упркос бројним ранијим великим студијама, персонализовани приступ је вероватно најбољи.

Кључне речи: фузиформна вертебробазиларна анеуризма; базиларна артерија; понтоцеребеларни угао

Acute Myocardial Infarction during Induction Chemotherapy for Acute *MLL t(4;11)* Leukemia with Lineage Switch and Extreme Leukocytosis

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SUMMARY

Introduction In patients with acute leukemias hemorrhage is the most frequent problem. Vein thrombotic events may appear rarely but arterial thromboses are exceptionally rare. We present a patient with acute leukemia and bilateral deep leg vein thrombosis who developed an acute myocardial infarction (AMI) during induction chemotherapy. The etiology and treatment of AMI in patients with acute leukemia, which is a rare occurrence, is discussed.

Case Outline In April of 2012 a 37-year-old male presented with bilateral deep leg vein thrombosis and malaise. Laboratory data were as follows: Hb 118 g/L, WBC $354 \times 10^9/L$ (with 91% blasts in differential leukocyte count), platelets $60 \times 10^9/L$. Bone marrow aspirate and immunophenotype revealed the presence of acute lymphoblastic leukemia. Cytogenetic analysis was as follows: 46,XY,t(4;11)(q21;q23)[2]/62-82,XY,t(4;11)[18]. Molecular analysis showed *MLL-AF4* rearrangement. The patient was on low molecular weight heparin and combined chemotherapy according to protocol HyperCVAD. On day 10 after chemotherapy he got chest pain. Three days later AMI was diagnosed (creatinase 66 U/L, CK-MB 13 U/L, troponin 1.19 µg/L). Electrocardiogram showed the ST elevation in leads D1, D2, aVL, V5 and V6 and "micro q" in D1. On echocardiography, hypokinesia of the left ventricle and ejection fraction of 39% was found. After recovering from AMI and restoring left ventricle ejection fraction to 59%, second course of HyperCVAD was given. The control bone marrow aspirate showed 88% of blasts but with monoblastic appearance. Flow cytometry confirmed a lineage switch from lymphoblasts to monoblasts. In further course of the disease he was treated with a variety of chemotherapeutic combinations without achieving remission. Eventually, palliative chemotherapy was administered to reduce the bulk of blasts. He died five months after the initial diagnosis.

Conclusion AMI in young adults with acute leukemia is a very rare complication which may occur in patients with very high white blood cell count in addition with presence of a CD56 adhesion molecule and other concomitant thrombophilic factors. The treatment of AMI in patients with acute leukemias should include antiplatelet and anticoagulant therapy, even with more aggressive methods depending on patient's age and clinical risk assessment.

Keywords: acute myeloid leukemia; chest pain; myocardial infarction; chemotherapy; leukocytosis

INTRODUCTION

Although hemorrhagic diathesis usually accompany acute leukemias, thrombotic events may occur at diagnosis, or later during the course of the disease. Thromboses are described most frequently in connection with acute promyelocytic and acute lymphoblastic leukemia, in which treatment with all-trans-retinoic acid or L-asparaginase causes impairment of anticoagulant mechanisms producing prothrombotic state [1, 2]. But in other types of acute myeloid leukemias (AML) the thrombosis is not negligible, as it was found in 3.2% of patients at presentation [2].

Multiple prothrombotic factors have been identified including effects of antileukemic therapy [3], hyperleukocytosis [3, 4, 5], heritable thrombophilias [6], indwelling central vein catheters and an acquired hypercoagulable state as antiphospholipid syndrome, heparin-induced thrombocytopenia and disseminated intravascular coagulation (DIC) [7].

Arterial thromboses are extremely rare as most thrombotic events occur in veins. Acute myocardial infarctions (AMI) in younger patients with AML were rarely reported [3-7]. We present a patient with a rare acute leukemia associated with t(4;11)(q21;q23), switched immunophenotype from acute lymphoblastic to acute monoblastic lineage, in whom AMI developed during the course of induction chemotherapy. According to PubMed survey of the world literature, there are 11 reported cases, but, to the best of our knowledge, this is the first case of AMI associated with a lineage switch acute leukemia.

CASE REPORT

A 37-year-old male presented in April of 2012 with a history of four-week bilateral thrombosis of deep leg veins. He was put on low molecular weight heparin (LMWH) and cardiopirin. During regular checkups, leukocytosis was noticed

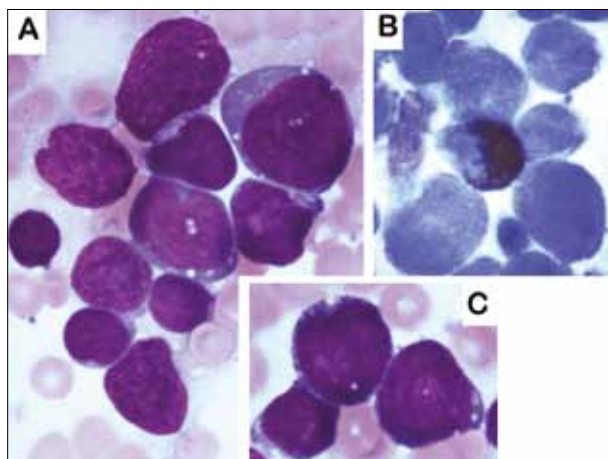


Figure 1. Bone marrow cytology at diagnosis. Leukemic cells are poly-morphous, with scarcely basophilic cytoplasm, without azurophilic granules. (A and C, MGG, 1000 $\times$). Myeloperoxidase staining is negative (B, POX, and 1000 $\times$).

and hospitalization was advised to him. His past medical history was unremarkable, without any cardiologic past history. He had smoked 20 cigarettes a day for eight years. On the day of admission, on April 30, 2012, physical examination revealed normal vital signs and petechiae. The liver and spleen were palpable at the costal ribs. Initial laboratory work-up was significant for a low platelet count of $60 \times 10^9/L$, hemoglobin 118 g/L, and white blood cell (WBC) count of $354 \times 10^9/L$ with blasts 94%. Blood biochemistry was within normal limits except for a lactic dehydrogenase level of 22,642 U/L. Hemostatic tests were as follows: fibrinogen 2.16 g/L, prothrombin time 52%, activated partial thromboplastin time (aPTT) 24.4s, D-dimer 35.2 $\mu g/L$, the International Society of Thrombosis and Haemostasis score for DIC was 5. Abdominal ultrasonography revealed enlarged both the liver (168 mm) and the spleen (138 mm). Conventional cytogenetic analysis showed 46,XY, t(4;11)(q21;q23) [2]/62-82,XY, t(4;11)[18]. A bone marrow aspirate was hypercellular with 91% of mononuclear blasts which were myeloperoxidase and periodic-acid-Schiff negative, consistent with acute lymphoblastic leukemia, L2 type according to the French-American-British classification (Figure 1) [8].

Immunophenotype of the mononuclear marrow cells disclosed a population of blasts HLA-DR, CD38, nTdT, CD19, CD22, cCD79a, cIgM, CD15+, which was in ac-

cordance with cytomorphologic type of leukemia. He was started with 6-mercaptopurine and prednisolone until the drop in WBCs to $60 \times 10^9/L$. On May 5, 2012, the protocol Hyper-CVAD (cyclophosphamide 600 mg in D1, D2 and D3, Dexasone 40 mg in D1–D14, Daunoblastin 40 mg in D4, Vcr 2 mg in D4 and D11, with G-CSF in D3–D21) was administered, with intrathecal prophylaxis. On the seventh day of the protocol WBCs dropped to $0.6 \times 10^9/L$ and the patient developed fever. Broad spectrum antibiotics (meronem, vancomycin, Diflucan, and G-CSF) were introduced. Ten days after the beginning of chemotherapy (May 15, 2012) the patient developed chest pain, became hypotensive, with systolic blood pressure of 85 mmHg. The ECG at that time was normal. Myocardial enzymes were not elevated (CK 26 U/L, CK-MB12 U/L, troponin 0.190 $\mu g/L$). Dopamine infusions and nitroglycerin tablets were administered. The next day the chest pain persisted, but during that day the enzymes and ECG, that were monitored, didn't show evolution to myocardial infarction. On the third day the patient was transferred to Emergency Unit as the chest pain did not stop. The ECG showed ST-elevation myocardial infarction in leads D1, D2, aVL, V5 and V6 with micro q in D1. At the same time cardiac biomarkers were tested and the results showed elevation (CK 66 U/L, CK-MB 13 U/L, troponin 1.19 $\mu g/L$). These findings corresponded to an anterolateral AMI (Figure 2) with a second-degree AV block. Echocardiography showed hypokinesia of the left ventricle, with the ejection fraction of 39%. In the cavity of the left ventricle there was an echo contrast showing presence of prethrombotic mass without clear signs of thrombus formation. The patient was treated with infusions of dopamine, oxygen, LMWH, carvedilol 12.5 mg ($2 \times \frac{1}{4}$ tab.), diuretics, G-CSF, antibiotics (vancomycin, tienam, acyclovir, ciprocalin). Cardiac catheterization and percutaneous coronary intervention was offered to the patient, however he refused, preferring conservative medical treatment as he knew the main diagnosis of acute leukemia. Antiplatelet therapy was contraindicated because of the increased risk of bleeding due to thrombocytopenia. Also ACE-inhibitors were not given as the patient was hypotensive because of weakened left ventricular ejection fraction. During the next ten days WBC count increased from $0.7 \times 10^9/L$ to $3.4 \times 10^9/L$, platelets increased from $19 \times 10^9/L$ to $78 \times 10^9/L$. The patient recovered after ten days, chest

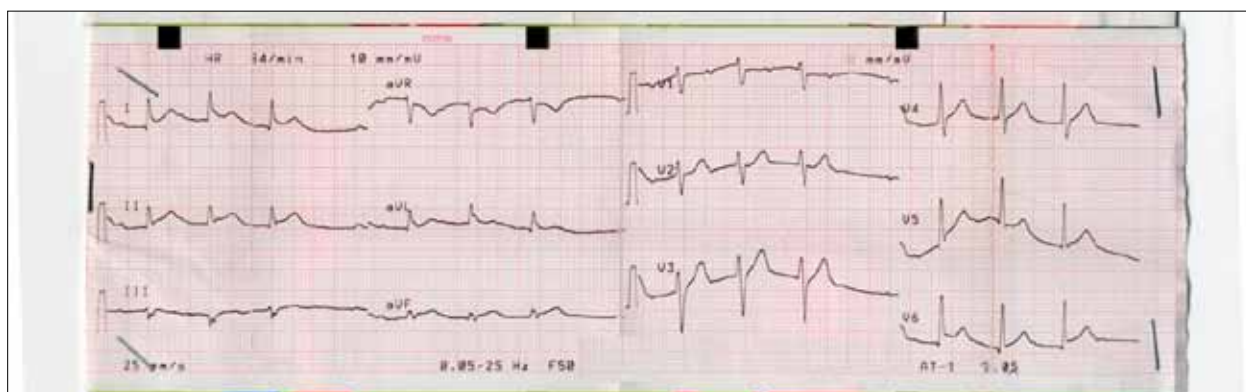


Figure 2. Electrocardiogram showing ST segment elevation in leads D1, D2, aVL, V5 and V6 with micro q in D1

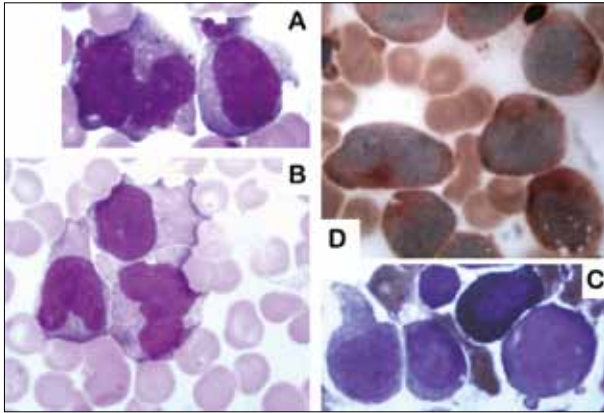


Figure 3. Bone marrow cytology at the time of immunophenotype switch. Leukemic cells are polymorphous, occasionally with lobulated or reniform nucleus, moderate to abundant cytoplasm, rare vacuoles and azurophilic granules (A and B, MGG, 1000 $\times$). Myeloperoxidase staining negative (C, POX, 1000 $\times$). ANAE staining positive in cytoplasm and Golgi region in blast and monocytoid cells (D, ANAE, and 1000 $\times$)

pain disappeared, dopamine infusions were discontinued, and ECG changes resolved to normal. After a complete cardiologic recovery (including echocardiography ejection fraction improvement to 59%), he was transferred again to Clinic of Hematology, where the bone marrow aspirate examination showed 60% of blasts. He received a second cycle of the same protocol Hyper-CVAD (methotrexate 2,000 mg on D1, Cytosar 2 $\times$ 6 g on D2 and D3). After the recovery, the bone marrow contained 88% of blasts with monoblastic morphology, myeloperoxidase and PAS negative (Figure 3). There was a switch in the immunophenotype pattern from lymphoblasts to monoblasts (HLA-DR, CD38, CD33, CD15, cCD68, cLysozyme^{high}, CD11b, CD11c, CD64, CD36, CD24, CD56)⁺. A minor population (0.1%) of (CD19+, CD79a+) cells were also found corresponding to leukemic B-cells, which predominated at the time of diagnosis. This evidence suggested the diagnosis of CD56+/AML with monocytoid differentiation. Cytogenetic analysis showed also the evolution of karyotype (46,XY,t(4;11)(q21;q23))[19]/47,XY,t(4;11)(q21;q23),+C[1]. The patient was treated with HiDAC+DA (ara-C 2 $\times$ 6 g in D1, D2 and D3 and Daunoblastin in D2, D4 and D6).

After this therapy his condition was complicated with severe aplasia and secondary bronchopneumonia, abscess of the spleen, pulmonary aspergillosis, but without any sign of cardiac dysfunction. The patient finally recovered and became afebrile, but with 17% residual blasts in the bone marrow. He was treated additionally with mitoxantrone and vepeside without achieving complete remission. Further on during its course, the disease was treated as a resistant one, with palliative chemotherapy (6-mercaptopurine) just to reduce the WBC count. He died five months after initial diagnosis without a recurrence of the cardiac disease.

DISCUSSION

AML is a hematopoietic stem cell disorder characterized by somatically acquired genetic changes in progenitor cells

which alter the normal mechanism of proliferation and differentiation [9]. AML is classified according to WHO classification into several distinct entities depending on morphologic and molecular-genetic characteristics [10]. Acute leukemia with t(9;11)(p22;q23) may be found in 2% of adult patient population. These patients may present with DIC and extramedullary myeloid sarcomas within different tissues. A “lineage switch” phenomenon is occasionally observed within this high-risk group of patients when at the time of the initial diagnosis the disease meets the criteria for a lymphoid or myeloid leukemia with an opposite lineage at relapse [9, 11, 12]. When lineage switch is diagnosed, it may represent either the emergence of an independent ancestral leukemic clone or a relapse of the original clone with heterogeneity at the morphological level but usually more resistant to chemotherapy [9].

It is also well known that expression of CD56 molecules, which we observed in our patient's leukemic cell membrane, is an adverse prognostic factor with capability to adhere to cells in different tissues and as such might contribute to a local myeloid sarcomas' formation [13].

Our patient, without previous history of coronary disease, presented with extremely high WBC count and within 10 days of induction chemotherapy experienced an acute coronary STEMI event (ST segment elevation myocardial infarction), most probably caused by bulky tumor mass. We were not able to perform coronary angiography and find out the real cause of coronary artery occlusion, but our suspicion was a formation of leukemic thrombi as it is well-known that they represent a complication in patients with acute and chronic leukemias and high WBC count. Additional contributing thrombogenic factor was DIC and infection, and finally expression of adhesion CD56 molecules on leukemic cells, which modulates adhesion between leukemic cells and endothelium.

Reviewing the literature we found 11 relevant cases of AMI in patients with acute leukemias but with different etiopathogenetic mechanisms leading to coronary arterial occlusion [3-7, 14-19], including leukostasis syndrome, leukemic thrombus formation [3, 4, 5], less deformable blast cells contributing to atherothrombosis [14, 16], effects of antileukemic chemotherapy, DIC [4, 6, 7, 18], leukemic myocardial infiltration, preponderance of leukemic cells to adherence due to having CD56 molecule on cell surface, thrombocytopenia, and a possible hemorrhage into the myocardial wall or intima of coronary arteries [7, 13] and deficiency of some coagulation and antithrombotic factors [6, 7]. Even in AML with normal WBC count STEMI may occur, but mechanisms of thrombotic vascular occlusion in such patients include alterations in microcirculatory rheology, increased adhesiveness of leukemic cells which are less deformable than corresponding mature cells, and increased procoagulant activity induced by cytokines [13].

It has also been found that coronary arteries vasospasms, which may be provoked by cytokines released from activated platelets, inflammatory cells or leukemic cells, play a significant role in occlusive coronary artery thrombosis [14]. Some chemotherapeutic agents have prothrombotic tendency such as L-asparaginase which induc-

es hypercoagulability and AMI which has been reported in patient with acute lymphoblastic leukemia, although in this report the authors suspect that contributing factor was administration of prednisone, vincristine and anthracyclines, which caused activation of coagulation and direct endothelial vascular damage [18]. Platelet-fibrin thrombus formation is possible in spite of thrombocytopenia [14, 18]. In circumstances of coronary arteries occlusion antithrombotic therapy should be carefully considered. Thrombolytic therapy was tried once, however the patient died due to fatal hemorrhage and such treatment is not recommended any more [17]. Usually dual antiplatelet therapy and anticoagulation should be administered as coronary arteries thrombi consist of platelets and fibrin. Administration of these drugs can prevent further clot progression [14]. However, concomitant AML and AMI are accompanied by thrombocytopenia and an increased risk of bleeding, so there is considerable danger of cardiac interventions, especially in circumstances of dual antiplatelet and anticoagulation therapy. This procedure could be recommended according to European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization only

in patients in whom there is a chance of favorable outcome of antileukemic treatment and after rigorous preparations for the procedure [20]. The prognosis of AMI and AML is especially poor in the elderly, much more so than if either of the conditions appeared separately.

This report represents the first case of acute leukemia with hyperleukocytosis and the "lineage switch" phenomenon, from the acute lymphoblastic to acute monoblastic leukemia and STEMI. The case shows that a leukostatic coronary occlusion can occur in acute leukemia with extreme hyperleukocytosis, accompanied with DIC, infection, in association with the presence of adhesion molecules on leukemic cells in a relatively young patient without the preexisting coronary artery disease.

The study was approved by the Institutional Ethical Board.

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REFERENCES

- Kwaan HC, Barnett MC, Cull HE. The coagulopathy in acute promyelocytic leukemia-What have we learned in the past twenty years. *Best Pract Res Clin Haematol*. 2014; 27:11-8. [DOI: 10.1016/j.bjha.2014.04.005] [PMID: 24907013]
- De Stefano V, Sorà F, Rossi E, Chiusolo P, Laurenti L, Fianchi L, et al. The risk of thrombosis in patients with acute leukemia: Occurrence of thrombosis at diagnosis and during treatment. *J Thromb Haemost*. 2005; 3:1985-92. [DOI: 10.1111/j.1538-7836.2005.01467.x] [PMID: 16102104]
- Kotla SK. Leukocytosis: a risk factor for myocardial infarction. *Res Rep Clin Cardiol*. 2012; 3:23-5. [DOI: 10.2147/RRCC.S30023]
- Cohen Y, Amir G, Da'as N, Gillis S, Rund D, Polliack A. Acute myocardial infarction as the presenting symptom of acute myeloblastic leukemia with extreme leukocytosis. *Am J Hematol*. 2002; 71(1):47-9. [DOI: 10.1002/ajh.10155] [PMID: 12221675]
- Muniz AE. Myocardial infarction and stroke as the presenting symptoms of acute myeloid leukemia. *J Emerg Med*. 2012; 42:651-4. [DOI: 10.1016/j.jemermed.2009.04.061] [PMID: 19500934]
- Chang H, Lin TL, Ho WJ, Hsu LA. Acute myeloid leukemia associated with acute myocardial infarction and dural sinus thrombosis: the possible role of leukemia-related hyperhomocysteinemia. *J Chin Med Assoc*. 2008; 71(8):416-20. [DOI: 10.1016/S1726-4901(08)70093-5] [PMID: 18772122]
- Pervez H, Potti A, Mehdi SA. Challenging and unusual cases: Case 1. Simultaneous presentation of acute myelogenous leukemia and acute myocardial infarction. *J Clin Oncol*. 2003; 21:1416-21. [DOI: 10.1200/JCO.2003.06.168] [PMID: 12663736]
- Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. *Br J Haematol*. 1976; 33(4):451-8. [DOI: 10.1111/j.1365-2141.1976.tb03563.x] [PMID: 188440]
- Schlenk RF. Post-remission therapy for acute myeloid leukemia. *Haematologica*. 2014; 99(11):1663-70. [DOI: 10.3324/haematol.2014.114611] [PMID: 25420282]
- Arber DA, Brunning RD, Le Beau, Falini B, Vardiman JW, Porwit A, et al. Acute myeloid leukemia with recurrent genetic abnormalities. In: Swerdlow SH, Campo E, Harris NL, et al., editors. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2008. p.110-29.
- Imataki O, Ohnishi H, Yamaoka G, Arai T, Kitanaka A, Kubota Y, et al. Lineage switch from precursor B cell acute lymphoblastic leukemia to acute monocytic leukemia at relapse. *Int J Clin Oncol*. 2010; 15(1):112-5. [DOI: 10.1007/s10147-009-0007-3] [PMID: 20066454]
- Dorantes-Acosta E, Pelayo R. Lineage switching in acute leukemias: a consequence of stem cell plasticity. *Bone Marrow Res*. 2012; 2012:406796. [DOI: 10.1155/2012/406796] [PMID: 22852088]
- Chang H, Brandwein J, Yi QL, Chun K, Patterson B, Brien B. Extramedullary infiltrates of AML are associated with CD56 expression, 11q23 abnormalities and inferior clinical outcome. *Leuk Res*. 2004; 28:1007-11. [DOI: 10.1016/S1726-4901(08)70093-5] [PMID: 15289011]
- Jao GT, Knovich MA, Savage RW, Sane DC. ST-elevation myocardial infarction and myelodysplastic syndrome with acute myeloid leukemia transformation. *Tex Heart Inst J*. 2014; 41(2):234-7. [DOI: 10.14503/THIJ-12-2905] [PMID: 24808792]
- Jachmann-Jahn U, Cornely OA, Laufs U, Hopp HW, Meuthen I, Krakai M, et al. Acute anterior myocardial infarction as the first manifestation of acute myeloid leukemia. *Ann Hematol*. 2001; 80(11):677-81. [DOI: 10.1007/s002770100353] [PMID: 11757728]
- Lisker SA, Finkelstein D, Brody JL, Beizer LH. Myocardial infarction in acute leukemia. Report of a case in a young man. *Arch Intern Med*. 1967; 119(5):532-5. [DOI: 10.1001/archinte.1967.00290230170010] [PMID: 5228977]
- Solomons HD, Stanley A, King PC, Plenaar N, Atkinson PM. Acute promyelocytic leukemia associated with acute myocardial infarction. A case report. *S Afr Med J*. 1986; 70(2):117-8. [PMID: 3460182]
- Yang W, Kovacic J, Cromwell C, Groskreutz C, Mascarenhas J. Myocardial infarction in a young man receiving chemotherapy for acute lymphoblastic leukemia. *Clin Adv Hematol Oncol*. 2013; 11:672-5. [PMID 24518380]
- Lou Y, Mai W, Jin J. Simultaneous presentation of acute myocardial infarction and acute promyelocytic leukemia. *Ann Hematol*. 2006; 85(6):409-10. [DOI: 10.1007/s00277-006-0106-4] [PMID: 16557379]
- Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular interventions (EAPCI). *Eur Heart J*. 2014; 35(37):2541-619. [DOI: 10.1093/eurheartj/ehu278] [PMID: 25173339]

Акутни инфаркт миокарда током индукционог лечења *MLL t(4;11)* леукемије са линијском променом и екстремном леукоцитозом

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КРАТАК САДРЖАЈ

Увод Код болесника с акутним леукемијама најчешћи проблем су крварења. Врло ретко могу се јавити венске, а изузетно ретко артеријске тромбозе. Приказујемо болесника с акутном леукемијом и тромбозом дубоких вена на обе ноге код којег се током индукционе хемиотерапије развио акутни инфаркт миокарда (АИМ). У раду су разматрани етиологија и лечење АИМ код болесника с акутном леукемијом.

Приказ болесника Приказан је 37-годишњи болесник који се разболео априла 2012. године са дубоком венском тромбозом на обе ноге. Лабораторијске анализе су показале следеће: хемоглобин 118 g/l, леукоцити $354 \times 10^9/l$ (са 91% бласта у диференцијалној леукоцитарној формули) и тромбоцити $60 \times 10^9/l$. Анализом ћелија аспирата костне сржи и проточном цитометријом постављена је дијагноза акутне лимфобластне леукемије. Цитогенетском анализом утврђен је кариотип 46,XY,t(4;11)(q21;q23)[2]/62-82,XY,t(4;11)[18], а молекуларна анализа је показала *MLL-AF4* реаранжман. Болесник је лечен нискомолекуларним хепарином и протоколом *HyperCVAD*. Десетог дана од почетка терапије јавио се бол у грудима, а трећег дана од појаве бола дијагностикован је АИМ с елевацијом ST-сегмента у одводима D1, D2, aVL, V5 и V6 и *micro q* у D1. На ехокардиографском налазу устано-

вљене су хипокинезија леве коморе и ејекциона фракција од 39%. Када се болесник потпуно опоравио, примењен је други циклус протокола *HyperCVAD*. Након аплазије костне сржи у контролном аспирату поново је нађено 88% бласта монобластног изгледа, што је потврђено и проточном цитометријом. Болесник је даље лечен разним комбинацијама хемотерапеутика којима се није могла постићи ремисија, те је на крају примењена палијативна терапија само ради смањења туморске масе. Пацијент је умро пет месеци након почетка болести.

Закључак АИМ код младих одраслих особа с акутном леукемијом је ретка компликација која се јавља код болесника с изразито високим бројем леукоцита уз присуство других тромбогених фактора, као што су експресија адхезионог молекула *CD56* на леукемијским ћелијама, дисеминована интраваскуларна коагулација, тромбоцитопенија и инфекција. Лечење АИМ се врши применом антиромбоцитне и анти-коагулантне терапије, инвазивним процедурама уз одговарајућу припрему, и то уколико је реч о млађем болеснику, у зависности од процене исхода лечења акутне леукемије.

Кључне речи: акутна мијелоидна леукемија; бол у грудима; инфаркт миокарда; хемиотерапија; леукоцитоза

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JAK2V617F Mutation in a Patient with B-cell Chronic Lymphocytic Leukemia and Prefibrotic Primary Myelofibrosis

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SUMMARY

Introduction Secondary malignancies, particularly solid tumors, are common in patients with chronic lymphocytic leukemia (CLL), but association of myeloproliferative neoplasms and chronic lymphocytic leukemia in the same patient is very rare.

Case Outline We report of a 67-year-old man with B-cell chronic lymphoid leukemia (B-CLL) who developed primary myelofibrosis (PMF) nine years after initial diagnosis. Patient received alkylation agents and purine analogue, which can be a predisposing factor for the development of myeloproliferative neoplasms. *JAK2V617F* mutation was not present initially at the time of CLL diagnosis, but was found after nine years when PMF occurred, which indicates that B-CLL and PMF represent two separate clonal origin neoplasms.

Conclusion Pathogenic mechanisms for the development of myeloproliferative and lymphoproliferative neoplasms in the same patient are unknown. Further research is needed to determine whether these malignancies originate from two different cell clones or arise from the same pluripotent hematopoietic stem cell.

Keywords: chronic lymphocytic leukemia; myelofibrosis; *JAK2V617F* mutation

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Europe. Patients with CLL are predisposed to develop a secondary malignancy due to impaired immune system or chemotherapy [1]. Secondary neoplasms, mainly solid tumors, are common in CLL, but coexistence of myeloproliferative neoplasms (MPN) and CLL is very rare. Janus kinase 2 (*JAK2*) is a cytoplasmic protein tyrosine kinase which plays an important role in cellular proliferation and survival. *JAK2V617F* mutation has been detected in patients with Philadelphia chromosome negative myeloproliferative neoplasms (Ph-MPN) [2]. Here, we present a patient who developed *JAK2V617F* mutation positive primary myelofibrosis (PMF) with excessive platelet count nine years after CLL.

BloodMini Kit (Qiagen, Hilden, Germany). The *JAK2V617F* mutation was detected using allele-specific polymerase chain reaction (PCR) described elsewhere [2].

Detection of *BCR-ABL* fusion transcript

Peripheral blood mononuclear cells were isolated on a Ficoll gradient according to the manufacturer's instructions. RNA extraction was performed using TRI Reagent solution (Ambion, Waltham, MA, USA) according to the manufacturer protocol. Complementary DNA (cDNA) was prepared from 1 µg of RNA using RevertAid Reverse Transcriptase (Thermo Scientific, Waltham, MA, USA) and random hexamer primers. RT PCR for *BCR-ABL* fusion transcript was performed using protocol described elsewhere [3].

Materials and methods

Detection of *JAK2V617F* mutation

Peripheral blood granulocytes were isolated on Ficoll gradient (Sigma-Aldrich, St. Louis, MO, USA) according to the manufacturer's instructions. Genomic DNA was extracted from granulocytes using the QIAampDNA

CASE REPORT

A 67-year-old male patient was admitted to the Department of Hematology (Clinical Hospital Center Dr. Dragiša Mišović, Belgrade) in April 2014 with severe headache and elevated platelet count ($1,323 \times 10^9$ platelets/L, reference range $150\text{--}400 \times 10^9$ platelets/L). Nine years previously he was diagnosed with B-cell chronic

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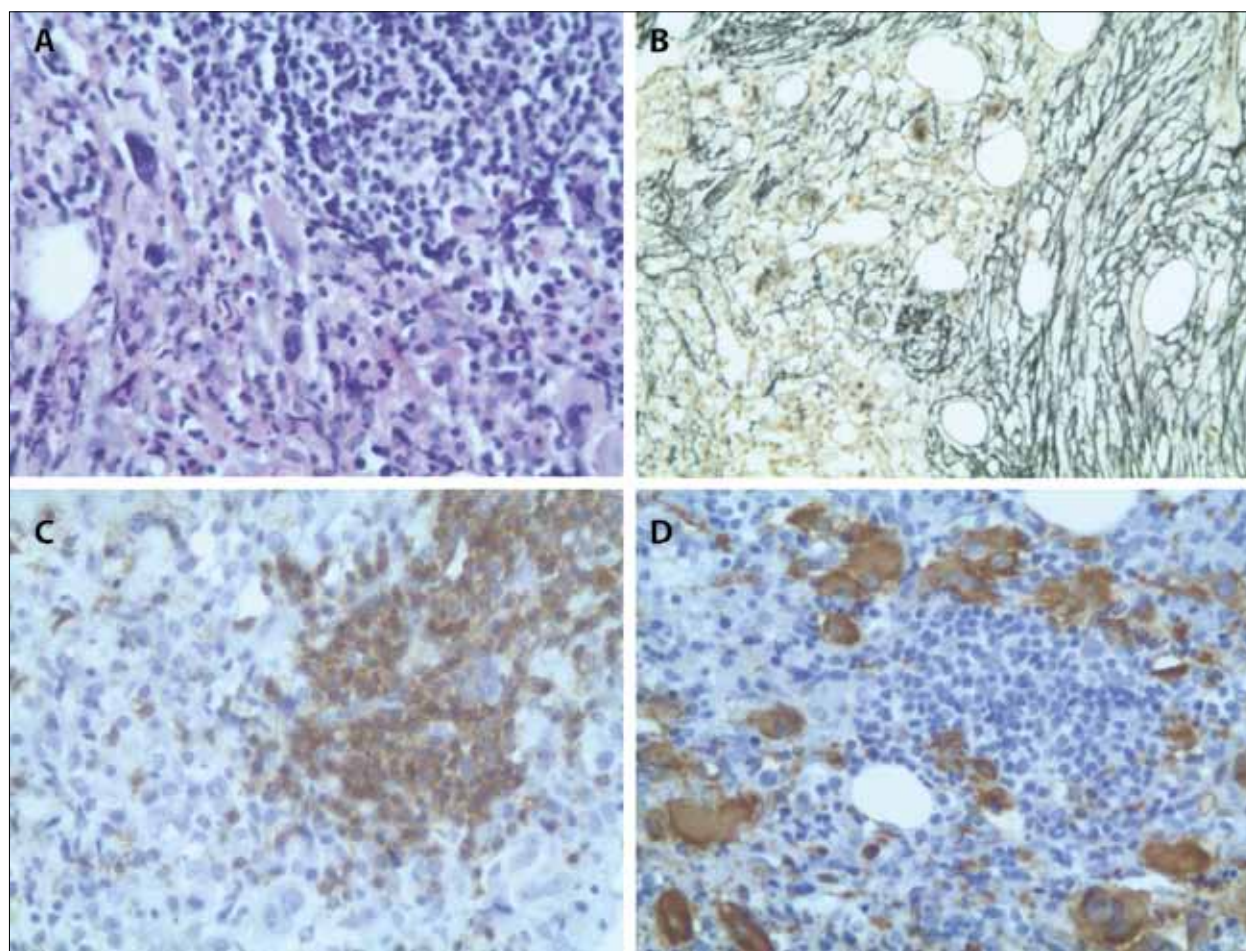


Figure 1. A) Bone marrow biopsy (hematoxylin-eosin) showing a population of small lymphoid cells, increased number of large megakaryocyte and fibrosis (magnification 400 $\times$); B) Bone marrow biopsy revealing significant reticulin fibrosis (magnification 200 $\times$); C) Bone marrow biopsy showing a population of neoplastic lymphocytes with strong CD5 immunopositivity (magnification 400 $\times$); D) Bone marrow biopsy showing increased number of CD61+ megakaryocyte (magnification 400 $\times$).

lymphocytic leukemia in 0/I Rai stage. The patient was monitored without therapy for four years. Subsequently, due to the elevation of white blood cell (WBC) count, he was occasionally treated with chlorambucil. In April 2012 CLL progressed to IV Rai stage. The bone marrow biopsy showed 60% nodular/interstitial infiltration with small mature lymphocyte, with expression of CD5, CD20, CD23, CD79a, and zeta chain associated protein kinase 70 (ZAP 70). The patient was treated with COP (cyclophosphamide, vincristine, prednisone) chemotherapy, and from May 2013 received FC (fludarabine, cyclophosphamide), VI cycles with partial response. The patient was in good condition until March 2014, when he felt fatigue and permanent headache. Physical examination showed cervical and axillar lymphadenopathy and splenomegaly, 2 cm below the costal margin. Splenomegaly with a diameter of 16 cm was present on ultrasound examination. Neurological examination, electroencephalogram and endocranial scan were normal. The hemoglobin (Hb) was 80 g/L, WBC count was 20×10^9 cells/L and differential count (neutrophils 8%, lymphocytes 88%, eosinophils 1%, basophils 2% and monocytes 1%, absolute lymphocyte count $17,600 \times 10^9$ cells/L). Platelet count was elevated ($1,581 \times 10^9$ platelets/L). Review of peripheral blood smear showed increased num-

ber of small lymphocytes, numerous platelets, anisocytosis and poikilocytosis. Erythrocyte sedimentation rate, fibrinogen level and C-reactive protein level were within normal range. The serum lactate dehydrogenase activity was elevated (877 U/L, normal range 160–410 U/L). Direct and indirect Coombs tests were negative. Coagulation status and D-dimer level were normal. Markers of neoplasm (CEA, CA19-9, PSA) were negative. Serum iron level and iron binding capacity were normal. Quantitative immunoglobulin test showed decreased serum immunoglobulin level (IgG 2.5 g/L, IgM 0.37 g/L, IgA 0.10 g/L). Causes for secondary thrombocytosis were excluded.

The bone marrow biopsy was performed, and showed hypercellularity with 30% nodular and interstitial infiltration by small lymphocytes, the megakaryocyte compartment was increased, with dysplastic megakaryocytes and reticulin proliferation grade II (Figure 1). The finding was consistent with diagnosis of CLL and prefibrotic phase of myelofibrosis.

Cytogenetics analysis detected normal male karyotype (46XY). Molecular assay revealed *JAK2V617F* mutation (Figure 2) and the absence of *BCR-ABL* fusion gene. When detection of *JAK2V617F* mutation was performed on a DNA sample which was obtained and preserved when di-

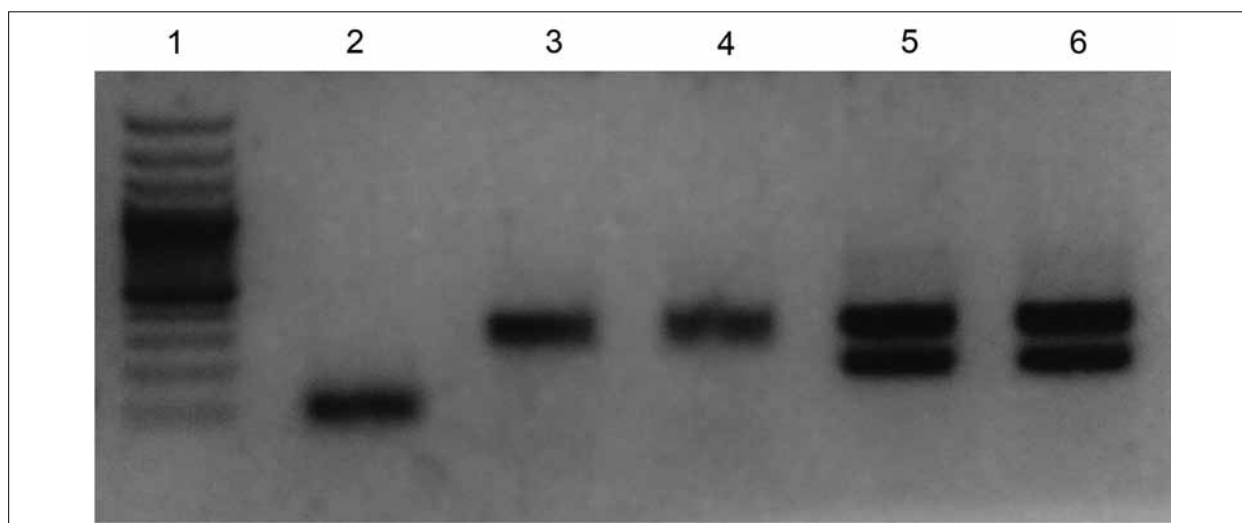


Figure 2. Detection of *JAK2V617F* mutation by allele-specific PCR (1 – 100 bp ladder; 2 – Water control; 3 – *JAK2V617F*-negative control; 4 – Patient before acquisition of myeloproliferative phenotype; 5 – Patient after acquisition of myeloproliferative phenotype; 6 – *JAK2V617F*-positive control)

agnosis of CLL was established, *JAK2V617F* mutation was not detected. Cyto-reductive treatment with hydroxyurea (2 g/day) was started with a low dose of aspirin, as well as management of anemia with red blood cell transfusions. Platelet count decreased to 350×10^9 platelets/L after one month, hydroxyurea dose was reduced to 1 g/day and discontinued after three months. Normalization of platelet count was associated with the disappearance of headaches. Platelet count stayed within normal range, but due to low hemoglobin concentration the patient received blood cell transfusions and prednisone therapy. The patient died in February 2015 because of progression of leukemia and associated pneumonia.

DISCUSSION

The development of chronic myeloproliferative disorder in a patient with lymphoproliferative neoplasm is very rare. Sequential or simultaneous occurrence of CLL and PMF in the same patient has been reported in literature in only 17 cases, with particular male predominance [4]. Simultaneous diagnosis of both diseases at presentation was noticed in nine patients [5], and in the case of subsequent diagnoses of diseases, myelofibrosis preceded CLL in the majority of patients [6, 7]. Our patient suffered from CLL and after nine years developed prefibrotic PMF. Impaired immune surveillance in chronic lymphocytic leukemia might be a triggering factor for the development of secondary malignancy [1]. In this case myelofibrosis occurred subsequent to previously treated CLL, and might be induced by the chemotherapy. The increased risk of therapy-related myeloid malignancies is reported in patients who received purine analogue [8]. However, in most patients with co-occurrence of myelo- and lymphoproliferative diseases, CLL patients were in Rai stage 0/I, without administered chemotherapy. Our patient had a progressive CLL and severe anemia, in contrast to literature data according to which patients having a combination of lymphoprolifera-

tive and myeloproliferative disease often show indolent clinical course [9].

Myelofibrosis is a very heterogeneous disease. A characteristic of prefibrotic myelofibrosis is elevated serum lactate dehydrogenase level, increased peripheral blood CD34+ cell count and a leucoerythroblastic peripheral blood smear [10]. Early prefibrotic myelofibrosis can mimic essential thrombocythemia and careful morphologic examination is necessary for distinguishing between the two diseases. Elevated platelet count is found in about one third of patients with PMF. In essential thrombocythemia megakaryocytes are giant with cluster formations, while those in prefibrotic PMF display abnormal maturation with hyperchromatic and irregularly folded nuclei. Our patient had very high platelet count, intense headaches, resistant to analgesics. Thrombohemorrhagic complications were ruled out, and the normalization of platelet count led to disappearance of headaches. Causes of headache associated with elevated platelet count and platelet dysfunction include increased plasma levels of serotonin, hypersensitivity of serotonin receptors, increased levels of platelet adenosine diphosphate and microcirculatory disturbance [11].

JAK2V617F mutation has been described in patients with Philadelphia chromosome negative myeloproliferative neoplasms (Ph-MPN), in majority of patients with polycythemia vera, in 50% of patients with primary myelofibrosis and essential thrombocythemia, in a small number of other myeloid malignancies, and rarely in lymphoid malignancies [2, 12]. The role of *JAK2V617F* mutation in B cell CLL is controversial. ZAP-70 expression, which is present in 30% of CLL cases, correlates with non-mutated immunoglobulin genes and predicts poor prognosis [13]. In most reported MPN cases which coexist with CLL, ZAP-70 was positivity present, as in our patient. Tabaczkowski et al. [6] proposed hypothesis that in cases of co-existence of CLL with MPN (*JAK2V617F*-positive essential thrombocythemia), initial genetic hit occurs early, during the pre-*JAK2* phase of progenitor cell development. Stem cells

then differentiate to lymphoid and myeloid cells, but due to genomic instability, acquire additional molecular mutations, as *JAK2* mutation within the myeloid lineage. *JAK2* mutation was not detected in B-cell lineage, which means that the two diseases arise from the same pluripotent stem cell but different cellular lineages. Our case favors this hypothesis because *JAK2* mutation was not present on CLL at presentation, and mutation is acquired during development of myeloproliferative disease, which suggests that B-CLL and PMF are two distinct clonal hematologic malignancies. Additionally, latency period between CLL and PMF appearance was very long, which favors hypothesis that impaired T-cell immunity might predispose the development of a second malignant clone [14]. Thus, neoplastic effect of received chemotherapy may be of importance. Different mutagenic events would independently induce the lymphoid and myeloid malignant proliferation, and the development of separate clonal origin malignant diseases. In contrast to this finding, Swierczek S. et al. [15] reported of three patients with concomitant development of polycythemia vera and chronic lymphocytic leukemia which arose independently from different hematopoietic stem cells.

JAK2 mutation is rarely present in lymphoid malignancies. In most of the reported cases with MPN and CLL, *JAK2* mutation was detected in myeloid, but not in lymphoid cells. Kodali et al. [5] identified *JAK2V617F* mutation in a patient with coexistent CLL and MPN. In 63 analyzed cases of B-cell CLL, only two were *JAK2V617F*-positive, but without a history of Ph-MPN [16]. *JAK2V617F* mutation was detected at low level in the peripheral blood of healthy donors, which indicates that mutation alone is not sufficient to induce Ph-MPN [17].

Pathogenesis of associated sporadic occurrence of myelo- and lymphoproliferative neoplasms is unclear and further studies are needed to find out whether these malignancies represent two distinct clonal hematological disorders or both derive from the same pluripotent stem cell.

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REFERENCES

- Bartik MM, Welker D, Kay NE. Impairments in immune cell functions in B-cell chronic lymphocytic leukemia. *Semin Oncol.* 1998; 25:27-33. [PMID: 9482524]
- Baxter EJ, Scott LM, Campbell PJ, East C, Fourouclas N, Swanton S, et al; Cancer Genome Project. Acquired mutation of the tyrosine kinase *JAK2* in human myeloproliferative disorders. *Lancet.* 2005; 365:1054-61. [DOI: 10.1016/S0140-6736(05)71142-9] [PMID: 15781101]
- Liang DC, Shih LY, Yang CP, Hung IJ, Chen SH, Jaing TH, et al. Multiplex RT-PCR assay for the detection of major fusion transcripts in Taiwanese children with B-lineage acute lymphoblastic leukemia. *Med Pediatr Oncol.* 2002; 39:12-7. [DOI: 10.1002/mpo.10092] [PMID: 12116073]
- Burgstaller S, Wimmer S, Mayrbaur B, Hoebeling W, Thaler J. Coexistence of primary myelofibrosis and chronic lymphocytic leukaemia: treatment of two different diseases with one agent. *Blood Cancer J.* 2011; 1(5):e20. [DOI: 10.1038/bcj.2011.18] [PMID: 22829155]
- Kodali S, Chen C, Rathnasabapathy C, Wang CJ. *JAK2* mutation in a patient with CLL with coexistent myeloproliferative neoplasm (MPN). *Leuk Res.* 2009; 33:e236-9. [DOI: 10.1016/j.leukres.2009.06.027] [PMID: 19625083]
- Tabaczewski P, Nadesan S, Lim SH. Zap-70 positive chronic lymphocytic leukemia co-existing with *Jak2V617F* positive essential thrombocythemia: a common defective stem cell. *Leuk Res.* 2009; 33:854-5. [DOI: 10.1016/j.leukres.2008.09.002] [PMID: 18849073]
- Chintapatla R, Battini R, Wiernik PH. Chronic lymphocytic leukemia with essential thrombocythemia: asbestos exposure association? *Clin Adv Hematol Oncol.* 2012; 10:752-5. [PMID: 23271264]
- Hisada M, Biggar RJ, Greene MH, Fraumeni JF, Travis LB. Solid tumors after chronic lymphocytic leukemia. *Blood.* 2001; 98:1979-81. [DOI: 10.1182/blood.V98.6.1979] [PMID: 11535538]
- Laurenti L, Tarnani M, Nichele I, Ciolli S, Cortezzi A, Forconi F, et al. The coexistence of chronic lymphocytic leukemia and myeloproliferative neoplasms: a retrospective multicentric GIMEMA experience. *Am J Hematol.* 2011; 86:1007-12. [DOI: 10.1002/ajh.22171] [PMID: 21953617]
- Tefferi A. Primary myelofibrosis: 2013 update on diagnosis, risk-stratification and management. *Am J Hematol.* 2013; 88:141-50. [DOI: 10.1002/ajh.23384] [PMID: 23349007]
- Frewin R, Dowson A. Headache in essential thrombocythaemia. *Int J Clin Pract.* 2012; 66:976-83. [DOI: 10.1111/j.1742-1241.2012.02986] [PMID: 22889110]
- Spasovski V, Tošić N, Kostić T, Pavlović S, Čolović M. *JAK2-V617F* mutation in patients with myeloproliferative neoplasms: association with *FLT3-ITD* mutation. *Srp Arh Celok Lek.* 2010; 138(9-10):614-8. [DOI: 10.2298/SARH1010614S] [PMID: 21180092]
- Leković D, Mihaljević B, Kraguljac-Kurtović N, Peruničić-Jovanović M, Bogdanović A, Čolović M, et al. Prognostic significance of new biological markers in chronic lymphocytic leukaemia. *Srp Arh Celok Lek.* 2011; 139(11-12):753-8. [DOI:10.2298/SARH1112753L] [PMID: 22338471]
- Kravić-Stevović T, Bogdanović A, Bumbaširević V. Higher percentage of in vitro apoptotic cells at time of diagnosis in patients with chronic lymphocytic leukemia indicate earlier treatment requirement: ten years follow up. *Srp Arh Celok Lek.* 2014; 142(1-2):48-53. [DOI: 10.2298/SARH1402048K] [PMID: 24684031]
- Swierczek S, Nausova J, Jelinek J, Liu E, Roda P, Kucerova J, et al. Concomitant *JAK2V617F*-positive polycythemia vera and B-cell chronic lymphocytic leukemia in three patients originating from two separate hematopoietic stem cells. *Am J Hematol.* 2013; 88:157-8. [DOI: 10.1002/ajh.23362] [PMID: 23280542]
- Yang Y-N, Qin Y-W, Wang C. *JAK2 V617F* detected in two B-cell chronic lymphocytic leukemia patients without coexisting Philadelphia chromosome negative myeloproliferative neoplasms: a report of two cases. *Oncology Lett.* 2014; 8:841-4. [DOI: 10.3892/ol.2014.2168] [PMID: 25013507]
- Sidon P, El Housini H, Dessars B, Heimann P. The *JAK2V617F* mutation is detectable at very low level in peripheral blood of healthy donors. *Leukemia.* 2006; 20:1622. [DOI: 10.1038/sj.leu.2404292] [PMID: 16775613]

JAK2V617F мутација код болесника са Б ћелијском хроничном лимфоцитном леукемијом и префибротичком примарном мијелофиброзом

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КРАТАК САДРЖАЈ

Увод Секундарни малигнитети, нарочито солидни тумори, чести су код болесника с хроничном лимфоцитном леукемијом (ХЛЛ), али ретко се среће удруженост мијелопролиферативних неоплазми и ХЛЛ.

Приказ болесника Приказујемо мушкарца старог 67 година са Б ћелијском ХЛЛ код кога се након девет година развила примарна мијелофиброза (ПМФ). Болесник је лечен алкилишућим агенсима и аналозима пурина, што може бити предиспонирајући фактор за развој мијелопролиферативног обољења. JAK2V617F мутација није откривена приликом постављања дијагнозе ХЛЛ, али је утврђена после

девет година, када се развила ПМФ, што указује на то да су Б ћелијска ХЛЛ и ПМФ неоплазме које потичу од различитих ћелијских клонова.

Закључак Патогенетски механизми удружености мијело-пролиферативне и лимфо-пролиферативне неоплазме код болесника нису разјашњени. Потребна су даља истраживања ради утврђивања да ли ове малигне болести потичу од два различита ћелијска клона или настају од исте плурипотентне матичне ћелије хематопоезе.

Кључне речи: хронична лимфоцитна леукемија; мијелофиброза; JAK2V617F мутација

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Extreme Hypertriglyceridemia in an Infant with Hemophagocytic Lymphohistiocytosis and Hydroxycobalamin Deficiency

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SUMMARY

Introduction Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory condition characterized by fever, cytopenias, hepatosplenomegaly and hemophagocytosis. HLH may be primary or secondary to infection, autoimmune disease or malignancy. Hypertriglyceridemia is a common abnormality in HLH and one of the HLH-2004 diagnostic criteria.

Case Outline We present an infant with severe hypotonia and hypoproteinemic edema who also had extreme hypertriglyceridemia (21 mmol/l) and was diagnosed with HLH based on six of eight HLH-2004 criteria (fever, hepatosplenomegaly, bicytopenia, hypertriglyceridemia with hypofibrinogenemia, sIL-2R > 2400 IU/ml, hemophagocytosis). The presence of IgM antibodies to Epstein-Barr virus and cytomegalovirus indicated a probable infectious trigger. The child was cured by the HLH-2004 protocol for secondary HLH (consisting of dexamethasone and cyclosporine). He was also found to have low serum hydroxycobalamin levels, promptly corrected upon hydroxycobalamin administration.

Conclusion The presented case history underlines the need to ascertain the presence or absence of each of the eight HLH-2004 criteria in any patient suspected to suffer from HLH.

Keywords: hemophagocytic lymphohistiocytosis; infant; hypertriglyceridemia; hydroxycobalamin deficiency

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory condition characterized by prolonged fever, cytopenias, hepatosplenomegaly and the phenomenon of hemophagocytosis, exerted by abnormally and excessively activated macrophages that cause a 'cytokine storm' [1]. HLH may be caused by a genetic defect (primary HLH, either a separate disease designated familial HLH or part of certain primary immunodeficiency disorders) or it may be secondary to other conditions, such as infection (particularly that caused by herpesviruses and *Leishmania*) [2, 3], autoimmune disease (where it is often called macrophage activation syndrome) [4] or malignancy (i.e. lymphoma) [5]. As envisaged by analyzing the functions of the genes involved in primary HLH, it appears that the common element in the pathogenesis of all types of HLH is a defect in immune functions that are dependent on exocytosis of vesicles containing cytotoxic granules – the action of natural killer (NK) cells and cytotoxic T-lymphocytes (CTL). The functional impairment of these cells leads to inefficient immune response with the persistence of invading microorganism and consequent inflammatory hyperstimulation, as well as to inefficient termination phase of the immune response, where NK cells and CTL also appear to play a key physiological role. It is less

clear what causes the impairment of cytotoxic functions in secondary HLH, and the extent of underlying genetic predisposition toward the abnormal response that characterizes HLH is difficult to measure against the contribution of exogenous factors. Since the initial clinical course of secondary HLH resembles closely the expected course of infection or other triggering condition, it is important that treating clinician bears in mind the possibility of this disorder. In addition to fever, cytopenias and hepatosplenomegaly, diagnostic criteria for HLH proposed by the Histiocyte Society [6] include hypertriglyceridemia, hyperferritinemia, hypofibrinogenemia, increased concentration of the receptor for interleukin (IL)-2 in the plasma, as well as decreased NK cell functional capacity. Hemophagocytosis (as demonstrable by bone marrow aspirate) may or may not be present, and its absence by no means excludes the diagnosis of HLH, a fact that is often overlooked, delaying the diagnosis. Although hypertriglyceridemia is a diagnostic criterion for HLH, its presence in patients affected with this disorder is far from universal, and its severity, where present, tends to be highly variable [7].

CASE REPORT

A seven-month-old male infant of body length of 72 cm and body mass of 6,530 g (body mass

index of 12.6 kg/m², under the 5th percentile: underweight) was admitted at the University Children's Hospital, Belgrade, Serbia, due to extreme hypotonia, high fever and hepatosplenomegaly. His mother indicated that the hypotonia was first apparent at the age of 4.5 months. However, the child had been diagnosed with perinatal asphyxia and a slight hypotonia had been medically documented since birth. Upon examination, the child was revealed to have moderate hepatomegaly (later confirmed by ultrasonography at 100 mm right lobe craniocaudal diameter). The spleen was also slightly enlarged (craniocaudal diameter of 80 mm). Blood analyses showed bicytopenia (red blood cell count 2.71×10^{12} cells/l, hemoglobin 9.9 g/l, white blood cell count 6.6×10^9 cells/l, absolute number of granulocytes 0.6×10^9 granulocytes/l, platelet count 527×10^9 platelets/l) with high mean corpuscular volume (110 fl). There was an extreme hypertriglyceridemia (21 mmol/L) and hypofibrinogenemia (1.1 g/l), while serum ferritin level was normal (147.6 µg/ml). Findings in the cerebrospinal fluid were also normal. The patient was an exclusively breast-fed infant, and his personal and family histories were unremarkable, as was the nutritional history of the mother. The patient is the only child of his non-consanguineous parents, who showed a normal lipid profile. Bone marrow aspiration showed a reduced myeloid precursor count with predominance of erythroid lineage exhibiting megaloblastic appearance. Scarce hemophagocytosis was noted. Bone marrow biopsy confirmed dysplastic/megaloblastic changes of the erythroid lineage.

Biochemical blood analyses also demonstrated hypoalbuminemia (14 mg/dl) and hypoproteinemia (31 mg/dl), as well as elevated lactate dehydrogenase (1,270 IU/l), alanine-aminotransferase (350 IU/l) and aspartate-aminotransferase (128 IU/l), while prothrombin and partial thromboplastin times were normal. The patient's lipid profile, apart from elevated triglycerides, showed a normal level of cholesterol (2.6 mmol/l), elevated lipoprotein A (867 mg/dl), reduced apolipoprotein A-I (54.1 mg/dl) and slightly reduced apolipoprotein B (53.9 mg/dl). Metabolic screening of the patient's urine showed increased excretion of all amino acids, positive cyanonitroprusside test (due to cystinuria) and mild proteinuria. Excretion of phenolic acids, organic acids, imidazoles, proline and hydroxyproline were all normal, as well the as anthron test, ferrichloride test, 2,4-DNPH test and toluidin blue test. There was no excretion of glucose or ketones.

Serological assays revealed IgM antibodies specific for Epstein-Barr virus (EBV), as well as both IgM and IgG antibodies specific for cytomegalovirus (CMV), while the antibodies to rubella virus, herpes simplex virus, human immunodeficiency virus and *Toxoplasma* were all absent. Lymphocyte populations, as evaluated by flow cytometry, were all within age-appropriate reference range. The receptor for IL-2 in the serum (sIL-2R) was markedly elevated (3,736 IU/ml). Although NK and cytotoxic T-cell function was not evaluated due to technical limitations, six of the eight HLH-2004 criteria were fulfilled: fever, hepatosplenomegaly, bicytopenia, hypertriglyceridemia with hypofibrinogenemia, and sIL-2R above 2,400 IU/ml. The

diagnosis of HLH was established. The child was subsequently treated according to the HLH-2004 protocol for secondary HLH: dexamethasone daily 10 mg/m² for two weeks, then 5 mg/m² for two weeks, then 2.5 mg/m² for two weeks, then 1.25 mg/m² for a week; cyclosporine 6 mg/kg daily divided into two doses, later corrected aiming at plasma level of 200 µg/l; however, no VP16. Shortly after the initiation of treatment, hypertriglyceridemia and neutropenia resolved. After the lipidemia improved, low levels of hydroxycobalamin (<60 pg/ml; reference range >200 pg/ml) were detected in the serum, and 1 mg/kg hydroxycobalamin was given i.m. three times weekly. In a matter of weeks after the institution of hydroxycobalamin treatment, mean corpuscular volume was reduced to 95 fl and signs of megaloblastosis disappeared from the bone marrow. In the course of two months, neurological problems also receded. Upon completion of HLH-2004 treatment, the child has been subjected to follow-up in regular intervals and appears to be in good health. By the time of writing, more than three years have passed without problems. A follow-up measurement of hydroxycobalamin serum level showed that it is now within the normal range (348 pg/ml). Serum hydroxycobalamin level of the mother was also measured and found to be moderately reduced (138 pg/ml).

Statement on ethics

Written informed consent for the publication of this case history was obtained from the child's parents in accordance with the Declaration of Helsinki, institutional Ethical Committee guidelines and relevant legal requirements.

DISCUSSION

HLH was reported to be the presentation in a case of transcobalamin II deficiency [8]. In the light of this finding, it is possible that very low levels of hydroxycobalamin in our patient could have increased the likelihood of occurrence of secondary HLH upon an appropriate trigger. This trigger was most probably EBV or CMV infection documented by the presence of anti-EBV and anti-CMV IgM antibodies, respectively. Transcobalamin II deficiency in our patient remains a possibility, particularly given the ever-widening clinical spectrum of this disorder of cobalamin metabolism [9]. However, the fact that we found a subclinical deficit of hydroxycobalamin in the mother argues in favor of the explanation that the child simply did not receive a sufficient quantity of hydroxycobalamin from his mother. Rapid resolution of anemia and disappearance of megaloblasts upon hydroxycobalamin treatment are also in accordance with this explanation. Since the mother insisted that her dietary habits were not vegan or vegetarian and did not appear to suffer from any disorder known to be associated with secondary hydroxycobalamin deficiency, the reason(s) for her mild hypohydroxycobalaminemia remain elusive. We had no means to explore potential genetic causes.

Even though hypertriglyceridemia is a diagnostic criterion for HLH, the exact mechanism(s) that cause it are not yet fully clarified. It is thought that cytokines that abound in the plasma, above all tumor necrosis factor, inhibit lipoprotein lipase, thereby hampering the uptake of triglycerides from very low density lipoproteins into the adipose tissue [10]. In addition to the role of tumor necrosis factor, IL-18 may also be partly responsible for hypertriglyceridemia in HLH, since it is shown to be specifically present in high concentrations in the plasma of HLH patients [11]. Thus it may be reasonable to assume that the level of triglycerides, which is routinely measurable, reflects the level of cytokines, which cannot be measured but in highly specialized institutions, usually in research settings. Although found to be of uncertain prognostic value so far [7], extreme hypertriglyceridemia, such as that found in our patient, should, at the very least, prompt the physician to include HLH in the differential diagnosis, particularly if other signs of congenital hyperlipidemia syndromes are absent, as was the case here.

The diagnosis of HLH in our patient was established on the basis of six of eight HLH-2004 criteria. However, one of the fulfilled criteria was bicytopenia. Since our patient had a megaloblastic anemia that may be interpreted as a consequence of reduced hydroxycobalamin levels, it is somewhat questionable whether this criterion was legitimately fulfilled, i.e. whether the co-occurrence of leukopenia and anemia still constitutes bicytopenia for diagnostic purposes if there is good reason to believe that their causes are separate and their mechanisms unrelated. In the presented case, this dilemma was compounded by the unusual fact that the child had thrombocytosis rather than thrombocytopenia. There is no specific provision for the above question in the HLH-2004 criteria and, to the

best of our knowledge, no 'official' interpretation. In the absence of the latter, and given that there was little support for any alternative diagnosis, and that, in total, six criteria were fulfilled, we felt compelled to conclude that the diagnosis of HLH was valid. Our confidence in the diagnosis was, to a certain degree, strengthened by the fact that plasma level of sIL-2R was very high, and this parameter showed a considerable promise of high specificity in previous experiences, including our series of children affected by HLH [12].

It is interesting that our patient had a marked hypoalbuminemia and hyperproteinemia. Although this is not a diagnostic criterion for HLH, the severity of hypoalbuminemia was recently reported to be correlated with poor prognosis in adult HLH patients [13]. The most plausible explanation for this correlation is that albumin levels closely reflect the degree of liver damage. It is also worth noting that the presented child did not exhibit hyperferritinemia at any time. Intriguingly, it has recently been shown in Japanese children that hyperferritinemia is associated with poor prognosis in EBV-triggered HLH [14]. The suggested strategy of using ferritin levels as a simple screening test for HLH would clearly not have been useful in establishing the diagnosis in our patient [15], further strengthening the case for the need to ascertain the presence or absence of each of the eight HLH-2004 criteria in any patient suspected to suffer from HLH.

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REFERENCES

- Rosado FGN, Kim AS. Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. *Am J Clin Pathol.* 2013;139:713-27. [DOI: 10.1309/AJCP4ZDKJ4ICOUAT] [PMID: 23690113]
- Gagnaire MH, Galambun C, Stéphan JL. Hemophagocytic syndrome: a misleading complication of visceral leishmaniasis in children – a series of 12 cases. *Pediatrics.* 2000; 106(4):E58. [DOI: 10.1542/peds.106.4.e58] [PMID: 11015553]
- Rouphael NJ, Talati NL, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. *Lancet Infect Dis.* 2007; 7(12):814-22. [DOI: 10.1016/S1473-3099(07)70290-6] [PMID: 18045564]
- Atteritano M, David A, Bagnato G, Beninati C, Frisina A, Iaria C, et al. Haemophagocytic syndrome in rheumatic patients. A systematic review. *Eur Rev Med Pharmacol Sci.* 2012; 16(10):1414-24. [PMID: 23104659]
- Blatt J, Weston B, Belhorn T, Hamrick H, Maia D. Childhood non-Hodgkin lymphoma presenting as hemophagocytic syndrome. *Pediatr Hematol Oncol.* 2002; 19(1):45-9. [DOI: 10.1080/088800102753356185] [PMID: 11787866]
- Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007; 48(2):124-31. [DOI: 10.1002/pbc.21039] [PMID: 16937360]
- Okamoto M, Yamaguchi H, Isobe Y, Yokose N, Mizuki T, Tajika K, et al. Analysis of triglyceride value in the diagnosis and treatment response of secondary hemophagocytic syndrome. *Inter Med.* 2009; 48:775-81. [DOI: 10.2169/internalmedicine.48.1677] [PMID: 19443971]
- Unal S, Tezol O, Oztas Y. A novel mutation of the transcobalamin II gene in an infant presenting with hemophagocytic lymphohistiocytosis. *Int J Hematol.* 2014; 99(5):659-62. [DOI: 10.1007/s12185-014-1545-7] [PMID: 24563082]
- Trakadis YL, Alfares A, Bodamer OA, Buyukavci M, Christodoulou J, Connor P, et al. Update on transcobalamin deficiency: clinical presentation, treatment and outcome. *J Inher Metab Dis.* 2014; 37(3):461-73. [DOI: 10.1007/s10545-013-9664-5] [PMID: 24305960]
- Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. *Annu Rev Med.* 2012; 63:233-46. [DOI: 10.1146/annurev-med-041610-134208] [PMID: 22248322]
- Kogawa K, Lee SM, Villanueva J, Marmer D, Sumegi J, Filipovich AH. Perforin expression in cytotoxic lymphocytes from patients with hemophagocytic lymphohistiocytosis and their family members. *Blood.* 2002; 99:61-6. [DOI: 10.1182/blood.V99.1.61] [PMID: 11756153]
- Krivokapić-Dokmanović L, Krstovski N, Janković S, Lazić J, Radlović N, Janić D. Clinical characteristics and disease course in children with haemophagocytic lymphohistiocytosis treated at the University Children's Hospital in Belgrade. *Srp Arh Celok Lek.* 2012; 140(3-4):191-7. [DOI: 10.2298/SARH120491K] [PMID: 22650106]
- Parikh SA, Kapoor P, Letendre L, Kumar S, Wolanskyj AP. Prognostic factors and outcomes of adults with hemophagocytic lymphohistiocytosis. *Mayo Clin Proc.* 2014; 89(4):484-92. [DOI: 10.1016/j.mayocp.2013.12.012] [PMID: 24581757]

14. Kogawa K, Sato H, Asano T, Ohga S, Kudo K, Morimoto A, et al. Prognostic factors of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in children: report of the Japan histiocytosis study group. *Pediatr Blood Cancer*. 2014; 61(7):1257-62. [DOI: 10.1002/pbc.24980] [PMID: 24535916]
15. Switala JR, Hendricks M, Davidson A. Serum ferritin is a cost-effective laboratory marker for hemophagocytic lymphohistiocytosis in the developing world. *J Pediatr Hematol Oncol*. 2012; 34(3):e89-92. [DOI: 10.1097/MPH.0b013e31824227b9] [PMID: 22322940]

Екстремна хипертриглицеридемија код одојчета с хемофагоцитном лимфохистиоцитозом и недостатком хидроксикобаламина

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КРАТАК САДРЖАЈ

Увод Хемофагоцитна лимфохистиоцитоза (ХЛХ) је тешко запаљењско стање које се одликује грозницом, цитопенијама, хепатоспленомегалијом и хемофагоцитозом. ХЛХ може да буде примарна или секундарна услед инфекције, аутоимунских болести или малигнитета. Хипертриглицеридемија је чест поремећај код ХЛХ и један од дијагностичких критеријума ХЛХ-2004.

Приказ болесника Представљено је одојче с тешком хипотонијом и хипопротеинским едемима које је имало и екстремну хипертриглицеридемију (21 mmol/l), а дијагноза ХЛХ је постављена на основу шест од осам критеријума ХЛХ-2004 (грозница, хепатоспленомегалија, бицитопени-

ја, хипертриглицеридемија с хипофибриногемидијом, *sIL-2R* > 2400 IU/ml, хемофагоцитоза). Постојање *IgM* антитела на Епстин-Бар вирус и цитомегаловирус указало је на инфекцију као вероватни покретач. Дете је излечено протоколом ХЛХ-2004 за секундарну ХЛХ (дексаметазон и циклоспорин). Такође је утврђен низак ниво хидроксикобаламина у серуму, који се брзо кориговао по давању хидроксикобаламина. **Закључак** Приказана историја болести наглашава потребу да се постојање или изостанак сваког од осам критеријума ХЛХ-2004 утврди код сваког болесника за којег се посумња да болује од ХЛХ.

Кључне речи: хемофагоцитна лимфохистиоцитоза; одојче; хипертриглицеридемија; дефицит хидроксикобаламина

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Pseudo-Bartter's Syndrome in Patients with Cystic Fibrosis: A Case Series and Review of the Literature

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SUMMARY

Introduction Pseudo-Bartter syndrome (PBS) is characterized by hyponatremic, hypochloremic metabolic alkalosis that mimics Bartter syndrome but with no pathology in the renal tubules. We present five patients with cystic fibrosis (CF) and PBS.

Cases Outline Four children aged between three and five-and-one-half months with previously diagnosed CF and one aged 17 months with previously undiagnosed disease, were hospitalized during the summer season, with severe dehydration, oliguria, apathy and adynamia. Additionally, one of them had an ileostomy due to meconium ileus after birth. All children were on a diet without additional salt intake. Laboratory analysis on admission showed hyponatremia (115–133 mmol/L, mean 122.4 mmol/L), high plasma renin activity (229–500 pg/ml, mean 324 pg/ml) and metabolic alkalosis (pH 7.5–7.6, mean 7.56) in all the patients, and in four of them high blood level of aldosterone (74–560 pg/ml, mean 295.9 pg/ml), hypokalemia (2.3–2.8 mmol/L, mean 2.6 mmol/L), hypochloremia (59–71 mmol/L, mean 66 mmol/L) and low urinary sodium (5–12 mmol/L, mean 9 mmol/L). After intravenous rehydration followed by additional use of sodium and chloride in mean dosis of 1.78 mmol/kg per day, all the patients made a complete recovery. With advice for additional use of salt in the mentioned amount, the patients were discharged from the hospital.

Conclusion PBS is one of CF complications, especially in infants and young children in situations accompanied by increased sweating and/or other causes of additional loss of sodium and chlorine. Sometimes, as was the case with one of our patients, PBS may be the initial presentation form of the disease.

Keywords: cystic fibrosis; pseudo-Bartter syndrome; infants

INTRODUCTION

Cystic fibrosis (CF) is a disease of exocrine gland dysfunction caused by genetic mutation on chromosome 7, which results in abnormalities in the production and/or function of protein called cystic fibrosis transmembrane conductance regulator (CFTR) that acts as a chloride channel and regulator of epithelial chloride and bicarbonate transport [1, 2]. The widespread presence of CFTR throughout the body leads to multisystem involvement [1, 2]. Although it primarily affects the respiratory and gastrointestinal tracts, it can also involve other organs [1, 2]. It may also cause electrolyte and acid base disturbances, especially in countries with warm climate during hot summer months. However, the rare episode of dehydration, metabolic alkalosis and hypochloremia in CF patients is presented as pseudo-Bartter syndrome (PBS) [3, 4].

PBS is characterized by hyponatremic, hypochloremic metabolic alkalosis that mimics Bartter syndrome but with no pathology in the renal tubules [5]. Sometimes PBS may be the first manifestation of CF [6, 7, 8].

We present five patients with CF and PBS. In one of them PBS was the initial presentation of CF.

REPORT OF CASES

During the summer period of 2012 and 2013, the PBS was diagnosed in five patients with CF. The reason for hospitalization in all patients was severe dehydration, oliguria, apathy and adynamia. The diagnosis of CF in four children is determined by the first month after birth (neonatal screening), while one, a 17-month-old girl, basic disease is diagnosed by the picture of PBS (Table 1). Basic data related to the age of children at the time of hospitalization, nutritional status, diet, factors that preceded dehydration and initial laboratory parameters are given in Tables 2 and 3. The important fact is that none of the children, except a two-month female infant who was fed unmodified cow's milk, had no additional salt intake. An additional risk factor for the development of PBS had a patient number five, which had an increased loss of water and electrolytes through ileostomy.

DISCUSSION

It is well known that CF patients may fail to thrive despite adequate intake of calories. In those cases it is important to think of the existence of electrolyte disturbances due to PBS.

PBS is a rare syndrome characterized with hypochloremic metabolic alkalosis, hyponatremia,

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Table 1. Results of newborn screening (IRT level, sweat test), CFTR mutations and fecal elastase level

Patient	IRT (ng/ml)	CFTR mutation	Sweat test (mmol/L)	Fecal elastase (µg/g)
1	80 and 100	621+1G>T//2789+5G>A	79 and 85	200
2	/	F508 del homozygote	68 and 98	15
3	129 and 133	F508 del homozygote	58 and 62	146
4	236 and 175	F508 del homozygote	87 and 96	15
5	460 and 229	F508 del / G 542X	78 and 86	19

IRT – immunoreactive trypsinogen; CFTR – cystic fibrosis transmembrane conductance regulator

Table 2. Characteristics of patients with cystic fibrosis and pseudo-Bartter syndrome and therapy they received

Patient	Age (months)	Sex	Symptoms before onset of PBS	Predisposing factors	Feeding	Body weight at admission (g)	Substitution therapy
1	3	Female	Failure to thrive	High air temperature	Cow's milk	4250 (<3 pct)	NaCl 0.5 mmol/kg/day KCl 1 mmol/kg/day
2	17	Female	None	High air temperature	Standard diet	13500 (50 pct)	NaCl 2 mmol/kg/day KCl 1 mmol/kg/day
3	4	Female	Recurrent respiratory infections	High air temperature	Formula	5700 (<50 pct)	NaCl 1.7 mmol/kg/day KCl 1.5 mmol/kg/day
4	5.5	Male	Failure to thrive	High air temperature	Formula	5700 (3 pct)	NaCl 1.7 mmol/kg/day KCl 1.3 mmol/kg/day
5	5	Male	Meconium ileus, ileostomy, failure to thrive	High air temperature and ileostomy	Formula	5200 (3 pct)	NaCl 3 mmol/kg/day

pct – percentile

Table 3. Initial laboratory findings on admission of patients with cystic fibrosis and pseudo-Bartter syndrome

Patient	pH	Na (mmol/l)	K (mmol/l)	Cl (mmol/l)	Urea (mmol/l)	SCr (µmol/l)	PRA (IU/ml)*	Aldosterone (pg/ml)*	UNa (mmol/l)	UK (mmol/l)	UCL (mmol/l)
1	7.6	119	2.8	69	2.8	10.4	320	560	12	5.5	10
2	7.5	115	2.8	58.8	20	120	279	37.8	5	60	6
3	7.6	124	2.3	71	8.3	33.9	229	74	34	1.1	14
4	7.6	121	2.5	65	30	64	500	97.6	7	11	10
5	7.5	133	4.2	109	10	46	296	452	12	/	6

Na – sodium; K – potassium; Cl – chloride; SCr – serum creatinine; PRA – plasma renin activity; UNa – urinary sodium; UK – urinary potassium; UCL – urinary chloride

* Referent range: PRA to 46 IU/ml; Aldosterone 16–40 pg/ml

hypokalemia, hyperreninemia, hyperaldosteronism and persistent failure to thrive. Hypochloremic metabolic alkalosis with elevated aldosterone and rennin occur both in Bartter syndrome, as well as in PBS within the CF. The main difference is that in the PBS renal tubules are not affected, while in classic Bartter syndrome renal tubules are not able to reabsorb electrolytes. In classic Bartter syndrome chloride loss in urine is high, while in PBS chloride loss in urine is low (<10 mmol/l) [3, 4, 9].

The CFTR dysfunction in the sweat glands results in excessive loss of sodium and chloride. This is especially true during hot summer months. The excessive loss of sodium chloride leads to a significant loss of the extracellular volume and secondary activation of the rennin-angiotensin-aldosterone system. Hyperaldosteronism leads to an increased loss of potassium through sweat, as well as through urine, causes hypokalemia and stimulates sodium cation exchange (hydrogen, potassium) which in addition results with hypokalemia and alkalosis occurrence. In reduced extracellular space relative increase in the concentration of bicarbonate occurs, and low levels of chloride leads to an increased reabsorption of bicarbonate in kidneys. In addition, reduced extracellular volume decreases bicarbonate filtration in urine due to the reduction of glomerular filtration rate. All this leads to metabolic alkalosis. On the other hand, hypokalemia itself may cause metabolic alkalosis [9].

Yalcin et al. [10] found the incidence of PBS in patients with CF to be 12%, Ballesterio et al. [11] 16.8%, and Fustik et al. [12] 16.5%. The first attack of PBS was most often before the age of one [9, 11]. In our patients only one patient had PBS beyond the first year of life (the patient was 17 months old at the time).

PBS is a usual complication in patients with established CF, but sometimes PBS can be the initial manifestation of CF [3]. In four of our patients the diagnosis of CF was based on neonatal screenings. In only one of our patients, in whom newborn screening was not performed, initial presentation of PBS and failure to thrive were followed by the diagnosis of CF. Marah [13] also described a case of an infant in which PBS was an initial manifestation of CF.

Risk factors for the development of PBS in CF patients include warm weather conditions (profuse sweating), severe respiratory or pancreatic disease and gastrointestinal losses (vomiting and diarrhea) [13]. Due to hyponatremia and hypochloremia, which appear in these diseases, the appetite is reduced, which additionally decreases the salt intake [14]. None of our patients had vomiting, but salt loss was caused by profuse sweating, and only a single patient had salt loss by ileostomy due to meconium ileus.

It is well known that PBS in patients with CF usually presents during warm summer months [15]. In four of our patients the trigger of PBS was high air temperature during

hot summer. In addition, in one patient with ileostomy, due to meconium ileus after birth, who had great losses through it, PBS appeared during winter.

In patients with PBS, differential diagnosis includes: cyclical vomiting (pyloric stenosis), congenital chloride-losing diarrhea, sustained gastric suction, misuse of laxatives, Gitelman syndrome, use of diuretics (in which case chloride in urine is low!) and primary hyperaldosteronism [9]. Igrutinović et al. [16] described a case of an infant with congenital chloride diarrhea and PBS.

All of our patients had a usual diet appropriate for their age, before the onset of PBS. Despite sodium intake being appropriate, they had extreme salt loss. The patient who was on cow's milk, which contains larger amounts of sodium, developed PBS as well. In most studies with CF PBS, majority of infants has been breast feeding. In a study by Fustik et al. [12], all the patients with CF PBS were breastfed. Kennedy et al. [5] described seven patients with CF PBS, all of who were on cow's milk.

After the initial intravenous fluid rehydration during one or two days, and electrolyte supplementation, oral substitution therapy with sodium and potassium was performed for all patients during further hospitalization. The substitution of potassium was performed for three to four days, because the stabilization of sodium homeostasis, that is elimination of secondary hyperaldosteronism, the cause of excessive renal loss, disappeared.

The substitution of sodium was continued for all patients after the hospital discharge (up to six months). Oral substitution with sodium and/or potassium can be carried out in all patients with CF PBS over months, and

even years. To date there is no clear position on how long the supplementation with sodium chloride or potassium chloride should be applied. It is suggested that the treatment is recommended until normal growth of the child is restored and until serum electrolyte levels are satisfactory, even after the abolition of supplementary therapy [17].

Yalcin et al. [10] published a review of as many as 29 patients with PBS. The average age at diagnosis of CF PBS was four months. In 11 patients CF was not diagnosed until CF PBS occurred. There were no differences in age, gender, genotype or severity of PBS attacks between those with pre- and post-PBS-diagnosed CF. Nine of the 29 patients were being fed breast milk, and the rest were taking formula milk. In all patients acid-base status and serum electrolyte levels were normalized after two to four days. Most of the patients had a respiratory exacerbation when PBS occurred (profuse sweating, loss of appetite and high fever). All of them had vomiting, loss of appetite, failure to thrive during the PBS episode [10].

In all the patients the values of rennin were high. Aldosterone values were high in four patients and within borderline range in one patient. This can be explained by the fact that the low serum potassium suppresses the secretion of aldosterone.

In conclusion, PBS is one of complication of CF, especially in infants and young children in situations accompanied by increased sweating and/or other causes of additional loss of sodium and chlorine. Sometimes, as was the case with one of our patients, PBS may be the initial presentation form of the disease. Hence, patients with CF in a state of increased sweating or other situations accompanied by increased loss of electrolytes require appropriate compensation.

REFERENCES

- Bush A, Alton EFW, Davies JC, Griesenbach U, Jaffe A, editors. Cystic Fibrosis in the 21st Century. In: Bolliger CT, editor. Progress in Respiratory Research. Vol. 34. Basel: Karger; 2006. p. 1-329. [DOI: 10.1159/isbn.978-3-318-01240-8]
- Radlović N. Cystic fibrosis. *Srp Arh Celok Lek.* 2012; 140(3-4):244-9. [DOI: 10.2298/SARH1204244R] [PMID: 22650116]
- Kose M, Pekcan S, Ozcelik U, Cobanoglu N, Yalcin E, Dogru D, et al. An epidemic of pseudo-Bartter syndrome in cystic fibrosis patients. *Eur J Pediatr.* 2008; 167:115-6. [DOI: 10.1007/s00431-007-0413-3] [PMID: 17323076]
- Dahabreh MM, Najada AS. Pseudo-Bartter syndrome, pattern and correlation with other cystic fibrosis features. *Saudi J Kidney Dis Transpl.* 2013; 24:292-6. [DOI: 10.4103/1319-2442.109579] [PMID: 23538352]
- Kennedy JD, Dinwiddie R, Daman-Willems C, Dillon MJ, Matthew DJ. Pseudo-Bartters syndrome in cystic fibrosis. *Arch Dis Child.* 1990; 65:786-7. [DOI: 10.1136/adc.65.7.786] [PMID: 2386386]
- Nahida el-R, Mohammed H, Guy L. Pseudo-Bartter's syndrome revealing cystic fibrosis in an infant caused by 3849 + 1G>A and 4382delA compound heterozygosity. *Acta Paediatr.* 2011; 100(11):e234-5. [DOI: 10.1111/j.1651-2227.2011.02294.x] [PMID: 21449922]
- Fustik S, Jakovska T, Spirevska L. PO-0074 Pseudo-Bartter's syndrom as a first manifestation of cystic fibrosis in infancy. *Arch Dis Child.* 2014; 99:A274. [DOI: 10.1136/archdischild-2014-307384.744]
- Maia C, Garrido A, Carvalho I, Pinto H, Vaz LG, Ferreira G. Pseudo-Bartter syndrome as an initial presentation of cystic fibrosis. *Port J Nephrol Hypert.* 2014; 28(4):348-51.
- Veizis IE, Cotton CU. Role of kidney chloride channels in health and disease. *Pediatr Nephrol.* 2007; 22(6):770-7. [DOI: 10.1007/s00467-006-0355-4] [PMID: 17109136]
- Yalcin E, Kiper N, Dogru D, Ozcelik U, Tana AA. Clinic features and treatment approaches in cystic fibrosis with pseudo-Bartter syndrome. *Ann Trop Paediatr.* 2005; 25:119-24. [DOI: 10.1179/146532805X45719] [PMID: 15949200]
- Ballesterio Y, Hernandez MI, Rojo P. Hyponatremic dehydration as a presentation of cystic fibrosis. *Pediatr Emerg Care.* 2007; 22:725-7. [DOI: 10.1097/01.pec.0000245170.31343.bb] [PMID: 17110865]
- Fustik S, Jandanova-Pop N, Slaveska N, Koceva S, Eftremov G. Metabolic alkalosis with hyponatremia in infants with cystic fibrosis. *Pediatr Int.* 2002; 44:289-92. [DOI: 10.1046/j.1442-200X.2002.01563.x] [PMID: 11982899]
- Marah MA. Pseudo-Bartter as an initial presentation of cystic fibrosis. A case report and review of the literature. *East Mediterr Health J.* 2010; 16(6):699-701. [PMID: 20799601]
- Radlović V, Leković Z, Radlović N, Lukač M, Ristić D, Simić D, et al. Significance of the application of oral rehydration solution to maintain water and electrolyte balance in infants with ileostomy. *Srp Arh Celok Lek.* 2013; 141(5-6):325-8. [DOI: 10.2298/SARH1306325R] [PMID: 23858801]
- Kintu B, Brightwell A. Episodic seasonal pseudo-Bartter syndrome in cystic fibrosis. *Paediatr Respir Rev.* 2014; 15(Suppl 1):19-21. [DOI: 10.1016/j.prrv.2014.04.015] [PMID: 24821548]
- Igrutinović Z, Peco-Antić A, Radlović N, Vuletić B, Marković S, Vujić A, et al. Pseudo-Bartter syndrome in an infant with congenital chloride diarrhea. *Srp Arh Celok Lek.* 2011; 139(9-10):677-80. [DOI: 10.2298/SARH1110677I] [PMID: 22070007]
- Tutar E, Boran P, Oktem S, Akinci O, Ilk S, Guven S. Pseudo-Bartter's syndrome in patients with cystic fibrosis. *Turkish J Pediatr Dis.* 2012; 6(4):206-10.

Псеудо-Бартеров синдром код болесника са цистичном фиброзом: приказ случајева и преглед литературе

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КРАТАК САДРЖАЈ

Увод Псеудо-Бартеров синдром (ПБС) се одликује хипона-тремијском и хипохлоремичком метаболичком алкалозом, као и Бартеров синдром, али без поремећаја функције реналних тубула. Приказано је пет болесника са цистичном фиброзом (ЦФ) и ПБС.

Приказ болесника Четири детета узраста од три месеца до пет и по месеци са претходно дијагностикованом ЦФ и једно дете од 17 месеци са дотада недијагностикованом ЦФ примљена су на болничко лечење током летњег периода због тешке дехидратације, олигурије, апатије и адинамије. Једно дете је такође имало илеостому због меконијумског илеуса по рођењу. Сва деца су била на исхрани без додатног уноса соли. Лабораторијске анализе на пријему су код свих показивале хипонатријемiju (115–133 *mmol/l*, просечно 122,4 *mmol/l*), повишену плазма-ренинску активност (229–500 *pg/ml*, просечно 324 *pg/ml*) и метаболичку ал-

калозу (*pH* 7,5–7,6, просечно 7,56), док су код четворо деце забележени висок ниво алдостерона у крви (74–560 *pg/ml*, просечно 295,9 *pg/ml*), хипокалемија (2,3–2,8 *mmol/l*, просечно 2,6 *mmol/l*), хипохлоремија (59–71 *mmol/l*, просечно 66 *mmol/l*) и снижена вредност натријума у мокраћи (5–12 *mmol/l*, просечно 9 *mmol/l*). Након интравенске рехидратације и наставка додатног уноса натријума и хлора у просечној дози од 1,78 *mmol/kg* дневно, сва деца су се потпуно опоравила. Са саветом за додатни унос соли у поменутој дози деца су пуштена кући.

Закључак ПБС је једна од компликација ЦФ, посебно код одојчади и мале деце, у условима појачаног знојења и/или постојања других разлога праћених повећаним губитком натријума и хлора. Некада, као у случају једног од наших болесника, ПБС може бити прва манифестација ЦФ.

Кључне речи: цистична фиброза; псеудо-Бартеров синдром; одојчад

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A Novel Frameshift Mutation of the *IKBKG* Gene Causing Typical Incontinentia Pigmenti

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SUMMARY

Introduction Incontinentia pigmenti (IP) is a rare X-linked dominant genodermatosis. Mutations of the *IKBKG* gene are responsible for IP. A deletion of exons 4–10 can be found in 80% of patients with IP. There are 69 different mutations of the *IKBKG* gene that have been reported.

Case Outline A proband, female patient from a family without previously diagnosed IP is reported. She had skin and dental changes typical of IP. The diagnosis was made according to updated IP criteria. Pathohistological and ultrastructural analysis of skin biopsy confirmed the diagnosis. However, the common deletion of exons 4–10 in the *IKBKG* gene could not be detected. Sequencing revealed the indel (deletion/insertion) mutation c.641_647delGCATGGAT (p.Arg214HisfsX38) in exon 5 of the *IKBKG* gene. Because this mutation could not be detected in the unaffected mother of the proband, it seems to be a *de novo* mutation.

Conclusion The registered novel frameshift *IKBKG* mutation c.641_647delGCATGGAT (p.Arg214HisfsX38) can be considered to be the cause of IP in this case.

Keywords: incontinentia pigmenti; *IKBKG* gene; frameshift mutation; genodermatosis; diagnosis

INTRODUCTION

Incontinentia pigmenti (IP) is a rare X-linked dominant genodermatosis that appears almost exclusively in females and is usually lethal *in utero* for males [1]. The *IKBKG* (*inhibitor of kappa-B kinase gamma*, previously *NEMO*) gene is the only gene known to be associated with IP [2]. Mutations of the *IKBKG* gene are responsible for IP. A deletion of exons 4–10 in the *IKBKG* gene can be found in 80% of IP patients [1]. To date, in IP patients 69 different mutations in the *IKBKG* gene have been reported [3, 4, 5]. These mutations originate from different molecular mechanisms [6]. The *IKBKG* gene product NEMO/IKK γ is required for activation of NF- κ B (nuclear factor kappa-B) transcription factor. As a consequence of the *IKBKG* gene mutation, its accurate product does not arise and NF- κ B activation does not occur [1]. At the skin level, NF- κ B appears to have a dual role in cell growth and apoptosis. The phenotypic expression of *IKBKG* gene mutation is highly variable [1]. No genotype–phenotype correlation is apparent from the comparison of patients with different loss-of-function mutations [7].

It is noteworthy that some hypomorphic mutations in the *IKBKG* gene, reducing but not eliminating NF- κ B activation, were found in surviving male patients. These males are affected by a different disease, named hypohidrotic ectodermal dysplasia associated with severe immunodeficiency (EDA-ID) or occasionally associated with osteopetrosis and lymphoedema (OL-EDA-ID) [7].

CASE REPORT

In this study, a female patient from a family without previously diagnosed IP is reported. IP diagnosis was made according to updated criteria [8]. The family pedigree was constructed, and routine laboratory findings for the proband and the mother were obtained. The investigation protocol followed the guidelines of the Helsinki Declaration and was approved by the Clinical Center of Serbia Ethics Committee. Written informed consent was obtained from all participants or their parent/guardian.

The pedigree analysis revealed that there were no other family members with IP stigmata. The proband's mother had two sisters. One died one month after birth (of unknown reason), and the other was healthy. The proband from clinically healthy nonconsanguineous parents was born at term by Caesarean section. She was the first child from a first normal pregnancy. At birth she had vesiculo-bullous lesions, typical for IP stage 1, grouped along Blaschko's lines. The lesions were located on the extremities, trunk, and back, with more on the left side. A skin biopsy was taken, and skin samples were prepared for light and electron microscopic investigation in a routine way [9]. Pathohistologically intraepidermal vesicles with eosinophils, apoptotic keratinocytes, and eosinophils infiltrating the epidermis and dermis were found, indicating IP stage 1 [10]. On light microscopy, apoptotic keratinocytes are characterized by a condensed and basophilic nucleus and eosinophilic homogenization of the cytoplasm, which sometimes contains

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irregular basophilic materials. Ultrastructural analysis revealed keratinocytes and dermal cells in the process of apoptosis. Eosinophilia of 29% was registered. After a couple of months the skin lesions evolved through stages 2 and 3.

The proband was 32 months old. Some of the skin changes already evolved into stage 4. In addition to hyper- and hypopigmented macules, proband had conical teeth, and her dentition had been delayed. There were no abnormal neurological and ophthalmological findings. To confirm IP diagnosis, molecular genetic testing for *IKBK*G gene mutation was performed.

Blood samples were collected and used to extract DNA using standard protocols. Molecular genetic testing was done at Diagenos, Center for Medical Genetics, Osnabrueck, Germany. For testing a modified polymerase chain reaction (PCR) protocol was performed [1]. However, the common deletion of exons 4–10 in the *IKBK*G gene could not be detected. Sequencing revealed the indel (deletion/insertion) mutation c.641_647delGCATGGGinsAT (p.Arg214HisfsX38) in exon 5 of the *IKBK*G gene, a heterozygous frameshift mutation with a premature termination signal. This mutation could not be detected in the unaffected mother of the proband.

DISCUSSION

The proband developed skin and dental changes typical for IP, and with an unambiguous clinical diagnosis she met updated IP diagnostic criteria [8]. Slightly higher expression of skin lesions on the left side was consistent with literature data [10]. Pathohistological findings corresponded to the stage 1 of IP and confirmed the diagnosis [11]. Ultrastructural analysis revealed apoptotic changes of keratinocytes that are typical for IP [1]. The mutation c.641_647delGCATGGGinsAT (p.Arg214HisfsX38) that was found in the proband has not been described as a causative mutation in the previous literature or in mutation databases (HMGD, Cardiff) [3]. The mutation resulted in an altered amino acid sequence beginning at position 214 and subsequently in a premature termination signal. Because this mutation could not be detected in the unaffected mother of the proband, it seems to be a *de novo* mutation. The local high frequency of micro/macro-homologies, tandem repeats, and repeat/repetitive sequences makes the *IKBK*G gene locus susceptible to novel pathological IP alterations [12]. The novel muta-

tion has probably been generated by *de novo* events during parental gametogenesis, whose origin could be due to the peculiar genomic architecture of the *IKBK*G gene locus [6, 12]. However, gonadal mosaicism can't be ruled out – either maternal or paternal.

The phenotypic expression of *IKBK*G gene mutation is highly variable, even among related patients with the same mutation [1]. In contrast, patients with different *IKBK*G mutations may have the same clinical phenotype [1]. The presented patient has a typical IP phenotype with an accelerated course of skin changes but novel *IKBK*G gene mutation. Variability of the IP phenotypic expression was likely to be the result of the skewed X-chromosome inactivation [1], the pleiotropic role of the NEMO/IKK γ [6], or dimer-specific regulatory mechanisms within the NF- κ B family of transcription factors [12, 13].

A large scale of different deletions of exons 4–10 has been identified in the *IKBK*G gene [10]. The presence of common *IKBK*G exons 4–10 deletion in six Serbian IP patients has been reported [14]. This mutation corresponds to the majority (80%) of *IKBK*G mutations in IP [1, 10]. In the remaining 20% of patients with IP, the mutation is hidden by the second copy of the *IKBK*G gene and the presence of a highly homologous *IKBK*G pseudogene [10]. In cases of hidden mutations [10], when no large deletion is identified in the gene, while phenotypical expression of the disease is highly suggestive of an *IKBK*G gene anomaly, a microrearrangement can be searched for using direct sequencing of the coding regions [7]. Besides the 69 different *IKBK*G gene mutations published, in the presence of a single IP minor criterion when other IP major criteria are absent, the newly detected novel mutation c.641_647delGCATGGGinsAT (p.Arg214HisfsX38) would be acceptable for making a diagnosis among female first-degree relatives [3, 8].

In conclusion, in the proband with typical IP skin and dental phenotype the novel *IKBK*G gene mutation c.641_647delGCATGGGinsAT (p.Arg214HisfsX38) was registered. This novel *IKBK*G frameshift mutation can be considered to be the cause of IP in this case.

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REFERENCES

- Smahi A, Courtois G, Vabres P, Yamaoka S, Heuertz S, Munnich A, et al. Genomic rearrangement in *NEMO* impairs NF- κ B activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium. *Nature*. 2000; 405:466-72. [DOI: 10.1038/35013114] [PMID: 10839543]
- Scheuerle A, Ursini MV. Incontinentia pigmenti (Bloch-Sulzberger syndrome). *GeneReviews* [Internet]. Seattle (WA): University of Washington; 2008. [accessed 26th January 2015]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1472/>.
- Leiden Open Variation Database. View transcript variants in *IKBK*G. [accessed 26th January 2015]. Available from: http://databases.loud.nl/shared/variants/IKBK?search_var_status=%3D%22Marked%22%3D%22Public%22.
- Conte MI, Pescatore A, Paciolla M, Esposito E, Miano MG, Lioi MB, et al. Insight into *IKBK*G/*NEMO* locus: report of new mutations and complex genomic rearrangements leading to incontinentia pigmenti disease. *Hum Mutat*. 2014; 35:165-77. [DOI: 10.1002/humu.22483] [PMID: 24339369]

5. Kim MJ, Lyu SW, Seok HH, Park JE, Shim SH, Yoon TK. A healthy delivery of twins by assisted reproduction followed by preimplantation genetic screening in a woman with X-linked dominant incontinentia pigmenti. *Clin Exp Reprod Med*. 2014; 41:168-73. [DOI: 10.5653/term.2014.41.4.168] [PMID: 25599040]
6. Fusco F, Paciolla M, Napolitano F, Pescatore A, D'Addario I, Bal E, et al. Genomic architecture at the Incontinentia Pigmenti locus favours *de novo* pathological alleles through different mechanisms. *Hum Mol Genet*. 2012; 21:1260-71. [DOI: 10.1093/hmg/ddr556] [PMID: 22121116]
7. Fusco F, Pescatore A, Steffan J, Royer G, Bonnefont JP, Ursini MV. Clinical Utility Gene Card for: incontinentia pigmenti. *Eur J Hum Genet*. 2013; 21(7). [DOI: 10.1038/ejhg.2012.227] [PMID: 23047738]
8. Minić S, Trpinac D, Obradović M. Incontinentia pigmenti diagnostic criteria update. *Clin Genet*. 2014; 85:536-42. [DOI: 10.1111/cge.12223] [PMID: 23802866]
9. Hayat MA. Basic techniques for transmission electron microscopy. Orlando: Academic Press; 1986.
10. Hadj-Rabia S, Rimella A, Smahi A, Fraitag S, Hamel-Teillac D, Bonnefont JP, et al. Clinical and histologic features of incontinentia pigmenti in adults with nuclear factor-κB essential modulator gene mutations. *J Am Acad Dermatol*. 2011; 64:508-15. [DOI: 10.1016/j.jaad.2010.01.045] [PMID: 21255870]
11. Fraitag S, Rimella A, de Prost Y, Brousse N, Hadj-Rabia S, Bodemer C. Skin biopsy is helpful for the diagnosis of incontinentia pigmenti at late stage (IV): a series of 26 cutaneous biopsies. *J Cutan Pathol*. 2009; 36:966-71. [DOI: 10.1111/j.1600-0560.2009.01206.x] [PMID: 19674201]
12. Ghosh G, Wang VY, Huang DB, Fusco A. NF-κB regulation: lessons from structures. *Immunol Rev*. 2012; 246:36-58. [DOI: 10.1111/j.1600-065X.2012.01097.x] [PMID: 22435546]
13. Smale ST. Dimer-specific regulatory mechanisms within the NF-κB family of transcription factors. *Immunol Rev*. 2012; 246:193-204. [DOI: 10.1111/j.1600-065X.2011.01091.x] [PMID: 22435556]
14. Minić S, Trpinac D, Gabriel H, Gencik M, Obradović M. First *IKBKG* gene mutation study in Serbian incontinentia pigmenti patients. *Srp Arh Celok Lek*. 2013; 141(7-8):490-4. [DOI: 10.2298/SARH1308490M] [PMID: 24073555]

Нова *frameshift* мутација гена *IKBKG* као узрок инконтиненције пигменти

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КРАТАК САДРЖАЈ

Увод Инконтиненција пигменти (ИП) је ретка генодерматоза која се наслеђује доминантно везано за X-хромозом. За појаву ИП одговорне су мутације гена *IKBKG*. Код 80% болесника са ИП нађена је делеција на егзонима 4–10 гена у *IKBKG* гену. Досад је код болесника са ИП утврђено 69 различитих мутација на овом гену.

Приказ болесника Пробанд је била девојчица из породице у којој досад није дијагностикована ИП. Она је на кожи и зубима имала промене типичне за ИП. Дијагноза је постављена применом унапређених критеријума за ИП. Дијагнозу су потврдиле патохистолошка и ултраструктурна анализа би-

опсије коже. Код пробанда није откривена делеција егзона 4–10 гена *IKBKG*. Секвенционирањем је показано присуство indel (deletion/insertion) мутације *c.641_647delGCATGGGinsAT (p.Arg214HisfsX38)* егзона 5 на гену *IKBKG*. Пошто ова мутација није откривена код мајке пробанда, изгледа да је у питању мутација *de novo*.

Закључак Новооткривена *frameshift* мутација гена *IKBKG c.641_647delGCATGGGinsAT (p.Arg214HisfsX38)* може се сматрати узрочном ИП.

Кључне речи: инконтиненција пигменти; ген *IKBKG*; *frameshift* мутација; генодерматоза; дијагноза

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Acute Diarrhea in Children

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SUMMARY

Acute diarrhea (AD) is the most frequent gastroenterological disorder, and the main cause of dehydration in childhood. It is manifested by a sudden occurrence of three or more watery or loose stools per day lasting for seven to 10 days, 14 days at most. It mainly occurs in children until five years of age and particularly in neonates in the second half-year and children until the age of three years. Its primary causes are gastrointestinal infections, viral and bacterial, and more rarely alimentary intoxications and other factors. As dehydration and negative nutritive balance are the main complications of AD, it is clear that the compensation of lost body fluids and adequate diet form the basis of the child's treatment. Other therapeutic measures, except antipyretics in high febrility, antiparasitic drugs for intestinal lamblasis, anti-amebiasis and probiotics are rarely necessary. This primarily regards uncritical use of antibiotics and intestinal antiseptics in the therapy of bacterial diarrhea. The use of antiemetics, antidiarrhetics and spasmolytics is unnecessary and potentially risky, so that it is not recommended for children with AD.

Keywords: acute diarrhea; etiopathogenesis; diagnostics, therapy

INTRODUCTION

Acute diarrhea is the most frequent gastrointestinal disorder and the main cause of dehydration in childhood [1, 2, 3]. It is characterized by a sudden occurrence of three or more watery or loose stools daily [1-5]. In addition, the initial phase of the disease is often accompanied by anorexia, vomiting, abdominal pain and elevated body temperature [1, 2, 3].

Acute diarrhea primarily occurs in children during the first five years after birth, and particularly in the second half-year and in small children [1, 2, 3]. Although it is present worldwide, the highest incidence is recorded in the developing countries. Except for neonatal pathological conditions and pneumonia, acute diarrhea is globally primarily due to dehydration, i.e. hypovolemia, electrolyte disbalance and acidosis, and in recurrent cases and general malnutrition, the leading cause of mortality in children until completed fifth year of life (Table 1) [1, 2, 3, 6, 7]. According to the data of the World Health Organization (WHO) from 2004, one-and-a-half million children

in the world die of acute diarrhea, mainly in countries with low standard of living [7]. The same WHO document reports that over 80% of children who died of acute diarrhea are from African and South Asian countries, where most were from India (380,600), Nigeria (151,700), Democratic Republic of Congo (899,000), Afghanistan (82,100) and Ethiopia (73,700).

ETIOPATHOGENESIS

The most frequent cause of acute diarrhea are gastrointestinal infections, viral and bacterial, and rarely parasitic (Tables 2 and 3) [1-5, 8, 9, 10]. The infections are spread by fecal-oral transmission, i.e. contaminated food and water or direct or indirect contact with an infected individual [9, 10]. Particularly high contagiousness show rotavirus, norovirus and *Shigella* [10, 11]. Viral causes of acute diarrhea, in addition to the classical manner, can be spread through aerogenic transmissions [10]. Prevalence of specific intestinal pathogens is age-related but it also depends on the stage of development of the child's surroundings [3, 9]. The most frequent etiological factors of acute infective diarrhea in Europe, North America and Australia, the developed countries, particularly at the age range from six months to five years, are viruses (rotavirus, norovirus, adenovirus, calicivirus, astrovirus and others), while bacterial causes of the disease (*Campylobacter jejuni*, *Salmonella*, *Shigella* and pathogenic species of *Escherichia coli*), which primarily affect children in the first six months after birth and after five years of age, are much rarer [1, 2, 3, 8]. *Giardia lamblia*, *Entamoeba histolytica* and *Cryptosporidium*

Table 1. Etiological factors of mortality of children under the age of five in the world [7]

Factors	%
Neonatal factors	Total
	Prematurity
	Intrapart complications
	Sepsis and meningitis
	Other
Pneumonia	14.1
Diarrhea	9.9
Malaria	7.4
Injuries, AIDS, meningitis, morbilli and other	28.3

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Table 2. Causes of acute infective diarrhea [8, 10]

Viruses (~70%) [8]	Rotavirus, norovirus (norwalk-like virus), adenovirus (serotypes 40 and 41), astrovirus, enterovirus
Bacteria (10-20%) [8]	<i>Campylobacter jejuni</i> , <i>Salmonella</i> (animal/non-typhoidal species), <i>Shigella</i> , <i>Yersinia enterocolitica</i> , <i>Escherichia coli</i> (enteropathogenic and enterotoxigenic), <i>Yersinia pseudotuberculosis</i> , <i>Clostridium difficile</i> , <i>Salmonella typhi</i> and <i>paratyphi</i> , <i>Vibrio cholerae</i>
Protozoa (<10%) [8]	<i>Giardia lamblia</i> , <i>Cryptosporidium</i> , <i>Entamoeba histolytica</i> , <i>Dientamoeba fragilis</i> , <i>Blastocystis hominis</i>
Helminths	<i>Strongyloides stercoralis</i>

ridium are even more rare causes of acute diarrhea [1, 2, 3, 8]. Although this country is not considered part of the economically developed group of countries, owing to unenviable level of children's healthcare insurance, as well as to people's education level, the situation is also similar in our surroundings. In children in developing countries, especially in tropical and subtropical regions, bacterial diarrheas were significantly more frequent, including cholera, typhoid and paratyphoid fever, although there as well as in developed countries rotavirus ranks as the leading single cause of the disease [3]. In these environments parasitic diarrheas were significantly more frequent as well [3].

In addition to gastrointestinal infections, acute diarrheal disorders are caused by alimentary intoxications, wide-spectrum antibiotics, oral iron preparations, laxatives, cytostatics, gastric secretion suppressors, stress-related conditions and severe extraintestinal infections in infancy period, such as sepsis, urinary tract infection, otitis media, pneumonia and other [1]. It is necessary to point out that a prolonged usage of wide-spectrum antibiotics even in children, particularly those with chronic inflammatory intestinal diseases and malignancies, can cause most severe *Clostridium difficile* (pseudomembranous) enterocolitis [9, 12, 13].

Infectious causes of acute diarrheal disorder colonize the small bowel and/or the large bowel (Table 4) [3, 9, 14, 15]. Viral infection affects only the small bowel causing invasion and destruction of the mature epithelium, while bacteria and parasites, depending on the type, exert their pathogenic effect in both bowel segments.

From the pathogenetic point of view, infectious diarrheal disorders are classified into three basic groups, i.e. secretory, osmotic-secretory and exudative-secretory [1, 9, 15]. Secretory diarrhea is caused by *Vibrio cholerae* and toxigenic strains of *E. coli*, osmotic-secretory by viruses, and exudative-secretory by enteroinvasive bacteria (*Salmonella*, *Shigella*, *Campylobacter*) and *Entamoeba histolytica* [3, 8, 15]. Accordingly, osmotic and osmotic-secretory diarrhea is characterized by liquid stools, and exudative-secretory by aqueous-mucilaginous and often blood-stained stools [3]. Enteropathogenic *E. coli*, *Giardia lamblia* and *Cryptosporidium* adhere to mucosal surface of the proximal small bowel, thus, by compromising its function, primarily causing a malabsorptive form of diarrheal disorder [3].

Alimentary intoxications are characterized by a secretory diarrheal disorder caused by the ingestion of food contaminated by enterotoxins of *Staphylococcus aureus*, *Clostridium perfringens* and *Bacillus cereus* [3, 16, 17]. Contrary to infections, there is no bacterial colonization of bowels. *Staphylococcus aureus* excretes a thermostabile,

Table 3. Categorization of most frequent causes of acute diarrhea in Europe, according to children's age [5]

Year	Virus
<1	Rotavirus
	Norovirus
	Adenovirus
	<i>Salmonella</i> *
1-4	Rotavirus
	Norovirus
	Adenovirus
	<i>Salmonella</i> *
	<i>Campylobacter</i>
	<i>Yersinia</i>
>5	<i>Campylobacter</i>
	<i>Salmonella</i> *
	Rotavirus

* non-typhoidal species

Table 4. Localization of the causes of gastrointestinal infections [9, 14]

Cause	Localization
<i>Salmonella</i>	Distal ileum and colon
<i>Campylobacter</i>	
Enteroinvasive <i>Escherichia coli</i>	
<i>Yersinia enterocolitica</i>	
<i>Vibrio cholerae</i>	Small bowel
Enterotoxigenic <i>Escherichia coli</i>	
Viruses (rotavirus and other)	
<i>Giardia lamblia</i>	
<i>Cryptosporidium</i>	Colon
<i>Shigella</i>	
<i>Entamoeba histolytica</i>	

while *Clostridium perfringens* and *Bacillus cereus* excrete a thermolabile enterotoxin.

Diarrhea, as a component of antibiotic therapy occurs as the consequence of the disintegration of colonic bacterial flora [18, 19]. The most severe disorder of this type is *Clostridium difficile* enterocolitis [12, 13]. Erythromycin, azithromycin and other macrolides, except for antibiotic effect, also act stimulatory on the gastrointestinal motility, thus it is not rare that their application is followed by feelings of nausea, vomiting, abdominal pain and diarrhea [20].

Other medications cause a diarrheal disorder by various mechanisms – oral iron preparations by irritative (pro-oxidative) effect, purgatives by laxative, chemotherapeutics by cytotoxic, gastric secretion suppressors (proton pump inhibitors and H2 blockers) by prokinetics, etc [21].

Stress conditions disturb vegetative body function, including the gastrointestinal motility and secretion, which constitute the bases for diarrheal episodes in persons with irritable bowel syndrome [22].

Pathogenesis of diarrhea, as a component of extraintestinal infections, is highly complex and insufficiently clear. It occurs as a consequence of antibiotics use, but also as a consequence of other, numerous factors that disturb the gastrointestinal integrity [23].

CLINICAL FEATURES

Basic clinical characteristics of acute infective diarrhea are relatively short incubation period, sudden onset manifested by frequent watery or loose stools and a complete recovery within 14 days (Table 5) [1, 2, 3, 19, 24, 25]. Enteritis is characterized by watery and postprandial, and colitis by mucous or mucous-hemorrhagic stools [3, 26]. In most cases the initial phase of the disease is followed by increased fever (one to three days), vomiting, loss of appetite, abdominal pain, and in case of colitis a false need to pass stools, and tenesmus. Owing to the natural passive immunity acquired prenatally, in infants aged six to nine months, particularly in those who are breastfed, gastrointestinal infections in gen-

eral, and in particular viral ones, are usually asymptomatic or with mild clinical symptoms [3, 24].

Contrary to infections, alimentary intoxications are characterized by a very short latent period (usually 10–12 hours, sometimes 30 minutes) and clinical course (mostly one day), as well as the absence of febrility [16, 17]. Besides watery diarrhea, the disease is almost regularly followed by an intensive feeling of nausea, vomiting and abdominal colic.

Basic complication of acute diarrheal disorder is dehydration developing due to diarrhea, vomiting and fever [1, 2, 3]. According to severity, it can be mild, moderate or severe, while according to osmolality, which is primarily defined by the level of sodium in serum, isotonic, hypotonic or hypertonic (Table 6) [8, 27, 28, 29].

Electrolyte deficit is equivalent to the degree of dehydration (Table 7) [28]. It is the highest in hyponatremic, followed by that in isonatremic, and it is the lowest in hypernatremic dehydration. Owing to compensatory mechanisms, in most children diarrheal dehydration is isonatremic (85%), and much rarer hypernatremic (5–15%) or hyponatremic (5–10%) [28, 30]. Hypernatremic dehydration occurs most often in infants, particularly six to nine months after birth, who are febrile, with osmotic diarrhea and on a diet of non-adapted cow's milk, while hyponatremic dehydration occurs in infants who are primarily inadequately rehydrated, i.e. without sufficient sodium substitution, undernourished and with prolonged diarrheal disorder [30]. In addition, more severe dehydration is followed by decompensated metabolic acidosis, hypo- or hyperkalemia and hypoglycemia, and the most severe sensorial disorder, convulsions and anuria [2, 30]. As a consequence of severe hypovolemia, i.e. prolonged hypoperfusion and renal hypoxia, tubular necrosis is also possible [31].

Second most frequent complication that occurs due to anorexia, vomiting, diarrhea and fever is negative nutritional status followed by reversible loss of body weight (BW) [1]. However, in cases with frequent and prolonged diarrheal episodes, particularly in children of the youngest age, poorly nourished or treated with an overly restrictive diet, the loss of BW can progress to severe overall malnutrition [2, 3]. In children during the first years of life, febrile (benign) convulsions are also common [32]. Rarer complications of the disease are bacteremia and consequential metastatic infections (osteomyelitis, meningitis, endocarditis, liver and spleen abscesses, etc.) that primarily develop in younger infants and immunocompromised children with *Salmonella enterocolitis*, as well as chronic post-infective diarrhea induced by overly restrictive diet and/or unnecessary antibiotic therapy, mostly present in the first and rarely in the second year of life, intestinal invagination and perforation, paralytic ileus, toxic megacolon, rectal mucosal prolapse, amebic liver abscesses and others [2, 3, 9].

Rare complications of acute infections also involve immune-mediated extra-intestinal manifestations, which usually occur after the cessation of diarrhea (Table 8) [3, 4, 9].

Table 5. Incubation period in acute infective diarrheas [10]

Cause	Incubation period (days)
Rotavirus	3 (1–3)
Norovirus	1 (1–2)
Astrovirus	1–2
<i>Salmonella</i> (non-typhoidal)	1 (0.3–1)
<i>Campylobacter</i>	3 (1–7)
<i>Shigella</i>	3 (1–7)
<i>Giardia lamblia</i>	9 (7–14)
<i>Cryptosporidium</i>	7 (1–14)

Table 6. Classification of dehydration

According to	Classification
Degree of body weight loss [27]	Mild (<5%)
	Moderate (5–10%)
	Severe (>10%)
Osmolality [29]	Isotonic (275–295 mOsm/kg)
	Hypotonic (<275 mOsm/kg)
	Hypertonic (>295 mOsm/kg)
Blood level of sodium [27, 29]	Isonatremic (Na^+ 130–150 mmol/L)
	Hyponatremic (Na^+ <130 mmol/L)
	Hyperosmolar (Na^+ >150 mmol/L)

Table 7. Water and electrolyte deficit in isotonic diarrheal dehydration [27, 28]

Parameter	Deficit
Loss of body weight (%)	5
	10
	15
Water (ml/kg)	50
	100
	150
Na^+ (mmol/kg)	4
	8
	12
K^+ (mmol/kg)	3
	6
	9

Table 8. Immune-mediated complications of acute infective diarrhea [9]

Complications	Causes
Erythema nodosum	<i>Yersinia</i> , <i>Campylobacter</i> , <i>Salmonella</i>
Guillain–Barré syndrome	<i>Campylobacter</i>
Hemolytic-uremic syndrome	<i>E. coli</i> O157:H7, <i>Campylobacter</i> , <i>Yersinia</i>
Hemolytic anemia	<i>Campylobacter</i> , <i>Yersinia</i>
IgA nephropathy	<i>Campylobacter</i>
Reiter syndrome	<i>Shigella</i> , <i>Salmonella</i> , <i>Campylobacter</i> , <i>Yersinia</i>
Glomerulonephritis	<i>Shigella</i> , <i>Campylobacter</i> , <i>Yersinia</i>
Reactive arthritis	<i>Salmonella</i> , <i>Shigella</i> , <i>Yersinia</i> , <i>Campylobacter</i> , <i>Cryptosporidium</i>

DIAGNOSTICS

Diagnosis of acute diarrhea is based on anamnesis, complete clinical examination and adequate laboratory analyses [1–5, 9]. Data on the frequency and appearance of stools, acceptance and tolerance of food, diuresis, as well as the presence of vomiting, fever, abdominal pain and other complaints, are obtained by parents or a custodian, or by the child itself if of older age. It is also important to acquire knowledge about the presence of identical problems in the child's surroundings (family, collective), as well as the consumption of unsafe food or water. Within physical examination, which must always be all-inclusive, special attention should be paid to the degree of dehydration, the state of consciousness, as well as other complications, either intestinal or extraintestinal. Laboratory analyses involve serum values of Na, K, Cl, acid-base status, creatinine, glucose, biochemical parameters of inflammation (C-reactive protein, leukocytosis, erythrocyte sedimentation rate), standard urine examination, and in certain cases hemoculture as well. Patients suspected of lactose intolerance, which represents a frequent manifestation of viral diarrheas, it is useful to determine the presence of reductive substances in stool [3, 4, 9]. Confirming viral particles in stool by the use of the agglutination test is a practical, highly reliable and most frequent procedure in the diagnosis of rotavirus and adenovirus gastroenteritis [33]. Similarly, the verification of antigens of *Giardia lamblia*, *Entamoeba histolytica* and *Cryptosporidium* and *Clostridium difficile* toxins A and B in stool currently present the method of choice in the diagnosis of parasitic and pseudomembranous enterocolitis [12, 13, 34]. Patients with suspected intestinal invagination or perforation require radiological and ultrasound examination of the abdomen, or other examinations depending on the type of complications.

THERAPY

In children acute diarrhea mostly withdraws spontaneously, thus the treatment basis consists of replacement of lost water and electrolytes and adequate nutrition [1, 2, 3, 5]. Probiotics and symbiotics can be useful, while the application of antibiotics is justified only in certain cases [1,

2, 3, 5]. There is evidence that Smecta (diosmectite) and racecadotril represent useful adjuvants in the therapy of this pathologic condition [5]. Antipyretics are not indicated for children with fever below 39°C, except if there is an additional reason for their administration [35]. Antipyretic of choice for children's age is paracetamol, but if a child is older than three months (BW>5 kg), then ibuprofen is the medicine of choice as well [36]. The treatment of acute diarrheal disorder, except in the case of severe dehydration or some other serious complication, does not require hospitalization [37].

Rehydration of children with acute diarrhea

Mild and moderate dehydration caused by acute diarrheal disorder are in about 95% of cases successfully corrected orally, i.e. by the use of oral rehydration solutions (ORSs), while in conditions of severe dehydration rehydration is performed by intravenous route [3, 27, 38]. Therapy with water and electrolytes does not involve only deficit correction but also coverage of the present pathologic and physiologic losses [27].

Intravenous rehydration

In the initial phase of rehydration of the patient with severe dehydration followed by shock or preshock condition, in order to restore circulating volume, it is necessary to use intravenous infusion of 0.9% NaCl or Ringer's lactate in the dosage of 10–30 ml/kg BW during one to three hours [27]. If the patient's condition does not improve, the same treatment is repeated again once or twice during the next one to three hours. To restore volemia, bolus or more rapid infusion is applied, i.e. in doses of 20 ml/kg BW of 0.9% NaCl during 10–20 minutes, which can be repeated up to twice within one hour [39]. During this procedure, in addition to the insight into the patient's condition, it is also necessary to keep assessing central venous pressure and diuresis. In cases of restored volemia and absent diuresis, acute tubulonecrosis should be kept in mind, and accordingly further treatment is to be continued [30]. If the patient's condition is stabilized, which is almost always the case, a full correction of fluid deficit in isonatremic and hyponatremic dehydration requires a period of 24–36 hours, and in hypernatremic dehydration 36–48 hours [27, 30]. In isonatremic and hyponatremic dehydration 50% of fluid restoration is achieved during the first eight hours, and the remaining 50% during the next 16–24 hours, while in hypernatremic dehydration this procedure must be more gradual [27]. Sodium deficit in hypotonic dehydration is calculated by the following formula: $\text{Na}^+ \text{ (mmol)} = \text{BW (kg)} \times 0.6 \times (135 - \text{actual serum Na}^+ \text{ in mmol/L})$. With the aim of preventing a relative hypernatremia, the normalization of serum sodium must be slow, i.e. not faster than 0.5 mmol/L per hour [27, 38]. This must be strictly taken into account, because a rapid correction of hyponatremia can cause myelinolysis (demyelination) at the level of the

central nervous system, particularly the pons, followed by permanent sequelae, and even lethal outcome [27]. In symptomatic hyponatremia, bolus NaCl 3% is administered at a speed rate of 1 ml/min until the rise of sodium concentration in the serum up to 120 mmol/L, i.e. until the clearly visible improvement of consciousness and cessation of seizures [38]. As 1 ml/kg of 3% NaCl increases sodium for 1 mmol/L, its intravenous application in the dosage of 4–6 ml/kg usually results in the withdrawal of symptoms [38]. Because of the danger of brain edema as well as cerebral hemorrhage and thrombosis, the speed rate of serum sodium decrease in hypernatremic dehydration also must not be higher than 10–12 mmol/L per 24 hours or 0.5 mmol/L per hour [27, 38]. So as to prevent the abovementioned complications, the correction of hyponatremia and hypernatremia requires control of serum sodium level every two to four hours [27, 38].

Decompensated metabolic acidosis with blood pH below 7.25 or HCO_3^- below 10 mmol/L requires bicarbonate administered intravenously according to the following formula: $\text{NaHCO}_3 \text{ (mmol/L)} = \text{BW (kg)} \times 0.3 \times -\text{BE}$ [32]. In most cases it is sufficient to compensate one third to one half of the calculated dose.

Precondition for the compensation of potassium is patient's recovery from the state of shock, i.e. restored diuresis [27, 38]. The concentration of potassium in infusion fluid should not be higher than 40 mmol/L and is administered via a continuous intravenous infusion in the dose of 3–4 mmol/L per 24 hours. More severe forms of acute diarrhea also present hyperkalemia that is normalized after the correction of dehydration and metabolic acidosis.

Oral rehydration

Rehydration by natural (oral) route is based on the active sodium-glucose cotransport [40–43]. Intake of ORSs, composed of a determined combination of sodium, glucose, potassium and bicarbonate or citrate, begins immediately after the appearance of diarrhea and/or vomiting and is continued until a complete normalization of digestive functions [2, 3, 41]. To prevent dehydration, either initially or after oral or intravenous rehydration, an ORS is administered at a rate of 10 ml/kg BW after each watery stool or 2 ml/kg BW after each episode of vomiting, while to correct moderately severe dehydration the administered dose is 100 ml/kg BW and for mild 50 ml/kg BW over a course of three to four hours [2, 3, 40].

An ORS is administered in frequent and small sips using a small spoon, bottle or cup [2]. It can be also given through the nasogastric tube [37]. Therapy is applied under both hospital and home conditions. By adhering to the abovementioned principles, about 50% of patients achieve rehydration after 24 hours [40]. In about 5% of cases oral fluid resuscitation remains unsuccessful and replaced with the intravenous one.

ORSs produced by Galenika in this country is available on the market under the brand name Orosal 65. The composition of the preparation is adopted to this region

Table 9. ESPGHAN and World Health Organization (WHO) recommendations for composition of ORS and Orosal 65 [42, 43]

Parameter		ESPGHAN, 1992	WHO, 1994	Orosal 65** Galenika
Electrolytes (mmol/l)	Na^+	60	60–90	65
	K^+	20	15–20	20
	Cl^-	60	50–80	60
	$\text{HCO}_3^-/\text{citrate}^{3-}$	10*	25–35	25
Glucose (g/l)		13–20	≤20	20
Osmolality (mOsm/kg)		225–260	225–331	281

* Citrate (1 mmol=3 mEq); **By prescription of N. Radlović and R. Stepanović, 1992

pathogenesis of diarrheal disorder and it fully corresponds to the guidelines of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and WHO (Table 9) [5, 43, 44].

Finally, it should be pointed out that the compensation of water and electrolyte loss in patients with acute diarrheal disorder with drinking water, sweetened tea, fruit juices and other drinks, 5% or 10% glucose, physiological solution and similar means have no physiological basis and therefore cannot produce adequate results [40].

Nutrition

After three to four hours of rehydration, either oral or intravenous, the patient is offered food [1, 2, 3, 5]. In milder forms of the disease, i.e. without manifest dehydration and with an adequate ORS intake, diet is not interrupted [3]. This also refers to breastfed infants, whose diet is in no case interrupted [3, 37]. According to current recommendations, the menu of a child should be identical to that before the onset of the disease [1, 2, 3, 5, 37]. The only exception are children with transient lactose intolerance associated with viral diarrhea who are, in regard to artificially-fed children, given lactose-free milk formula, i.e. fermented milk products (yoghurt, sour milk, cheese) if the child is older than one year [8, 37, 45].

Antimicrobial therapy

As mentioned above, acute diarrheal disorder represents a pathological condition which, with compensation of lost fluids and adequate nutrition, withdraws spontaneously within one to two weeks. Thus, antibiotic therapy for acute bacterial diarrheas, generally viewed, is most often unnecessary [5, 9]. Moreover, in some cases it is counterproductive, because, if routinely applied in *Salmonella* enterocolitis, except in favoring germ spreading, it has no other effects, while in enterohemorrhagic *E. coli* strain infection it can contribute to the development of hemolytic-uremic syndrome [5, 9]. Absolute indication for antibiotic therapy of bacterial diarrheal disorders that occur in Europe are only salmonellosis in younger infants (< 3 months old) and patients with immunodeficiency, malignancy and chronic inflammatory bowel disease and moderately severe forms of *Clostridium difficile* enterocolitis [5]. It is

Table 10. Antibiotics in therapy of bacterial diarrhea [4, 5]

Cause	Antibiotic	Daily dose of drug and mode of application	Duration of treatment (days)
<i>Salmonella</i>	Ampicillin	50–100 mg/kg per os or IV in 4 doses	5–7
	Ceftriaxone	50–100 mg/kg IV or im in 1 dose	5–7
	Ciprofloxacin	20–30 mg/kg per os in 2 doses	7–10
<i>Shigella</i>	Ampicillin	50–100 mg/kg per os or IV in 4 doses	5–7
	Ceftriaxone	50–100 mg/kg IV or im in 1 dose	5–7
	Ciprofloxacin	20–30 mg/kg per os in 2 doses	7–10
<i>Campylobacter jejuni</i>	Erythromycin	50 mg/kg per os in 3–4 doses	5
	Azithromycin	5–10 mg/kg per os in 1 dose	5
<i>Yersinia enterocolitica</i>	TMP/SMX	10/50 mg/kg per os in 2 doses	7–10
	Gentamicin	3–5 mg/kg im or IV in 1–3 doses	7
EPEC, ETEC, EIEC	Ampicillin	100 mg/kg per os or IV in 4 doses	5
	TMP/SMX	10/50 mg/kg per os in 2 doses	5
	Ciprofloxacin	20–30 mg/kg per os in 2 doses	5–10
<i>Clostridium difficile</i>	Metronidazole	30 mg/kg per os in 3–4 doses	5
	Vancomycin	40 mg/kg per os in 4 doses	7

EPEC – enteropathogenic *E. coli*; ETEC – enterotoxigenic *E. coli*; EIEC – enteroinvasive *E. coli*; TMP/SMX – trimethoprim-sulfamethoxazole; IV – intravenous

understood that it's indicated in patients with threatening or manifested *Salmonella* bacteremia, as well as in cases of metastatic infections [9, 46]. Also, it is fully justified in severe forms of shigellosis [5]. In other bacterial diarrheas the application of antibiotics can only contribute to some shortening of disease course and faster elimination of the cause [5]. The list of antibiotics to be used in the treatment of acute bacterial diarrhea is presented in Table 10 [4, 5]. *Salmonella* bacteremia requires antibiotic therapy of two weeks, meningitis of four weeks and osteomyelitis of four to six weeks [46]. Antimicrobial drug of choice for fighting intestinal lambliasis and amebiasis is metronidazole [4].

Additional therapeutic measures

Probiotics, racecadotril and diosmectite have a favorable effect on the clinical course of the disease [4, 5, 37, 47, 48]. Probiotics and their combination with prebiotics (symbiotics) essentially contribute to the alleviation and shortening of the disease course, while racecadotril and diosmectite decrease fecal water and electrolyte loss. Due to the high risk of adverse side effects, loperamide

and other antidiarrheal drugs, as well as antiemetics (ondansetron and similar) are not recommended for children [8, 37]. Microencapsulated probiotics and prebiotics, due to their higher stability and resistance to acid peptic and biliary pancreatic activity, have advantage over standardly designed preparations of the same type [49, 50, 51].

PREVENTION

Strict adherence to basic hygienic and sanitary measures related to food and water represents the basis in the prevention of alimentary infections and intoxications, and in regard to infections, avoiding contact with the diseased is just as important [2, 3, 4]. Apart from contact with the diseased, rotavirus vaccine is practically the only efficient measure in the prevention of rotavirus gastroenteritis [1–5, 8, 9]. There is no doubt that breastfeeding is the essential component in the prevention of the development and alleviation of infective diarrhea, particularly viral [1–4]. Also, probiotics and symbiotics have a significant role in the prevention of *Clostridium difficile* enterocolitis, and partially in the prevention of rotavirus gastroenteritis [1, 18, 47].

REFERENCES

- Guandalini S, Kahn SA. Acute diarrhea. In: Kleinman RE, Sanderson IR, Goulet O, Sherman PM, Mieli-Vergani G, Shneider B, editors. Walker's Pediatric Gastrointestinal Disease. 5th ed. Hamilton: BC Decker Inc; 2008. p.253–64.
- Koletzko S, Osterrieder S. Acute infectious diarrhea in children. Dtsch Arztebl Int. 2009; 106(33):539–47. [DOI: 10.3238/arztebl.2009.0539] [PMID: 19738921]
- Farthing M, Salam MA, Lindberg G, Dite P, Khalif I, Salazar-Lindo E, et al.; WGO. Acute diarrhea in adults and children: a global perspective. J Clin Gastroenterol. 2013; 47(1):12–20. [DOI: 10.1097/MCG.0b013e31826df662] [PMID: 23222211]
- Bhutta ZA. Gastroenteritis in children. In: Kliegman RM, Stanton BF, Schol NF, St Geme III JW, Behrman RE, editors. Nelson Textbook of Pediatrics. 19th ed. Philadelphia: Elsevier; 2011. p.1323–39.
- Guarino A, Albano F, Ashkenazi S, Gendrel D, Hoekstra JH, Shamir R, et al; European Society for Paediatric Gastroenterology, Hepatology; Nutrition/European Society for Paediatric Infectious Diseases. European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe. J Pediatr Gastroenterol Nutr. 2008; 46(Suppl 2):S81–122. [DOI: 10.1097/MPG.0b013e31816f7b16] [PMID: 18460974]
- Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al.; Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012; 379(9832):2151–61. [DOI: 10.1016/S0140-6736(12)60560-1] [PMID: 22579125]
- UNICEF/WHO. Diarrhoea: Why children are still dying and what can be done. Geneva/New York: UNICEF, WHO; 2009.
- Elliott EJ. Acute gastroenteritis in children. BMJ. 2007; 334(7583):35–40. [DOI: 10.1136/bmj.39036.406169.80] [PMID: 17204802]

9. Pickering LK. Approach to diagnosis and management of gastrointestinal tract infections. In: Long SS, Pickering LK, Prober CG, editors. *Principles and Practice of Pediatric Infectious Disease*. 2nd ed. New York: Churchill Livingstone; 2003. p.362-8.
10. Musher DM, Musher BL. Contagious acute gastrointestinal infections. *N Engl J Med*. 2004; 351(23):2417-27. [DOI: 10.1056/NEJMr041837] [PMID: 15575058]
11. Radlovic NP, Trisic B, Radlovic NP, Vuletic BP, Djurdjevic J, Berenji K, et al. The prevalence of intrahospital-acquired Rotavirus gastroenteritis at a pediatric gastroenterology department. *Child Care Health Dev*. 2010; 36(1):82.
12. Nylund CM, Goudie A, Garza JM, Fairbrother G, Cohen MB. Clostridium difficile infection in hospitalized children in the United States. *Arch Pediatr Adolesc Med*. 2011; 165(5):451-7. [DOI: 10.1001/archpediatrics.2010.282] [PMID: 21199971]
13. Sammons JS, Toltzis P, Zaoutis TE. Clostridium difficile Infection in children. *JAMA Pediatr*. 2013; 167(6):567-73. [DOI: 10.1001/jamapediatrics.2013.441] [PMID: 23460123]
14. Roy CC, Silverman A, Alagille D. *Pediatric Clinical Gastroenterology*. 4th ed. St Louis: Mosby; 1995.
15. Hodges K, Gill R. Infectious diarrhea: cellular and molecular mechanisms. *Gut Microbes*. 2010; 1(1):4-21. [DOI: 10.4161/gmic.1.1.11036] [PMID: 21327112]
16. Argudin MA, Mendoza MC, Rodicio MR. Food poisoning and Staphylococcus aureus enterotoxins. *Toxins*. 2010; 2(7):1751-73. [DOI: 10.3390/toxins2071751] [PMID: 22069659]
17. Grass JE, Gould LH, Mahon BE. Epidemiology of foodborne disease outbreaks caused by Clostridium perfringens, United States, 1998-2010. *Foodborne Pathog Dis*. 2013; 10(2):131-6. [DOI: 10.1089/fpd.2012.1316] [PMID: 23379281]
18. Hood K, Nuttall J, Gillespie D, Shepherd V, Wood F, Duncan D, et al. Probiotics for Antibiotic-Associated Diarrhoea (PAAD): a prospective observational study of antibiotic-associated diarrhoea (including Clostridium difficile-associated diarrhoea) in care homes. *Health Technol Assess*. 2014; 18(63):1-84. [DOI: 10.3310/hta18630] [PMID: 25331573]
19. Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA*. 2012; 307(18):1959-69. [DOI: 10.1001/jama.2012.3507] [PMID: 22570464]
20. Zuckerman JM. Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. *Infect Dis Clin North Am*. 2004; 18(3):621-49, xi. [DOI: 10.1016/j.idc.2004.04.010] [PMID: 15308279]
21. Abraham B, Sellin JH. Drug-induced diarrhea. *Curr Gastroenterol Rep*. 2007; 9(5):365-72. [PMID: 17991336]
22. Qin HY, Cheng CW, Tang XD, Bian ZX. Impact of psychological stress on irritable bowel syndrome. *World J Gastroenterol*. 2014; 20(39):14126-31. [DOI: 10.3748/wjg.v20.i39.14126] [PMID: 25339801]
23. Reisinger EC, Fritzsche C, Krause R, Krejs GJ. Diarrhea caused by primarily non-gastrointestinal infections. *Nat Clin Pract Gastroenterol Hepatol*. 2005; 2(5):216-22. [DOI: 10.1038/ncpgasthep0167] [PMID: 16265204]
24. Radlovic N, Milosavljevic S, Deura L, Andrejic B, Paripovic V, Jovanovic I, et al. Rotavirus gastroenteritis in children: our clinical experience. *G Mal Infett Parassit*. 1990; 42:683-5.
25. Radlovic N, Stepanovic R, Milosavljevic S, Paripovic V, Miličević J, Andrejic B, et al. Treatment of Campylobacter enterocolitis in children. *Zoonoses Congress, Brno 1988; Abstracts*, p.4.18.
26. Radlovic N, Trisic B, Radlovic P, Djurdjevic J, Vuletic B, Vujnovic Z, et al. Clinical characteristics of rotavirus gastroenteritis in children. *Acta Paediatr*. 2011; 100(Suppl 463):35.
27. Lewy JE. Nephrology: Fluid and electrolytes. In: Behrman RE, Kliegman RM, editors. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders Comp; 1994. p.573-610.
28. Shelov S, Stewart CL, Kaskel FJ. Principles of pediatric nutrition, fluids and electrolytes. In: Bernstein D, Shelov S, editors. Philadelphia: Williams & Wilkins; 1996. p.69-90.
29. Greenbaum LA. Pathophysiology of body fluids and fluid therapy. In: Kliegman RM, Stanton BF, Schor NF, Geme III JW, Behrman RE, editors. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia: Elsevier Saunders; 2011. p.212-42.
30. Finberg L. Dehydration in infancy and childhood. *Pediatr Rev*. 2002; 23(8):277-82. [PMID: 12154234]
31. Needham E. Management of acute renal failure. *Am Fam Physician*. 2005; 72(9):1739-46. [PMID: 16300036]
32. Motoyama M, Ichiyama T, Matsushige T, Kajimoto M, Shiraishi M, Furukawa S. Clinical characteristics of benign convulsions with rotavirus gastroenteritis. *J Child Neurol*. 2009; 24(5):557-61. [DOI: 10.1177/0883073808327829] [PMID: 19168832]
33. Altindis M, Yavru S, Simsek A, Ozkul A, Ceri A, Koc H. Rotavirus infection in children with acute diarrhea as detected by latex agglutination, ELISA and polyacrylamide gel electrophoresis. *Indian Pediatr*. 2004; 41(6):590-4. [PMID: 15235165]
34. Garcia LS, Shimizu RY, Bernard CN. Detection of Giardia lamblia, Entamoeba histolytica/Entamoeba dispar, and Cryptosporidium parvum antigens in human fecal specimens using the triage parasite panel enzyme immunoassay. *J Clin Microbiol*. 2000; 38(9):3337-40. [PMID: 10970380]
35. Powell KR. Fever. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors. *Nelson Textbook of Pediatrics*. 18th ed. Philadelphia: Elsevier; 2007. p.1084-7.
36. Section on Clinical Pharmacology and Therapeutics; Committee on Drugs, Sullivan JE, Farrar HC. Fever and antipyretic use in children. *Pediatrics*. 2011; 127(3):580-7. [DOI: 10.1542/peds.2010-3852] [PMID: 21357332]
37. Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. *J Pediatr Gastroenterol Nutr*. 2014; 59(1):132-52. [DOI: 10.1097/MPG.0000000000000375] [PMID: 24739189]
38. Greenbaum LA. Maintenance and replacement fluid therapy. In: Kliegman RM, Stanton BF, Schol NF, St Geme III JW, Behrman RE, editors. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia: Elsevier; 2011. p.242-9.
39. Whyte DA, Fine RN. Acute renal failure in children. *Pediatr Rev*. 2008; 29(9):299-306. [DOI: 10.1542/pir.29-9-299] [PMID: 18765468]
40. WHO/UNICEF. The management of diarrhoea and use of oral rehydration therapy. A joint WHO/UNICEF statement; 1985.
41. Binder HJ, Brown I, Ramakrishna BS, Young GP. Oral rehydration therapy in the second decade of the twenty-first century. *Curr Gastroenterol Rep*. 2014; 16(3):376. [DOI: 10.1007/s11894-014-0376-2] [PMID: 24562469]
42. Radlović V, Leković Z, Radlović N, Lukac M, Ristić D, Simić D, et al. Significance of the application of oral rehydration solution to maintain water and electrolyte balance in infants with ileostomy. *Srp Arh Celok Lek*. 2013; 141(5-6):325-8. [DOI: 10.2298/SARH1306325R] [PMID: 23858801]
43. Report of an ESPGAN Working Group. Recommendations for composition of oral rehydration solutions for the children of Europe. *J Pediatr Gastroenterol Nutr*. 1992; 14:113-5. [PMID: 1573500]
44. World Health Organization. 25 years of ORS – Joint WHO/ICDDR, B Consultative meeting on ORS formulation – Dhaka, Bangladesh, 10-12 December 1994.
45. Vuletić B, Radlović N, Leković Z, Ristić D, Mladenović M, Pavlović M, et al. Ishrana odojčadi sa rotavirusnim gastroenteritisom. *Hrana i ishrana*. 2008; 49:30-6.
46. Fassano A. Intestinal infections. In: Walker AW, Durie PR, Hamilton RJ, Walker-Smith JA, Watkins JB, editors. *Pediatric Gastrointestinal Disease*. 3rd ed. Hamilton: BC Decker Inc; 2000. p.463-84.
47. Guarner F, Khan AG, Garisch J, Eliakim R, Gangl A, Thomson A, et al; World Gastroenterology Organization. World Gastroenterology Organisation Global Guidelines: probiotics and prebiotics October 2011. *J Clin Gastroenterol*. 2012; 46(6):468-81. [DOI: 10.1097/MCG.0b013e3182549092] [PMID: 22688142]
48. Faure C. Role of antidiarrhoeal drugs as adjunctive therapies for acute diarrhoea in children. *Int J Pediatr*. 2013; 2013:612403. [DOI: 10.1155/2013/612403] [PMID: 23533446]
49. Del Piano M, Carmagnola S, Andorno S, Pagliarulo M, Tari R, Mogna L, et al. Evaluation of the intestinal colonization by microencapsulated probiotic bacteria in comparison with the same uncoated strains. *J Clin Gastroenterol*. 2010; 44(Suppl 1):S42-6. [DOI: 10.1097/MCG.0b013e3181ed0e71] [PMID: 20697290]
50. Del Piano M, Carmagnola S, Ballarè M, Sartori M, Orsello M, Balzarini M, et al. Is microencapsulation the future of probiotic preparations? The increased efficacy of gastro-protected probiotics. *Gut Microbes*. 2011; 2(2):120-3. [DOI: 10.4161/gmic.2.2.15784] [PMID: 21637030]
51. Riaz QU, Masud T. Recent trends and applications of encapsulating materials for probiotic stability. *Crit Rev Food Sci Nutr*. 2013; 53(3):231-44. [DOI: 10.1080/10408398.2010.524953] [PMID: 23215997]

Акутна дијареја код деце

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КРАТАК САДРЖАЈ

Акутна дијареја је најчешћи гастроинтестинални поремећај и главни узрок дехидратације у деçкој доби. Манифестује се наглом појавом три или више течних или обилних столица дневно у трајању од седам до десет дана, најдуже 14 дана. Најчешће погађа децу у првих пет година по рођењу, а посебно одојчад у другом полугођу и децу узраста до три године. Њени примарни узроци су гастроинтестиналне инфекције (вирусне и бактеријске), а ређе алиментарне интоксикације и други фактори. Будући да су дехидратација и негативан нутритивни биланс главне компликације акутне дијареје, јасно је да ће надокнада губитка телесне течности

и одговарајућа исхрана чинити основу њеног лечења. Друге терапијске мере, изузимајући антипиретике ако је дете високо фебрилно, антипаразитне лекове уколико су заступљене интестинална ламблијаза и амебијаза, и пробиотике, ретко су потребне. То се примарно односи на некритичку употребу антибиотика и цревних антисептика у лечењу бактеријских дијареја. Примена антиеметика, антидијареика и спазмолитика је беспотребна и потенцијално ризична, те се не саветује код деце с акутном дијарејом.

Кључне речи: акутна дијареја; етиопатогенеза; дијагностика; лечење

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Accurate Completion of Medical Report on Diagnosing Death

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SUMMARY

Diagnosing death and issuing a Death Diagnosing Form (DDF) represents an activity that carries a great deal of public responsibility for medical professionals of the Emergency Medical Services (EMS) and is perpetually exposed to the control of the general public. Diagnosing death is necessary so as to confirm true, to exclude apparent death and consequentially to avoid burying a person alive, i.e. apparently dead. These expert-methodological guidelines based on the most up-to-date and medically based evidence have the goal of helping the physicians of the EMS in accurately filling out a medical report on diagnosing death. If the outcome of applied cardiopulmonary resuscitation measures is negative or when the person is found dead, the physician is under obligation to diagnose death and correctly fill out the DDF. It is also recommended to perform electrocardiography (EKG) and record asystole in at least two leads. In the process of diagnostics and treatment, it is a moral obligation of each Belgrade EMS physician to apply all available achievements and knowledge of modern medicine acquired from extensive international studies, which have been indeed the major theoretical basis for the creation of these expert-methodological guidelines. Those acting differently do so in accordance with their conscience and risk professional, and even criminal sanctions.

Keywords: expert-methodological guidelines; medical report; diagnosing death

INTRODUCTION

Cardiopulmonary resuscitation (CPR) represents a sequence of procedures with the goal of restoring spontaneous circulation and breathing in resuscitated persons [1].

CARDIAC ARREST

Cardiac arrest (CA) is the leading cause of death in the world, with an annual incidence of about 700,000 cases in Europe alone [2]. As one of the most emergent medical conditions, CA is the most frequent out-of-hospital (OH) occurring event [1]. According to the Utstein definition, CA is the cessation of cardiac mechanical activity as confirmed by the absence of consciousness, palpable pulse and apnea or agonal breathing [3].

Clinical death is the condition occurring immediately after the cessation of breathing and heartbeat, and before the brain cells die, when it is still possible to resuscitate the person by CPR. The time period from the cessation of breathing and/or heartbeat until the brain cells die is variable, but it mostly lasts from three to five minutes. Hypoxic brain injury develops four minutes after CA and is irreversible unless CPR is initiated during the next 12 minutes. Exceptions are children, patients with hypothermia or acute poisoning [1].

The norm is to resuscitate any patient who has a chance of recovery, or when there are no sufficient data on the mechanism of injury, i.e. on the course of the patient's pathological con-

dition [4, 5, 6]. In hypothermic and drowning persons or if CA cause is unclear, the process of resuscitation should be immediately initiated.

CPR is not initiated if CA had lasted for more than 20 minutes, if asystole confirmed in two leads lasts for over 30 minutes, in terminal phase of incurable diseases, in case of evident signs of sure death, signs of tissue decomposition and in case of severe destructive injuries evidently incompatible with life [6, 7].

There are general rules on the duration of CPR [1, 3]. CPR should be continuously applied until spontaneous circulation has been restored or as long as there is pulseless VF/VT. CPR is prolonged in a CA caused by hypothermia.

Cessation of CPR is justified when there are signs of irreversible cardiac death (asystole confirmed in two leads lasting for over 30 minutes despite CPR) [3].

CA is diagnosed by rapid triage of certain and uncertain signs [8].

A. Certain signs of CA: loss of consciousness, cessation of breathing (agonal breathing or apnea) and absent carotid pulses.

B. Uncertain signs of CA: changed color of the skin and visible mucosa, mydriasis and EKG recording.

DIAGNOSING DEATH

Diagnosing death is performed based on the signs of death, which, defined on their confirmed values, are divided into three groups: uncertain, probable and certain [9].

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Type of death

Agony or death rattle is a collection of all events that precede a quick or slow death.

Apparent death is the condition when life activities are reduced to a minimum compatible with life. It can last for hours, but 24 hours at the most. Apparent death can be suspected in the following cases:

- if minimal life activities can be noted,
- if probable and certain signs of death have not manifested within the usual time,
- in sudden death of adults and children,
- in poisoning with psychoactive substances, hypothermia, apoplexy, uremia.

In such cases CPR should be applied rapidly and without exception, in accordance with official protocols.

True death implies an irreversible cessation of the activity of the central nervous system and essential life functions, circulation and breathing, which is followed by the occurrence of the signs of death.

COMPLETION OF MEDICAL REPORT FORM

In the Medical Report Form (MRF) (Figure 1), check the box indicating the degree of emergency, state the time the call was received by the medical emergency telephone service and the time of dispatching it to the Emergency Medical Team (EMT).

State the patient's personal data obtained by the dispatcher and the patient's address, and whether the intervention is in a public place or at the patient's residence or other location. State the reason for the call to the EMT. Unless police officers are already present, and the EMT assesses that their assistance would be needed, inform the dispatcher about it. Call the police in case of any of the following:

- Unsafe approach to event location;
- Verbal or physical attack on the EMT;
- Impossibility to identify the deceased;
- Death of a foreigner or death at someone else's residence;
- Sudden death;
- Obscure circumstances of death occurrence;
- Violent death;
- Evidence of violence;
- Death at a public site;
- Death in the emergency vehicle during transport and
- Unwitnessed death.

On arrival at the site, state data from the identification document (ID) with a photo of the bearer (ID card, passport, refugee ID, driver's license): patient's first name and surname, Unique Master Citizen Identifier (UMCI), address, place of residence and ID number [10].

For deceased newborns without a registered name in the Register of Births prior to death, the following data is stated: male/female newborn with maternal first name, middle name and surname.

If reliable identification of the deceased is not possible in any of the aforementioned ways, the physician is obliged

to pass the information immediately to the competent police office. MRF with personal data obtained heteroanamnestically cannot be issued for an unidentified deceased person; instead, such a person is referred to by a placeholder name N.N., with stated gender and approximately assessed age.

For children up to the age of seven days, also fill in hour and minute of birth from the medical record or heteroanamnesis in case of newborns born at home before the arrival of the EMT.

State the place of residence from the ID, house number and name of the street or inhabited settlement, municipality, and the republic of the last (permanent) place of residence of the deceased.

For foreigners who die on the territory of Serbia the following is to be stated: place of residence and the country of origin, i.e. permanent place of residence until the moment of death.

For refugees and displaced persons from the territory of Kosovo and Metohija state the following: name of the street and house number, place and municipality of the last residence.

As the place of residence of a deceased newborn state the paternal place of residence if father is the citizen of the Republic of Serbia while mother is a foreigner with the place of residence abroad.

Stated time entries are the crucial part of the MRF and sometimes only they can successfully defend us at court proceedings! [5]

For these reasons it is necessary to indicate exact date of intervention and precisely fill in all the times in the MRF:

- Time of call received by the medical emergency telephone service;
- Time when the call was dispatched to the EMT;
- Time of the EMT arrival at site of event and
- Time when the intervention is completed and the EMT informs the dispatcher of being free for the next dispatch.

Taking anamnesic/heteroanamnesic data

This is the most significant part of the MRF in case of diagnosing death; therefore, data should be taken precisely and carefully filled in. It is necessary to state data on previous diseases and treatment obtained anamnestically/heteroanamnestically and from medical records if available [11].

If the patient is encountered with vital signs, but death occurred during the intervention [12], the following should be done:

- Describe main complaints;
- Indicate the time of complaints onset, describe their course and dynamics;
- Indicate the time of CA onset during intervention and previously applied diagnostic and therapeutic measures;
- Describe encountered body position;
- Describe circumstances under which CA developed;

MEDICAL REPORT FORM

PATIENT: ☐ M ☐ F Street: _____ Municipality: ☐ street ☐ courtyard ☐ entrance floor ☐ Flat No: _____ Reason for calling EMS: _____ Caller's tel: _____ WHO CALLED? _____ ☐ PRESENT POLICE ☐ PUBLIC PLACE ☐ APARTMENT		AGE NUMBER _____ TEAM _____		PATIENT'S ADDRESS: type _____ healthcare booklet No. _____ HEALTH INSURANCE NUMBER _____ UNIQUE MASTER CITIZEN IDENTIFIER _____ REPUBLIC FOUND OF HEALTH INSURANCE _____ Price _____ din. registration number: _____		DAY MONTH YEAR _____ : _____ : _____ Call received at TC _____ : _____ : _____ EMS team received call at: _____ : _____ : _____ EMS team arrival at site of event: _____ : _____ : _____ Time of intervention: _____ : _____ : _____																																																				
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Legend:

RTS – revised trauma score; SBP – systolic blood pressure; RR – respiratory rate; GCS – glasgow coma scale; BP – blood pressure; ECG – electrocardiography; SVES – supraventricular extrasystoles;

SVT – supraventricular tachycardia; VES – ventricular extrasystoles; VT – ventricular tachycardia; VF – ventricular fibrillation; AV – atrioventricular blocks; SPINE (C – cervical; TH – thoracic; L – lumbar; S – sacral); L – left; R – right.

Figure 1. Medical Report Form

DEATH DIAGNOSING FORM

0000000

SURNAME, PATERNAL NAME AND FIRST NAME OF DECEASED

SEX

M ☐

F ☐

PLACE AND DATE OF BIRTH:

TIME OF DEATH DIAGNOSING:

PLACE OF DEATH:

PRESENT

YES ☐

(CALLED) POLICE

NO ☐

(Street and number)

In

year

(Signature and facsimile of physician certifying death)

Note: This form cannot be used to bury the deceased. For further procedures contact the Office for Certification of Time and Cause of Death, and in suburbs a relevant healthcare center. Tel. 011/323-14-23; 0-24h.

Figure 2. Death Diagnosing Form

- Indicate initial rhythm of CA and state the changes of rhythm if developed;
 - Indicate if CPR was performed and define the diagnostic algorithms, and describe the response to applied CPR measures;
 - If CPR is not performed, state reasons for this decision.
- If the patient is encountered without vital signs, state the following significant heteroanamnesic data obtained by the present persons:
- Whether CA occurred in the presence of witnesses, and state as precisely as possible the time from which the person was without signs of life, and duration of the state;
 - Whether basic resuscitation measures were applied by witnesses before EMT arrival, which ones and their duration;
 - If CA occurred without the presence of witnesses, state the time of the last contact with the victim;
 - Circumstances under which CA occurred;
 - Position in which the person was encountered;
 - All visible signs of CA, visible signs of violence, visible injuries [5];
 - Uncertain, probable or certain signs of death if present;
 - Data on previous diseases and treatment;

- If CPR is not performed, state reasons for this decision [13].
- If indications are determined for CPR initiation or CPR continuation if already started by laymen, state the following: whether CPR was performed and under which algorithms [1]; time of CPR initiation; initial rhythm of CA; response to applied CPR measures, state changes of CA initial rhythm if developed; final outcome of CPR.
- In physical findings describe vital functions, changes of vital parameters, if developed, and the time when the changes were detected. Also, describe visible injuries and signs of violence if present, and mark initial arrest rhythm and its changes, if developed [14].
- In the part of the MRF referring to therapeutic measures and procedures state the following:
- Applied CPR measures;
 - Administered drugs, the dosage, as well as the mode and time of drug administration [1, 5].
- If the outcome of CPR was negative, record EKG findings and note asystole in at least two leads. Attach the recording to the Death Diagnosing Form (DDF) – it is advised to make the recording in two copies; a copy is filed with a copy of the DDF [15, 16].
- In the adequate box of the MRF state the number of the DDF and the time of the diagnosed death [17]. Also, in

the provided box, state the working diagnosis, as well as other diagnoses, with appropriate ICD codes. The physician has an obligation to confirm the completed MRF with a signature and a valid facsimile[10].

COMPLETION OF THE DEATH DIAGNOSING FORM

If an intervention ends with a lethal outcome for the patient, the physician is under obligation to complete the DDF (Figure 2). This form is printed in duplicate. The original of the form is left to the relatives of the deceased or police officers if present at the intervention, while the duplicate is kept by the physician [18].

Paternal first name, deceased's name, surname and place and date of birth – these data are obtained from the ID with a photo of the bearer. If such a document is unavailable, then the deceased is given a placeholder name N.N., and only gender and age according to the physician's evaluation are stated.

Place of death – state the exact address where death was pronounced.

Time of ascertained death (day, hour and minute) [10, 15]. If, based on the available data and performed examination, the physician assesses that there are no indications for initiating CPR, the time when this decision is made as well as the time of diagnosed death are filled into the form.

If CPR was necessary and performed sufficiently long according to the corresponding protocol, but with a negative outcome, the time of ascertained death is the time when the decision was made to stop CPR, which is when, at the end, asystole is confirmed by EKG in at least two leads. It is also recommended that such an EKG recording should be attached to the DDF.

The number of the DDF is entered into the MRF in the appropriate box, as well as the time of diagnosed death.

And finally, the physician is obliged to put a readable signature and a valid facsimile at the end of the form.

Note: It is not allowed to bury the deceased using this form only. The Office for the Certification of the Time and Cause of Death is authorized for further procedures regarding deceased persons on the territory of Belgrade, Serbia. Telephone number of this Office is stated at the right footer of the page. In the city suburbs the relevant healthcare center has the same role.

At the end, moral obligation of each EMT physician is to apply, in the process of diagnostics and treatment, all available achievements and knowledge of modern medicine acquired from extensive international studies, which have been indeed the major theoretical basis for the creation of these expert-methodological guidelines [19]. Those acting differently do so in accordance with their conscience and risk professional, and even criminal sanctions [20].

REFERENCES

- Andjelic S. A prediction survival model for out-of-hospital cardiopulmonary resuscitations. *J Crit Care.* 2011; 26(2):223.e11-8. [DOI: 10.1016/j.jcrc.2010.06.001] [PMID: 20655699]
- Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA.* 2008; 300(12):1423-31. [DOI: 10.1001/jama.300.12.1423] [PMID: 18812533]
- Andjelic S, Djordjevic N. Out-of-hospital cardiopulmonary resuscitation in four Serbian university cities: outcome follow-up according to the "Utstein style". *Signa Vitae.* 2010; 5(1):27-33.
- British Medical Association. Decisions relating to cardio-pulmonary resuscitation. A joint statement from the British Medical Association, The Resuscitation Council and the Royal College of Nursing. London: Ethics Department, British Medical Association; 2002.
- Andjelic S, Panic G, Sijacki A. Emergency response time after out-of-hospital cardiac arrest *Eur J Intern Med.* 2011; 22(4):386-93. [DOI: 10.1016/j.ejim.2011.04.003] [PMID: 21767757]
- Andjelić S, Ivančević N, Bogunović S. Reaction times as indicators of the quality of expert work of Belgrade municipal institutions for emergency medical services. *Central European Journal of Medicine.* 2012; 8(1):90-5. [DOI: 10.2478/s11536-012-0102-0]
- Savić S. Smrt i utvrđivanje smrti. In: Vučović D i sar., editors. *Urgentna medicina.* Beograd: Obeležja; 2002. p.1235-6.
- Andjelić S, editor. *Vanbolnička kardiopulmonalna reanimacija odraslih.* Beograd: Zadužbina Andrejević; 2008.
- International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). Geneva: Center for Health Statistics. Centers for Disease Control and Prevention (CDC); 2010.
- Pravilnik o postupku izdavanja potvrde o smrti i obrascu potvrde o smrti. Službeni glasnik RS, br. 25/2011.
- Zollinger U, Plattner T. The unusual cause of death – a special assignment for the doctor in emergency service. *Ther Umsch.* 2005; 62(6):413-8. [DOI: 10.1024/0040-5930.62.6.413] [PMID: 15999940]
- Canas F, de la Grandmaison GL, Guillou PJ, Jeunehomme G, Durigon M, Bernard MH. Medical and legal problems of death certificates. *Revue Prat.* 2005; 55(6):587-94. [PMID: 15913109]
- Lockey AS. Recognition of death and termination of cardiac resuscitation attempts by UK ambulance personnel. *Emerg Med J.* 2002; 19(4):345-7. [DOI: 10.1136/emj.19.4.345] [PMID: 12101156]
- Savić S. Hirurška intervencija i lekarska odgovornost. In: Stevović D. i sar., editors. *Hirurgija za studente i lekare.* Beograd: Savremena administracija; 2000.
- Nguyen F, Mathy F, Hervé C, Lorin de la Grandmaison G, Charlier P. How to complete a death certificate? *Rev Prat.* 2012; 62(6):759-63. [PMID: 22838264]
- Savić S. Physicians' responsibility between social criticism, legal rules, and medical ethics. *Medical Data Rev.* 2009; 1(3):37-41.
- Robbins JA. Commentary: death certificate reporting needs to be fixed. *J Public Health Policy.* 2012; 33(2):215-7. [DOI: 10.1057/jphp.2012.5] [PMID: 22358122]
- Walker S, Rampatige R, Wainiqolo I, Aumua A. An accessible method for teaching doctors about death certification. *HIM J.* 2012; 41(1):4-10. [PMID: 22408110]
- Monsó i Fernández C. Signing the death certificate: legality and ethics. *Aten Primaria.* 2012; 44(4):e20-2. [DOI: 10.1016/j.aprim.2011.07.012] [PMID: 22019061]
- Collier R. Managing an expected home death. *CMAJ.* 2012; 184(4):396-7. [DOI: 10.1503/cmaj.109-4101] [PMID: 22311948]

Правилно попуњавање лекарског извештаја приликом констатације смрти

Слободан Савић¹, Ђорђе Алемпијевић¹, Слађана Анђелић²

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²Градски завод за хитну медицинску помоћ, Београд, Србија

КРАТАК САДРЖАЈ

Дијагностиковање смрти и издавање потврде о утврђивању смрти је одговорна и професионална јавна активност лекара службе хитне медицинске помоћи (ХМП), која је стално изложена контроли грађана и јавности уопште. Дијагностиковање смрти је неопходно како би се потврдила права смрт и искључила привидна смрт, тј. да би се на тај начин избегло сахрањивање живих, односно привидно мртвих особа. Циљ овог стручно-методолошког упутства, заснованог на савременим медицинским подацима, јесте да помогне лекарима ХМП при правилном попуњавању лекарског извештаја о дијагностиковању смрти. Уколико је исход примењених мера реанимације негативан или када је особа пронађена мртва, лекар је дужан да дијагностикује смрт и

правилно попуни формулар о дијагностиковању смрти. Такође се препоручује ЕКГ преглед и да се региструје асистолија у најмање два одвода. Морална обавеза сваког лекара ХМП јесте да током поступка дијагностиковања и лечења примени сва расположива достигнућа и знања савремене медицине, стечена на основу екстензивних међународних студија, што је свакако била главна теоријска основа за стварање овог стручно-методолошког упутства. Они који се у своме раду понашају другачије чине то по својој савести, долазећи у ситуацију да због тога професионално – па и кривично – одговарају.

Кључне речи: стручно-методолошко упутство; извештај лекара; дијагностиковање смрти

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Сарадња лекара Емериха Линденмајера и архитекте Јана Невола на обнови амама у Сокобањи

Гордана Митровић, Марина Нешковић

Републички завод за заштиту споменика културе – Београд, Београд, Србија

КРАТАК САДРЖАЈ

Амам у Сокобањи је изузетан пример дводелних амама, карактеристичан у стилском, типолошком и технолошком груписању здања ове врсте. Један је од само два овога типа која су остала сачувана на територији Србије и једини који је до данас остао у својој првобитној функцији. О његовој изградњи сазнаје се из дефтера Видинског санџака из друге половине 16. века. У корпусу богатог градитељског наслеђа амама су јединствена остварења профаног јавног типа која су одиграла значајну улогу у развоју здравствене културе. Заснована првенствено на специфичној функцији, она имају посебан архитектонски израз и често су монументална, декоративна, маштовита у богатству облика и украса. Оправку купатила и бањских извора иницирао је кнез Милош одмах по прикључивању Сокобање Кнежевини Србији 1834. године. Тада су предузети радови на поправци мушког купатила уз које је формиран засебан простор са „кадом“ кнеза Милоша, док је женско купатило остало зарушено. Министарство унутрашњих дела је 1847. године послало тадашњег начелника Санитетског одељења др Емериха Линденмајера и архитекту Јана Невола у стручну комисију, да испитају стање амама, како би се његова оправка уврстила у радове финансиране из државног буџета. После њиховог заједничког сагледавања стања и испитивања постојећих проблема, на основу исцрпног извештаја који су доставили Министарству унутрашњих дела, током 1850. године обављени су сложени радови на обнови – на основу пројекта архитекте Јана Невола и уз његов стални надзор. Приступ који је примењен у архитектонском поступку обнове заснивао се на принципима који су владали у време градње, чиме је очувана како основна функција, тако и вредна архитектура овог здања.

Кључне речи: лековите воде; амам; обнова; лекар; архитекта

УВОД

Почетак истраживања минералних вода у Србији у новије доба везује се за период владавине кнеза Милоша, који је уследио после вишевековног раздобља сталног присуства Отоманске империје на том простору и њен непрекидни утицај на све видове живота, што је оставило за собом и бројне материјалне трагове, као и споменике духовне културе. Посебну врсту наслеђа представљају градитељска дела везана непосредно за коришћење минералних и термалних извора, као непобитни докази о организованом животу у њиховој близини, али и о њиховом коришћењу за хигијенске потребе у складу с обичајима и религијом источњачких народа. Као једно од значајнијих питања којем се кнез Милош посветио било је и стварање услова за здрав живот народа, а нарочито успостављање хигијенских навика. Његовим залагањем Србија је хатишерифом из 1830. године добила право да оснива здравствене установе и да сама брине о здравственој заштити становника, док је Сртењским уставом из 1835. године знатно унапредила однос према овом за државу значајном питању [1]. Интересовање кнеза Милоша за здравствену заштиту народа заснивало се на моралним и економ-

ским разлозима, али и жељи да постане цењени владар успешне и признате европске државе. Током прве владавине кнез Милош је допринео успостављању здравствене културе у Србији оснивањем првих болница и апотека, организовањем карантина и карантинског кордона, испитивањем хемијског састава минералних вода и првим активностима око уређивања бања [2].

Посебан проблем био је недостатак образованих људи у Србији који би својим знањем допринели изградњи и уздизању државе, због чега су одређену улогу имали странци. У Србији кнеза Милоша здравствену заштиту и послове у области градитељства вршили су најпре странци: лекари, апотекари и инжењери, потом и образовани Срби из Хабзбуршке монархије, који су краће или дуже ту остајали. Огроман удео у унапређивању земље после стицања државне независности, нарочито у решавању питања законодавства, имали су Срби из Аустроугарске, који су доносили вредности културно-цивилизацијског круга у којем су се формирали. Први лекари били су др Константин Александриди, др Вито Ромита, др Бартоломео Куниберт, др Јован Стејић, др Карло Пацек, др Емерих Линденмајер, др Стеван Мачај, др Георгије Новаковић, др Антоније Славуј и други [2-5]. Прве обра-

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зоване архитекте и инжењери у Србији били су Франц Јанке, Јан Неволу, Франц Доби, Константин Радотић, Атанасије Николић, Аугуст Церман и други [6-11].

ДОПРИНОС ЛИНДЕНМАЈЕРА И НЕВОЛА ОБНОВИ БАЊА СРБИЈЕ

У сложеном процесу уређења и изградње бања Србије посебан допринос дала је сарадња лекара Емериха Линденмајера (*Emmerich Lindenmayer*, 1806–1883) и архитекте Јана Неволу (*Jan Nevole*, 1812–1903), два државна службеника – странца.

Доласком др Линденмајера у Санитетско одељење Министарства унутрашњих дела држава је почела да организовано испитује минералне изворе и планира уређивање бањских и климатских лечилишта и насеља за лечење и опоравак [12]. Током четрнаест година рада као начелник санитета (1845–1859) Линденмајер се посветио испитивањима, уређењу и развоју српских бања организујући хемијске анализе воде, сређивање извора, откуп земљишта око извора и изградњу зграда за смештај пацијената [12]. Припремао је правна акта о обавезном присуству лекара током сезоне у бањама, о пословима бањског чувара, о општем реду у бањама. Незадовољан недовољним коришћењем бања, јер у њима нема никаквих услова за пристојан боравак, залагао се за градњу конака за смештај посетилаца и слање лекара с одговарајућим инструкцијама о саветима које треба да деле гостима током сезоне. Подстицао је коришћење минералних вода и тиме што је осмислио начин како да се она флашира и доставља корисницима. Посебно је допринео популаризацији Србије и српских бања објављивањем многих текстова у новинама, магазинима и часописима. Његова књига „Опис минералних вода и њихова употреба уопште, а понаособ лековитих вода у Књажевству Србији“ објављена је на српском и немачком језику 1856. године у Београду [13]. У овој књизи он детаљно описује лековите воде уз прецизна упутства за њихову употребу. Његово друго дело, „Србија, њен развој и напредак у санитету са напоменама о целокупном санитетском стању на Оријенту“, објављено је на немачком језику 1876. године у Темишвару [12]. Ове књиге су полазиште у изучавању историје српске медицине 19. века. Линденмајерова залагања за исправну употребу лековитих вода, која је заснована на хемијским испитивањима, заштити извора и одређивању начина примене према медицинској процени, и омогућавање њиховог коришћења изградњом одговарајућих грађевина за смештај и лечење могу се сматрати пресудним за развој бања. Његов рад на унапређењу ових специфичних насеља у заосталој и конзервативној Србији је својеврстан напор да се уведу нови културни модели по узору на државе средње Европе.

Инжењер Јан Неволу међу првим је школованим градитељима који су дошли у ослобођену Србију [6, 8, 14]. Као већ искусног архитекту по препоруци професора Јанка Шафарика, а на предлог Министарства унутрашњих дела, Совјет га је примио на рад на три

године, да израђује планове за грађевине свих врста, да надзире њихово извршење и да се стара да се јавна здања тачно и уредно подижу по плану, као и да ради на изградњи путева, регулисању села и вароши и слично [15]. Био је постављен за главног инжењера Одељења грађевина у Попечитељству унутрених дела (Министарству унутрашњих дела) 1852. године.

ПРВА КОМИСИЈА ЗА ОБНОВУ БАЊА

Од осамостаљења Србије изградњу државе и њено јачање одликују током 19. века политичка превирања и смене династија. Тако је и за време владавине кнеза Александра Карађорђевића, који је такође разумео велику важност уређивања минералних извора, настављено испитивање њихове лековитости, те су такви послови уведени „у редовно буџетирање“ [2]. Министарство унутрашњих дела добило је задатак да 1844. предвиди за следећу годину поправке у бањама. За планирање ових послова били су значајни стручни извештаји. Може се претпоставити да је почело постављање окружних инжењера на основу расписа Министарства од 18. јуна 1846. године упућеног свим окружним начелствима у којем се каже да морају водити бригу о грађевинама у своме округу [16]. Захваљујући извештајима окружних лекара и физикуса које је добијао о стању у бањама, као и сопственим запажањима, начелник Санитета Линденмајер могао је закључити да су неке од њих биле потпуно природне, без трагова деловања људи, да су у неким постојали остаци купатила, а да су негде она била у веома лошем стању [2]. Због оваквог стања у бањама, нехигијенских услова и недостатка смештаја, Министарство унутрашњих дела наложило је Линденмајеру да са државним инжењером Јаном Неволом обиђе 1849. године Брестовачку Бању, Рибарску Бању и Сокобању, како би прегледали државне грађевине и предложили мере за њихово побољшање [2]. На основу исцрпног извештаја који је Линденмајер доставио Министарству, урађени су планови за проширење бањских имања и откупљивање потребне земље [2]. Затим су започети радови на заштити и уређењу извора, обнови и изградњи купатила, као и зграда за смештај гостију.

АМАМ КАО СПЕЦИФИЧНО ГРАДИТЕЉСКО ОСТВАРЕЊЕ

У исламској архитектури амами су јединствена градитељска дела, профаног јавног карактера, која су одиграла значајну улогу у развоју здравствене културе на Балкану. Заснована првенствено на специфичној функцији, она су често монументална, декоративна, маштовита у богатству облика и украса [17, 18, 19]. Основна функција допуњавана је вештим постављањем у оквир потпуног пријатног доживљаја. Градитељи амама показивали су уметност у решавању сложених архитектонских питања, примени разних техника

градње и материјала, као и различитих конструктивних склопова. Градња оваквих грађевина је сложен и компликован посао који су обављали изузетно вешти и обучени мајстори различитих специјалности: клесари, зидари, сујолције (мајстори за градњу водовода), куршумције (мајстор за топљење олова), столари, стаклари, ковачи, казанције.

Да би се сагледала комплексност ове врсте грађевина и разумео процес њиховог коришћења, потребно је знати које су уобичајене основне просторије амама у којима се знањима градитеља усмеравају и контролишу два основна елемента – ватра и вода. То су: шадрван (чекаоница и гардероба); капалук (просторија за одмор после купања); халвате (простор за купање); трашхана (кабина – просторија ограђена даскама у којој се депилало помоћу тинктура сачињених од трава); хазна (резервоар за воду или просторија из које се вода разводила у просторије за купање кроз цеви положене у зидове; у хазну се могло ући кроз један отвор из халвата); курна (камено издубљено корито – базен); нужник (често је био у самој згради, у њега се улазило углавном из капалука, а каналима су се одводиле отпадне воде даље ван амама или у базен цехенемлук изван амама, а одатле каналом хериз даље је отицао); ђулхан (ложионица) са предпросторијом, одакле се ложило (чине га два дела – *hyrpsaustum* и *praeformium*; *hyrpsaustum* је укупани део испод целе грађевине осим испод шадрвана, сличан подруму, али не велике висине, у који се улазило из малог предворја, *praeformium*, што се надовезивало на хазну, а по унутрашњости личило на капалук. Дobar део предворја укупан је у земљу тако да је у истој висини с подом хипокауста. Улаз у хипокауст је испод казана у хазни, и ту је било огњиште у којем је ватра непрестано горела. Топли ваздух је циркулисао испод плоча и кроз многобројне цеви скривене у зидовима амама, или кроз отворе сличне димњаку, излазио на мале отворе сличне шупљим ваљцима што су били око тамбура кубета. Тако се загревала зграда, али и вода ако није била термална. Хипокауст је имао гвоздена врата). Друга врста амама имала је мејдан (предворје слично холу између купатила и халвата). Вода је довођена са извора кроз глинене (керамичке) цеви (чункове) везиване најчешће оловом. При извору се налазила једна терезија (вага или мали базен где се вода даље усмеравала), а исто тако и пред хазном, где се завршавао „водовод“. Из терезије у хазну је текла вода посебним цевима у амам, а посебним у хазну, и према потреби се могла ту и зауставити. Вишак воде је пуштан у шадрван и чесме на улици, којих је било уз амаме. У терезији се налазио цевцир (решетка или цедиљка) [20].

Извори за истраживање, као што су бројни путописи, путне белешке са цртежима, успутни осврти у разним списима у којима су описивана и дела ове монументалне архитектуре, садрже значајне податке корисне за проучавање специфичних грађевина какве су амами. Путници са Запада који су у 16. и 17. веку путовали по Истоку, према многим описима амама, очигледно су били њима опчињени, будући да се у својим крајевима нису сусретали с оваквим здањима.



Слика 1. Амам у Сокобањи – женско купатило (фото: Завод за заштиту споменика културе Ниш)

Figure 1. Hammam in Sokobanja – women's bath (photograph: Institute for Protection of Cultural Monuments Niš)

Они их описују с усхићењем, али су се чудили њиховој честој употреби, томе што се купању посвећује толика пажња и у ту сврху граде посебне монументалне грађевине. Тако је путописац Пуле (*Pouillet*) средином 17. века оставио детаљан опис изгледа и начина коришћења амама. Према његовом опису, купатила имају три просторије: у првој, са водоскоком у средини и зиданим клупама по ободу, скида се одећа и потом се прелази у другу, мању просторију, где се тело припрема за купање у главној, трећој просторији, са базеном надвишеним кубетом са малим стакленим отворима и подом поплочаним мермером (Слика 1). Он је забележио „да оно што је добро у овим купатилима јесте то што она не само што одржавају гипкост удова и нежност коже, већ и заустављају ток многих болести“ [21].

Други значајан опис амама и посебно свих фаза процеса употребе купатила, као обавезног дела друштвеног живота, обичаја и навика у јавном простору, дао је Никола де Николе (*Nicolas de Nicolay*, 1517–1583) [20]. Према његовом опису, то су раскошно грађене зграде с неколико просторија, обложене мермером или каменим плочама. Он је нагласио да се у амам одлази ради здравља и зато што то људе чини лепшим. Третман у амаму састоји се од неколико поступака према утврђеном редоследу, при чему се прелази из просторије у просторију. После свлачења и одлагања одеће у првој просторији, која је имала улогу чекаонице и гардеробе, а на чијој се средини налазио водоскок (шадрван), људи су седели на миндерлуцима (каменим клупама уз зид). Потом су одлазили у следећу просторију, где се обављала депилација, затим у собу у којој је била виша температура, са столовима или великом каменом плочом на средини. Ту се лежало и знојило, после чега су амамске слуге (телаци) посетиоцу детаљно прали и трљали тело, а затим масирали, па поново прали и трљали. У просторије где су биле каде или базени одлазило се после депилације и темељног прања, а тек после базена обављала се масажа. На крају се одлазило поново у прву просторију са шадрваном, где се чекало да се тело осуши и где се често водио некакав друштвени живот.

РАДОВИ НА ОБНОВИ АМАМА У СОКОБАЊИ

Амам у Сокобањи изузетан је пример, карактеристичан у стилском, типолошком и технолошком груписању здања ове врсте [22]. Овај репрезентативни дводелни амам до данас је у непромењеној употреби, а како се налази у једној од најпознатијих бања, и веома је посећен. Амам је двострука (чифте) лековита бања (каплица) за истовремено одвојено купање мушкараца и жена (Слика 2).

Старо купатило у Сокобањи међу ретким је сачуваним аутентичним комплексима ове врсте, а чине га четири спојене грађевине из различитих епоха – дводелни амам (16. век), крило с кадама и улазним тремом с аркадама (из 1880. године) и инхалаторијум (20. век) [23]. Сокобањски амам саграђен је од камена неправилног облика повезаног кречним малтером, углавном измешаним са „кечетом“ – саструганом длаком са говеђе коже. Зидови су знатне ширине, при чему су спољни дебљи од унутрашњих. Унутрашњи зидови малтерисани су водонепропусним кречним малтером црвенкасте боје. Подови су поплочани дебелим каменим плочама. И мушко и женско купатило су засведени по једном куполом коју носе декоративно обрађени пандантифи (Слика 3). Најстарији турски покривач био је олово, док је после обнове кнеза Милоша амам био покривен ћерамидом.

Прву поправку у 19. веку оштећеног бањског извора и купатила наредио је кнез Милош одмах по прикључивању Сокобање Кнежевини Србији 1834. године [2]. Суд Нахије Бањске обавестио је кнеза писмом од 28. марта 1834. године, уз које је био приложен једноставан цртеж основе [2], да су радови отпочели, али да је због опалог малтера унутра и трагова ложења ватре питање да ли поново све треба малтерисати. У одговору је наложено да посао заврши сердар расински Милета Радојковић према упутствима кнеза Милоша [2]. Тада је поправљено само мушко купатило и у једној споредној просторији уређен је простор с кадом за кнеза Милоша (Слика 4). Женско купатило је и даље остало зарушено, будући да се недовољно вешти мајстори нису смели упустити у већи обим радова [2].

Следећи радови обављени су 1842. године, када је извршена оправка чесме хладне воде „која је к разлађивању топле воде у Амаму сведена била, са свим порушена и искварена“ [2]. Пет година касније појавио се нови проблем слабог дотока воде и недовољног пуњења резервоара. Тада је Министарство унутрашњих дела одредило комисију са задатком „да се бања потанко и тачно прегледа, да се утврди узрок опадања воде за купање и да предложи шта би и како би се томе могло помоћи“ [2]. За чланове комисије одређени су др Емерих Линденмајер, начелник Санитета, и Јан Неволе, главни државни инжењер [8]. Они су добили пуно овлашћење да могу предузети све радове који би уједно служили као припрема за темељну оправку амама. Треба напоменути и чињеницу да је Линденмајер био упознат с резултатима истраживања барона Сигмунда Аугуста Волфганга Фрајхера фон Хердера (*Sigmund*



Слика 2. Амам у Сокобањи (фото: Републички завод за заштиту споменика културе)

Figure 2. Hammam in Sokobanja (photograph: Institute for Protection of Cultural Monuments of Serbia)



Слика 3. Амам у Сокобањи – мушко купатило (фото: Завод за заштиту споменика културе Ниш)

Figure 3. Hammam in Sokobanja – men's bath (photograph: Institute for Protection of Cultural Monuments Niš)



Слика 4. Амам у Сокобањи – када кнеза Милоша (фото: Завод за заштиту споменика културе Ниш)

Figure 4. Hammam in Sokobanja – men's bath with the Prince Milos' bathtub (photograph: Institute for Protection of Cultural Monuments Niš)

August Wolfgang Freiherr von Herder, 1776–1838) [24] крајем септембра и почетком октобра 1835. године у Сокобањи (Алексиначкој бањи). Фон Хердер је написао да су у Сокобањи на старим римским зидинама саграђене турске, односно да је изнад главног извора „сазидана зграда опасана зидинама, која има куполу у којој се налази велики округли базен пречника 12 лаката, са седиштима која су постављена околу, а његова дубина је два и по лакта. Из овога базена вода отиче у такозвано сиротињско купатило, које се налази у непосредној близини, где се купају жене и деца. Све је у нареду. Надам се да ће државне власти које се баве установама од општег интереса око овог извора саградити објекте за боравак гостију и запослити бањског лекара с годишњом платом и спровести све неопходне мере. А то значи да је потребно да се сагради неколико посебних купалишта, као и једно опште купалиште за мушкарце из нижих сталежа, јер за то има довољно места, а и капацитет извора је довољан. Овај лековити извор на једном тако повољном месту могао би у том случају да постане веома благородни окрепљујући.“ Он је навео да су два извора у Сокобањи по својствима слична изворима у Пфеферу у Швајцарској и у Гаштајну код Салцбурга [24]. Линденмајер је преузео Хердеров опис [2, 24] и навео у свом извештају: „Вода има само два јака извора, по четири хазне у којима се вода сабира; један је извор с поља у хошету између они два обшти купатила с горње стране, а други у самом женском купатилу.“ [2]

Детаљан извештај о стању амама с предлогом за његову обнову Комисија је послала Министарству [2]. На основу закључака до којих је Комисија дошла може се претпоставити да су приликом испитивања наведеног проблема извршени и одређени истражни радови у темељној зони амама и на проверавању стања изворишта, каптаже и развођења воде. Подаци о начину фундаирања применом дрвених шипова могли су бити добијени само путем сондажних ископавања. У извештају се као први разлог недовољног дотока воде наводи управо конструктивно решење темеља „на кратким кочевима“, за које се даље наводи да су дуже време били у води и да, иако нису потпуно иструлили, имају знатне шупљине кроз које вода несметано отиче испод темеља. Овај разлог се може повезати и са следећом констатацијом која се у извештају наводи а то је да су две блиске грађевине (мушки и женски амам) делом сазидане над изворима. Сматрају да се престанак коришћења женског купатила може везати управо за недостатак воде, што је могао бити проблем још од његове изградње. Овај закључак може потврдити одломак опширног дефтера Видинског санцака из друге половине 16. века, који уз опис села Градашнице садржи белешку с навођењем значајног податка да је Јахја-бег завештао приходе од своје воденице за обнављање купатила „која је озидао у Сокобањи“ [25]. Испитивањем извора констатовано је да воде има довољно како за постојећа два купатила, тако и за проширење „за више од двадесет појединачних купатила“ [2]. Из свега наведеног може се закључити да је истраживање

показало да су проблеми везани за стање грађевине, а не за капацитет изворишта.

У извештају је описано и неуредно окружење амама са бројним приватним баракама које онемогућавају развој бање, с предлогом да се откупи земља и уреди простор. Према одобреном плану, Неволе је током 1848. године надгледао припремне радове „за предстојећу темељну оправку која је и 1850. с пролећа започета трудом првога Правитељственог Инжинира Г. Неволе за неколико месеци свршена“ [13]. Обнова амама била је сложен и компликован посао који је могао да обави добар познавалац технологије његовог функционисања, али и зналац технике градње и материјала. Ово је један од најсложенијих задатака који је Неволе добио да уради у некој од бања после комисијског утврђивања стања с Линденмајером. Његов приступ санирању и обнови овог специфичног здања заснивао се на начелима које данас можемо окарактерисати као начела поштовања функције и аутентичности историјске грађевине, очувања њеног просторног и конструктивног склопа и архитектонског израза. Пројекат према којем је архитекта Јан Неволе извео радове није до данас познат. О резултатима изведене обнове и изгледу амама после радова остаје до даљег да сведочи само запис др Емериха Линденмајера: „Можемо се дакле дичити са тим купатилима, и само је сажаљевати што она стара здања с поља ни у чему оправљена нису, премда то обстојатељство нешто и доброга има, јер се из тога види стародревност ти купатила.“ [13]

Због великог знања и искуства, Неволе је уживао огромно поверење власти, која му је давала многе одговорне задатке [6]. Поред обнове амама у Сокобањи, био је ангажован и у обнови старих купатила у Брестовачкој и Рибарској Бањи и надгледао је радове редовно 1850. године. Када је откупљена земља у Буковичкој Бањи 1852. године, имао је удела у планирању њеног уређења.

ЗАКЉУЧАК

Почетак истраживања минералних вода у Србији везује се за период владавине кнеза Милоша, који је посебну пажњу посвећивао побољшању основних услова живота и унапређењу здравствене културе становништва. У остваривању ових циљева посебну улогу имали су образовани стручњаци – странци које је ангажовао на пословима у различитим областима. За процес уређења и изградње бања Србије значајан допринос дала је сарадња лекара др Емериха Линденмајера и архитекте Јана Неволу, два државна службеника. Као чланови комисије Министарства унутрашњих дела они су крајем четрдесетих година 19. века извршили преглед државних грађевина у Брестовачкој, Рибарској бањи и Сокобањи, на основу чега су предложили мере за њихово побољшање. Захваљујући њиховом знању и искуству, а по свему судећи и креативној и плодној сарадњи, може се рећи да су тада остварена једна од првих мултидисциплинарних истраживања

преточена у радове на заштити и уређењу извора, обнови и изградњи купатила. У томе је несумњив удео имао др Линденмајер, као изванредан познавалац коришћења лековитих вода и њиховог „благоделатног“ дејства на здравље људи.

Сложена питања обнове амама у Сокобањи архитекта Јан Неволе успешно је решио кроз јединство поштовања основне функције и процеса коришћења

лековитих вода и очувања аутентичности и историчности здања у којима се тај процес одвија. Задржавањем затеченог просторног и конструктивног склопа грађевине, првобитних облика, примењених материјала и техника градње, први модерни архитекта у Србији представио се и као конзерватор који је обновом овог јединственог двоструког амама сачувао његове вредности.

ЛИТЕРАТУРА

1. Ђорђевић Т. Србија пре сто година. Београд: Просвета; 1946.
2. Милајковић В. Из историје санитета у обновљеној Србији од 1804–1860 (posebna izdanja, knj. CLXXX – Odeljenje medicinskih nauka, knj. 4). Београд: SAN; 1951.
3. Stanojević V. Organizatori zdravstvene službe i istaknuti bolnički lekari starog Beograda. Godišnjak grada Beograda. 1962/1963; (9-10):171-98.
4. Stojanović V. Kultura i zdravstvo: zdravstvena služba. In: Istorija Beograda 2. Београд: Просвета; 1974. p.791-804.
5. Čolović R. 800 godina srpske medicine i 140 godina Srpskog lekarskog društva. In: Zbornik radova Trećeg naučnog skupa „800 godina srpske medicine“ (Sokolski zbornik). Београд: Српско lekarsko društvo; 2012. p.11-45.
6. Nestorović N. Građevine i arhitekti u Beogradu prošlog stoleća. Београд: Удружење Jugoslovenskih inženjera i arhitekata – Klub arhitekata; 1937.
7. Roter-Blagojević M. Nastava arhitekture na višim i visokoškolskim ustanovama u Beogradu tokom 19. i početkom 20. veka, uticaj stranih i domaćih graditelja. Godišnjak grada Beograda. 1997; (44):125-68.
8. Đurić-Zamolo D. Graditelji Beograda 1815–1914. Београд: Музеј града Београда; 1981.
9. Nestorović B. Arhitektura Srbije u XIX veku. Београд: Art Press; 2006.
10. Trgovčević L.J. Planirana elita: O studentima iz Srbije na evropskim univerzitetima u 19. veku. Београд: Službeni glasnik; Istorijski institut; 2003.
11. Trgovčević L.J. Školovanje inženjera iz Srbije na Visokoj tehničkoj školi u Berlinu do Prvog svetskog rata. PINUS Zapisi. 1997; (7):1-19.
12. Dimitrijević B, Vacić Z, editors. Dr Emerih Lindenmajer – život i delo. In: Zbornik radova 38. sastanka Sekcije za istoriju medicine Srpskog lekarskog društva, 26. oktobar 2013. godine. Београд: Српско lekarsko društvo; 2013.
13. Lindenmaer E. Opis mineralni voda i njino upotrebljenje vaopšte, a ponaosob lekoviti voda u Knjažestvu Srbiji do sada poznati. Београд: Pravitelstvenom knjigopečatnom Knjaž. Srskog; 1856.
14. Roter-Blagojević M. Jan Nevole: prvi moderni arhitekta u Beogradu. Limes plus 2013; (2):129-48.
15. Peruničić B. Aleksinac i okolina. Београд: SO Aleksinac; 1978.
16. Đurić-Zamolo D. Najraniji pravni propisi iz oblasti arhitekture i urbanizma u Srbiji XIX veka (1835–1865). In: Zbornik radova Gradska kultura na Balkanu (XV–XIX vek). Београд: Balkanološki institut SANU; 1988. p.155-157.
17. Đorđević S. Hamam u Novom Pazaru. In: Zbornik radova Raška baština 1. Kraljevo: Zavod za zaštitu spomenika kulture Kraljevo; 1975. p.137-144.
18. Andrejević A. Dva novopazarska amama. In: Godišnjak Balkanološkog instituta Balkanika VII. Београд: SANU; 1976. p.291-307.
19. Andrejević A. Islamska monumentalna umetnost XVI veka u Jugoslaviji. Kupolne džamije. Београд: Institut za istoriju umetnosti; 1984.
20. Kreševljaković H. Banje u Bosni i Hercegovini. Sarajevo: Svjetlost; 1952.
21. Samardžić R. Beograd i Srbija u spisima francuskih savremenika XVI–XVII vek. Београд: Istorijski arhiv Beograda; 1961.
22. Klinghardt K. Türkische Bäder. Stuttgart: Julius Hoffmann; 1927.
23. Mitrović G. Spas in Serbia, Hammams – old Turkish baths, Old spa baths complex in Sokobanja. In: Halacoglu Y, editor. XVth Turkish Congress of History, Ankara 2010. p.2119-2124.
24. Fon Herder S. Rudarsko putovanje po Srbiji 1835. godine (u izvodu u Beogradu 1845. fototipsko izdanje). Београд: Službeni glasnik; 2014.
25. Knežević B. Oblast Banja prema opširnom defteru iz 1560. godine. Istorijski časopis. 1995/1996; (42-43):263-6.

Collaboration between Physician Emerich Lindenmayer and Architect Jan Nevole in Restoring the Sokobanja Turkish Bath

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SUMMARY

The Sokobanja Turkish bath is an exceptional example of two-section baths and quite particular in its style, structure type and technology used. It is one of the two of the same type that remained in Serbia and the only one that has retained its original function. About its construction we learn from the Vidin sanjak defter from the second half of the 16th century. In the lavish built heritage inventory, Turkish baths are quite unique secular public structures, playing a prominent role in the development of health culture. Based upon their specific function, these baths possess a special architectural expression, are often monumental, decorative and imaginative in their forms and ornamentation. Prince Miloš initiated repair works of the Soko Banja baths and spa springs immediately after the settlement became a part of the Serbian Principality in 1834.

When work on restoring the men's baths started, a separate room with a tub was built for Prince Miloš, while the women's bath remained in ruins. In 1847, the Ministry of Interior sent Dr Emerich Lindenmayer and architect Jan Nevole, as an expert team, to assess the state of the hammam so that it could be included in the undertakings funded from the state budget. After the assessment and review of the existing issues and upon a detailed report submitted to the Ministry of Interior, complex repairs were conducted in 1850, according to Nevole's architectural design and his constant supervision. The approach implemented in the architectural renovation process was based on highly regarded principles of the time, thus preserving both the hammam's original function and its valuable architecture. **Keywords:** medicinal waters; Turkish bath; restoration; physician; architect

Pharmacology of the Renin-Angiotensin System (Farmakologija renin-angiotenzin sistema)

Author: Rajko Igić

Publisher: Medical Faculty, Banja Luka, 2014.

Book volume: 10 + 122 pages, illustrated

The renin-angiotensin system (RAS) and kallikrein-kinin systems (KKS) were discovered more than a century ago. Interestingly, both systems emerged from initial observations involving the urinary system. Renin was discovered when it was noted that extracts of rabbit kidney caused a hypertensive effect, while the hypotensive effect of intravenously injected urine led to discovery of kallikrein. Kallikrein was named according to the Greek name kallikréas (pancreas), where the highest concentration was found. The discovery of renin was dormant for several decades, until it was found that the occlusion of the renal artery in dogs caused hypertension. Soon afterwards it was discovered that renin releases an inactive decapeptide, angiotensin (Ang) I, from a substrate, angiotensinogen, and this peptide is further cleaved by Ang-converting enzyme (ACE) to octapeptide Ang II, a very strong hypertensive material.

The KKS participates in various vascular processes by the generation of two peptides: a nonapeptide, bradykinin (BK), and a decapeptide, lys-bradykinin (kallidin). Bradykinin causes hypotension, cough, and relaxation/contractions of smooth muscles. It is ten times more potent on a molecular basis than histamine. The enzyme, ACE, has a dual function – it activates Ang and inactivates BK. Thus, ACE inhibitors decrease formation of Ang II, and increase the level of BK. These effects contribute to both the therapeutic properties and the side effects of ACE inhibitors.



tors. The first orally active ACE inhibitor, captopril, was discovered by the researchers of the Squibb Company, in 1977; today we have sixteen ACE inhibitors in clinical use.

The book *Pharmacology of the Renin-Angiotensin System* has eleven chapters. The introductory ones provide a short history of the RAS and KKS. Components of the RAS (prorenin/renin, synthesis and secretion of renin) are explained with emphasis on the fast synthesis and secretion of renin by sympathetic nerve stimulation, long-lasting renin release by renal baroreceptors, and the chronic adaptive system of renin release by the ions via the macula densa. Pharmacological and clinical data of ACE inhibitors, Ang receptor blockers, and renin inhibitors are presented in three longer chapters. Another chapter examines the vasopeptidase inhibitors, including omapatrilat,

ilepatril, bosentan, and inhibitors of endothelin-1-converting enzyme (ECE-1). The final chapter is devoted to future research on the RAS.

The appendix includes a discussion of the following medical conditions relative to the RAS: arterial hypertension, heart failure, myocardial infarction, and sleep apnea. These short chapters are prepared for the non-physicians, such as pharmacists, medical biochemists, and biomedical students. Perhaps the appendix should include a chapter on nephrology as well.

The original illustrations are simple and will help the reader follow the complex relationships of the various systems (the RAS, KKS and vasopeptidases). The book includes 92 references, 15 of which are in the appendices as footnotes, and after a short biographical note about the author, there are 57 references to his publications in various journals.

Clinicians, students, and biomedical investigators dealing with study or treatment of cardiovascular disease will find this book to be an excellent guide. It may also be useful to anyone who wants to review this complex subject of pharmacology and therapeutics.

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Critical Review of the Book *The Integrated Medical Curriculum* by Raja C Bandaranayake and Strategies to Implement Integrated Medical Curriculum

Author: Raja C Bandaranayake

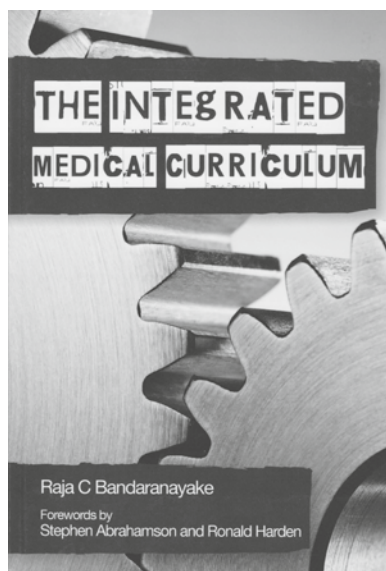
Publisher: Redcliffe Publishing Ltd, London, 2011

Book volume: 124 pages, 9 chapters

The Integrated Medical Curriculum is a book written by educationist Raja C Bandaranayake and published by Redcliffe Publishing Ltd in 2011 in London. In its nine chapters and 124 pages the author describes how to evaluate the integrated medical curriculum.

In the first chapter "Integration and the medical curriculum" the author describes the terms. Term 'integration' is defined as 'brought together into a whole' and it is illustrated through examples from mathematics, history of medicine, family, and education. Integration is not summation, but rather harmonization of already existing parts, into a meaningful composite (pre-experienced in the past). Integration has different approaches, from spiral shape to integrated curricula, where the content is presented in a more meaningful way to improve its relevance to the student. The author explained the process of applied integration and the roles of the teacher as a facilitator and the learner as a person in whose mind the integration is taking place. In general sense, education is preparation for life.

The second chapter presents the history of the integrated medical curriculum and the story of how medicine was taught, from the time of Hippocrates and his disciples until today. In the beginning, with limited medical and other knowledge, it was easy to become a polymath, who, more or less, existed until industrial times and the rapid development of technical skills. The exponential growth of knowledge led to the development of different specialties, and from 1965 to numerous subspecialties. Consequently, medical schools developed conglomerate of



complex departments, which led to the so called centrifugal curriculum, which in turn pulled students in all directions. At the same time the lack of pedagogical skills was noticed among medical teachers who weren't prepared to undertake the task of education. Very soon the disadvantage of the centrifugal curriculum appeared through dearth of generalists in the USA as significant slice of that centrifugal curriculum was designated elective. After Flexner Report the main changes happened with the development of centripetal curriculum, which engaged reflective thinking, self-directed learning, problem solving and integrating as the foundation of integrated medical curriculum. The author explains a common misconception that remains even to date – if somebody is an excellent practitioner, he must be a good medical teacher.

The last subtitle of the second chapter, "Integration of humanities with medicine," is very interesting.

It brings a meaningful explication on how doctor–patient relationship was being eroded with lack of communication abilities, which had never been taught to medical students. The importance of having the patient and not the disease as the focus of clinical practice and curriculum is clearly stated and valued. The differences in focus are due to imbalance between the disease-oriented and patient-oriented curriculum. Two different approaches are currently used for solving this problem: clinical psychologist and role-model of clinical teacher. The book is worth reading and very remarkable if only for this one paragraph. The author's view of medicine as a union of science and the art of medicine is impressive and should be widely spread among medical practitioners and students.

In the third chapter the levels and types of integration in medical curriculum and the main characteristics of integration are explained. These characteristics are correlation of components, appropriate sequencing of content, synchronization (team-teaching or "block system") and early exposure to the patient. At the same time, all advantages are potential threats to integration if not properly applied. The change from discipline-oriented or classic curriculum to an integrated one can be facilitated through the "ladder of integration," step-by-step instructions in 11 stages to reach the highest level, which is a real-life trans-disciplinary situation. The integration can be horizontal (themes at the same level) or vertical (different levels). Vertical integration is very rare in practice, due to organization of healthcare itself. Organizing themes within integrated curriculum

is still a demanding task for medical schools and is usually solved in one of three approaches: "organ-system," chronological or "multi-system unit."

In the fourth chapter integrative practices in medical curriculum and many different experiences in integration are summarized. Component-focused integration as its goal has the preparation of the basic doctor after graduation if he wants to undertake further education in some field of specialization. Horizontal integration can be applied on preclinical and clinical levels and even the author himself had a horizontal integration project in 1974. Vertical integration seems to be a supreme way of integration, where student can see the application and usefulness of knowledge, while horizontal one gives better idea of wholeness. Problem-based integration is another approach described in this chapter and it started almost simultaneously in Canada, the Netherlands and Australia in 1970/71, and its main characteristic is that students are placed in similar environment they will face later in professional life – the world of problems. Community-based integration is a learning process outside the hospital or clinic, and it has many advantages for rural areas and distant places, as well as for students who will later be in charge of these communities' health. The Philippines' experience is presented as lasting multiprofessional integration where the nucleus of health service is team work. Integration can be applied in many different ways. The best integration should envelop science and the art of medicine, with communication skills and medical ethics, with the aim of developing knowledge-based critical thinking and interprofessional collaboration, as well as emphasizing team work in health professions.

Reading this chapter demands a great deal of attention and concentration. Whatever the integration process is applied, it seems to be better than without any integration at all. We can find the statement that after graduation the basic doctor should be able to upgrade and specialize in any branch of medicine. This in turn means that they are not supposed to

be specialists when they become doctors. In many medical schools the professors are only aware of their own subject, without a holistic approach to education, which is a very common mistake. The author illustrated the advantages and even his own experience in the application of horizontal integration, but also touched on the core of difficulties by explaining the lack of logistic support and understanding of clinicians to join the team-teaching activity. The idea of vertical integration is surely more useful for students, but at the same time needs more team work than horizontal integration. From reading the author's opinion it can be concluded that a clinician is better than a basic scientist at impressing students and becoming their role model, a leader.

In the fifth chapter advantages and disadvantages of curriculum for both teachers and students are explained. The main advantages for students is the improvement of retention – they recall better and exhibit deeper learning. There is no duplication of knowledge, no redundancy; they can transfer learning, the knowledge from different subjects. The benefits are achieved only if students take part in the process and undertake integrative learning to link the knowledge for themselves. The main advantages for the teachers are self-development, and development of mutual respect for colleagues and other disciplines, as well as cooperation. Disadvantages are very few and all are consequences of poor application or misunderstanding of the concept of integration. The main disadvantage is the cost of integration in faculty time. For students it is increased anxiety at the beginning of medical school. Also, they can rarely venture deep into a specific discipline of interest.

This chapter is the crucial one. The question whether integration is a worthwhile or wasted investment finally found the answer. In brief, it is good if teachers are well prepared and if students are ready to integrate for themselves. The author however didn't forget to speak about the particular advantages and drawbacks for both students and teachers. It seems that the success of integration

depends on both parts equally. The main difficulty in implementation and success of integration comes from teachers and their willingness to spend more time in preparation, in discussion with colleagues and in readiness to change the basic approach to the problem. Students will study in whichever way, but after initial trepidation, they will get used to integration. The author also discussed a very important remark that we can still hear very often – "with integration, students have no time to go deeper into any particular field." One of the major difficulties is also defined in this chapter – it is student assessment which needs to be integrated as well. Without integrated assessment the process is not complete, and it is the responsibility of teachers alone.

In the sixth chapter the integrated student assessment is explained. Integrated curriculum needs integrated assessment. Usually, multiple choice questions are not integrated as it is difficult to make them this way, however it is possible, and this is illustrated with the example of Arabian Gulf University, which had organ-system based curriculum and integrated examination system. Free-response questions seem to be the best way of assessment to support integration. Clinical examination in the form of OSCE (objective structured clinical examination) and OSPE (objective structured practical examination) can be set in an integrated way especially if examiners use the long-lasting cases, which allow better testing of students' knowledge and understanding. The problem with integrated exams is of administrative nature, since regulatory and licensing bodies still prefer discipline to overall scores.

The author considers the possibility of testing higher cognitive abilities. These abilities are necessary for the art of being a good doctor. Unfortunately, most of medical schools have a simpler goal – to make a doctor. For many years the universal rule has been the following: the medicine has nothing to do with how smart you are, but how much time you spend learning... It's a sad reality, but with the new approach, hopefully we will

have smart doctors with applicable knowledge, instead of doctors with only brilliant marks.

In the seventh chapter the evaluation of integrated programs is discussed as very important feedback and guideline for improvement. The most suitable model of evaluation is to evaluate each of the elements of integration separately: INPUT (physical components of curriculum-actors), PROCESS (what actors do) and PRODUCTS (the outcomes and results of their doings), all under one hat of CONTEXT (traditional approach and requirement of higher education and accreditation). The use of this evaluation is to find the weak points and to improve them. The evaluation can be undertaken by internal or external evaluators, which have to be completely familiarized with all elements of curriculum.

Also, as the author says, everything happens within CONTEXT: tradition and requirements by higher authorities and accreditation bodies. The context is changeable – very inert,

but people make the context. The requirements, rules and regulation for licensing, may be less inert in comparison to tradition. But probably the best way would be self-evaluation, when schools replace the traditional curriculum with integrated. Further implementation of any process needs time and adjustment – it is not enough to have a good plan, the basic key to success is how the plan is applied. The author has pointed out that the program evaluation must be planned before its implementation. This is a very important point of view, and it may improve the implementation itself when we know in advance what measurable components of the program are.

In the eighth chapter the most important implementation guideline keywords are provided. The first and the most important problem in the implementation is resistance and traditionalism of faculty. But this seems to be inevitable, as every innovation had to travel a difficult road until acceptance, according to known history.

However, the guidelines are clearly enumerated: understanding of the concept is first, and acceptance of philosophy of integration, which indeed seems to be more important, is second. In this manner the ultimate representation of integration can be shown, especially to a resistant faculty.

In the ninth chapter there are examples: four different case reports of implementation given by order of success in the integration process. Schools A and B were unsuccessful and C and D successful. School A had tried with just one topic; school B one organ system; in school C the integration was complete but obstructed by an old-fashioned faculty; in school D the integration was successful as faculty members were fully committed. Tradition is the main factor of obstruction, and it always comes from faculty's side.

Overall, the book explains the process of integration with useful tips and offers experience necessary for its implementation. Highly recommended!

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Vladimir Albert Lovrić

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(June 14, 1926 – October 14, 2015)



The haematologist Vladimir Albert Lovrić, originator of the 'Lovric-Wisdom circle pack', a storage system for donated blood, has died peacefully after a short illness. Lovrić's innovations in component separation and anticoagulant solutions fundamentally altered blood banking in Australia, enabling up to five patients to benefit from any single blood donation.

Lovrić was born on June 14th 1926 in Belgrade, capital of the former Yugoslavia. He was the first son of a prosperous family; his brother, Ivan, was born two years later. His father, Erwin Lovrić, was born in 1892 in Osijek, Croatia; his mother, Sofia Herzl, was born in 1902 in Zemun, Serbia.

A comfortable life in Belgrade with much continental travel was suddenly interrupted by World War II: deadly bombings by the Luftwaffe on April 6th 1941 and the arrival of German troops a week later. The family fled the city, spending the war in a village in the mountains.

Lovrić entered military service in the (Partisan) People's Liberation Army in Valjevo on September 3rd 1944. Still a teenager, he was put in charge of a cavalry unit of 200 men, 100 horses and three canons. He explained that he had been so commissioned because he was the only soldier educated enough to calculate canon trajectories. Lovrić would later acknowledge that the experience of war had a profound impact on the rest of his life. Decorated for bravery, he was finally discharged in January 1948 holding the rank of lieutenant.

Sofia Lovrić did not survive the war. Erwin married a widow, Jelena, in 1946. With the marriage, a step-sister Mira also came into the family.

Lovrić had completed four years of medicine at the University of Belgrade when he had what he described as a personal disagreement with the political regime. He and his extended family moved in 1951 to Australia, where he was accepted into the third year of the medical course at the University of Sydney. He graduated with a Bachelor of Medicine and Bachelor of Surgery in 1956 and began a two-year residency at the Royal Newcastle Hospital. It was there that he met his wife Barbara, with whom he would have five children.

He returned to Sydney, working as a resident medical officer, registrar and then staff haematologist at the former Royal Alexandra Hospital for Children ('the Children's Hospital') in Camperdown, later becoming head of the Department of Haematology.

Lovrić spent 17 years at the Children's Hospital. As well as his clinical duties, he undertook research into anaemia, haemophilia, childhood leukaemia and sickle cell anaemia, subjects on which he would publish extensively, producing more than 80 scientific papers and articles.

He gained his Graduate Diploma in Clinical Pathology in 1962 and a Graduate Diploma in Public Health in 1974, both from the University of Sydney. In the same year he was made a fellow of the Royal Australasian College of Physicians. In 1967 he was appointed a fellow of the Royal College of Pathologists (UK).

At the Children's Hospital, he saw many cases of erythroblastosis foetalis. Before the introduction of rhesus immunization, the only treatment for the condition was exchange transfusion. His work in that field brought him into regular contact with the Australian Red Cross Blood Service and in 1975 he moved to the Sydney Blood Bank, where he was appointed Deputy Director and Director of Country Blood Banks NSW under Gordon Archer.

His position entailed making regular visits to the state's 29 country blood banks, rationalising and networking the state's facilities. One of his drivers in this work was ensuring an efficient supply of blood for haemophiliacs. To this end, he was instrumental in both changing health policy and securing funding to permit the production of separate components by the regional centres, with surplus material being sent to Sydney to meet chronic metropolitan shortages.

Back in the Sydney laboratory, he devoted himself to research, developing new methods of blood utilisation and storage. His quadruple-bag system, developed in collaboration with other specialists at the Blood Bank, became known as the Lovric-Wisdom circle pack. It allowed for better component collection – mainly plasma for immunoglobulins, clotting factors and platelets. He was by then also improving the physical and biochemical properties of packed red blood cells, thereby facilitating surgical transfusions and increasing shelf-life and usage. Up to five patients could, as a result, benefit from every donor's individual contribution.

He also developed new testing techniques for hepatitis C.

His position at the Blood Bank in the early 1980s put him in the front line at the time of the AIDS crisis. The Blood Bank was picketed in 1983 when it was announced that the homosexual community should refrain from giv-

ing blood until a fully workable solution was found to the possible transmission of HIV via transfusion. In 1985, Australia became the first country in the world to screen its entire blood supply for the HIV-1 virus.

In 1990, his wife, Barbara, an anthropologist, died of cancer.

He retired from the Blood Bank in 1991, though he continued as a consultant pathologist in the hospitals within the South-East Health Region and also with his clinical work as a Visiting Medical Officer in Haematology at the Repatriation General Hospital, Concord.

Throughout his career he was a significant contributor to the education of young specialists, supervising PhD candidates, as well as lecturing and teaching undergraduates and postgraduates at the University of Sydney. Later in life he acted as a consultant to pathology companies and again took on a teaching role.

He shared a passion for Indonesia with his wife Barbara, whose work focussed on medical anthropology in Bali. He served as Secretary-General of the Asian-Pacific division of the International Society of Hematology from 1975 until 1982. From 1977 until his retirement, he undertook numerous consultancies and teaching assignments for the World Health Organization (WHO) in South-East Asia and Geneva. WHO first sent Lovrić to Jakarta in 1989, on a project to deal with HIV transmission. For more than 15 years, he ran courses in transfusion techniques in various Indonesian cities, even organising the recycling of equip-

ment from Australia. He also taught in Thailand, the Philippines and Korea.

In 1998, Lovrić received the Distinguished Service Medal of the Australian Red Cross, the highest award of the Society.

Until his death, Lovrić remained active in the Haematology Society of Australia and New Zealand and in the Australian and New Zealand Society of Blood Transfusion.

Since the 1970s, 'Doc' was a well-known figure at the Gordon's Bay Amateur Fishing Club. Lovrić loved fishing but had an aversion to eating fish himself. Instead, on successful trips, he would phone family members from his tinny to announce the imminent arrival of a fish supper.

In his private life, Lovrić took pleasure in classical music, theatre, literature and cake. He enjoyed the Australian countryside as much he loved the sea. In his retirement he undertook many solo camping trips into the bush in his four-wheel drive.

He maintained an interest in his country of birth, reading Serbian newspapers online. His accent retained certain Serbo-Croatian resonances six decades after his arrival in Australia. His sense of humour was robust and black, like the coffee he brewed in a professional machine at home.

He is survived by his brother Ivan, his step-sister Mira; his five children, Michelle, Kathryn, Jenny, Melissa and Michael and three grandchildren, Miko, Zaia and Kio.

Michelle Lovric

Имена рецензената који су рецензије радова доставили крајем 2014. и у 2015. години (закључно са 22. децембром 2015)

Поштовани рецензенти, чланови Уређивачког одбора, лектори и сарадници,

Захваљујем вам на ангажовању у реализацији 143. волумена и прилога објављених у „Српском архиву за целокупно лекарство“. Значајно смо напредовали у увођењу стандарда за међународне часописе. Квалитет рецензија и укупна обрада рада до публиковања су побољшани и убрзани. Достигли смо ниво да у истој години када је предат Уредништву прихваћени рад буде и објављен, што до сада, сем изузетно, није био случај. Очекујемо да ће преуређењем и усавршавањем сајта часописа комуникација с Уредништвом бити још више олакшана и убрзана. Верујем да ће даље ангажовање новоизабраног Уређивачког одбора, ентузијаста у стручном и научном раду, допринети подизању квалитета и статуса часописа у оквиру домаће и међународне медицинске публицистике, уз жељу да нам наступајућа 2016. године донесе још више успеха.

- | | |
|---|--------------------------------|
| 1. Аврамов Светолик | 38. Вучковић-Декић Љиљана |
| 2. Алексић Петар | 39. Вучовић Драган |
| 3. Антонијевић Небојша | 40. Гига Војислав |
| 4. Апостолски Слободан | 41. Гојковић-Букарица Љиљана |
| 5. Арсовић Ненад | 42. Голднер Вуков Мила |
| 6. Аткинсон Хенри Душан Едвард
(Atkinson, Henry Dushan Edward) | 43. Голубовић Слободан |
| 7. Ач-Николић Ержебет | 44. Грга Ђурица |
| 8. Бабић Никола | 45. Грујичић Даница |
| 9. Балинт Бела | 46. Гучев Зоран |
| 10. Беслаћ-Бумбаширевић Љиљана | 47. Давидовић Лазар |
| 11. Билановић Драгољуб | 48. Дамјановић Александар |
| 12. Бјеговић-Микановић Весна | 49. Дачић Драгица |
| 13. Бјеловић Милош | 50. Делић Драган |
| 14. Божановић Татјана | 51. Димитријевић Иван |
| 15. Божић Марија | 52. Димитријевић Јован |
| 16. Божић Милена | 53. Димић Драган |
| 17. Боричић Иван | 54. Димковић Нада |
| 18. Брашанац Димитрије | 55. Динчић Евица |
| 19. Бреберина Милан | 56. Докић Дејан |
| 20. Брковић Божидар | 57. Драгојевић-Симић Викторија |
| 21. Брмболић Бранко | 58. Дробњак Томашек Олика |
| 22. Бумбаширевић Марко | 59. Дуњић Душан |
| 23. Бурић Никола | 60. Дучић Синиша |
| 24. Васиљевић Зорана | 61. Ђорђевић Владимир |
| 25. Васиљевић Младенко | 62. Ђорђевић-Дикић Ана |
| 26. Вејновић Тихомир | 63. Ђорђевић Момчило |
| 27. Вељковић Снежана | 64. Ђукић Војко |
| 28. Влашки Јован | 65. Ђуровић Александар |
| 29. Војиновић Милорадов Мирјана | 66. Живковић Зорица |
| 30. Вујисић-Тешић Босиљка | 67. Жувела Маринко |
| 31. Вујић Драгана | 68. Здравковић Вера |
| 32. Вујчић Исидора | 69. Зидверц-Трајковић Јасна |
| 33. Вуковић Оливера | 70. Ивовић Владимир |
| 34. Вукомановић Владислав | 71. Игњатовић Миле |
| 35. Вукомановић Горан | 72. Игрутиновић Зоран |
| 36. Вучетић Чедомир | 73. Илић Драган |
| 37. Вучинић Предраг | 74. Илић Слободан |
| | 75. Илле Татјана |

76. Ињац Раде
77. Јаковљевић Бранко
78. Јанковић Борисав Борко
79. Јанковић Љиљана
80. Јаношевић Љиљана
81. Јаношевић Мирјана
82. Јанчић Јасна
83. Јашовић-Гашић Мирослава
84. Јелић Светлана
85. Јеремић Ивица
86. Јовановић Ида
87. Јовановић Марина
88. Јовановић-Марковић Загорка
89. Јовановић Б. Милан
90. Јовановић-Симић Јелена
91. Јовановић Томислав
92. Јовићевић Ана
93. Јовић Рајко
94. Јокић Радојица
95. Каменов Борислав
96. Катанић Драган
97. Кесић Весна
98. Кесић Љиљана
99. Ковачевић Мирослав
100. Ковачевић Слободан
101. Константинович Нада
102. Константиновић Љубица
103. Контић Ђорђе
104. Костић Владимир
105. Костић Гордана
106. Костовски Ацо
107. Коцић Биљана
108. Коцић Бранислава
109. Кривокапић Зоран
110. Крстев Срмена
111. Кузмановић Милош
112. Лаврнић Драгана
113. Лазаревић Ивана
114. Лакић Анета
115. Лалић Катарина
116. Лалошевић Душан
117. Латас Милан
118. Латковић Зоран
119. Лековић Зоран
120. Лепић Топлица
121. Лечић-Тошевски Душица
122. Лешић Александар
123. Лилић Деса
124. Лукач Марија
125. Маглајлић Свјетлана
126. Мазих Сања
127. Мандић-Стојменовић Гордана
128. Марић-Бојовић Нађа
129. Марковић Вук
130. Марковић-Денић Љиљана
131. Мартиновић Жарко
132. Мачукановић-Голубовић Лана
133. Месарош Шарлота
134. Мијајловић Милија
135. Микић Антон
136. Микић Драган
137. Миков Момир
138. Миланков Мирослав
139. Милашин Јелена
140. Милашиновић Горан
141. Миленковић Бранислава
142. Милетић Весна
143. Милетић-Турк Душанка
144. Миловановић Бранислав
145. Милојевић Предраг
146. Милошевић Павле
147. Миљић Предраг
148. Мирановић Весна
149. Мирковић Љиљана
150. Митић Марија
151. Митковић Милорад
152. Митровић Предраг
153. Мицев Марјан
154. Младеновић Властимир
155. Младеновић Марија
156. Мостарица-Стојковић Марија
157. Мујовић Небојша
158. Муњиза Марко
159. Нагорни Александар
160. Нагорни-Обрадовић Људмила
161. Недок Александар
162. Ненадовић Милутин
163. Несторовић Бранимир
164. Николић Живорад
165. Николић Предраг
166. Николић Слободан
167. Николић Татјана
168. Новаковић Маријан
169. Ножић Дарко
170. Обрадовић-Ђуричић Косовка
171. Оташевић Петар
172. Павлица Душан
173. Павловић Александра
174. Павловић У. Синиша
175. Пашић Срђан
176. Пејовић Милованчевић Милица
177. Пејчић Љиљана
178. Перишић Мирјана
179. Петровић Владимир
180. Петровић Жељко
181. Петровић Игор
182. Половина Снежана
183. Поповић-Деушић Смиљка
184. Потпара Татјана
185. Простран Милица
186. Путниковић Биљана
187. Путник Светозар
188. Радак Ђорђе
189. Радловић Недељко
190. Радовановић Бојан
191. Радовановић Зоран
192. Радовановић Небојша
193. Радовановић Саша

194. Радовић Милан
195. Радојковић Милица
196. Радоњић-Лазовић Гордана
197. Радуновић Горан
198. Ранђеловић Томислав
199. Ранковић Јаневски Милица
200. Ребић Предраг
201. Ристић Александар
202. Ристић Арсен
203. Ристић-Медић Данијела
204. Савић Александар
205. Сајковски Александар
206. Самарџић Мира
207. Самарџић Мирослав
208. Сарајлија Адријан
209. Светел Марина
210. Сето Чеук-Чун (*Szeto, Cheuk-Chun*)
211. Симић Снежана
212. Симић-Огризовић Сања
213. Симоновић-Бабић Јасмина
214. Спремовић Рађеновић Светлана
215. Стаменковић Драгослав
216. Станимировић Виолета
217. Станковић Горан
218. Станковић Милан
219. Станојевић Горан
220. Станојловић Светлана
221. Старчевић Владан
222. Стефанова Елка
223. Стефановић Владисав
224. Стојановић Душица
225. Стојановић Јован
226. Стојановић Мирослав
227. Стојановић Роксанда
228. Стојић Драгица
229. Стојић Синиша
230. Стојковић-Анђелковић Анђелка
231. Стојковић Миодраг
232. Стокић Едита
233. Стомпор Томаш (*Stompór, Tomasz*)
234. Суботић Драган
235. Тарабар Дино
236. Татић Вујадин
237. Тахировић Хусреф
238. Тодоровић Љубомир
239. Томашевић Милоје
240. Тончев Гордана
241. Тотић Познановић Сања
242. Трбојевић Божо
243. Тричковић-Јањић Оливера
244. Хабиб Наги (*Habib, Nagy*)
245. Царевић Момир
246. Цветковић Добросав
247. Цвијановић Радован
248. Церовац Наташа
249. Чакић Саша
250. Чобељић Горан
251. Човичковић-Штернић Надежда
252. Чолић Сњежана
253. Чоловић Милица
254. Чоловић Радоје
255. Чутурило Горан
256. Џодић Радан
257. Шаранац Љиљана
258. Шешлија Игор
259. Шубаревић Владан
260. Шуловић Ненад

Проф. др Павле Миленковић
главни и одговорни уредник

Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво може одложити објављивање рада или чак одбити његово публиковање. Стога се ауторима и потенцијалним сарадницима саветује да пажљиво прочитају ово упутство пре него што приступе припреми рукописа за штампу у „Српском архиву за целокупно лекарство“.

ОПШТА УПУТСТВА. Оригинални и стручни радови се у целини достављају на енглеском језику са сажетком на енглеском и српском. Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 pt). Све четири маргине подесити на 25 mm, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 mm, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лежиру и *Toolbars*. За прелазак на нову страну документа не користити низ ентера, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ⁹⁹Tc, IL-6, O₂, B₁₂, CD8).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања.

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања која се односе на једну здравствену интервенцију или на више њих, а ради испитивања утицаја на здравствени исход. Регистарски број истраживања треба да се наведе у последњем реду Кратког садржаја.

ЕТИЧКА САГЛАСНОСТ. Рукописи о хуманим медицинским истраживањима или историјама болести пацијената треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с локалним правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME*; <http://www.wame.org>) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало би да буду наведени у Захвалници с описом њиховог рада, наравно, уз писани пристанак.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установе у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

КРАТАК САДРЖАЈ. Уз оригинални рад, саопштење, преглед литературе, приказ болесника, рад из историје медицине, рад за рубрику „Језик медицине“ и рад за праксу, на другој по реду страници документа треба приложити кратак садржај рада обима 100–250 речи. За оригинале радова кратак садржај треба да има следећу структуру: Увод, Циљ рада, Методе рада, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. За приказе болесника кратак садржај треба да има следеће делове: Увод, Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Кратког садржаја навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH* (<http://www.nlm.nih.gov/mesh>).

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установе у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити кратак садржај (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан кратак садржај на енглеском језику. Превод појмова из стране литературе треба

да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом.

Уколико је рад у целости на српском језику (нпр. рад из историје медицине, језика медицине и др.), потребно је превести називе прилога (табела, графикана, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад обавезно треба да има следеће поднаслове: Увод, Циљ рада, Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор прегледног рада мора да наведе бар пет аутоцитата (референце у којима је био први аутор или коаутор рада) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ болесника чине: Увод, Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од седам аутора.

Прилоге (табеле, графиконе, слике итд.) сместити на крај рукописа, а у самом телу текста назначити место које се односи на дати прилог. Крајња позиција прилога пре штампања рада зависиће од прелома текста.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у кратком садржају, али ако су неопходне, сваку скраћеницу поново објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. $12,5 \pm 3,8$). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм – *kg*, литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса ($^{\circ}\text{C}$), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РУКОПИСА. Целокупни рукопис рада – који чине насловна страна, кратак садржај, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, саопштење, рад из историје медицине и преглед литературе до 5.000 речи, а за приказ болесника, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3.000 речи; радови за остале рубрике могу имати највише 1.500 речи.

Провера броја речи у документу може се извршити у програму *Word* кроз подмени *Tools–Word Count* или *File–Properties–Statistics*.

ТАБЕЛЕ. Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле.

Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

СЛИКЕ. Сlike се означавају арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолюције 300 dpi и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватити за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати као *Grayscale* (или у боји) у резолуцији 300 dpi и снимити их у оригиналној величини.

Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Сlike се у свесци могу штампати у боји, али додатне трошкове штампе сноси аутор.

ГРАФИКОНИ. Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикана.

Уколико је рукопис на српском језику, приложити називе графикана и легенду на оба језика.

СХЕМЕ (ЦРТЕЖИ). Схеме цртати у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме.

Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести DOI број чланка (јединствену ниску карактера која му је додељена) и PMID број уколико је чланак индексан у бази PubMed/MEDLINE.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публикације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не треба да буде старија од пет година. Избегавати коришћење апстракта као референце, а апстракте старије од две године не цитирати. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (<http://www.icmje.org>), чији формат користе U.S. National Library of Medicine и базе научних публикација. Примере навођења публикација (чланака, књига и других монографија, електронског, не-објављеног и другог објављеног материјала) могу се пронаћи на интернет-страници http://www.nlm.nih.gov/bsd/uniform_requirements.html. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (SUBMISSION LETTER). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (<http://www.srp-arh.rs>).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА И ПРЕТПЛАТА. Да би рад био објављен у часопису Српски архив за целокупно лекарство, сви аутори морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва), док први аутор мора бити и претплатник на часопис, за годину у којој се рад предаје Уредништву. Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату, као доказ о уплатама. Аутори из иностранства нису дужни да буду чланови Српског лекарског друштва, нити претплатници на часопис за текућу годину. Додатне информације о чланарини и претплати могу се добити на телефоне 011/3245-149 и 011/3346-963, односно имејлом ([srparhiv@bvcom.net](mailto:srp-arh@bvcom.net)) и на интернет-страници часописа (<http://www.srp-arh.rs>).

СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад могу се доставити имејлом ([srparhiv@bvcom.net](mailto:srp-arh@bvcom.net)), електронски преко система за пријављивање на интернет-страници часописа (<http://www.srp-arh.rs>), препорученом поштом или лично, доласком у Уредништво. Уколико се рад шаље поштом или доноси у Уредништво, рукопис се доставља одштампан у три примерка и нарезан на CD (снимљени материјал треба да је истоветан оном на папиру).

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