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TREATMENT OF ROTATOR CUFF TEARS

TERAPIJA RUPTURE ROTATORNE MANŽETNE

Srđan NINKOVIĆ

The shoulder is the most mobile joint in the human body, which enables three-dimensional hand motion in space. Evolutionary changes have led to the adjustment of the shoulder region and it has become a very mobile and dynamic junction of the arms and torso. A large number of muscles move the arm in space and provide strength of movement that is extremely important for proper functioning of the shoulder [1].

The rotator cuff of the shoulder joint is the most important functional structure of the shoulder. It consists of the subscapularis, supraspinatus, infraspinatus and teres minor tendons. Its main function is the dynamic stabilization of the humeral head during arm movements and the formation of support (hypomochlion) during contractions of the deltoid muscle of the shoulder. In addition to moving the arm and stabilizing the shoulder, the attachments of the rotator cuff tendons are also very important for the vascularization of the upper part of the humerus [2].

A rotator cuff injury is a common cause of shoulder pain. The structure of the rotator cuff is very solid. During normal daily activities, approximately 140 to 200 newtonts (N) of force is transmitted through these tendons. The maximum load that an undamaged rotator cuff tendon can withstand is 600 to 800 N [3]. The diagnosis of rotator cuff muscle injuries is made based on medical history data, clinical examination, analysis of radiographic images and magnetic resonance imaging [4, 5].

According to epidemiological data, rotator cuff injuries account for 9% to as much as 39% of soft tissue shoulder lesions in the population older than 40 years [6]. The incidence of rotator cuff rupture in people over 50 is thought to be 50% and even 80% after the age of 80, but epidemiological data show that less than 40% of patients with shoulder pain after the age of 70 seek medical attention [2]. The mechanism of rupture is in most cases a combination of recurrent microinjuries and poor tendon nutrition, but may also be a consequence of high-intensity force or the use of corticosteroids [1]. The supraspinatus tendon is most commonly affected. Namdari and Green [7] reported 62% of isolated supraspinatus injuries, studying range of motion in 345 operated injuries, and in other studies, this muscle is also the most common site of injury [8–10].

Non-operative treatment of patients with chronic rotator cuff injury is recommended in patients whose painful component is marked and the weakness of the arm is not dramatic and progressive. If no significant improvement is found after 3 to 6 months of physical treatment, surgical treatment is suggested [11]. Basset and Cofield [12] found that the optimal time for the management of rotator cuff tendon complete rupture is up to three weeks from acute injury. In cases when the weakness is marked or progressive, it is necessary to decide faster on surgical treatment, because surgical reinsertion should be performed before the tendon is retracted, its tissue lost and the muscle volume reduced.

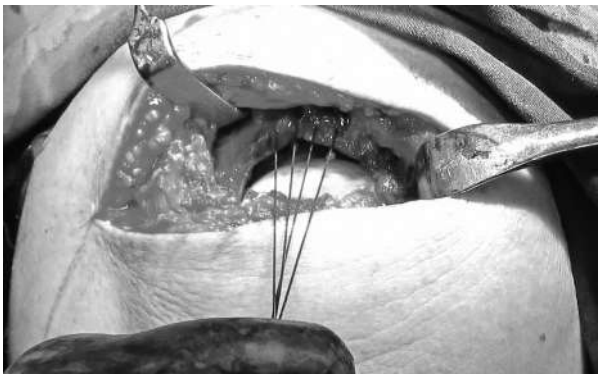

Figure 1. Mobilized supraspinatus muscle tendon with supported sutures (open repair)
Slika 1. *Mobilisana tetiva nadgrebenog mišića podržnim šavovima (otvorena tehnika)*

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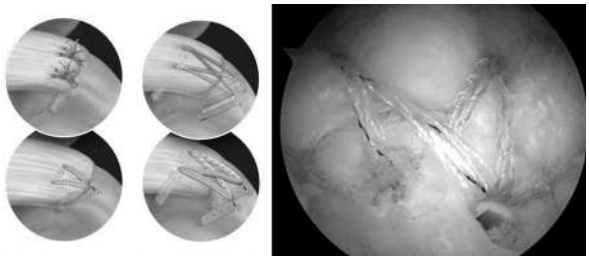

Figure 2. Arthroscopic image after rotator cuff muscles repair
Slika 2. *Artroskopski snimak nakon reparacije mišića rotatorne manžetne*

The rotator cuff management technique was first described by Codman in 1911 [13]. Neer perfected the existing open technique in 1972, and established the principles of modern rotator cuff injuries treatment [14]. Since then, according to Murray [15] et al., the number of patients satisfied with the results of surgical treatment has ranged from 70% to 95%. Today, rotator cuff tendon repair is done with a minimally invasive approach **(Figure 1)** or using arthroscopic techniques **(Figure 2)**. The next step in treatment was made by using arthroscopy, providing greater visibility during surgery and reduced incidence of certain complications, as well as simultaneous surgical treatment of other associated shoulder injuries. However, there are many published papers stating that there are no differences in postoperative results [16–18].

The traumatic rotator cuff injuries are often unrecognized at the first clinical examination by physicians, due to poor physical findings. Patients in whom shoulder fractures or dislocations have been ruled out based on radiography are often referred for physical treatment, without further diagnosis. A study conducted by Sorensen [19] and co-workers in Danish emergency centers investigated whether rotator cuff injuries remained unrecognized by doctors. It has established that most patients were discharged from hospital and referred for physical treatment, although additional diagnostics revealed a rotator cuff injury. The research has shown that special care should be paid in cases when there are no clear clinical signs of tendon rupture and that early diagnosis must be improved. A long period from injury to diagnosis and surgery is one of the negative factors that reduces the possibility of restoring the range of motion to the range prior the injury. Retraction of the tendon towards the muscular body increases over time, which makes successful repair impossible. Mayer [20] and co-workers pointed out that the muscle is reduced first, and then the length of the injured tendon is shortened. These pathogenic mechanisms lead to a decrease in range of motion and strength in the shoulder after surgical treatment. Namdari and Green [7] confirmed that in chronic injuries, damage to the subscapularis tendon and the long biceps tendon reduce the range of motion of external shoulder rotation.

The study of Mansat [21] included 2,948 operated shoulders and the most common postoperative complications were adhesive capsulitis ("frozen shoulder") and deep infection that were found in 10.5% of cases.

Today, it is a fact that rotator cuff surgery yields better and better results. About 75,000 of these procedures are performed annually in the United States. At the Clinic of Orthopedic Surgery and Traumatology of the Clinical Center of Vojvodina in Novi Sad, the treatment of these injuries has been performed since 2006. Several studies have found that after repair of the rotator cuff injuries, shoulder function is significantly improved, but that there is a slight decrease in the range of motion and strength compared to the opposite healthy shoulder [5, 23, 24]. Despite this discrepancy, the fact that 95% of patients can perform all activities of daily living and that 95% of patients are satisfied with the results of surgical treatment, indicates that the results are very good [24].

Surgical treatment of a rotator cuff injury is reliable, time-tested and gives good clinical results, especially in patients operated in the first three weeks after the injury, without associated bone lesions.

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ORIGINAL STUDIES
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RISK FACTORS FOR HAND OSTEOARTHRITIS

FAKTORI RIZIKA ZA NASTANAK OSTEOARTROZE ŠAKE

Jelena ZVEKIĆ SVORCAN[1, 2], Bojana STAMENKOVIĆ[3, 4], Ivana MINAKOVIĆ[1, 5], Rastislava KRASNIK[1, 6], Tanja JANKOVIĆ[1, 2] and Aleksandra MIKOV[1, 6]

Summary

Introduction. Hand osteoarthritis is a joint degenerative disease characterized by hand deformities affecting the hand strength and function, leading to greater disability and increased healthcare utilization. The objective of this study was to estimate the impact of different risk factors on the incidence of hand osteoarthritis. **Material and Methods.** The study was a prospective cross-sectional study conducted at the Special Hospital for Rheumatic Diseases Novi Sad, Serbia, during a one year period (2017 - 2018). It included 100 postmenopausal women aged 60 to 70 years presenting with pain in the hands ≥ 3 according to the visual analogue scale. All respondents were divided into two groups, according to radiographic findings graded using the Kellgren-Lawrence scale. Risk factors responsible for the development of hand osteoarthritis were examined and the research procedure included medical history data, physical examination of the hand joints, anthropometric measurements, and laboratory tests. Statistical processing and analysis was performed using Statistical Package for the Social Sciences ver. 25. **Results.** Statistically significant differences were found between the two groups in relation to positive family history of degenerative changes in the hand joints (p = 0.000), as well as in relation to metabolic syndrome (p = 0.001). **Conclusion.** A positive family history of degenerative changes of the hands and presence of metabolic syndrome are significant risk factors for the development of hand osteoarthritis.

Key words: Osteoarthritis; Hand Joints; Wrist; Metacarpus; Risk Factors; Menopause; Postmenopause; Female

Sažetak

Uvod. Osteoartroza šake predstavlja degenerativnu bolest zglobova za koju su karakteristični deformiteti šake koji utiču na snagu i funkciju šake, a koji vode većoj invalidnosti, te povećanju učestalosti korišćenja zdravstvene zaštite. Cilj rada je procena uticaja različitih faktora rizika na pojavu osteoartroze šake. **Materijal i metode.** Istraživanje je sprovedeno u vidu prospektivne studije preseka u Specijalnoj bolnici za reumatske bolesti u Novom Sadu, Srbija, u periodu od jedne godine (2017−2018). Studija je obuhvatila 100 žena u menopauzi starosti od 60 do 70 godina, koje su imale bolove u šakama ≥ 3 označeno prema vizuelnoj analognoj skali. Ispitanice su bile podeljene u dve grupe u odnosu na radiografski nalaz na šakama prema Kelgren-Lorencovoj skali (*Kellgren-Lawrence*). Ispitivani su faktori rizika koji bi mogli biti odgovorni za nastanak osteoartroze šake, a istraživački postupak je uključivao dobijanje anamnestičkih podataka, fizikalni pregled zglobova šake, antropometrijska merenja i laboratorijske analize. Statistička obrada i analiza urađena je u statističkom paketu SPSS ver. 25. **Rezultati.** Statistički značajna razlika je primećena između dve grupe u odnosu na postojanje pozitivne porodične anamneze o strukturnim promenama na zglobovima šaka (p = 0,000) kao i u odnosu na postojanje metaboličkog sindroma (p = 0,001). **Zaključak.** Pozitivna porodična anamneza o strukturnim promenama na šakama i prisustvo metaboličkog sindroma predstavljaju značajan faktor rizika za nastanak osteoartroze šake.

Ključne reči: osteoartritis; zglobovi ruke; šaka; metakarpus; faktori rizika; menopauza; postmenopauza; žensko

Introduction

Osteoarthritis (OA) is the most predominant degenerative joint disease [1]. It is characterized by chronic musculoskeletal pain which is related to physical disability and dysfunction [2]. The most common form of arthritis is OA, and its prevalence has been increasing in the United States probably due to population aging and more frequent obesity. Risk factors for OA include factors at the joint level in terms

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Abbreviations
OA – osteoarthritis
BMI – body mass index
MetS – metabolic syndrome

of joint loading, and factors at the personal level such as – age, sex, obesity and genetic factors [3]. Risk factors for OA include biomechanical and systemic factors and they are not fully understood, which means harmful health behaviour may possibly contribute to OA affecting joint tissues [4]. One of the most frequent locations affected by OA is the hand [5]. Human hand is the evolutionary culmination in the development of all living beings [6]. It is composed of numerous bones and muscles and its complex structure allows heterogeneous functions and daily activities [7]. Hand OA is characterized by deformities which affect hand strength and function, leading to greater disability and increased health care utilization [5]. Hand OA is associated with hand pain, stiffness, loss of mobility which all lead to a reduction in quality of life [8]. A longitudinal study conducted in several European countries within the European project on OA that included individuals aged 65 - 85 years, indicated that the overall prevalence of clinical OA at any site was 30.4% and 16.3% had hand OA [9]. The proportion of the population who will develop symptomatic hand OA is defined as a lifetime risk. This risk was estimated from models using generalized estimating equations and had included the development of symptomatic hand OA in at least one hand by the age of 85 years. The lifetime risk of symptomatic hand OA was 39.8% and it was particularly high among women. It was estimated that 1 in 2 women will develop symptomatic hand OA by the age 85 years, compared to 1 in 4 men [5]. Considering there is no disease-modifying drug for OA, it is important to reduce the risk for developing hand OA by decreasing modifiable risk factors [2]. The OA is related to an extremely high economic burden and indirect costs for OA are also high which is caused by both work-related losses and home care cost [10]. Regarding all the above mentioned, our study aimed to estimate the impact of different risk factors on the incidence of hand OA.

Material and Methods

A prospective cross-sectional study was conducted at the Special Hospital for Rheumatic Diseases Novi Sad, Serbia, during a one year period (2017 – 2018). The Research was approved by the Ethics Committee of the Special Hospital for Rheumatic Diseases Novi Sad and the Ethics Committee of the Faculty of Medicine Novi Sad, Serbia. First, all respondents signed informed consent forms to take part in the study. The research included 100 postmenopausal women who met the inclusion criteria: age from 60 to 70 years, hand pain ≥ 3 according to the visual analogue scale [11]. All respondents were divided into two groups, according to radiographic findings of hands which were in line with Kellgren–Lawrence scale [12, 13]. The study group included respondents with radiographic progression on their hand joints classified as II – IV grade, while the control group included respondents with 0 and I grade according to the Kellgren–Lawrence scale. The exclusion criteria were as follows: inflammatory rheumatic disease, tenosynovitis of the hand and carpal tunnel, previous hand surgery, use of corticosteroid therapy and physical therapy 3 months before enrollment into the study.

Research procedure: obtaining medical history data, physical examination of the hand joints, anthropometric measurements – body height (cm), body weight (kg), calculation of the body mass index (BMI) (kg/m^2), waist circumference measurement with a tape measure (cm), blood pressure measurement with a sphygmomanometer (mmHg), laboratory tests – glycemia (mmol/l), cholesterol (mmol/l), high-density lipoprotein cholesterol (mmol/l) and triglycerides (mmol/l) – which were measured in the morning, on an empty stomach. The components of the metabolic syndrome (MetS) were determined according to the clinical definition of the MetS by National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATPIII) [14]. All respondents were examined for potential risk factors that may be responsible for hand OA: occupation (work that requires repeated finger movements, lifting and carrying heavy loads - strong grips, work that requires precise grip and work in administration), BMI, cigarette smoking, alcohol consumption, physical activity, time of onset of menopause (entering menopause before and after the age of 45), duration of menopause, fractures or minor trauma, family history of fractures, family history of structural changes in the hands and diagnosed MetS.

Numerical variables were analyzed by arithmetic mean and standard deviation, while categorical variables were analyzed by frequencies and percentages. Chi-square test and Student's t-test were used for testing differences. The univariate logistic regression was performed first to distinguish the predictors of hand OA. The hand OA was used as a dependent variable coded as a dummy variable. Categorical independent variables have undergone some categorization, to better define reference categories. Before conducting the logistic regression, multicollinearity of the dependent variables was examined. Multicollinearity was investigated to provide stable and precise regression coefficients. Tolerance level and variance inflation factor (VIF) were used as indicators of multicollinearity. The univariate binary and multivariate models were used to determine the risk factors for hand OA. The Odds ratio was used in the interpretation of the results combined with the 95% confidence interval. The multivariate model was conducted by the forward method. Statistical processing and analysis were performed in the statistical package SPSS ver. 25.

Results

The research included 100 subjects, postmenopausal women, 60 in the study and 40 in the control group. A comparison was made between the 2 groups in relation to potential risk factors for hand

Table 1. Demographic characteristics of patients
Tabela 1. *Demografske karakteristike pacijenta*

	Study group *Eksperimentalna grupa* (*n* = 60)	Control group *Kontrolna grupa* (*n* = 40)	p	All respondents *Svi ispitanici* (*n* = 100)
Occupation, n (%)/*Zanimanje, n* (%)				
Lifting and carrying heavy loads, strong grips *Dizanje i nošenje teškog tereta, snažni hvatovi*	17 (28.3%)	14 (35.0%)		31 (31.0%)
Work that requires repeated finger movements *Rad koji zahteva ponavljane pokrete prstiju*	11 (18.3%)	3 (7.5%)	0.061[a]	14 (14.0%)
Work that requires precise grip *Rad koji zahteva precizni hvat*	11 (18.3%)	2 (5.0%)		13 (13.0%)
Work in administration/*Rad u administraciji*	21 (35.1%)	21 (52.5%)		42 (42.0%)
BMI, n (%)/*ITM, n (%)*				
Underweight/*Pothranjenost* (< 18,5)	1 (1.7%)	1 (2.5%)		2 (2.0%)
Normal weight (18,5 - 25) *Normalna uhranjenost (18,5-25)*	7 (11.7%)	10 (25.0%)	0.203[a]	17 (17.0%)
Overweight and obesity (25 and more) *Prekomerna uhranjenost i gojaznost (25 i više)*	52 (86.7%)	29 (72.5%)		81 (81.0%)
Smoking status, n (%)/*Pušački status, n (%)*				
Smoker/*Pušač*	9 (15.00%)	5 (12.50%)	0.327[a]	14 (14.00%)
Ex-smoker/*Bivši pušač*	12 (20.00%)	4 (10.00%)		16 (16.00%)
Non smoker/*Nepušač*	39 (65.00%)	31 (77.50%)		70 (70.00%)
Alcohol consumption, n (%)/*Konzumiranje alkohola, n (%)*				
Yes/*Da*	0 (0%)	1 (2.50%)	0.218[a]	1 (1.00%)
No/*Ne*	60 (100%)	39 (97.50%)		99 (99.00%)
Physical activity, n (%)/*Fizička aktivnost, n (%)*				
Low/*Niska*	32 (53.30%)	24 (60.00%)	0.511[a]	56 (56.00%)
Moderate/*Umerena*	28 (46.70%)	16 (40.00%)		44 (44.00%)
Time of menopause onset, n (%)/*Vreme ulaska u menopauzu, n (%)*				
Before the age of 45/*Pre 45. godine*	10 (16.7%)	10 (25.0%)	0.307[a]	20 (20.0%)
After the age of 45/*Nakon 45. godine*	50 (83.3%)	30 (75.0%)		80 (80.0%)
Duration of menopause, M ± SD *Trajanje menopauze, M±SD*	16.2±5.62	17.9±5.74	0,147[b]	16.9±5.70
Fractures to minor trauma, n (%)/*Prelomi i male trume, n (%)*				
Yes/*Da*	12 (20.0%)	10 (25.0%)	0.383[a]	22 (22.0%)
No/*Ne*	48 (80.0%)	30 (75.0%)		78 (78.0%)
Family history of fractures among relatives, n (%) *Porodična anamneza o prelomima kod srodnika, n (%)*			0.515[a]	
Yes/*Da*	17 (28.3%)	9 (22.5%)		26 (26.0%)
No/*Ne*	43 (71.7%)	31 (77.5%)		74 (74.0%)
Family history of structural changes in the hand joints, n (%) *Porodična anamneza o strukturnim promenama na zglobovima šaka, n (%)*			0.000[a]	
Yes/*Da*	49 (81.7%)	8 (20.0%)		57 (57.0%)
No/*Ne*	11 (18.3%)	32 (80.0%)		43 (43.0%)
Metabolic syndrome, n (%)/*Metabolički sindrom, n (%)*				
Yes/*Da*	49 (81.7%)	20 (50.0%)	0.001[a]	69 (69.0%)
No/*Ne*	11 (18.3%)	20 (50.0%)		31 (31.0%)

Legend: [*a]χ2 – Chi-square test; [b]Student's t-test; p – statistical significance
*Legenda: [*a]χ2 – Hi-kvadrat test; [b]Studentov t-test; p – statistička značajnost, ITM - indeks telesne mase*

OA. No statistically significant difference was found between the study and control group (p > 0.05) in relation to the previous occupation, including lifting and carrying heavy loads and strong grips, work that requires repeated finger movements, work that requires precise grip and work in administration. Most

Table 2. Prediction of hand osteoarthritis using univariate logistic regression
Tabela 2. *Predikcija osteoartroze šake, univarijantna logistička regresija*

	Wald	p	OR	95% Confidence interval/*95% Interval pouzdanosti*		Cox & Snell R^2
				Lower limit *Donja granica*	Upper limit *Gornja granica*	
Occupation - Work that requires repeated finger movements *Zanimanje - Rad koji zahteva ponavljane pokrete prstiju*	6.698	0.082				
Lifting and carrying heavy loads, strong grips (1) *Dizanje i nošenje teškog tereta, snažni hvatovi (1)*	2.203	0.138	0.331	0.077	1.425	0.077
Work that requires precise grip (2) *Rad koji zahteva precizni hvat (2)*	0.162	0.687	1.500	0.208	10.807	
Work in administration (3)/*Rad u administraciji (3)*	3.250	0.071	0.273	0.066	1.120	
BMI - Normal weight/*ITM - Normalna uhranjenost*	3.067	0.216				
Underweight (1)/*Pothranjenost (1)*	0.057	0.812	1.429	0.076	26.895	0.031
Overweight and obesity (2)/*Prekomerna uhranjenost i gojaznost (2)*	2.983	0.084	2.562	0.881	7.448	
Smoking status/*Pušački status*	1.761	0.184	1.855	0.745	4.618	0.018
Physical activity/*Fizička aktivnost*	0.432	0.511	0.762	0.339	1.714	0.004
Time of menopause onset (years) *Vreme ulaska u menopauzu (godine)*	1.030	0.310	0.600	0.224	1.609	0.010
Duration of menopause/*Trajanje menopauze*	2.089	0.148	0.948	0.882	1.019	0.021
Fractures to minor trauma/*Prelomi i male traume*	0.348	0.555	0.750	0.289	1.949	0.003
Family history of fractures among relatives *Porodična anamneza o prelomima kod bliskih srodnika*	0.423	0.515	1.362	0.537	3.454	0.004
Family history of structural changes in the hand joints *Porodična anamneza o strukturnim promenama na zglobovima šaka*	31.004	0.000	17.818	6.465	49.109	0.326
Metabolic syndrome/*Metabolički sindrom*	10.561	0.001	4.45	1.809	10.967	0.106

Legend: The variable alcohol consumption was excluded from the regression model, due to the small number of respondents by category (N = 1)
Legenda: Varijabla konzumiranja alkohola isključena je iz regresionog modela, zbog malog broja ispitanika po kategorijama (N=1), ITM - indeks telesne mase
p – statistical significance; OR – odds ratio/*p – statistička značajnost, OR – količnik šansi*

of the examinees from both groups were overweight (81%), but no statistically significant difference was observed between the groups comparing the BMI. Most of the respondents were non-smokers (70%), while the percentage of smokers and ex-smokers was similar (14% vs. 16%) and no statistically significant difference was found between groups in relation to smoking status. Almost all participants reported that they did not consume alcohol (99%) and there was no statistically significant difference between the groups. Likewise, there was no statistically significant difference ($p > 0.05$) between the groups in relation to low and moderate levels of physical activity. In most respondents, menopause occurred after the age of 45 years (80%), and the average duration of menopause in the study group was 16.2 ± 5.62 years, while in the control group it was 17.9 ± 5.74. There was no statistically significant difference between the groups either in relation to the time of onset of menopause or the duration of menopause. Similarly, there was no statistically significant difference between two groups with regard to the existence of fractures to minor trauma or positive family history of fractures among relatives. Statistically significant differences were observed between two groups in relation to positive family history of structural changes in the hand joints ($p = 0.000$), as well as in relation to the existence of MetS ($p = 0.001$) **(Table 1)**. First, a binary logistic regression was performed, and then, in order to explain the existence of hand OA, the contribution of each individual variable was evaluated. As statistically significant predictors for hand OA, using univariate regression analysis, the following were distinguished: family history of structural changes in the hand joints (Wald = 31.00, $p = 0.000$) and MetS (Wald = 10.56, $p = 0.001$). Individuals with a positive family history of structural changes in the hand had a 17 times higher chance of developing OA of the hand than women with a negative family history (OR: 17.81; 95% CI (6.46 – 49.10)). This variable alone explained 32% of the variance of the dependent variable. Individuals with MetS had a 4 times higher chance of

Table 3. Prediction of hand osteoarthritis using multivariate logistic regression
Tabela 3. *Predikcija osteoartroze šake, multivarijantna logistička regresija*

		Wald	p	OR	95% Confidence interval *95% Interval pouzdanosti*	
					Lower limit *Donja granica*	Upper limit *Gornja granica*
Step 1 *Korak 1*	Family history of structural changes in the hand joints *Porodična anamneza o strukturnim promenama na zglobovima šaka*	31.004	0.000	17.818	6.465	49.109
	Constant/*Konstanta*	9.334	0.002	0.344		
Step 2 *Korak 2*	Family history of structural changes in the hand joints *Porodična anamneza o strukturnim promenama na zglobovima šaka*	26.620	0.000	15.288	5.426	43.078
	Metabolic syndrome/*Metabolički sindrom*	3.936	0.047	3.046	1.014	9.156
	Constant/*Konstanta*	11.151	0.001	0.176		

hand OA than subjects who did not have MetS (OR: 4.45; 95% CI (1.80 - 10.96)). This variable alone explained 10% of the variance of the dependent variable **(Table 2).** When both variables are observed together a final regression is obtained - individuals with a positive family history are 15 times more likely to have hand OA than those without a positive family history, and subjects with MetS are 3 times more likely to have hand OA than those without MetS **(Table 3).**

Discussion

The aim of this study was to compare the association between different risk factors for radiographic hand OA. We found no statistically significant correlation between radiographic hand OA and potential risk factors which include earlier occupation, BMI, smoking, alcohol consumption, physical activity, and time of onset of menopause, duration of menopause, fractures to minor trauma or family history of fractures. The studies that have researched hand OA mostly analyzed occupation-related data for men and women combined. Currently, there are no standardized criteria for assessing the connection between work exposures and OA, which shows that highly diverse criteria were used in the studies. Some of the studies reported strong and moderate evidence for a lack of association among several activities and increased risk of hand OA [15–17] which is in line with our results. Meta-analysis conducted by Hammer et al. provided limited evidence that work activities required repeated and/or sustained pinch grip may increase the risk of the wrist or finger OA. However, the included studies were mostly cross-sectional, and there is a lack of prospective cohort studies [18]. In our research, we found no association between hand OA and overweight which is in line with the Norwegian study on obesity and hand OA [2, 19]. A different result was reported by O' Neil et al. who found that increased BMI is moderately associated with the progression of hand OA. They suggested that overweight/obesity may also increase the risk of progression of OA through systematic factors [20]. There are different definitions of OA, so that may cause different results. Considering the known connection between obesity and pain, it is more likely that there is an association between obesity and clinical OA definitions, than with radiographic definitions [2]. There have been different studies which have shown opposite results about the effect of smoking on hand OA. While some studies reported a protective role of smoking on OA, others reported an association between smoking and increased risk for cartilage loss [21]. We found no evidence for the association between cigarette smoking and hand OA, comparing smokers, ex-smokers and nonsmokers. Haugen et al. reported less severe hand OA in smokers as compared to never smokers in cross-sectional analyses, whereas longitudinal analyses did not confirm the inverse association [2]. Meta-analysis conducted a few years ago concluded that the protective role of smoking in OA development is likely to be false [21]. We did not find a statistically significant difference in the prevalence of hand OA between women who consumed alcohol and those who did not. It was established that ultrasound detected inflammation on a joint level could predict radiographic progression on that joint [22], hence, synovitis presents the risk factor for radiographic progression of OA [23]. The result of the musculoskeletal pain in Ullensaker study analysis had shown that moderate frequency of alcohol consumption was associated with prevalent ultrasound detected synovitis. Hougen et al. reported that moderate alcohol consumption was associated with prevalent hand OA [2]. We must emphasize that the participants in our study were divided into two groups depending on whether they consumed alcohol or not, and they were not classified according to the amount of alcohol they consumed. On the other hand, we cannot exclude the fact that some of the participants did not want to report consuming alcohol. It could be the cause of different results. In this study, we also compared patients with low and moderate physical activity, and there was no statistically significant difference between groups. Studies conducted in the general population have shown that a moderate level of physical activity is not associated with OA [3], but research

has mostly been conducted on the knee joint. The explanation of the increased risk for developing OA among women after menopause has been a challenge for researchers for years [24]. We did not find a statistically significant difference either in relation to the time of onset of menopause or the duration of menopause between the 2 groups. The results of different studies are contradictory. One Australian study suggests that a later age at menopause and longer duration of the interval between menarche and menopause are associated with more severe distal interphalangeal OA, stating that estrogen in the early course of the disease can lead to the development of severe form of OA either symptomatic or radiographic [25]. On the other hand, studies which examined the association between estrogen replacement therapy and hand OA showed different results. One study showed that those who do not take hormone therapy are at higher risk to develop hand OA [26], while another study [27] found no association between hormone replacement therapy and hand OA [24]. The effects of estrogen on the joint level are still not clear enough and future research in this area is required [28]. One Rotterdam study reported that individuals with vertebral fractures had a 74% increased risk of developing radiographic hand OA, and to the contrary, non-vertebral fractures were not associated with the incidence of progression of hand OA [29]. Another result was in line with the result of our study which is likely due to the fact we did not separate the study participants by the location of the previous fracture. The mentioned study suggests, as one of the explanations for a different result in two groups, the fact that individuals with a prevalent vertebral fracture are more dependent on the use of walking aid which increases the risk of hand OA [29]. Our results did not show an association between family history of fractures and the prevalence of hand OA. In their study, Bergin et al. mentioned the possibility of a heritable bone characteristic which affects both vertebral fracture risk and frequency of hand OA [29]. As statistically significant predictors, family history of structural changes in the hands and MetS were distinguished. Genetic factors have a significant role in the development of OA, and heritability of hand OA is more than 60% [10, 30]. The results of our study showed that patients who have a positive family history of structural changes in the hands have a 15 times higher chance of hand OA compared to patients with a negative family history. When it comes to MetS as a predictor of hand OA, there are also disagreements in the foreign research reports. Two Dutch studies which had examined the association between MetS and hand OA reported higher prevalence of MetS among individuals with hand OA [31, 32]. The first showed that overweight persons with diabetes and hypertension had a significantly higher risk of radiographic hand OA, pointing to the metabolic component in the etiology of OA [31]. Our study showed that individuals with MetS had a 3 times higher chance for hand OA compared to subjects without MetS. On the other hand, Marshall et al. established that metabolic risk factors were not associated with higher incidence or progression of hand OA over 7 years, whether observed together or separately [33]. This contradiction could be explained by different study methodologies, and the use of different definitions of MetS. The last-mentioned study included the following metabolic factors: BMI, hypertension, dyslipidemia, and diabetes [33], while in our study we used the clinical definition mentioned in the methodology of these study [14]. However, they have used BMI which is defined on height and weight, so there is no information about the distribution of adipose tissue, whilst we used data relating to waist circumference. One Dutch study reported an association between visceral fat and hand OA in men. It has been suggested that visceral fat secretes bioactive cytokines which likely act locally in joint tissues [34]. Furthermore, we did not consider the influence of individual metabolic factors, so the two studies cannot be compared in that segment. Although intrinsic factors, such as genetic, increase the risk for hand OA, MetS also has a significant role as a modifiable factor which indicates a notable potential for prevention [35]. This original scientific paper is part of a doctoral dissertation: The link between hand functionality in osteoarthritis and bone density in postmenopausal women as measured by central dual-energy X-ray a absorptiometry.

Conclusion

A positive family history of structural changes in the hand is the most significant risk factor for the development of hand osteoarthritis. Likewise, metabolic syndrome presents another important predictor of hand osteoarthritis. Considering the contradictory results of previous studies in relation to other potential predictors, future longitudinal studies are needed.

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COMPARISON OF SERUM INTERLEUKIN-33 LEVELS IN CHILDREN WITH ALLERGIC RESPIRATORY DISEASES

POREĐENJE SERUMSKIH NIVOA INTERLEUKINA-33 KOD DECE SA ALERGIJSKIM BOLESTIMA RESPIRATORNOG SISTEMA

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Summary

Introduction. Recent studies point to the importance of interleukin-33 in the pathogenesis of allergic respiratory diseases. The relationship of interleukin-33 and certain allergic respiratory diseases as well as their characteristics is not fully elucidated. The basic aim of this research was to determine interleukin-33 serum levels in children with allergic asthma and allergic rhinitis, as well as to examine the relationship between obtained interleukin-33 levels and individual clinical characteristics of these patients. **Material and Methods.** Serum interleukin-33 levels were measured in a total of 91 children. The study group included 39 children with both allergic asthma and allergic rhinitis, and also 22 children with allergic asthma without allergic rhinitis. The control group included 30 healthy children. **Results.** Serum levels of interleukin-33 in children with both allergic asthma and allergic rhinitis were significantly higher compared to those in children with allergic asthma only ($\chi^2 = 7.01$; $p = 0.008$; $p < 0.01$). Both groups of patients had significantly higher interleukin-33 serum levels compared to healthy children ($\chi^2 = 7.01$; $p = 0.008$; $p < 0.01$). The correlation between serum interleukin-33 levels and allergic asthma severity was statistically significant ($rs = 0.289$; $p = 0.024$; $p < 0.05$). **Conclusion.** Serum levels of interleukin-33 were significantly higher in children with allergic respiratory diseases compared to healthy examinees. Significantly higher levels of serum interleukin-33 levels were found in children with both allergic asthma and allergic rhinitis, compared to children with allergic asthma only. Patients with higher interleukin-33 serum levels also had a more severe type of allergic asthma.

Key words: Interleukin-33; Respiratory Tract Diseases; Interleukins; Allergens; Respiratory Hypersensitivity; Child; Rhinitis, Allergic; Asthma; Hypersensitivity, Immediate

Sažetak

Uvod. Dosadašnja ispitivanja ističu značaj interleukina-33 u patogenezi alergijskih bolesti disajnih puteva. Odnos interleukina-33 i pojedinih alergijskih bolesti disajnih puteva kao i njihovih karakteristika nije dovoljno preciziran. Osnovni cilj ovog istraživanja bio je odrediti vrednosti interleukina-33 u serumu kod dece sa alergijskom astmom i alergijskim rinitisom kao i ispitati odnos dobijenih vrednosti interleukina-33 sa pojedinim kliničkim karakteristikama ovih pacijenata. **Materijal i metode.** Izmerene su serumske vrednosti interleukina-33 kod ukupno 91 deteta. Ispitivanu grupu činilo je 39 dece sa alergijskom astmom i alergijskim rinitisom i 22 deteta koja su imala alergijsku astmu bez alergijskog rinitisa. Kontrolnu grupu činilo je 30 zdrave dece. **Rezultati**. Deca koja su imala alergijsku astmu udruženu sa alergijskim rinitisom, vrednosti interleukina-33 u serumu bile su signifikantno veće u odnosu na decu koja su imala alergijsku astmu bez alergijskog rinitisa ($\chi2 = 7{,}01$; $p = 0{,}008$; $p < 0{,}01$). Obe grupe pacijenata su imale signifikantno veće vrednosti interleukina-33 u serumu u odnosu na zdravu decu ($\chi2 = 7{,}01$; $p = 0{,}008$; $p < 0{,}01$). Korelacija između nivoa interleukina-33 u serumu i težine alergijske astme je statistički značajna ($rs = 0{,}289$; $p = 0{,}024$; $p < 0{,}05$). **Zaključak**. Serumske vrednosti interleukina-33 su značajno veće kod dece sa alergijskim bolestima disajnih puteva u odnosu na zdrave ispitanike. Značajno više vrednosti interleukina-33 u serumu imaju deca sa alergijskom astmom i alergijskim rinitisom u odnosu na decu sa alergijskom astmom bez alergijskog rinitisa. Pacijenti koji su imali više vrednosti interleukina-33 u serumu imali su i teži oblik alergijske astme.

Ključne reči: interleukin-33; oboljenja respiratornog sistema; interleukini; alergeni; respiratorna hiperosetljivost; dete; alergijski rinitis; astma; atopijska hiperosetljivost

Introduction

Allergic asthma (AA) is a chronic inflammatory lung disease. The disease is characterized by reversible airway obstructions and bronchial hyperactivity induced by direct and indirect stimuli [1].

Allergic asthma is the most common chronic inflammatory disease in children and adolescents. The incidence of AA has been increasing over time. The last estimate indicates that 334 million people suffer from AA worldwide [2].

Respiratory tract inflammation in AA happens due to the development of complex immunopathogenic mechanisms which lead to infiltration and activation of inflammatory cells and release of potent mediators. In most cases, inflammation in AA is the

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Abbreviations

IL-33 – interleukin-33
AA – allergic asthma
AR – allergic rhinitis
Th2 – T helper 2 lymphocytes
CD4+ – cluster of differentiation 4 +
GINA – Global Initiative for Asthma
SABA – short-acting beta agonist
BMI – body mass index
ATS – American Thoracic Society
ARIA – Allergic Rhinitis and its Impact on Asthma
ELISA – enzyme linked immunosorbent assay

consequence of type 2 T helper cells (Th2) activation, while mechanisms of "non-Th2" mediated inflammation are still poorly defined [3].

Interleukin-33 (IL-33) is a relatively new member of cytokine interleukin 1 family. Research studies published so far showed that IL-33 appears to have proinflammatory, anti-inflammatory and protective function in different diseases. Determination of IL-33 function in certain inflammatory diseases has been the subject of numerous ongoing researches [4–7]. The IL-33 has a significant role in the differentiation of naive cluster of differentiation 4 (CD4) + T cells into Th2 cells which cause activation of eosinophils and other inflammatory cells by complex cytokine- and cell-mediated interaction, thereby significantly impacting allergic inflammation in AA and allergic rhinitis (AR) [8]. Previous studies showed that there was a higher level of serum IL-33 in patients with AA compared to healthy examinees [9–11]. The relationship between serum IL-33 level and certain clinical characteristics of allergic respiratory diseases is not specified enough, especially in children. The basic aim of this research was to determine serum IL-33 levels in children with AA and AR, as well as to examine the relationship between obtained IL-33 levels and individual clinical characteristics of these patients.

Material and Methods

A prospective study was conducted at the Institute of Child and Youth Health Care of Vojvodina from September 2016 to March 2018. The study was approved by Ethics Committee of the Faculty of Medicine in Novi Sad and Institute of Child and Youth Health Care of Vojvodina. Informed consent and assent (for children aged 10 years and older) were obtained prior to inclusion into the study. The principles of the Declaration of Helsinki were respected during the trial.

The study group included 61 children, aged between 6 and 18 years, with mild or moderate clinical presentation of AA (newly and previously diagnosed children who did not receive prophylaxis with inhaled corticosteroids at least 6 months before the trial). The diagnostic protocol and classification of AA severity were performed according to Global Initiative for Asthma (GINA) guidelines [1].

Thirty healthy examinees were included in the control group and they were matched on sex and age with the study group.

The exclusion criteria were as follows: presence of urticaria, eczema, food allergies, chronic respiratory infections, parasite infections, uncontrolled gastroesophageal reflux, eosinophilic oesophagitis, any chronic disease, acute infection or other acute condition, earlier or current treatment with allergen specific immunotherapy and use of systemic, inhalatory, intranasal and local corticosteroids before and during the study.

Anamnestic/heteroanamnestic data were obtained for children of the study group. The type of symptoms and frequency of short-acting beta2-agonists (SABA) administration were recorded. The clinical examination was performed and the following parameters were recorded: weight and height, body mass index (BMI), Z score, percentiles. Pulmonary function test – spirometry was performed in all children of the study group by using MasterScreen IOS (Jaeger, Germany) spirometer, according to American Thoracic Society (ATS) instructions.

According to Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations, classification of AR was made based on the medical history data and clinical laboratory test results in the study group, to establish children who had been diagnosed with both AA and AR [12]. Based on the severity, AR cases were classified as mild and moderate/severe; in regard to the causal allergen type as perennial and seasonal, and based on the duration of symptoms as intermittent and persistent.

Laboratory tests also included determination of serum IL-33 levels in all the children in both the study and control group. Measurement of serum IL-33 levels was performed in the laboratory of the Clinical Center of Vojvodina, Novi Sad. The IL-33 levels were determined by direct (sandwich) enzyme linked immunosorbent assay (ELISA), a method which implies the use of Human IL-33 Quantikine®ELISA assay (R&D systems, USA) and polyclonal antibodies specific for IL-33 that was carried out on EUROIMMUN Analyzer I 2-P ELISA (EUROIMMUN AG, Luebeck, Germany) according to the manufacturer's protocol.

Anamnestic/heteroanamnestic data were collected for children in the control group (drug hypersensitivity, absence of acute infection signs and symptoms 2 weeks before examination, while absence of chronic diseases was specially recorded). Physical examination was also performed (weight, height and absence of clinical signs of acute infection were specially recorded). Serum IL-33 level (pg/ml) was measured in the same way in both groups of children.

The Statistical Package for the Social Sciences 23 was used for the statistical processing of the obtained data. Estimation of statistical significance was done by using Wilcoxon signed-rank test, independent samples T-test, Mann-Whitney U-test, median test and chi-squared test. Spearman's rank correlation coefficient was used for correlation assessment and $p < 0.05$ was considered statistically significant.

Results

The study group included 61 children (n = 61), average age of 9 years and 6 months. Thirty-two (52.5%) examinees were boys and 29 (47.5%) were girls. The control group included 30 healthy children (n=30), average age of 9 years and 8 months; 16 (53.3%) of them were boys and 14 (46.6%) girls. In the study group 52 (85.2%) patients had normal weight, 4 (6.6%) were overweight, 3 (4.9%) were obese and 2 (3.3%) were underweight. The control group included 25 (83.3%) examinees with normal weight, 4 were (13.3%) overweight and 1 was (3.3%) obese, while there were no underweight examinees.

Differences in sex ($\chi^2 = 0.006$; p = 0.937), age (t = 0.187; p = 0.852) and obesity level ($\chi^2 = 2.157$; p = 0.540) between the study and control group were not statistically significant (p > 0.05). **Table 1** shows serum IL-33 levels in children from the study group, i. e. in children with AA and with/without AR and also in healthy children in the control group.

Mann-Whitney U-test results show that there is a highly statistically significant difference (U = 509; p = 0.00; p < 0.01) in the serum IL-33 levels between the children aged 6 – 18 years with AA/without AR and healthy children of the same age.

Out of the total of 61 children with AA who participated in this study, 39 (64%) also had AR. The remaining 22 (36%) children had AA without AR.

The median serum IL-33 level in children with AA and AR was 1.80 pg/ml, which is above the median serum IL-33 level in the whole sample (1.49 pg/ml). The median serum IL-33 level in children without AA was 0.70 pg/ml, i. e. they had lower median levels compared to the median level in the whole sample (M = 1.49 pg/ml). The examinees who had extremely high serum IL-33 levels in regard to the median levels of other examinees in the group are shown in **Graph 1**.

The chi-square test showed that children with both AA and AR also had statistically significantly higher serum IL-33 levels compared to the children with AA but without AR ($\chi^2 = 7.01$; p = 0.008; p < 0.01).

The majority of examinees (34 children, 55.7%) presented with a mild AA, while 27 (44.3%) presented with moderate AA symptoms.

The relationship between serum IL-33 levels and AA severity was analyzed by Spearman's rank correlation coefficient. A statistically significant positive correlation was found between serum IL-33 level and AA severity (rs = 0.289; p = 0.024; p < 0.05).

The **Table 2** shows the prevalence of perennial and seasonal, mild and moderate/severe, intermittent and persistent AR relative to the median level of serum IL-33 in the whole sample.

The chi-square test results did not indicate that there was a statistically significant difference among serum IL-33 levels in the examinees with perennial and seasonal AR ($\chi^2(1) = 0.14$; p = 0.707; p > 0.05),

Table 1. Serum interleukin-33 levels (pg/ml) in the study and control group
Tabela 1. *Vrednosti serumskog nivoa interleukina-33 (pg/ml) u ispitivanoj i kontrolnoj grupi*

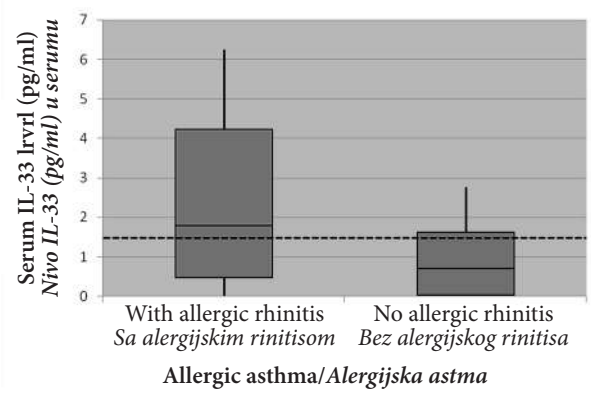
	N	Min.	Max.	Mode	M	AM	SD
Study group/*Ispitivana grupa*	61	0.00	14.745	0.041	1.491	2.550	3.387
Control group/*Kontrolna grupa*	30	0.00	2.682	0.00	0.261	0.573	0.632

Legend: N - number of examinees; Min. - minimal; Max. - maximal; Mode - value that appears most often, M - median; AM - arithmetic mean; SD - standard deviation
Legenda: N-broj ispitanika; Min.-minimalna vrednost; Max.-maksimalna vrednost; Mode - najčešće ponavljana vrednost, M-medijana; AS-aritmetička sredina; SD-standardna devijacija

Table 2. The prevalence of perennial and seasonal, mild and moderate/severe, intermittent and persistent AR relative to the median level of serum interleukin 33 in the whole sample
Tabela 2. *Zastupljenost perenijalnog i sezonskog, blagog i srednje teškog/teškog, intermitentnog i perzistentnog alergijskog rinitisa u odnosu na srednju vrednost interleukina-33 u serumu za ceo uzorak*

IL-33 level (pg/ml) *Nivo IL-33 (pg/ml)*	Allergic rhinitis/*Alergijski rinitis*	
	Perennial/*Perenijalni*	Seasonal/*Sezonski*
> Median/> *Medijana*	16	3
≤ Median/≤ *Medijana*	17	3
	Mild/*Blag*	Moderate/Severe/*Srednje težak/težak*
> Median/> *Medijana*	7	12
≤ Median/≤ *Medijana*	8	12
	Intermittent/*Intermitentni*	Persistent/*Perzistentni*
> Median/> *Medijana*	6	13
≤ Median/≤ *Medijana*	4	16

Legend**:** IL-33 - interleukin 33; Median – the median level in the whole sample
*Legenda**:** IL-33 - interleukin 33; Medijana - srednja vrednost za ceo uzorak*



Graph 1. Distribution of serum IL-33 levels in children with both AA and AR, and those with AA without AR
Grafikon 1. *Distribucija serumskih vrednosti IL-33 kod dece koja su imala dijagnozu AA i AR i kod dece koja su imala samo AA bez AR*
Legend: IL-33 - interleukin 33; AA – allergic asthma; AR – allergic rhinitis
Legenda: IL-33 – interleukin 33; AA – alergijska astma; AR – alergijski rinitis

mild and moderate/severe AR ($\chi^2(1) = 0.16$; $p = 0.899$; $p > 0.05$), and intermittent and persistent AR ($\chi^2(1) = 0.21$; $p = 0.645$; $p > 0.05$).

The **Table 3** shows the prevalence of examinees with a certain AR type (classified based on causal allergen type, duration and clinical severity) relative to the median serum IL-33 level in the whole sample.

The results of the chi-square test showed that the difference among serum IL-33 levels in examinees with different AR types was not statistically significant ($\chi^2 = 4.44$; $p = 0.618$; $p > 0.05$).

Discussion

There was no significant difference between the control group of healthy examinees and the children with AA with/without AR in regard to the sex distribution, age, and obesity level. Out of the total number of children with AA, the majority of our examinees (85.25%) had normal weight. Also, in another similar study, children with AA mostly had normal weight [13]. A study which analyzed the relationship of IL-33 level and inflammation associated with obesity showed that activation of IL-33/ST2 axis had an anti-inflammatory role [14].

In our study, the average serum IL-33 level, in children with AA and with /without AR, was 2.550 ± 3.387 pg/ml. A significantly higher average serum IL-33 level, compared to the level obtained in our examinees, was found in the study performed by Bahrami et al. and it was 15.17 ± 32.3 pg/ml [15]. This difference in the average serum IL-33 level in children with AA can be explained by different inclusion criteria of the examinees. In the study conducted by Bahrami et al., children were included regardless of the duration and severity of AA, unlike examinees in our study who had persistent, mild or moderate AA.

A study that included a series of adult examinees with AA detected higher serum IL-33 levels compared to our study. The serum IL-33 level in adult examinees with a mild form of persistent AA was 202.6 pg/ml, while in patients with moderate AA it was 380.4 pg/ml. These differences in serum IL-33 levels may be due to the fact that the study included a series of adult patients with other allergic diseases besides AA. Also, in the afore-mentioned study, IL-33 levels were determined using a test which differs from the one used in our study in terms of sensitivity, standard range, minimal detectable level, and the manufacturer [16]. The difference in serum IL-33 levels between examinees included in our study and adult examinees can additionally be explained by the characteristics of our examinees. One of the exclusion criteria in our study was, among others (except for AR), presence of other allergic diseases which probably could affect serum IL-33 level. Also, it should not be neglected that our study included children, while the study by Momen et al. tested adult population.

Table 3. The prevalence of certain AR types relative to the median serum interleukin-33 level
Tabela 3. *Zastupljenost određenih oblika alergijskog rinitisa u odnosu na srednju vrednost interleukina-33 u serumu*

IL-33 level (pg/ml) *Nivo IL-33 (pg/ml)*	Allergic rhinitis/*Alergijski rinitis*	
	Perennial/*Perenijalni*	Seasonal/*Sezonski*
> Median/> *Medijana*	16	3
≤ Median/≤ *Medijana*	17	3
	Mild/*Blag*	Moderate/severe/*Srednje težak/težak*
> Median/> *Medijana*	7	12
≤ Median/≤ *Medijana*	8	12
	Intermittent/*Intermitentni*	Persistent/*Perzistentni*
> Median/> *Medijana*	6	13
≤ Median/≤ *Medijana*	4	16

Legend: IL-33 - interleukin 33; Median - median level: 1-intermittent + mild; 2 - intermittent + moderate/severe; 3 - persistent + mild; 4 - persistent + moderate/severe; a-seasonal; b-perennial
Legenda: IL-33 – interleukin 33; Median – srednja vrednost: 1 – intermitentni + blagi; 2 – intermitentni + srednje teški/teški; 3 – perzistentni + blag; 4 – perzistentni + srednje teški/teški; a – sezonski; b – perenijalni

The median level of serum IL-33 recorded in healthy children in our study was 0.573 ± 0.632 pg/ml and it is similar to median levels of IL-33 in other studies that included healthy pediatric population. For example, the median level of IL-33 in healthy children from an Iranian study was 0.61 ± 2.16 pg/ml [15]. A higher median level of IL-33 in healthy adult examinees in the mentioned study compared to the levels in healthy children in our study suggests that the age of examinees may be a significant factor in defining normal serum IL-33 level range, which is a common practice in most laboratory findings.

The results of our study show that serum IL-33 levels in children with AA and with/without AR are significantly higher compared to those in healthy children. Higher serum IL-33 levels in children with AA compared to healthy children were also detected in studies with a large number of examinees. Meta-analysis of eight earlier studies which included 330 children with AA and 248 healthy children also showed that serum IL-33 levels were higher in children with AA [17].

The study of Bahrami et al. also showed that serum IL-33 levels were significantly higher in children with AA compared to the control group of children [15]. Furthermore, studies with adults also show that patients with AA have significantly higher serum IL-33 levels compared to healthy examinees [16, 18].

The coexistence of AA and AR is common [19]. In our study, 39 (63.9%) children were diagnosed with AR and AA. Similarly, results of other studies that analyzed the coexistence of these two allergic diseases showed that AA is accompanied by AR in 30 - 80% of AR cases [20, 21].

The importance of IL-33 in AR pathogenesis is suggested by a study conducted in an animal experimental model of AR caused by ambrosia pollen which proved that mice with a removed IL-33 gene have a decreased production of Th2 cytokine as well as decreased accumulation of eosinophils, basophils and Th2 lymphocytes in nasal mucosa and lower frequency of sneezing [22].

The children in our study with both AA and AR had significantly higher serum IL-33 levels compared to children with AA only.

Similarly, a study by Bonanno et al. which compared serum IL-33 levels in examinees with AA and AR and examinees with AR only showed that IL-33 levels were significantly higher in examinees who had both of these two allergic diseases (AA and AR) [23].

The significance of IL-33 in the exacerbation of AR is indicated in a study with adult patients in which serum IL-33 levels were significantly higher in adult patients with AR sensitized to Japanese cedar pollen in the pollination season, when the pollen concentration in the air is highest, compared to the IL-33 levels measured out-of-the pollination season [24].

In our study, children with higher serum IL-33 levels also had a more severe form of AA. These results are in accordance with the results of previous studies. Bahrami et al. showed that the lowest serum IL-33 levels were detected in children with mild AA, slightly higher in children with moderate AA, and the highest levels were identified in children with a severe form of AA [15]. The study including adult patients also showed that there was a significant difference among serum IL-33 levels in patients with mild, moderate and severe AA [17]. Guo et al. conducted a study including 45 adult patients and proved that there was a positive correlation between serum IL-33 level, thickening of the basal membrane in the bronchial biopsy samples, and AA severity [25].

The results of our study do not indicate that there is a difference among serum IL-33 levels in children with both AA and AR relative to causal allergen of AR (perennial, seasonal), AR severity (mild, moderate/severe) and AR duration (intermittent, persistent) as well as relative to different AR forms for which classification was done based on afore-mentioned AR features. However, a study by Yang et al. showed that the IL-33 levels in nasal secretion of patients with AR were significantly higher during the causal allergen pollination season compared to those identified out of the pollination season [24]. A study performed by Asak et al. showed that examinees with severe AR have higher IL-33 levels of nasal secretion [26].

Similar values of serum IL-33 in children with different causal allergens, severity, duration, and AR forms are a possible consequence of serum IL-33 level detection independently of pollination season i. e. examinee exposure to the causal allergen. Measuring of serum IL-33 level was done independently of severity and earlier duration of AR at the moment of blood sample collection. Furthermore, all the children in our study group had both AR and AA.

Conclusion

The results of our study indicate that serum interleukin-33 levels in children with allergic respiratory diseases are significantly higher than in healthy children. Children who had both allergic asthma and allergic rhinitis had higher levels of this cytokine compared to children who had only allergic asthma. Patients with higher serum interleukin-33 levels also had more severe forms of allergic asthma. The causal allergen type, severity and duration of allergic rhinitis, i. e. different forms of allergic rhinitis did not significantly impact serum interleukin-33 levels in children with allergic asthma. The results confirm that interleukin-33 may be a potent inflammatory biomarker for the diagnosis of allergic respiratory diseases and suggest a potential importance of interleukin-33 correlating with allergic asthma severity and respiratory inflammatory process extension assessment.importance of interleukin-33 correlating with allergic asthma severity and respiratory inflammatory process extension assessment.

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REVIEW ARTICLES
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ALCOHOLIC LIVER DISEASE

ALKOHOLNA BOLEST JETRE

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Summary

Introduction. Alcoholic liver disease is one of the most common liver disorders in Europe and in the United States of America. This paper highlights the clinical-pathological concept of alcoholic liver disease with an overview of current therapeutic approaches. **The spectrum** of alcoholic liver disorders includes liver steatosis, alcoholic steatohepatitis, alcoholic cirrhosis with a potential to culimate in hepatocellular carcinoma. Alcoholic steatohepatitis is a rapidly-progressive disorder that may be associated with severe clinical manifestations of alcoholic hepatitis and high mortality. There are large variations in alcohol consumption and consequent morbidity and mortality around the world. In addition to the amount of alcohol intake, different individual manifestations of alcoholic liver disease are affected by genetic and other risk factors. **Pathogenesis** with a potential to culminate in hepatocellular carcinoma of the disease is based on the toxic effects of acetaldehyde, oxidative stress, lipid metabolism disorders and alcohol-induced inflammation. **Diagnosis of alcoholic liver disease.** In the diagnosis of alcoholic liver disease, apart from clinical picture and laboratory findings, ultrasonography, transient elastography, magnetic resonance imaging, serum biomarkers and liver biopsy are important. **Therapy of alcoholic liver disease** includes abstinence, nutritional support, corticosteroid treatment and liver transplantation. New therapeutic modalities are being investigated. **Conclusion**. Despite abundant knowledge of the epidemiology, pathophysiology and clinical diagnostics of alcoholic liver disease, the therapy has not changed over the past few decades. The development of novel therapeutic modalities requires a multidisciplinary approach and close cooperation of doctors and pharmacists. The emphasis must be put on the disease prevention at both individual and community level.

Key words: Liver Diseases, Alcoholic; Hepatitis, Alcoholic; Liver Cirrhosis; Acetaldehyde; Lipid Metabolism; Inflammation; Diagnosis; Therapeutics; Risk Factors

Sažetak

Uvod. Alkoholna bolest jetre jedna je od najčešćih bolesti jetre u Evropi i Sjedinjenim Američkim Državama. U radu je istaknut kliničko-patološki koncept alkoholne bolesti jetre sa osvrtom na aktuelnu terapiju. **Spektar** alkoholne bolesti jetre čine steatoza jetre, alkoholni steatohepatitis i alkoholna ciroza jetre, koja može rezultirati hepatocelularnim karcinomom. Alkoholni steatohepatitis može biti rapidno progresivan i manifestovati se ozbiljnom kliničkom slikom alkoholnog hepatitisa sa visokom smrtnošću. Širom sveta postoje velike varijacije u konzumaciji alkohola i posledičnom morbiditetu i mortalitetu. Osim količine alkohola, na različito individualno ispoljavanje alkoholne bolesti jetre utiču genetski i drugi faktori rizika. **Patogeneza** alkoholne bolesti jetre zasniva se na toksičnom dejstvu acetaldehida, oksidativnom stresu, poremećaju metabolizma lipida i alkoholom indukovanoj inflamaciji. **U dijagnostici alkoholne bolesti jetre**, osim kliničke slike i laboratorijskih nalaza, značajni su ultrasonografija, tranzijentna elastografija, magnetna rezonancija, serumski biomarkeri i biopsija jetre. **Standardna terapija** alkoholne bolesti jetre uključuje apstinenciju, nutritivnu podršku, primenu kortikosteroida i, uz ispunjavanje kriterijuma, transplantaciju jetre. Istražuju se novi terapijski modaliteti. **Zaključak.** Iako se mnogo zna o epidemiologiji, patofiziologiji i kliničkoj dijagnostici alkoholne bolesti jetre, terapija se nije mnogo promenila tokom proteklih decenija. Potrebno je angažovanje kliničara i farmaceuta sa ciljem iznalaženja novije terapije alkoholne bolesti jetre. Lečenje alkoholne bolesti jetre mora biti multidisciplinarno. Akcenat mora biti na prevenciji bolesti na populacionom i individualnom nivou.

Ključne reči: alkoholna bolest jetre; alkoholni hepatitis; ciroza jetre; acetaldehid; metabolizam lipida; inflamacija; dijagnoza; terapija; faktori rizika

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Abbreviations

ALD – alcoholic liver disease
ASH – alcoholic steatohepatitis
AH – alcoholic hepatitis
HCC – hepatocellular carcinoma
AFL – alcoholic fatty liver
DNA – deoxyribonucleic acid
NAD – nicotinamide adenine dinucleotide
IL – interleukin
TNF-α – tumor necrosis factor-α
SREBP1 – sterol regulatory element-binding protein 1
PPAR-α – peroxisome proliferator-activated receptor-alpha

Introduction

Alcoholic liver disease (ALD) is one of the most common liver disorders in Europe and the United States of America. The disease is caused by chronic alcohol overconsumption at amounts exceeding standard daily quantities, which vary significantly between individuals. It commonly affects the working population resulting in extensive socio-medical consequences [1, 2]. As early as the 18th century, physicians drew the connection between heavy drinking and the distribution of liver diseases in population [3, 4].

Spectrum and epidemiology of alcoholic liver disease

The ALD spectrum includes alcoholic fatty liver (AFL), alcoholic steatohepatitis (ASH) and alcoholic cirrhosis with a potential to culminate in hepatocellular carcinoma (HCC). The ASH may manifest as a slowly-progressing condition, when chronic liver injury and inflammation lead to progressive fibrosis and liver cirrhosis. In some patients with ALD (with or without cirrhosis), ASH may progress rapidly and may be accompanied by severe clinical manifestations of alcoholic hepatitis (AH). Short-term mortality of AH remains high (20–30%), as well as six-month mortality, that can reach 40% in severe disease conditions [5, 6].

The majority (90–100%) of heavy chronic alcoholics develop liver steatosis. Those who consistently and excessively abuse alcohol are at risk of developing progressive ALD. Fibrosis is likely to occur in some 20% to 40% of patients with steatosis, while 8% to 20% of these patients will develop liver cirrhosis [7].

A large variation in alcohol consumption and related morbidity and mortality exists worldwide. According to the European Association for the Study of the Liver HEPAHEALTH Report, Serbia is categorized as a country with a stable alcohol consumption at low levels (on average below 10 L pure alcohol per person annually) [8]. A group of authors from Novi Sad reported that alcohol consumption in Vojvodina region is lower than in other regions of Serbia, but with significant health consequences [9].

In 2012, it was estimated that 3.3 million deaths, or 5.9% of all deaths worldwide, were attributable to alcohol consumption. An estimated 5.1% of the global burden of disease, as measured in disability-adjusted life-years, is attributed to alcohol consumption [10].

Global liver cirrhosis deaths increased from around 676,000 (95% uncertainty interval: 452,863 - 1,004,530) in 1980 to over 1 million (1,029,042; 670,216 - 1,554,530) in 2010 (about 2% of the global total) [11]. Due to cirrhosis and chronic liver disease, there were 1,256,900 deaths in 2016. Out of these, 334,900 (27%) were attributable to alcohol [12].

Risk factors for the development of ALD

Considering that a relatively small percentage of chronic alcoholics develop advanced ALD, the course of the disease is most likely determined not only by the amount of alcohol intake, but also by the predisposing factors such as genetics, female sex, underlying viral and metabolic liver diseases, overweight, use of some drugs and supplements (paracetamol, isoniazid, methotrexate, beta-carotene, vitamin A) and smoking [5–7].

The measurement of alcohol consumption includes determination of daily alcohol intake in grams and duration of drinking period. According to relevant guidelines, standardizing a "drink" to a measure of 10 g of alcohol is recommended. The number and type of alcoholic drinks are recorded and calculation to grams of alcohol per day is done [5–7].

Rehm et al. reported a continuous curve displaying increased risk for the development of liver cirrhosis proportional to increased alcohol consumption; however, increased risk is also associated with chronic consumption of small amounts of alcohol (12 g/day to 24 g/day) [14].

Chronic consumption of more than 40 g of alcohol per day over a period of several consequent years was identified as a risk factor for AFL by Seitz et al. [5]. The majority of patients with AH reported heavy drinking (more than 100 g of alcohol per day) during ten years and over, with escalated consumption as a response to recent life events and crisis [15].

Bellentani and Tiribelli reported development of ALD in patients consuming more than 30 g of alcohol per day during ten years. The incidence of cirrhosis increases linearly with increasing alcohol intake above this threshold [16]. Alcoholics taking 80 g of alcohol per day in the last 10 years are nearly certain to develop an advanced form of ALD [17]. As reported by Dunn and Shah, AH is associated with female sex and an irregular (i.e. binge drinking) pattern of alcohol consumption. Cirrhosis is associated with female sex, heavy alcohol use over a period of 15 years, and consuming over 200 g of alcohol per day [18].

In the United States, the type of alcohol and the prevalence of binge drinking changed during the period of 2000 – 2013, with a substantial increase observed in the consumption of distilled spirits,

wine and binge drinking. Binge drinking is particularly concerning in young adults [6, 19]. Early onset of alcohol consumption is a predictor of alcohol problems in adulthood. Today, many more young people drink at younger ages. Psychosocial factors play an important role [20]. Certain childhood risk factors may lead to alcohol addiction later in life [21].

Patatin-like phospholipase domain-containing protein 3 (PNPLA3) may be implicated in the genetic background of ALD. The PNPLA3 is associated with the development of ALD even in cases of significantly shorter drinking history and exposure to alcohol [5, 6, 18].

Females are more prone to alcohol than men. They develop ALD after consuming lesser amounts of alcohol over a shorter period. It may be due to their decreased gastric metabolism of alcohol, lower total body water content and alcohol-mediated increase of serum estrogen levels [5, 6].

Pathogenesis of ALD

Alcohol oxidation includes conversion of ethanol to acetaldehyde by alcohol dehydrogenase (ADH) in hepatocytes. Acetaldehyde is further metabolized down to acetate. Another pathway of alcohol conversion to acetaldehyde involves cytochrome P450 2E1. Acetaldehyde is a highly toxic and carcinogenic substance. It binds to the proteins leading to structural and functional damage predominantly in mitochondria and microtubules [5, 22].

Consumption of alcohol is also associated with oxidative stress. Formation of reactive oxygen species can be generated through *CYP2E1* induced by alcohol metabolism as well as alcohol-induced inflammation. The reactive oxygen species bind with proteins and deoxyribonucleic acid (DNA) either directly or via lipid peroxidation products, thus resulting in formation of DNA adducts [6, 7, 18, 23, 24].

Alcohol-induced epigenetic modifications include acetylation, phosphorylation, DNA hypomethylation as well as dysregulation of micro-ribonucleic acid (miRNAs) [25–27].

Lipid metabolism impairments in ALD

Early pathophysiological response to chronic alcohol consumption includes accumulation of lipids (triglycerides, phospholipids and cholesterol esters) in the hepatocytes. Alcohol drinking induces lipolysis resulting in elevation of circulating fatty acids and their accumulation in the liver, while increasing the lipid supply from the small intestines into the liver [28].

Alcohol consumption increases the reduced to oxidized forms of nicotinamide adenine dinucleotide reduced (NADH) and nicotinamide adenine dinucleotide(NAD) (NADH/NAD+) ratio in hepatocytes, thus disturbing the mitochondrial fatty acid β-oxidation. It also increases hepatic expression of sterol regulatory element-binding protein 1 (SREBP1c), a transcription factor stimulating the expression of lipogenic genes and consequent increase of fatty acid synthesis [29]. Alcohol inhibits the effects of negative SREBP1c regulators, such as adenosine monophosphate activated protein kinase and some other ones [6, 7, 18, 30, 31].

Alcohol inactivates the peroxisome proliferator-activated receptor-alpha (PPAR-α), a nuclear hormone receptor that, under physiological conditions, increases the expression of several genes involved in fatty acid transport and oxidation. Alcohol can reduce the activity of PPAR-α either directly (via acetaldehyde) or indirectly (via oxidative stress, adiponectin decrease and zinc deficiency) [18, 32].

Alcohol is an established cause of oxidative stress, inflammation and cell death in the adipose tissue. It induces an increase in serum leptin and decreases adiponectin levels. Alcohol inhibits the activation of farnesoid X-receptor, thus negatively affecting the lipogenesis via SREBP1 and positively regulating fatty acid oxidation via PPARα [6, 18, 33].

Liver inflammation in ALD

Pathogen-associated molecular patterns from the gastrointestinal tract, which stimulate the expression of cytokines and chemokines from Kupffer cells, as well as damage-associated molecular patterns released from dying hepatocytes, are implicated in the development of ASH [5]. Excessive use of alcohol results in alterations of intestinal microbiome composition. Intestinal barrier damage leads to increased intestinal permeability and small intestinal dysmotility, resulting in increased translocation of bacterial products from the gut towards the liver via the portal circulation [34].

Endotoxin (lipopolysaccharide) is sensed by immune system cells via the Toll-like receptor 4 leading to the activation of nuclear factor kappa B and formation of proinflammatory chemokines (chemokine (C-C motif) ligand 2 and interleukin (IL-8) and cytokines (tumor necrosis factor-α (TNFα) and IL-6) [5]. Processing of Pro-IL-1β to its active form (IL-1β) and its release is mediated by caspase activity and requires activation of inflammasome. The IL-1β amplifies the production of proinflammatory cytokines, renders hepatocyte susceptibility to cell death signals, increases synthesis of fatty acids and stimulates liver fibrosis [18, 35]. The IL-17 induces recruitment of neutrophils into the liver and stimulates production of IL-8 and chemokine (C-X-C motif) ligand 1 by hepatic stellate cells. Increased activity of other cytokines and chemokines has also been established [6, 7].

The loss of proteasome or inhibition of ubiquitin-proteasome pathway may result in cell damage, proliferation, apoptosis and formation of cellular inclusions comprising keratin aggregates [5]. Alcohol induces hepatocyte apoptosis by activating mitochondrial (intrinsic) apoptotic pathways, caspase-dependent and caspase-independent pathways, as well as by endosplasmic reticulum stress [36].

Progression of ALD - liver fibrosis and liver cirrhosis

Hepatic fibrosis is a wound-healing response, which may regress following absolute abstinence from alcohol. Continuation of alcohol consumption leads to a progressive course resulting in the replacement of the liver parenchyma by a scar tissue. In liver injury, hepatic stellate cells undergo complex activation processes and become the major source of excessive deposition of extracellular matrix. Activated hepatic stellate cells play a role in regulating the inflammatory response [37].

Cirrhosis is characterized by the formation of regenerative nodules of hepatic parenchyma surrounded by fibrous septa. It is associated with the development of portal hypertension and vascular abnormalities. Vasoconstriction occurs in the liver and kidneys, whereas vasodilatation is present in multiple vascular beds. Impairments occurring in individual vascular beds involve specific clinical manifestations thus requiring specific therapeutic modalities [38, 39].

Diagnosis of alcoholic liver disease

The diagnosis of ALD is frequently suspected upon documentation of excessive alcohol consumption (more than 40 g per day to 50 g per day) and the presence of clinical and/or biological abnormalities suggestive of liver injury. In its early stages, ALD is a silent disease and can only be detected by laboratory tests or imaging techniques [40].

Simple abdominal ultrasonography can be used to screen for AFL, but it has only moderate sensitivity and specificity. By contrast, ultrasonography techniques based on attenuation of shear waves such as controlled attenuation parameter are more accurate for the quantification of AFL. Magnetic resonance imaging has excellent accuracy for detecting liver fat [22].

Laboratory finding in ALD reveals aspartate aminotransferase/alanine aminotransferase ratio higher than 2, increased AST values at least twice the upper normal limit, increased gamma-glutamyl transferase and mean corpuscular volume. Decreased synthetic function of the liver, increased bilirubin and leukocyte counts and acute renal failure can occur. Liver biopsy is indicated in aggressive forms of ALD, if prospective modification of therapeutic options or establishment/confirmation of the accurate diagnosis is needed. Transjugular approach is the preferred biopsy method in cases with coagulopathy and ascites [13, 40].

Acute AH should be distinguished from decompensated alcoholic cirrhosis or acute or chronic liver disease [18]. Differential diagnosis may include severe sepsis, biliary obstruction, diffuse HCC, drug-induced liver injury and ischemic hepatitis [22]. The diagnosis of AH is frequently overlooked, especially in patients admitted for gastrointestinal bleeding or sepsis. The AH patients at significantly high risk for early mortality are identified according prognostic models such as Maddrey's discriminant function, the Model for End-Stage Liver Disease, the Glasgow AH score, and the age-bilirubin-International normalized ratio-creatinine score. After 7 days of medical therapy with prednisolone, physicians may identify responders using the Lille model [7, 40].

The assessment of liver fibrosis in patients with ALD is done by using non-invasive methods such as serum markers and liver stiffness measurements. The AST to platelet ratio index, FibroTest®, Fibrometer®, Hepascore®, and Fibrosure® can be useful in patients with ALD. Liver cirrhosis is diagnosed by clinical evaluation, using hepatic imaging techniques and, in some instances, liver biopsy. Esophagogastroduodenoscopy is used to assess the presence of esophageal varices, whereas liver/spleen ultrasound elastography is applicable for quantifying portal hypertension [40–42].

Therapy of alcoholic liver disease

Therapeutic strategies in the early stages of ALD implicate antioxidant administration, neutralization of intestinal bacterial endotoxins, and recovery of intestinal permeability by applying zinc, balancing the disturbed gut flora by using probiotics and specific antibiotics [7, 36].

Administration of inflammatory cytokines (e.g. TNF-α) blockers did not prove effective in patients with ALD, which is probably due to the fact that the majority of cytokines exhibit hepatoprotective properties besides their inflammatory effects. Corticosteroids reduce systemic inflammatory response, yet increasing the risk of infection and sepsis [36].

Inhibition of inflammasome signaling pathways by applying caspase inhibitors may be a new therapeutic target [35]. Preclinical studies open novel promising therapeutic options such as application of IL-22, anakinra, and IL-1 receptor antagonists. Potential application of farnesoid X receptor agonists also gains increased attention [6, 7, 36, 43, 44].

Key points in the therapy of ALD

The first and most important step in the therapy of ALD is absolute abstinence from alcohol. Combination of psychosocial intervention, pharmacotherapy and medical management is the most effective strategy in the treatment of patients with alcohol use disorders and ALD [45, 46].

Patients with advanced ALD manifest with severe clinical signs of protein-calorie malnutrition, so relevant nutritional support is needed. Reduced intake of vitamins and minerals and consequent impairment of their bioavailability results in clinical deficiency syndromes that require adequate supplementation [46–48].

Pharmacotherapy of ALD has not considerably changed over the past few decades as compared with tremendous advancements of treatment options for other liver diseases [7, 46]. Corticosteroids still remain the first-line therapy in AH. The majority of therapy protocols include 40 mg prednisolone per

day during a one-month period, with or without dose reduction [40]. After 7 days of prednisolone administration, Lille model can be used to identify the nonresponders, in which the risk greatly overwhelms the benefits of further corticosteroid therapy [13, 49]. Intravenous administration of N-acetylcysteine along with prednisolone (40 mg/day) can improve the 30-day survival of patients with severe AH. Pentoxifylline is not recommended in the treatment of AH any more [50].

Liver transplantation, as a rescue therapy in selected AH patients who do not respond to medicamentous therapy, dramatically improves their survival. Strict adherence to the rule of 6-month abstinence period before acceptance to the transplantation list is widely applied; however, the majority of AH patients die before the expiration of this period [51].

Decompensated alcoholic liver cirrhosis is most commonly manifested by portal hypertension complications such as ascites with or without complication and esophageal varices with or without bleeding. Treatment regimens for such clinical conditions are clearly defined [52].

Alcoholic liver cirrhosis is one of the most common indications for liver transplantation. Such patients often display multi-system manifestations of long-term ethanol consumption (peripheral and central nervous system disorders, alcoholic myopathy, hepatic osteodystrophy, and alcoholic cardiomyopathy, etc) [46, 47, 53, 54]. Treatment of alcoholic liver cirrhosis and preparing the patient for liver transplantation requires a multidisciplinary approach [46, 55].

Conclusion

Despite the abundant knowledge of the epidemiology, pathophysiology and clinical diagnostics of alcoholic liver disease, the therapy has not changed much over the past few decades. The development of novel therapeutic modalities for alcoholic liver disease requires a multidisciplinary approach and close cooperation of doctors and pharmacists. The emphasis must be put on the disease prevention at both individual and community level.

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CASE REPORTS
PRIKAZI SLUČAJEVA

University Clinical Center "Mother Theresa" Skopje,
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Case report
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A RARE CASE OF ADRENAL CAVERNOUS HEMANGIOMA

REDAK SLUČAJ NADBUBREŽNOG KAVERNOZNOG HEMANGIOMA

Ivo VUJICIK

Summary
Introduction. Adrenal cavernous hemangiomas are extremely rare non-functioning benign tumors. The majority of adrenal cavernous hemangiomas are diagnosed incidentally after surgery by histopathological examination. **Case Report.** We report a clinical case of a 57-year-old woman with adrenal cavernous hemangioma. On admission, the patient's adrenal-related hormones were in the reference range, so adrenal endocrine dysfunction was ruled out. The computed tomography scan revealed a well-circumscribed, round, heterogeneous right adrenal mass (32.3 x 55.4 mm). Iodinated contrast enhanced abdominal computed tomography showed a slight inhomogeneity. In this case, preoperative radiologic findings and absence of signs of local invasion indicated laparoscopic adrenalectomy. The patient underwent right transperitoneal adrenalectomy. Microscopic evaluation showed a sinusoidal dilatation and fibrotic septa, so postoperative diagnosis of adrenal cavernous hemangioma was made. **Conclusion.** In summary, we reported a case of an incidentally discovered non-functioning adrenal cavernous hemangioma treated by laparoscopic surgery. The diagnosis of adrenal cavernous hemangioma may be challenging, and it is commonly made after surgery, since it is frequently confirmed by histopathological examination.
Key words: Hemangioma, Cavernous; Adrenal Gland Neoplasms; Laparoscopy; Diagnosis; Incidental Findings

Sažetak
Uvod. Kavernozni hemangiomi nadbubrega su izuzetno retki nefunkcionalni benigni tumori. Većina kavernoznih hemangioma nadbubrega dijagnostikovana je nakon operacije histopatološkim pregledom. **Prikaz slučaja.** Prikazujemo klinički slučaj kavernoznog hemangioma nadbubrežne žlezde kod 57-godišnje žene. Pri prijemu, hormoni nadbubrežne žlezde kod pacijentkinje bili su u referentnom opsegu, tako da smo isključili bilo kakvu adrenalnu endokrinu disfunkciju. Skeniranjem kompjuterizovanom tomografijom videla se jasno ograničena, okrugla, heterogena masa u desnoj adrenalnoj žlezdi (32,3 x 55,4 mm). Kompjuterizovana tomografija abdomena sa jodnim kontrastom pokazala je neznatnu nehomogenost. U ovom slučaju preoperativni radiološki nalazi i nedostatak znakova lokalne invazije, naveli su nas da izvedemo laparoskopsku adrenalektomiju kako bismo uspostavili konačnu dijagnozu. Pacijentkinja je podvrgnuta desnoj adrenalektomiji transperitonealnog lumbalnog pristupa. Mikroskopska evaluacija pokazala je sinusoidnu dilataciju i fibrozne lezije sa postoperativnom dijagnozom kavernoznog hemangioma nadbubrežne žlezde. **Zaključak.** Ukratko, prikazali smo slučaj, slučajno otkriven nefunkcionalni adrenalni hemangiom tretiran laparoskopskim pristupom. Dijagnoza kavernoznog hemangioma najčešća je nakon operacije, a najčešće se potvrđuje histopatološkim pregledom.
Ključne reči: kavernozni hemangiom; neoplazme nadbubrežne žlezde; laparoskopija; dijagnoza; slučajni nalaz

Introduction

Adrenal masses are discovered with increasing frequency due to widespread use of radiological imaging techniques. It is estimated that adrenal masses are incidental findings in 1% to 5% of all abdominal computed tomography (CT) scans [1]. Adrenal cavernous hemangiomas are extremely rare non-functioning benign tumors [2]. The majority of adrenal cavernous hemangiomas are diagnosed after surgery by histopathological examination. Approximately 60 surgical cases have been reported in the literature so far [2].

The current report presents a case of an adrenal cavernous hemangioma which was confirmed histologically after laparoscopic surgery.

Case Report

We report a clinical case of adrenal cavernous hemangioma in a 57-year-old woman. An incidental right adrenal mass was discovered on ultrasonography when she visited a nephrologist due to a right flank discomfort. Her past medical history was positive for essential hypertension in the past year which was treated by 20 mg lisinopril + 12.5 mg hydrochlorothiazide twice daily. She also had type 2 diabetes mellitus in the past two years, and it was treated by glibenclamide 5 mg once daily in the morning. Physical examination did not reveal any abnormalities. The patient's blood pressure was 140/90 mmHg, with a pulse rate of 78 beats/min. On admis-

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Abbreviations
CT – computed tomography
MRI – Magnetic Resonance Imagining
H&E – Hematoxylin and Eosin

sion, laboratory findings **(Table 1)** and adrenal-related hormones and other hormones **(Table 2)** were in the reference range, so any adrenal endocrine dysfunction was ruled out. The abdominal CT scan revealed a well circumscribed, heterogeneous right adrenal mass (32.3 x 55.4 mm) **(Figure 1)**. Iodinated contrast enhanced abdominal CT showed a slight inhomogeneity. In this patient, abdominal magnetic resonance imaging (MRI) was not performed. The preoperative radiologic findings and the absence of signs of local invasion indicated laparoscopic adrenalectomy in order to establish the final diagnosis. The perioperative blood glucose level was 5.01 mmol/l (reference range: 3. 5 – 6.1 mmol/l) well controlled with glibenclamide. The antihypertensive therapy was continued on the day of surgery. The patient underwent a right transperitoneal adrenalectomy. Intraoperatively, an encapsulated adrenal mass without local invasion was found. The total operating time was 160 min, without any intraoperative or postoperative complications. The patient was discharged on postoperative day 6. Microscopic evaluation showed sinusoidal dilatation and fibrotic septa and a postoperative diagnosis of adrenal cavernous hemangioma was made **(Figure 2)**. Positive cluster of differentiation 31 and cluster of differentiation 34 immunostaining demonstrated a tumor of endothelial nature that supported the diagnosis [3].

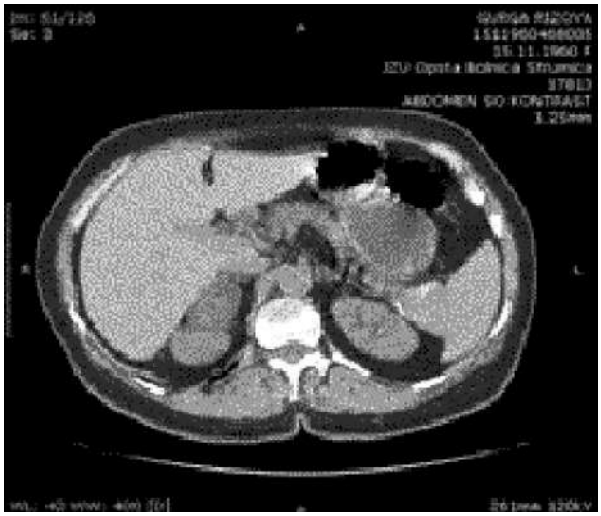

Figure 1. Abdominal CT scan revealed heterogenous right adrenal mass with regular margins
Slika 1. *Kompjuterizovana tomografija abdomena otkrila je heterogenu desnu nadbubrežni masu sa regularnim marginama*

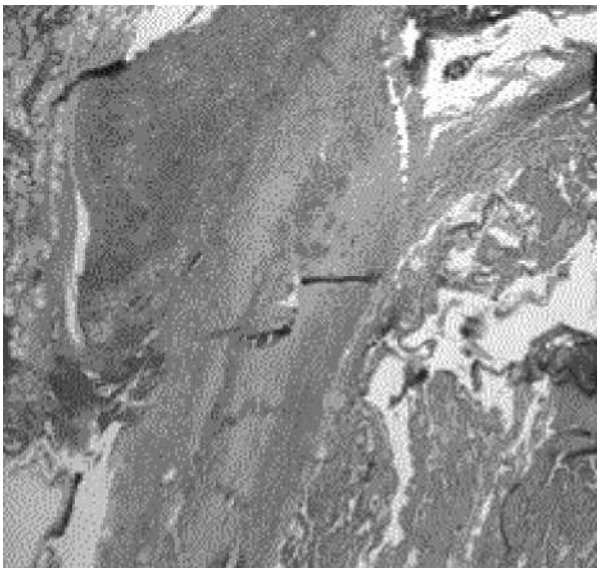

Figure 2. Histopatology. Thick walled vascular cavities are present adjancent to the adrenal cortex. (H&E stain original magnifaction 13x)
Slika 2. *Histopatologija. Vaskularne šupljine sa debelim udovima su prisutne u korteksu nadbubrežne žlezde (H&E obojeno originalno uvećanje 13x)*

Discussion

Cavernous hemangiomas of the adrenal gland are rare, benign and endocrinologically inactive tumors. The pathogenesis of these tumors is unclear; they are probably congenital, with involvement of hereditary factors and ectasia of blood vessels [3]. They are usually unilateral and appear in the sixth or seventh decade of life. The majority of tumors are asymptomatic lesions, but if they are large, the symptoms include flank pain and a palpable mass, or they may present with hypovolemic

Table 1. Laboratory test results
Tabela 1. *Laboratorijski nalazi*

Test/*Test*	Result/*Rezultat*	Reference range/*Referentne vrednosti*
WBC (white blood cells) x10^9/L/*Leukociti*	7.4	4.00 - 9.00
Hematocrit/*Hematokrit (rv)*	0.440	0.37 - 0.54
PLT (platelet count) x10^9/L/*Trombociti*	271	150 - 450
Glucose (mmol/l)/*Glukoza*	5.01	3.5 - 6.5
Urea (mmol/l)/*Urea*	4.5	2.7 - 7.8
Creatinine (umol/l)/*Kreatinin*	83	45 - 109
C-reactive protein mg/L/*C-reaktivni protein*	4	< 6

Table 2. Levels of the patient's adrenal hormones, other hormones, and electrolytes during the preoperative period
Tabela 2. *Vrednosti adrenalnih hormona, drugih hormona i elektrolita kod pacijentkinje u preoperativnom periodu*

Test *Test*	Result *Rezultat*	Reference range *Referente vrednosti*
Morning cortisol levels/*Jutarnji kortizol u serumu (nmol/l)*	120.96	55 - 690
Cortisol levels at night/*Večernji kortizol u serumu (nmol/l)*	20 h 145.5	55 - 690
Midnight serum cortisol/*Ponoćni kortizol u serumu (nmol/l)*	24 h 87.8	55 - 690
Adrenocorticotropic hormone/*Adrenokortikotropni hormon (ρg/ml)*	21	< 46
Aldosterone/*Aldosteron (ng/ml)*	11.2	5 - 14.5
Calcitonin/*Kalcitonin (ρg/ml)*	< 3	< 5.8
Sodium/*Natrijum (mmol/l)*	140	137 - 145
Potassium/*Kalijum (mmol/l)*	4	3.8 - 5.5
Ionized calcium test/Jonizovani *kalcijum (mmol/l)*	1.26	1 - 1.30
Dexamethasone suppression test *Test prekonoćne supresije deksametazonom(cortisol/kortizol nmol/l)*	42	55 - 690
Urinary metanephrines/*Metanefrini u urinu* Metanephrines/*Metanefrini (μg/24 h)*	68	< 90
Urinary normetanephrines/*Normetanefrini u urinu* Normetanephrines/*Normetanefrini (μg/24 h)*	134	< 180

shock caused by a spontaneous rupture. Adrenal hemangiomas are most commonly non-functioning tumors, and only three cases of functioning adrenal hemangiomas have been reported to date [4].

Adrenal masses are usually identified by imaging techniques performed for other reasons. The differential diagnosis of incidental adrenal masses includes: adrenal adenoma, adrenal cortical carcinoma, metastatic cancer, pheochromocytoma, adrenal cyst, myelolipoma, hematoma, ganglioneuroma and cavernous hemangioma. A CT scan finding of adrenal cavernous hemangioma includes a hypodense, heterogeneous lesion with calcifications. Spotty calcifications throughout the tumor are probably due to phleboliths in dilated vascular spaces [5]. Although nonspecific, abdominal MRI may show hyperintensity on T2-weighted images and a focal hyperintensity on T1-weighted images [6].

On histopathological examination, adrenal cavernous hemangioma is located in the adrenal cortex and consists of multiple dilated vascular cavities lined by a single layer of vascular endothelium surrounded by a collagenous wall [7]. The main indications for surgery of these adrenal masses are to relieve mass-effect-type symptoms, to exclude malignancy, and to treat complications such as spontaneous bleeding [8].

Conclusion

In summary, we reported a case of an incidentally discovered nonfunctionine adrenal cavernous hemangioma treated by laparoscopic surgery. The diagnosis of adrenal cavernous hemangioma may be challenging and it most often occurs after surgery, since it is frequently confirmed by histopathological examination. Surgical excision may be achieved by laparoscopic adrenalectomy, as a standard care for small to medium sized benign adrenal tumors (up to 6 – 7 cm in diameter).

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RUPTURE OF AN UNSCARRED UTERUS – A CASE REPORT

RUPTURA INTAKTNE MATERICE – PRIKAZ SLUČAJA

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Introduction. Rupture of an unscarred uterus is extremely rare and associated with severe maternal and fetal morbidity. Risk factors are second-stage dystocia, grand multiparity, high parity, labor induction or augmentation with oxytocin or prostaglandins, delivery after the 42nd week of gestation, neglected labor, fetal malpresentation, breech extraction, and instrumental delivery. **Case Report**. A 44-year-old multipara (gravid3 para3) underwent induction of labour at 40 + 3 weeks of gestation. The patient's medical history showed no uterine surgeries, but her first delivery was instrumental, with vacuum extractor. The induction of labour was initiated by oxytocin infusion of 6 mIU/min. Continuous fetal heart rate monitoring was performed and there were no signs of fetal distress. Fetal descent in the second stage of labor lasted an hour, which is slightly over than average duration for multiparas. A live female infant weighing 3380 g was born and the pediatrician started resuscitation of the baby. Apgar score was 1/3/3. Ten days following the delivery, the patient was admitted to Emergency Gynaecology Department of the Clinic of Gynecology and Obstetrics due to abdominal pain, left sided retrouterine hematoma, and foul-smelling vaginal discharge. Laparotomy was indicated due to suspected uterine rupture. The intraoperative findings showed subinvolution of the uterus with signs of panmetritis and on the left side below the round ligament there was a 2 cm long rupture, passing through and invading the lateral and posterior walls of the uterus. A total abdominal hysterectomy with bilateral salpingo-oophorectomy on the left side was performed. **Conclusion**. Although a reliable prediction and prevention do not exist, the obstetricians' awareness of this rare event in unscarred uterus may decrease maternal and neonatal morbidity. This case report is an example of a serious and difficult outcome after a seemingly low-risk situation.

Key words: Uterine Rupture; Obstetric Labor Complications; Labor, Induced; Rupture, Spontaneous; Risk Factors; Hysterectomy

Uvod. Ruptura intaktnog uterusa je izuzetno retka pojava sa ozbiljnim fetalnim i maternalnim morbiditetom. U faktore rizika spadaju distocija drugog porođajnog doba, multiparitet, veći broj porođaja, indukcija ili stimulacija porođaja oksitocinom ili prostaglandinima, porođaj nakon 42 nedelje, zapušteni porođaj, fetalna malprezentacija, karlična ekstrakcija, instrumentalni porođaj. **Prikaz slučaja**. Trećerotki, staroj 44 godine, određena je indukcija porođaja u 40 + 3 gestacijskoj nedelji. Anamnestički negira operacije na materici, navodi da je prvi porođaj završen instrumentalnim putem, vakuum-ekstrakcijom. Indukcija porođaja započeta je infuzijom oksitocina u dozi od 6 mIU/min. Kontinuirani fetalni monitoring tokom porođaja bio je normalan, bez znakova fetalnog distresa. Spuštanje fetalne glavice u drugoj fazi porođaja, trajao je jedan sat, što je nešto duže od prosečnog vremena za multipare. Rođeno je živo žensko novorođenče teško 3.380 g, uz prisustvo pedijatra, koji je pristupio zbrinjavanju deteta. Apgar skor bio je 1/3/3. Deset dana nakon porođaja pacijentkinja je primljena na Odeljenje opšte i urgente ginekologije zbog bolova u donjem delu stomaka, ultrazvučno viđenog retrouterinog hematoma s leve strane uterusa, pojačanog i neprijatnog mirisa vaginalnog sekreta. Zbog sumnje na rupturu uterusa, indikovana je laparotomija. Intraoperativni nalaz ukazao je na subinvoluciju materice, sa znakovima panmetritisa, levo ispod *ligg. rotunda* rupturu dužine 2 cm koja prožima i prolazi kroz lateralni i zadnji zid materice. Učinjena je totalna abdominalna histerektomija sa obostranom salpingektomijom i levom ovarijektomijom. **Zaključak.** Iako ne postoji klinički pouzdan način predikcije ili prevencije, svest i razmišljanje akušera o rupturi intaktne materice može da smanji maternalni i fetalni morbiditet. Ovaj prikaz slučaja primer je ozbiljnog i teškog ishoda nakon, naizgled, niskorizične situacije.

Ključne reči: ruptura uterusa; komplikacije opstetričkog porođaja; indukovani porođaj; spontana ruptura; faktori rizika; histerektomija

Introduction

Uterine rupture in pregnancy is rare, but it is associated with serious complications and severe maternal and fetal morbidity. The initial signs and symptoms of uterine rupture are typically nonspecific, and low suspicion of this event makes the diagnosis difficult, sometimes delaying the therapy.

A normal, unscarred uterus is least susceptible to rupture. Risk factors for rupture of unscarred uterus are second-stage dystocia, grand multiparity, high parity, labor induction or augmentation with oxytocin or prostaglandins, delivery after 42nd week

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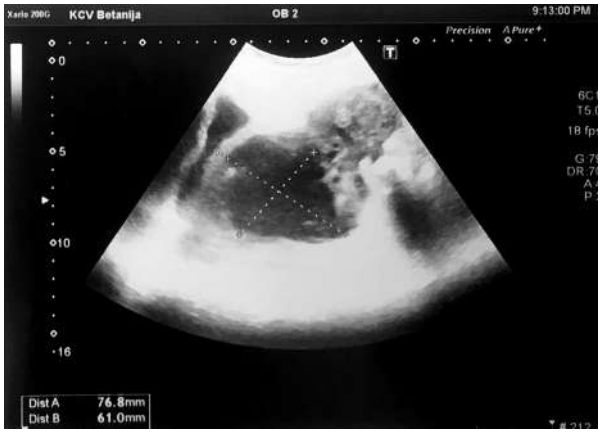

Figure 1. Transvaginal ultrasound of the pelvis showing retrouterine hematoma on the left side of the uterus
Slika 1. *Transvaginalni ultrazvuk karlice koji pokazuje retrouterini hematom sa leve strane uterusa*

of gestation, neglected labor, fetal malpresentation, breech extraction, and instrumental delivery [1].

The incidence of uterine rupture in women with unscarred uterus is low, only 0.012% (1 in 8.434) in developed countries, and 0.11% (1 in 920) in developing countries [2]. A higher incidence in developing countries is due to inadequate access to medical care and therefore more cases of neglected and obstructed labor.

Case Report

A 44-year-old multipara (gravid3 para3) was admitted to Emergency Gynaecology Department of the Clinic of Gynecology and Obstetrics 10 days after vaginal delivery due to abdominal pain, left sided retrouterine hematoma, and foul-smelling vaginal discharge.

In the most recent pregnancy, she was diagnosed with a polyhydramnios and gestational diabetes mellitus. She was on a diabetic diet, without medications. She had no history of any uterine surgeries, but her first delivery was instrumental, with vacuum extractor. The induction of labor was at 40 + 3 weeks of gestation, and started with oxytocin infusion of 6 mIU/min with diazepam. Spontaneuos rupture of membranes occurred after 90 minutes, and contractions became stronger. Continuous fetal heart rate monitoring was performed and there were no signs of fetal distress. Fetal descent in the second stage of labor lasted an hour, which was slightly over the average duration for multiparas. The delivery lasted 9 hours after the oxytocin infusion was initiated. A live female infant was born weighing 3380 g and the pediatrician performed a resuscitation of the baby. Apgar score was 1/3/3. The placenta was delivered spontaneously 13 minutes later. She had an episiotomy and rupture of the cervix uteri on the left side, which were sutured. The day after the delivery, at the maternity ward the patient complained about pain in the upper abdomen. Her vital signs were normal, laboratory findings suggested anemia (hgb: 76 g/l, hct: 0,22 l/l, er: 2.44 x 10^{12}/l). A transadominal ultrasound of the pelvis and upper abdomen was performed and there was no sign of free fluid in Douglas pouch, uterus was in good involution, length and width 113 x 75 mm, and the uterine cavity was empty. She received infusion of iron (III)-hydroxide (Ferrovin®). The control laboratory findings showed dropping values of red blood cells pointing to severe anemia (hgb: 69 g/l, hct: 0,20 l/l er: 2,23 x 10^{12}/l,). Blood transfusion (595 ml, two units of packed red blood cells) was administrated.

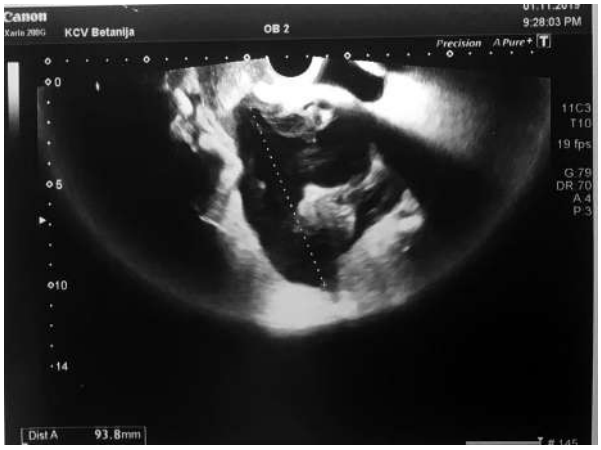

Figure 2. Transvaginal utrasound of the pelvis showing progression of the retrouterine hematoma
Slika 2. *Transvaginalni ultrazvuk karlice koji pokazuje progresiju retrouterinog hematoma*

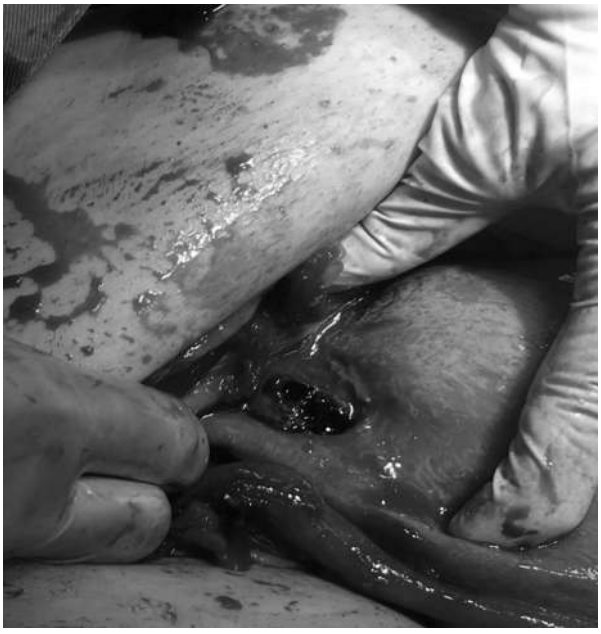

Figure 3. Uterine rupture below the round ligament passing through and invading the lateral and posterior walls of the uterus
Slika 3. *Ruptura materice ispod ligg. rotunda koja prolazi kroz lateralni i zadnji zid uterusa*

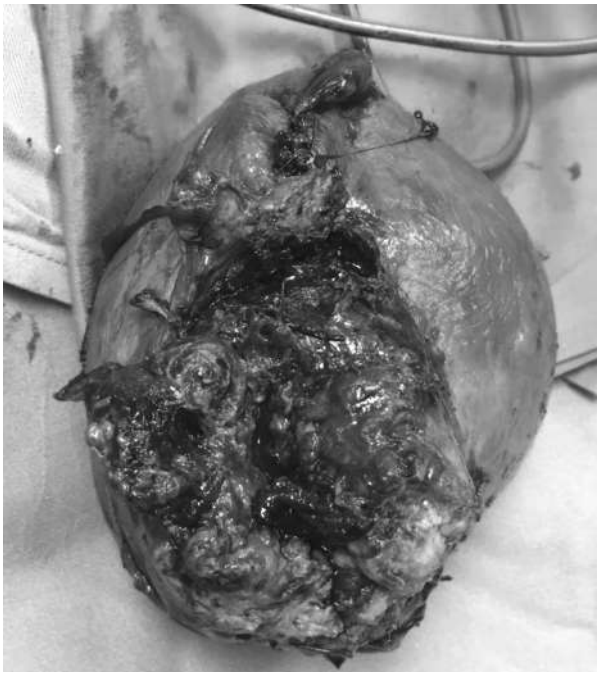

Figure 4. Uterine specimen after hysterectomy
Slika 4. *Preparat materice nakon histerektomije*

She was discharged on the fourth day postpartum, with a proscribed therapy for anemia.

Ten days following the delivery, she was admitted to our Clinic. Upon examination, her temperature was 38˚C, vital signs were stable, there was no rebound tenderness in the abdomen, abdominal rigidity or guarding. The transvaginal ultrasound scan showed a retrouterine hematoma on the left side of the uterus (61 x 76 mm) **(Figure 1**). Triple intravenous antibiotic therapy was introduced (Metronidazole, Cefuroxime, Ciprofloxacin). Later that day, she presented with heavy vaginal bleeding. The transvaginal ultrasound scan showed a progression of retrouterine hematoma that measured 93,8 mm **(Figure 2).** A laparotomy was indicated due to suspected uterine rupture. The intaoperative findings showed subinvolution of the uterus with signs of panmetritis and on the left side below the round ligament there was a 2 cm long rupture, passing through and invading the lateral and posterior walls of the uterus **(Figure 3).** There were adhesions between the sigmoid colon and posterior wall of the uterus, and organized hematoma (250 ml of blood) that communicated with the uterine cavity. A total abdominal hysterectomy with bilateral salpingo-oophorectomy on the left side was performed due to the extent of the rupture and signs of infection **(Figure 4).** The estimated intraoperative blood loss was 1300 mL and the patient received two units of packed red blood cells (575 ml) and two units of fresh frozen plasma (395 ml), postoperatively. The hematoma lodge and peritoneal fluid cultures, taken during surgery, were both positive on anaerobic bacteria Bacteroides fragilis. The patient made a recovery without any other medical complications and was discharged 7 days later in a good medical condition and antibiotic therapy.

Discussion

Uterine rupture is a very rare event in patients without any history of cesarean section or other uterine surgery [2]. Our patient had a history of two vaginal deliveries and no previous gynecological procedures, so the risk of rupture was extremely low, at the level of hypothesis. Studies show that due to delayed diagnosis and management of this event, uterine rupture of the unscarred uterus has a higher maternal and neonatal morbidity than rupture of a scarred uterus [3, 4]. In the study of Gibbins et al., cases of rupture of unscarred uterus had a greater mean blood loss, higher rate of blood transfusion and frequency of peripartum hysterectomy, and higher adverse neonatal neurologic outcomes, comparing to rupture of scarred uterus [4]. Unfortunately, our case report is an example of these facts. In patients with an unscarred uterus, risk factors that may lead to uterine rupture are macrosomia, shorter interval between deliveries, high parity, post-date pregnancies, advanced maternal age, labor induction or augmentation with prostaglandins or oxytocin, and dystocia during the first and second stage [5, 6]. Our patient's advanced maternal age, third pregnancy, induction of labor, use of oxytocin, dystocia during the second stage of labor are all individual factors that together resulted in this unfavorable outcome.

Conclusion

Delayed identification and management of uterine rupture in unscarred uterus results in severe maternal and fetal outcomes. Although a reliable prediction and prevention do not exist, the obstetricians' awareness of this rare event may decrease maternal and neonatal morbidity. This case report is an example of a serious and difficult outcome after a seemingly low-risk situation.

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SMALL BOWEL PERFORATION FOLLOWING BLUNT ABDOMINAL TRAUMA CAUSED BY AN ACCIDENTAL HAMMER BLOW – A CASE REPORT

PERFORACIJA TANKOG CREVA U SKLOPU TUPE TRAUME ABDOMENA IZAZVANA SLUČAJNIM UDARCEM ČEKIĆEM – PRIKAZ SLUČAJA

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Summary

Introduction. Trauma is among the leading causes of death. Undetected and untreated adequately and on time, traumatic small bowel injuries can be lethal. **Case Report.** We present a case of a small bowel perforation after a blunt abdominal injury, caused by an accidental self-inflicted hammer blow to the abdomen. The initial abdominal and chest x-rays and abdominal ultrasound did not indicate an injury to the abdominal organs. Due to the impaired clinical picture and the fact that the patient was hemodynamically stable, multi-detector computed tomography of the abdomen and small pelvis was performed, showing intraperitoneal free fluid and pneumoperitoneum, not seen by other imaging methods. A decision for surgical treatment was made. The intraoperative finding confirmed a small bowel perforation. **Conclusion.** Due to the possible false-negative imaging findings, clinical follow-up of patients with abdominal trauma is mandatory when making the decision for surgical treatment.

Key words: Intestinal Perforation; Wounds, Nonpenetrating; Abdominal Injuries; Household Articles; Accidental Injuries; Pneumoperitoneum; Signs and Symptoms; Diagnosis; Tomography, X-Ray Computed; Treatment Outcome

Sažetak

Uvod. Trauma je među vodećim uzrocima smrti. Neprimećene i nelečene na odgovarajući način i na vreme, traumatske povrede tankog creva mogu biti smrtonosne. **Prikaz slučaja.** Predstavljamo slučaj perforacije tankog creva nakon tupe traume trbuha, uzrokovane slučajnim samopovređivanjem u trbuh, udarcem čekićem. Prvobitni rendgenski snimci grudnog koša i abdomena, kao i ultrazvuk abdomena, nisu ukazivali na povredu trbušnih organa. Zbog pogoršanja kliničke slike, a zbog činjenice da je pacijent bio hemodinamički stabilan, urađena je kompjuterizovana tomografija abdomena i male karlice koja je pokazala slobodnu tečnost i pneumoperitoneum, što nije viđeno drugim imidžing metodama. Postavljena je indikacija za operativno lečenje. Intraoperativni nalaz − perforacija tankog creva. **Zaključak.** Zbog mogućih negativnih nalaza radiološke dijagnostike, kliničko praćenje bolesnika s trbušnom traumom obavezno je prilikom postavljanja indikacije za operativno lečenje.

Ključne reči: perforacija tankog creva; nepenetrirajuće rane; abdominalne povrede; kućni alati; slučajne povrede; pneumoperitoneum; znaci i simptomi; dijagnoza; ct; ishod lečenja

Introduction

Abdominal injuries caused by blunt trauma are in the 3rd place, right after head and chest traumas, blunt abdominal traumas (BAT) being the leading cause of mortality and morbidity in all age groups.

Isolated injuries of the small intestine and mesentery, as a part of BATs, are rare and occur in about 1–5% of cases, and high morbidity and mortality is often due to late diagnosis [1, 2].

Intestinal injuries in BAT may be caused by various forms of blunt traumas, but the main causes of BAT are direct traumas, motor vehicle accidents, and falls from height [3]. The authors present a case of a 58-year-old male with traumatic jejunal perforation caused by an accidental hammer blow to the abdomen.

Case Report

A 58-year-old man was admitted to the Department of General Surgery of the General Hospital Novi Pazar, Serbia, due to abdominal pain caused by an accidental self-injury to the abdomen with a hammer blow. The patient had a history of a previous surgery of a duodenal ulcer.

Initially, a laboratory test (all biochemical parameters were in reference range), abdominal and chest x-ray (no signs of pneumoperitoneum), abdominal ultrasound (no free fluid in the abdomen and pelvis) were performed. A muscle hematoma measuring 14 x 6 mm was observed in the suprapubic area on the left side of the abdominal wall. There were no visible signs of injury on the skin surface.

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Abbreviations

BAT – blunt abdominal trauma
CT – computed tomography
SBP – small bowel perforation
US – ultrasonography

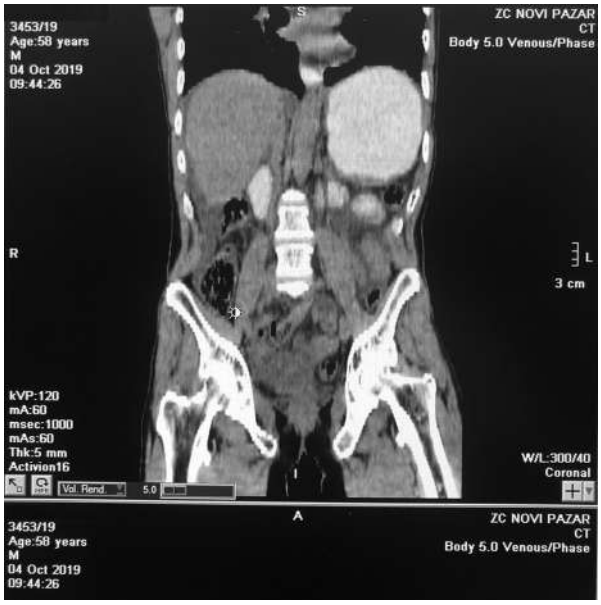

Figure 1. Abdominal CT scan A
Slika 1. *Kompjuterizovana tomografija abdomena - slika A*

Since the radiological and ultrasound diagnostics did not indicated injuries of internal abdominal organs, and the patient was in good overall condition, hemodynamically stable, conservative treatment was initiated. Eight hours after admission, the general condition of the patient got worse with an increase in abdominal pain. The abdomen was distended with diffuse tenderness and guarding over the lower quadrants of the abdomen. The laboratory test showed the following results: C-reactive protein 103.9 mg/L, white blood cells 11.6 x 10.9/L, red blood cells 4.64 x 10.12/L, hemoglobin 143 g/L, platelets 218 x 10.9/L, hematocrit 0.395 L/L, while the rest biochemical parameters were within the reference range. The patient was hemodynamically stable. The computed tomography (CT) of the abdomen and pelvis showed fluid around the liver and lower abdomen, whereas apparent solid organ injuries **(Figures 1 and 2)** were not found by other imaging methods. A decision for surgical treatment was made.

A median laparotomy was performed and approximately 800 cc of free fluid and intestinal contents was evacuated, and a portion of the contents was sent for microbiological analysis. Intraoperatively, a large number of small bowel adhesions to the anterior abdominal wall as well as to the small bowel were identified, probably as a result of the previous surgery. The small intestine was partially covered with fibrin deposits. Adhesiolysis was performed and the abdomen was explored. The small bowel was examined completely up to the ileocecal

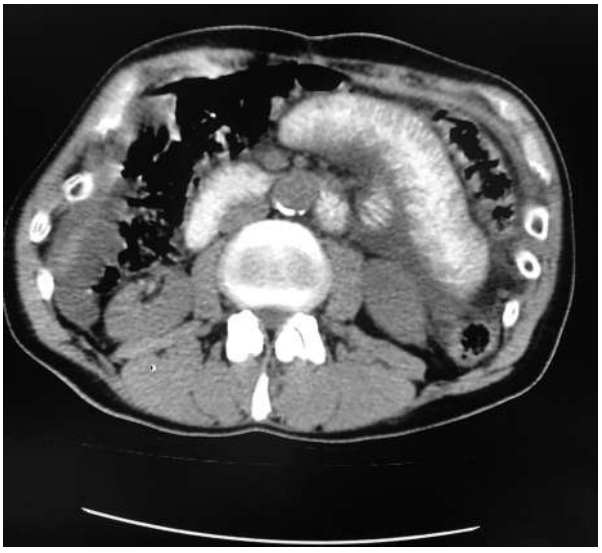

Figure 2. Abdominal CT scan B
Slika 2. *Kompjuterizovana tomografija abdomena - slika B*

valve. A perforation of the small intestine was found about 70 cm from the Treitz ligament, on the antimesenteric side, with no other signs of injury **(Figure 3)**. Abundant lavage of the abdominal cavity with a large amount of saline was done, after which the suture of the perforation site was made, in two layers, using absorption thread with a diameter 3/0. The first two postoperative days the patient was in intensive care after which he was transferred to the general surgery department, hemodynamically stable, afebrile with no signs of sepsis. Klebsiella spp. was isolated from the intra-abdominal fluid specimen sent for analysis. The treatment was continued with conservative therapy (crystalloids, analgesics, antibiotics (ceftriaxone, amikacin, metronidazole) and other supportive therapy). The postoperative recovery was satisfactory. There was no significant abdominal postoperative pain. The patient was discharged on the 12th postoperative day.

Discussion

Blunt abdominal trauma can cause injury to both the solid organs and intestines. Solid organ injuries usually involve liver and spleen injuries and they are manifested by internal bleeding. Enteric injuries usually do not have such a dramatic clinical picture initially and manifest with sepsis and peritonitis [4, 5]. Clinical assessment of the patient's condition and adequate diagnosis are crucial for the timely diagnosis of small bowel perforation (SBP) and surgical treatment. Delayed surgical management leads to an increase in morbidity and mortality. Because imaging methods have a degree of false-negative results, relying solely on them may delay surgery and endanger the patient [1, 6]. Different investigations reported low accuracy (16–45%) of clinical findings and unreliability in defining the need for laparotomy in BAT patients [7]. Due to the charac-

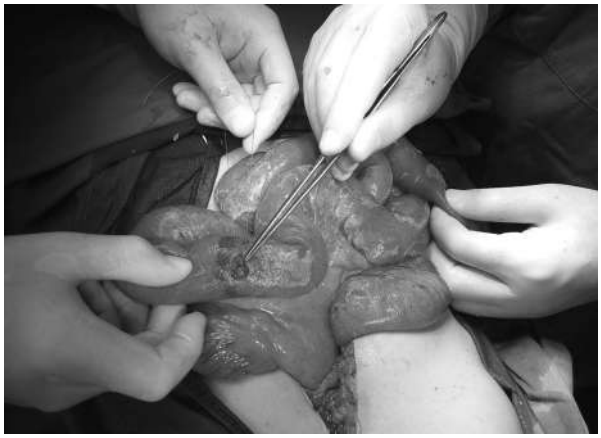

Figure 3. Intraoperative finding – small bowl perforation
Slika 3. *Intraoperativni nalaz – perforacija tankog creva*

teristics of the small bowel content, which is characterized by low bacterial content and almost neutral pH, peritoneal irritation develops slowly [8]. Pneumoperitoneum may not be specific for the diagnosis of SBP [8], especially if SBP is confined or temporarily covered, or only liquid is leaking. In this case, pneumoperitoneum may be absent [1]. Today, ultrasonography (US) is a very widespread diagnostic method, it is safe and reliable, simple, fast and it can be safely procured multiple times. Free fluid on abdominal US after abdominal trauma represents a positive finding. In case when there is no solid organ abdominal injury and there is a verified free fluid on abdominal US, Kahn et al. suggest a high probability of a bowel injury. However, free peritoneal fluid is not a specific finding of bowel injury [1, 9]. In our case, there were no signs of pneumoperitoneum on the graphs or free fluid on the US. Due to the abdominal pain and signs of peritonism and the fact that the patient was hemodynamically stable, and even though the surgical team made the decision for explorative laparotomy, an abdominal CT scan was performed. In hemodynamically stable patients, the method of choice in the diagnosis of blunt abdominal trauma is CT [10]. The CT allows detection of both parenchymal and hollow organ injury. If there are no CT signs of solid organ injuries, but there are pneumoperitoneum, free abdominal fluid, contrast extravasation in the abdomen, small bowel thickening and dilatation, there is a high suspicion of a bowel injury [3]. This finding has been reported in several studies [3, 11, 12]. The CT diagnosis of SBP has a sensitivity of 92–97.7% and a specificity of 94–98.5%, making it the gold standard for the diagnosis of SBP [2, 3]. Although some authors found CT findings to be unreliable for assessing the injury severity, they recommended mandatory laparotomy for patients with isolated free fluid on CT scans [13]. Surgical treatment of patients may be either open or laparoscopic surgery. The laparoscopic approach can be applied in hemodynamically stable patients with BAT, taking into account the patient's condition, surgical team experience, and equipment. Complications of laparoscopic surgery should also be considered, especially in patients who have previously had open abdominal surgical procedures, procedures which may complicate the laparoscopic exploration and a degree of conversion which can go up to 50% [1, 14]. Our patient was previously operated on for duodenal ulcer perforation. With all of the above in mind, the surgical team opted for an open surgical procedure. There were no postoperative complications and the outcome was successful.

Conclusion

Diagnosis of an isolated perforation of the small intestine in the context of blunt abdominal trauma can sometimes be difficult and can lead to delayed diagnosis, which increases morbidity and mortality. Due to the possible false-negative imaging findings, clinical monitoring of patients with abdominal trauma is mandatory when making the decision for surgical treatment. Due to the high sensitivity, computed tomography is necessary in the early diagnosis of minor blunt abdominal injuries.

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ULTRASOUND DIAGNOSIS OF PEPTIC ULCER PERFORATION - A CASE REPORT

ULTRAZVUČNA DIJAGNOSTIKA PERFORIRANOG PEPTIČKOG ULKUSA − PRIKAZ SLUČAJA

Danka PETROVIĆ[1], Predrag PETROVIĆ[2] and Nataša PRVULOVIĆ BUNOVIĆ[1,3]

Summary

Introduction. Peptic ulcer perforation is an urgent, life-threatening condition that requires prompt diagnosis and emergency surgical treatment. It is a focal defect of the pylorobulbar zone that affects all the layers and allows intraluminal content to leak into the peritoneal/retroperitoneal cavity. The aim of this study is point to ultrasonography as a good diagnostic modality in identifying peptic ulcer perforation when it is clinically unrecognized. **Case Report.** We report a case of a 36-year-old man who came to the Emergency Center of the Clinical Center of Vojvodina complaining of a sudden severe pain in the entire abdomen. The patient reported previous dyspeptic symptoms. Emergency transabdominal ultrasonography was perfomed, and a peptic ulcer perforation was suspected. It significantly shortened the time to urgent surgical treatment and the diagnosis was confirmed. **Conclusion.** Pneumoperitoneum, collection of extraluminal free fluid with gas bubbles around the lesion, inflammatory thickening and discontinuity of the pylorobulbar wall, with or without focal hyperechogenic line (perforation zone) are ultrasound findings suggestive of peptic ulcer perforation.

Key words: Peptic Ulcer Perforation; Ultrasonography; Diagnosis; Stomach Ulcer; Duodenal Ulcer; Signs and Symptoms

Sažetak

Uvod. Perforacija peptičkog ulkusa je urgentno, životno ugrožavajuće stanje koje zahteva brzu dijagnostiku i što raniji hirurški tretman. Predstavlja fokalni defekt koji zahvata sve slojeve zida pilorobulbarne regije i omogućava isticanje intraluminalnog sadržaja u peritonealnu/retroperitonalnu duplju. Cilj ovog članka je da podseti čitaoca da ultrasonografija može biti ponekad dobar dijagnostički modalitet u postavljanju sumnje na klinički neprepoznate perforacije peptičkog ulkusa. **Prikaz slučaja.** Predstavljamo 36-godišnjeg muškaraca koji dolazi u Urgentni centar Kliničkog centra Vojvodine zbog naglo nastalih jakih bolova u celom trbuhu. Od ranijih tegoba navodi dispeptičke tegobe. U sklopu urgentnog protokola načinjena je ultrasonografija abdomena zbog sumnje na perforaciju peptičkog ulkusa, što je značajno skratilo vreme do urgentnog hirurškog tretmana koji je potvrdio postavljenu dijagnozu. **Zaključak.** Pneumoperitoneum, perileziona ekstraluminalna slobodna tečna kolekcija sa mehurićima gasa i inflamatorna zadebljanja i prekid kontinuiteta zida pilorobulbarne regije sa/bez fokalne hiperehogene linije − zone perforacije su ultrazvučni kriterijumi za postavljanje sumnje na perforaciju peptičkog ulkusa.

Ključne reči: perforacija peptičkog ulkusa; ultrasonografija; dijagnoza; ulkus želuca; ulkus duodenuma, znaci i simptomi

Introduction

Peptic ulcer perforation is an urgent surgical, life-threatening condition with a high risk of mortality and morbidity (10 – 40%), especially in the elderly patients and patients with comorbidities, as well as in patients who presented late, i. e. 12 hours or later, after the onset of symptoms. The annual incidence of peptic ulcer disease in the world is 1.5 – 3%, and perforation occurs in 2 – 14% of patients with active ulcer. The 30-day mortality rate reaches 20% and 90-day mortality rate is over 30% [1]. It presents a focal defect which penetrates all the layers of the gastric or duodenal wall, allowing food and digestive juices to leak into the peritoneal or retroperitoneal cavity [1, 2]. The perforation usually occurs in small curvatures on the posterior wall of the pylorus, or in the anterior wall of the duodenal bulb. It is most commonly caused by the bacterium Helicobacter pylori. It may also occur due to excessive use of nonsteroidal anti-inflammatory drugs. Today, the incidence of perforated ulcer is in decline, because of the improvement in the eradication of Helicobacter pylori and peptic ulcer therapy [3]. Clinical manifestations of peptic ulcer perforation largely depend on the time when the first symptoms begin, on the size of the perforation, and whether there is leakage of luminal content into the peritoneum/retroperitoneum. The clinical symptoms may be nonspecific: severe pain in the upper abdomen that mimics acute pancreatitis, cholecystitis, pyelonephritis, appendicitis, as well as acute abdomen with abdominal wall rigidity. Due to these nonspecific symptoms, abdominal ultrasonography is often the initial diagnostic modality, because it is noninvasive, available, and easy to perform. This procedure easily excludes many entities of differential diagnosis. Also, ultrasonography is often the first step to detect the free peritoneal fluid, wall thickening of pylorobulbar region and to suspect the presence of free extraluminal gas (large-

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Abbreviations
CT – computed tomography
TUS – transabdominal ultrasound

ly depends on the experience of the sonographer and condition of the patient) [4, 5]. The definitive diagnosis is usually established by native abdominal X-ray and computed tomography (CT) of the abdomen. The CT scan is recommended, as its diagnostic accuracy is as high as 98% [6].

The purpose of this study was to point to ultrasonography as the first, only and irreplaceable diagnostic procedure in establishing peptic ulcer perforation, and not to diminish the importance of CT. Ultrasonography is a good diagnostic tool to identify patients with peptic ulcer perforation, especially in children and pregnant women, in order to reduce exposure to radiation [7]. Furthermore, "saving time" from the onset of symptoms and the surgical care of the patient is important in these patients, because it reduces potential complications [8, 9].

Case Report

A 36-year-old man came to the Emergency Center of the Clinical Center of Vojvodina complaining of a sudden severe pain in the abdomen that got worse in a supine position. The patient reported previous dyspeptic symptoms. The physical examination revealed a diffuse abdominal pain with abdominal wall rigidity, while the rest of the findings were unremarkable. Laboratory test results showed increased leukocytes (12.72 ... 22), while the remaining blood test results were within normal ranges. An emergency abdominal utrasonography was performed using a 3.5 – 5 MHz convex probe, with the patient lying in a supine position. Right subcostal, right parasagittal and epigastric scans were made. A circumscript, uniformly thickened wall, 12 mm in diameter, of pylorobulbar region was established **(Figure 1)**. In the locoregional area there was a small amount of free liquid. Also, in the liver hilum, free extraluminal gas was found with distal acoustic shadow **(Figure 2).**

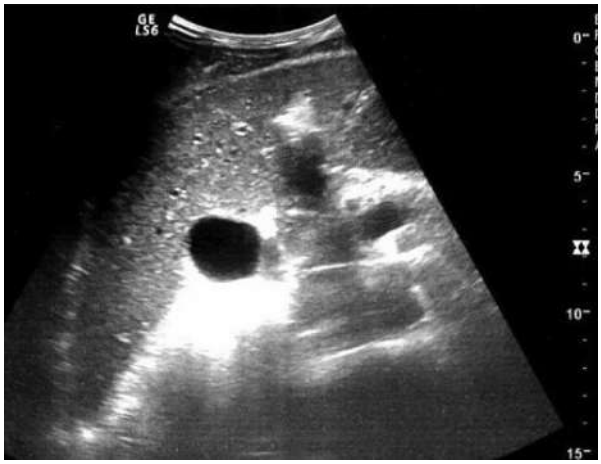

Figure 1. Abdominal transverse epigastric scan using 3.5 MHz transducer; Circular thickening of the duodenal wall points to peptic ulcer perforation (arrow)
Slika 1. *Sonogram sa transverzalnim presekom epigastrične regije abdomena ultrazvučnom sondom od 3,5 MHz. Cirkularno zadebljanje zida bulbusa duodenuma koje može ukazivati na perforirani peptički ulkus (strelica)*

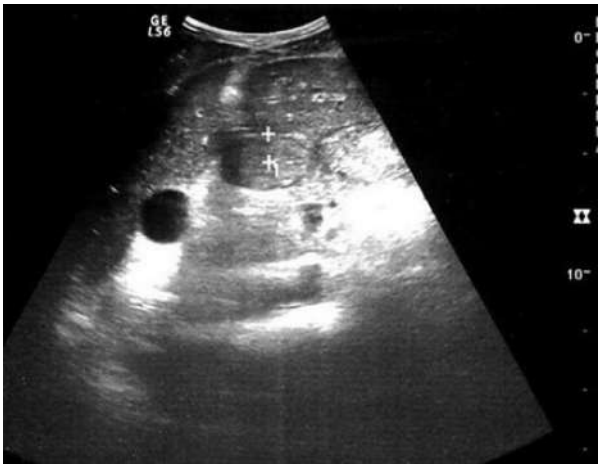

Figure 2. Abdominal transverse epigastric scan using 3.5 MHz transducer; Pocket of shadowing gas and free fluid adjacent to porta hepatis (arrow)
Slika 2. *Sonogram sa transverzalnim presekom epigastrične regije abdomena ultrazvučnom sondom od 3,5 MHz. Inkluzije ekstraluminalnog gasa i slobodna tečnost u regiji porte jetre (strelica)*

After a short preoperative preparation, an emergent surgery was performed. The intraoperative findings showed a perforated ulcer in the front of the pyloric stomach, 5 mm in size, with about 1000 ml of serous fluid spilled into the peritoneal cavity.

Discussion

Direct signs of peptic ulcer perforation are inflammatory thickening and stratified appearance of the wall of pyloric or bulbar region (normal thickness of gastric wall is up to 7 mm, so peptic ulcer disease is suspected when the gastric wall exceeds 8 mm in thickness and has lost its five-layer structure on transabdominal ultrasound (TUS); duodenal ulcer is suspected if the duodenal wall thickness exceeds 5 mm) and there is a focal discontinuity of the affected portion of gastric/bulbar wall [10]. Indirect signs of peptic ulcer perforation are pneumoperitonem - presence of free extraluminal gas in the peritoneal cavity, localized around the pylorus, duodenum, liver, subdiaphragmatic and perirenal space, etc, presence of free fluid in the peritoneal cavity, focal or diffuse peritonitis, focal "striped form" inflammatory infiltration of perigastric fat or diffuse inflammatory infiltration of mesenteric fat - "dirty mesenterium", locoregional reactive lymph nodes [2, 9]. Free fluid is usually around the lesion, subhepatic, intraperitoneal, etc. The pylorus is a 5-layer structure (mucosa,

submucosa, muscularis, subserosa and serosa) that tapers in cross-section and passes into the duodenal bulb which has a thinner wall and several strains are less recognizable, but three main layers: serosa, muscularis and mucosa are enough to visualize it [11–14]. A perforated peptic ulcer is seen on TUS as a focal thickening or discontinuity of the wall of pyloric or duodenal bulb with or without hyperechoic bright line that passes through the firewall (perforation zone) [7, 8, 12]. Sometimes it is possible to see free peritoneal gas in the form hyperechogenic foci or lines, providing dirty distal acoustic shadow and "ring down" artifacts. Also, there may be bubbles of gas which together with the intraluminal content leak through the perforated wall into the perigastric space or diffuse into the peritoneum [15]. It is difficult to distinguish the intraluminal from extraluminal gas, but the gas location may be helpful: intraluminal gas is deeper relative to the surface of the peritoneum, while the free gas can be detected on subdiaphragmatic surface of the liver, epigastric, in the lodge of the gallbladder, and in the fissure of ligamentum teres [11, 16].

It is possible to establish focal thickening and discontinuity of gastric wall, as well as pneumoperitonem using ultrasonography, but as it is not entirely reliable, it is generaly associated with a multidetector CT that has higher sensitivity to establish the cause of acute abdominal pain. Contrast enchanced CT is routinly used in late arterial and portalvenous phase with muliplanar recontruction of images, and it evaluates emergency signs of acute abdomen: free intraperitoneal extraluminal gas, focal diffuse peritonitis, contrast enchanced parietal peritoneum and/or focal o diffuse hyperdense stranding infiltration of perigastric/mesenteric fat – "dirty mesenterium", free intraperitoneal fluid, dilated bowel with gas–liquid level, extravasal leakage of blood, focal thickening or discontinuity of gastric/bulbar wall [19].

Ultrasound examination largely depends on the skills of a sonographer, ultrasonography machine, and preparation of the patient (meteorism, previous installment, constitution, etc.). The sensitivity of TUS in diagnosing peptic ulcer is 66.7%, 38.9% for duodenal ulcer, and 45.8% in total [9, 10, 20]. Peroral fluid-aided negative oral contrast or peroral cellulose-based gastric ultrasound contrast agent in TUS of the stomach and duodenum may increase the diagnostic sensitivity; it has recently been suggested as a valuable initial screening tool for evaluation of acute abdomen in group of patients such as children and pregnant women, to establish peptic ulcer perforation.

Conclusion

Ultrasound is used in the diagnosis of perforated peptic ulcer and that is in accordance with papers published in medical literature. Regardless of the type of diagnosis, earlier and more accurate diagnosis leads to faster therapy which reduces the number of serious complications and length of hospital stay.

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A MULTIDISCIPLINARY APPROACH TO THE MANAGEMENT OF GASTROENTERO-PANCREATIC NEUROENDOCRINE TUMORS – A CASE REPORT

MULTIDISCIPLINARNI PRISTUP U LEČENJU GASTROENTEROPANKREATIČNIH NEUROENDOKRINIH TUMORA – PRIKAZ SLUČAJA

Dijana KOSIJER[1, 2], Željka SAVIĆ[1, 2], Dragomir DAMJANOV[1, 2], Dimitrije DAMJANOV[1, 2], Đuro MACUT[3,4] and Nikica GRUBOR[4, 5]

Summary

Introduction. Gastroenteropancreatic neuroendocrine tumors comprise a heterogeneous group of neoplasms that originate from the cells of the diffuse endocrine system within the gastrointestinal tract and pancreas. The diagnostic procedures and therapy of patients with gastroenteropancreatic neuroendocrine tumors is complex and requires a multidisciplinary approach. **Case Report.** A 51-year-old patient visited a Gastroenterology Outpatient Clinic for examination complaining of redness, facial swelling and frequent watery diarrhea since the age of 48 years. The clinical examination revealed subicterus, systolic murmur, and hepatomegaly. The patient received an extensive examination that included specific laboratory tests and various imaging techniques (endoscopy, radiology, cardiology, nuclear imaging) at the regional medical center. He was referred to a tertiary medical center, including the national Center for the Treatment of Neuroendocrine Tumors, and a metastatic neuroendocrine tumor, most likely affecting the ileum, was established. After preoperative cardiac and anesthesiological assessments, an elective surgical procedure was performed, with a pathohistological/immunohistochemical confirmation of a grade 1 neuroendocrine tumor of the ileum. **Conclusion.** The process of diagnosing gastroenteropancreatic neuroendocrine tumors, after the onset of symptoms, is often long, associated with comorbidities, and requires a multidisciplinary approach to diagnosis, treatment and monitoring.

Key words: Neuroendocrine Tumors; Intestinal Neoplasms; Pancreatic Neoplasm; Stomach Neoplasms; Interdisciplinary Communication; Malignant Carcinoid Syndrome; Neoplasm Metastasis

Sažetak

Uvod. Gastroenteropankreatični neuroendokrini tumori predstavljaju heterogenu grupu neoplazmi porekla ćelija difuznog endokrinog sistema gastrointestinalnog trakta i pankreasa. Dijagnostički i terapijski pristup kod ovakvih bolesnika je složen i zahteva multidisciplinarnosti. **Prikaz slučaja.** Bolesnik star 51 godinu javio se na pregled u gastroenterološku ambulantu zbog naleta crvenila, oticanja lica i učestalih prolivastih stolica koje primećuje od 48. godine života. Klinički pregled je ukazao na subikterus, sistolni šum i hepatomegaliju. U regionalnom zdravstvenom centru, a zatim u tercijernim zdravstvenim centrima, od kojih je jedan referentni nacionalni centar za lečenje neuroendokrinih tumora, sprovedenim ekstenzivnim ispitivanjem uz korišćenje specifičnih laboratorijskih testova, endoskopskih, radioloških, kardioloških i nuklearnih metoda, ukazano je na postojanje metastatskog neuroendokrinog tumora, najverovatnije porekla ileuma. Nakon kardiološke i anestezioloških evaluacije, sprovedena je elektivna hirurška procedura uz patohistološku/imunohistohemijsku potvrdu gradus 1 neuroendokrinog tumora ileuma. **Zaključak.** Postavljanje dijagnoze od trenutka ispoljavanja prvih simptoma gastropankreatičnih neuroendokrinih tumora je često dugo, u vezi je sa ispoljavanjem komorbiditeta i zahteva multidisciplinarni pristup u dijagnostici, lečenju i praćenju.

Ključne reči: neuroendokrini tumori; intestinalni tumori; tumori pankreasa; tumori želuca; interdisciplinarna komunikacija; karcinoidni sindrom; metastaze

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) comprise a heterogeneous group of neoplasms that originate from at least 16 different types of cells of the diffuse endocrine system within the gastrointestinal tract and cells of the islets of Langerhans of the pancreas [1, 2].

It is thought that approximately 2/3 of all neuroendocrine tumors (NETs) are gastrointestinal or pancreatic tumors, most frequently located in the small intestine. The GEP-NETs account for about 2% of all gastrointestinal tumors [3]. The annual incidence of GEP-NETs is estimated to be 5.25 new cases per 100,000 people [4].

Approximately 1/3 of GEP-NETs are classified as functional, with cells that are releasing peptide

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Abbreviations

GEP	– gastroenteropancreatic
NETs	– neuroendocrine tumors
CCS	– Clinical Center of Serbia
CT	– computed tomography
5-HIAA	– 5-hydroxyindoleacetic acid
PH/IHC	– pathohistological and immunohistochemical
MR	– magnetic resonance

receptors on the surface, which can be useful for diagnosing the location and target therapy. The five-year survival rate is 30 – 90% [4, 5].

The clinical manifestations of GEP-NETs are diverse and usually non-specific. The clinical symptoms and signs of GEP-NETs located in the small intestine and proximal colon are known as the carcinoid syndrome [6].

Patients with GEP-NETs require a multidisciplinary approach. The diagnosis is made through the measurement of serum markers and visualization procedures [6, 7].

The treatment usually involves a combination of surgery and the use of somatostatin analogs, radiofrequency ablation of liver metastases and chemoembolization, peptide receptor radionuclide therapy and chemotherapy [8].

Case Report

A 51-year-old patient visited the Gastroenterology Outpatient Clinic for examination, complaining of redness, facial swelling and frequent watery diarrhea, since the age of 48 years. These symptoms were not accompanied by abdominal pain, loss of appetite or weight loss. The past medical history was negative, while the family history showed cardiovascular disease and malignancy. It was established through clinical examination that the patient was in good overall health, but he was diagnosed with subicterus, audible 3/6 systolic murmur on the xiphisternum, and enlarged right lobe of the liver (4 cm enlargement) behind the right portion of the rib cage. Ultrasonography, and then computed tomography (CT), confirmed liver enlargement with multiple secondary deposits up to 57 mm in diameter and paraaortic lymph nodes **(Figure 1)**. The esophagogastroduodenoscopy procedure indicated gastritis, while colonoscopy up to the terminal ileum revealed second-degree internal hemorrhoids. Biochemical analyses confirmed a mild form of normocytic anemia, with hyperbilirubinemia, as well as slightly elevated gamma-glutamyl transferase (GGT), elevated chromogranin A (CgA), neuron-specific enolase (NSE) and urine 5-hydroxyindoleacetic acid (5-HIAA), with alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen (CA) 19-9, and prostate-specific antigen (PSA) levels within the reference range **(Table 1).**

Based on the clinical presentation and the laboratory test results, radiological and endoscopic procedures, the suspicion of a NET was identified and the patient was referred to the Center for the Treatment of Neuroendocrine Tumors in Belgrade. At the Clinic of Endocrinology, Diabetes and Metabolic Diseases of the Clinical Center of Serbia (CCS), a metastatic NET was suspected, and a pathohistological confirmation of liver changes using CT of the chest and Magnetic Resonance (MR) Enteroclysis were suggested. Additional tests were conducted at the Gastroenterology and Hepatology Clinic of the Clinical Center of Vojvodina. The CT scan confirmed there was no infiltration of the pulmonary parenchyma; percutaneous ultrasound-guided focal liver change biopsy made by an interventional radiologist indicated a pathohistological and immunohistochemical (PH/IHC) analysis which revealed GEP-NET liver metastases, according to the proliferation index (Ki-67) of histological grade G2 (immunohistochemical profile: Synaptophysin +, Ki-67 cca. 10%). The MR Enterography revealed a short segment (2 cm) with a slightly thickened wall (up to 4 mm) in the ileum region that amplified the signal intensity and showed diffusion restriction post-contrast; pathologic lymph nodes, 12 – 24 mm in diameter, were registered in the mesentery and retroperitoneum **(Figure 2)**. As part of the preoperative preparation, echocardiography was performed at the Department of Endocrine Tumors and Hereditary Cancer Syndromes of the Endocrinology Clinic of the CCS that revealed a massive tricuspid regurgitation (TR 4+) and the cardiologist's consent for a planned surgery under local anesthesia was obtained. Somatostatin Receptor Scintigraphy (SRS; OstreoScan) was done at the Nuclear Medicine Center of the CCS and it showed a stripe-shaped zone of intense radiopharmaceutical accumulation (grade IV) in the middle part of the abdomen, right to the periumbilical region, as well as

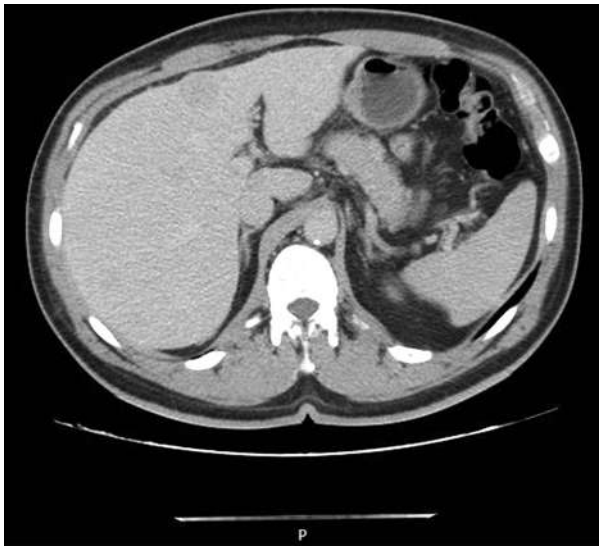

Figure 1. CT scan of the abdomen confirming enlarged liver with multiple secondary deposits
Slika 1. *Kompjuterizovana tomografija abdomena koja pokazuje uvećanu jetru sa brojnim sekundarnim depozitima*

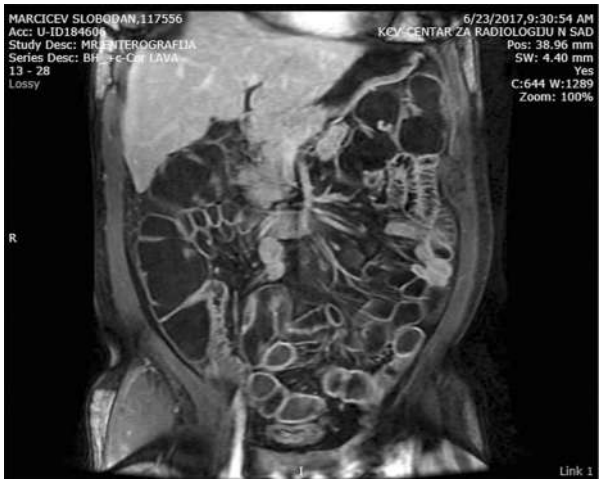

Figure 2. MR Enterography showing the location of the primary tumor in the ileum
Slika 2. *Magnetnorezonantna enterografija je pokazala lokalizaciju primarnog tumora u ileumu*

numerous zones of intense radioactive tracer accumulation in both lobes of the liver. An elective surgical procedure was performed at the Clinic for Digestive Surgery of the CCS, restricting the primary intestinal tumor together with fast-acting octreotide therapy during surgery in order to prevent intraoperative exacerbation of carcinoid syndrome. The final PH/IHC findings confirmed a G1 NET of the small intestine with liver metastases (mitotic index 1/10 HPF, Ki-67 index lower than 0.01%, Synaptophysin +++, CDX-2 +++, SSTR-2 +++, with no PAX-8 and TTF-1 immunoreactivity), tumor stage IV, residual status R0.

Discussion

Hereby we present a case of a patient diagnosed with a GEP-NET three years after the onset of symptoms. The delay was due to non-specific initial symptoms that resulted in the patient's late visit to the doctor. The diagnostic procedure relied on teamwork in the fields of gastroenterology, endocrinology, radiology, nuclear medicine, surgery, and finally pathology, and the patient was ultimately diagnosed with a metastatic GEP-NET of low proliferative potential.

The GEP-NETs are most frequently located in the small intestine (39–42%) and rectum (26%), which is followed by the colon (9–20%), stomach (9–20%), pancreas (7–12%) and the appendix (6%). Additionally, carcinoid tumors are the primary malignant tumors of the distal ileum whose incidence exceeds that of adenocarcinomas (44% compared to 33%) [9, 10].

In this case, MR Enterography revealed a possible localization in the small intestine, while liver biopsy indicated primary NET metastasis. Liver metastases are common in patients with GEP-NETs, occurring in 50 – 75% of cases, and their presence has a significant influence on the quality of life, as well as the overall prognosis [11, 12].

When 5-HIAA levels were compared among patients with different localizations of GEP-NETs, patients with functional midgut tumors exhibited the highest levels. A correlation between 5-HIAA levels and metastases, especially hepatic metastases, was also noted. In approximately 75% of cases, a correlation was found between NETs with embryologic origin in the midgut and urinary 5-HIAA, which was also the case in our patient. If carcinoid syndrome is present, the sensitivity and specificity of this test is 70 and 90%, respectively [13–15].

However, even when specific biomarkers and morphological methods are used, primary tumors are often difficult to locate. In a study by Wang et al., out of 15 patients with liver metastases, with unknown location of the primary tumor, the small intestine was identified as the primary tumor location in 87%, following explorative laparotomy [16].

Our patient was diagnosed with right-sided carcinoid heart disease. Carcinoid heart disease, as a unique carcinoid tumor manifestation, is seen in 72% of patients diagnosed with a primary GEP-NET of the small intestine. The exact mechanisms responsible for the development of this multifactorial phenomenon are not well known to this day, although

Table 1. Biochemical analysis results during the process of diagnosis
Tabela 1. *Rezultati biohemijskih analiza tokom dijagnostike pacijenta*

Analysis *Analiza*	Result *Rezultat*	Reference range *Referentna vrednost*
Hemoglobin/*Hemoglobin*	120 g/l	130 - 160 g/l
Total/Direct bilirubin/*Totalni/Direktni bilirubin*	37.7/12.8 µmol/l	3 - 21/0.1 - 5.2 µmol/l
Gamma-glutamyltransferase (GGT)/*γ-glutamil transferaza*	70 U/l	< 55 U/l
Chromogranin A (CgA)/*Hromogranin A*	246 µg/L	< 125 µg/L
Neuron-specific enolase (NSE)/*Neuron-specifična enolaza*	20 µg/L	< 16.3 µg/L
5-hydroxyindoleatic acid (5-HIAA)/5- *hidroksi indol sirćetna kiselina*	368.3 µmoL/24h	< 32 µmoL/24h
Alpha-fetoprotein (AFP)/*Alfa-fetoprotein*	2 ng/ml	< 7.08 ng/ml
Carcinoembryonic antigen (CEA)/*Karcinoembrionalni antigen*	1.8 ng/ml	3 ng/ml
Cancer antigen (CA 19-9)/*Karbohidratni antigen*	24 U/ml	< 37 U/ml
Prostate-specific antigen (PSA)/*Prostata-specifični antigen*	2 ng/ml	< 4 ng/ml

there is evidence that this is due to the chronic exposure of endothelium to a range of vasoactive substances secreted by the tumor, such as serotonin, prostaglandins, histamine, bradykinin, tachykinins, as well as the signaling through 5-hydroxytryptamine 2B receptor and transforming growth factor β1, which ultimately leads to fibrotic degeneration of cardiac valves and the subvalvular apparatus. Echocardiography should be mandatory in patients diagnosed with carcinoid syndrome, so that the potential signs of right-sided carcinoid heart disease, which is associated with poorer prognosis, may be recognized in a timely manner. A significant drop in the incidence of right-sided carcinoid heart disease was seen following the introduction of somatostatin analogs as a form of treatment, given that, up to that point, about two thirds of patients diagnosed with carcinoid syndrome also suffered from right-sided carcinoid heart disease [17–19].

The CT is the most widely used radiological method when it comes to diagnosing carcinoid tumors. In approximately 73% of patients, primary GEP-NETs are diagnosed by means of CT scanning, although detection rates vary significantly (39–94%). The NETs located in the small intestine are often small and multifocal, which means that they can go undetected on the CT scan in 50% of cases. When the location of the primary tumor is unknown, the CT detection rate is significantly lower (35%). The role of MR Enterography and enteroclysis in the detection of small intestine carcinoid has not been precisely evaluated. Although some studies showed 86–94% sensitivity and 95–97% specificity, the number of carcinoids detected in those studies was fairly small. In cases where the primary tumor's location is known, OctreoScan shows 80% sensitivity and 90% specificity, while the detection rate of primary tumors of unknown location is 24–39%. A study that compared MR, CT and OctreoScan findings in the detection of hepatic metastases, showed that MR has the highest level of sensitivity - 95.2%, CT - 78.5%, and OctreoScan - 49.3% [20–23].

Continuous administration of somatostatin analog infusion is a crucial part of the perioperative period for such patients. It should be administered at least two hours before the surgery and continued for 48 hours following the surgery, gradually decreasing the dose. The goal is to reduce the release of serotonin and prevent complications such as hypotension, carcinoid crisis and death. Treatment involving somatostatin analogs and/or tumor deblocking techniques (hepatic artery embolization, palliative hepatic cytoreductive therapy) can improve the symptoms of carcinoid syndrome and decrease the negative impact that vasoactive agents have on carcinoid heart disease and the occurrence of heart failure, although no conclusive evidence of their impact on the progression of carcinoid heart disease has been found to this day [24, 25].

Nowadays, the approach to the treatment of patients diagnosed with GEP-NETs is going through significant and rapid changes in line with new research and introduction of novel treatment options. Dramatic changes regarding the management of these patients and introduction of sophisticated new guidelines are a challenge that requires a multidisciplinary team of endocrinologists, gastroenterologists, radiologists, oncologists, surgeons and pathologists. Complex cases also require consultations with specialized centers for the treatment of neuroendocrine tumors [20].

Conclusion

The process of diagnosing a gastroenteropancreatic neuroendocrine tumor, once the symptoms start showing is difficult; regardless of the increase in their incidence, neuroendocrine tumors are rare and seldom come to mind. Although gastroenteropancreatic neuroendocrine tumors are usually diagnosed only after the disease has metastasized into the liver, early diagnosis has a significant influence on the positive outcome of the treatment. A correct and, most importantly, early diagnosis, together with appropriate gastroenteropancreatic neuroendocrine tumor treatment, results in a good prognosis in most patients. Therefore, diagnosis and treatment of patients with clinical suspicion of a gastroenteropancreatic neuroendocrine tumor requires a multidisciplinary approach, both in the process of diagnosis and initial treatment, and in the phase of long-term monitoring.

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RIMANOCZY SPA HOUSE RULES – A MODEL FOR THE NOVI SAD ARTESIAN SPA HOUSE RULES

KUĆNI RED BANJE RIMANOCZY KAO PRIMER KUĆNOG REDA U NOVOSADSKOM ARTEŠKOM KUPATILU

Rastislava KRASNIK[1, 2], Jelena ZVEKIĆ SVORCAN[1, 3], Viktor STRIKOVIĆ[4], Sara SAMARDŽIĆ[5], Branislav BOBIĆ[1, 3] and Mirjana KOLUNDŽIĆ[6]

Summary

Introduction. Artesian well drilling, water testing, obtaining all the necessary permits, as well as designing, equipping, and final organization of work, including hiring the necessary staff, is often time-consuming and complex, and so it was for the leaders of the Free Royal City of Novi Sad in establishing the future Novi Sad "Jodna banja" (Iodine Spa). **Spa House Rules.** The paper gives an overview of the Rimanoczy Spa House Rules, which served as a model for creating similar house rules and shaping the work in the future spa. The success of the Novi Sad City Artesian Spa in the late 19th and early 20th century was attributed to visionaries, architects, city leaders, doctors, as well as numerous employees, who invested their knowledge and abilities to the people's needs in order to improve the wellbeing and health of the Spa guests.

Key words: Water Wells; Baths; Guideline; History of Medicine; Serbia; History, 19th Century; History, 20th Century

Sažetak

Uvod. Put od kopanja arteškog bunara, analize vode, pribavljanja potrebnih dozvola, projektovanja, opremanja pa do finalne organizacije rada i angažovanja potrebnog osoblja, često je dugotrajan i složen, iskusili su i čelni ljudi slobodnog kraljevskog grada Novog Sada pri organizaciji rada buduće novosadske *Jodne banje*. **Kućni red Banje.** U radu je naveden osvrt na kućni red banje *Rimanoczy*, koji je poslužio kao uzor za formiranje sličnog kućnog reda i oblikovanje strukture rada u budućoj banji. Popularnosti novosadskog varoškog kupatila s kraja 19. i početka 20. veka doprineli su vizionari, arhitekte, čelni ljudi grada, lekari, ali i brojni zaposleni, koji su znanje, fokusiranost na korisnike i osluškivanje potreba usmerili na dobrobit i poboljšanje zdravlja svojih korisnika.

Ključne reči: arterski bunari; kupatila; preporuke; istorija medicine; Srbija; istorija, 19. vek; istorija, 20. vek

Introduction

At the turn of the twentieth century, a number of European countries started exensive use of mineral waters for healing purposes, and thus building of famous future spas. A similar trend was noted in the Vojvodina region, including drilling artesian wells in Novi Sad (1898), Bečej (1904), Kanjiža (1908), Senta, Bezdan (1911 – 1912), Prigrevica, Apatin (1913) and Temerin (1919) [1–3]. Artesian well drilling, water testing, obtaining all the necessary permits, as well as designing, equipping, and final organization of work, including hiring the necessary staff, is often time-consuming and complex, and so it was for the leaders of the Free Royal City of Novi Sad in establishing the future Novi Sad "Jodna banja" (Iodine Spa).

On June 7, 1909, the Novi Sad City Council received a letter from the then Mayor of Nagyvarad, today the city of Oradea in Romania, that was a response to their request from the same year, concerning the house rules for the Novi Sad City Artesian Spa that was in the process of being established. In the correspondence between the Mayor of Nagyvarad and the City Council of Novi Sad, there was an attached price list and rules of conduct, that is, the house rules for the employees of the Rimanoczy Spa Hotel, owned by the city of Nagyvarad, offering 12 baths to their guests [4]. Several generations of architects from the famed Rimanoczy family have

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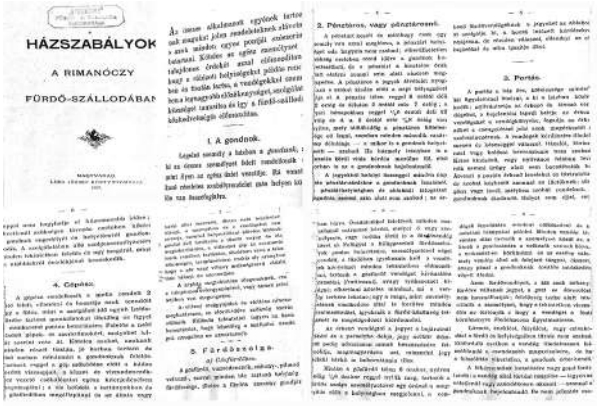
participated in the design of numerous monumental buildings in several European cities, some of which were for the purpose of continental and coastal health tourism, as the famous Miramare Hotel in Crikvenica (Republic of Croatia) [5, 6]. The architect Rimanóczy Kálmán Senior built the Rimanóczy Spa and Hotel buildings on the bank of the Körös river at his own expense, and then he bequeathed it to the city of Nagyvárad (Oradea) [5].

The structure of the employees, manner of conduct among the employees in the institution, as well as towards the guests at the Rimanoczy Spa Hotel, are defined in the very first sentences of this old copy of the House Rules: "All employees are obligated to respect these rules and to follow them in full. All employees are obligated to protect the interests of the owners by keeping in order and care for the hygiene of the premises they are entrusted with; they will be polite to the guests, provide all possible help and thus contribute to increase the popularity of the spa-hotel" [4]. There are rules that regulate the rights and responsibilities of the manager. The aforementioned text emphasizes that "the first person in the institution is the **manager** who is responsible for all employees and runs the entire institution" [4]. The above-mentioned House Rules do not define the rights and obligations of physicians, the terms of their employment and work. The later Statute of the Joint Company "Novi Sad Iodine Spa" states that "the Board of Directors meets once a month for the purpose of making decisions and for advisory purposes; makes decisions on who will be employed, the annual salary and bonuses for employees. The Administrative Board appoints the spa manager as well as the spa doctor, determines the period for which they were appointed, and the amount of their earnings. The members of the Administrative Board may appoint a Small Administrative Board of ex officio high-ranking employees of the spa, a spa doctor and two elected members of the Administrative Board" [7].

The duties of the **cashier** of the Rimanoczy Spa are defined very precisely. It is recommended that "in the event of any unclear situation during the work, the manager should be informed first. Under no circumstances should he have visits at the cash desk or at the counter. He should politely, but briefly, answer the guests' questions, check those who come in, and explain where they should go" **(Figures 1 and 2)** [4].

The importance of the **doorman's** position is particularly emphasized in the extensive segment of the House Rules regarding the day-to-day work responsibilities of the employees. According to the document, "the doorman is the guardian of the institution whose duty is to monitor the movements of all those who move in the institution. He keeps track of guests, coming and going. He registers guests in the guestbook based on the check-in list, greets the arriving guests and notifies the arrival by ringing the bell. He kindly and politely answers the guests' questions. Peddlers and beggars should not be allowed inside the spa. Under no circumstances should women of suspicious appearance, like those from a


HÁZSZABÁLYOK

A RIMANÓCZY

FÜRDŐ-SZÁLLODÁBAN

Figure 1. "House Rules of the Rimanoczy Spa-Hotel" Nagyvarad: Jozsef Lang printing shop, 1897 [4]
Slika 1. *„Kućni red Rimanoczy banje-hotela" Nagyvarad; štamparija Jožefa Langa; 1897. godine [4]*

brothel, be allowed in. He receives postal letters and telegrams and sends them immediately to those to whom they are intended. The telegrams or letters in which the rooms are booked are to be handed over to the manager. The doorman must not leave his post for long periods, day or night. In case he needs to go somewhere, he must seek the permission of the manager and must find a replacement. He is responsible in all respects for all employees as well as for himself and he must assure it" [4]. Great attention was also paid to the proper maintenance of the equipment and the entire spa inventory. The **head of the boiler room** was responsible for a large number of tasks related to the maintenance of the heating system. Thus, the document states that the head of the boiler room "is required to check the bath faucets in the morning before starting the machine, to check the full length of pipes leading to the toilets and to the pools, to establish the water temperature in the tanks and in the steam bath, and if he notices a defect, or someone reports a defect, to fix it immediately without bothering the guests. He should be economical, but only to the extent that it does not jeopardize the production of sufficient quantities of steam or electricity" [4]. The House Rules also pointed out that "the boiler room may be shown to a foreigner only with the permission or presence of the owner or manager of the spa" [4]. The House Rules of the Rimanoczy Spa Hotel also regulated the duties of the **spa attendants**. According to the rules "the steam baths, pools, shower rooms, restrooms and changing rooms are the responsibility of the spa attendants, male or female. They supervise that the House Rules are properly followed, do their work with other employees, and should endeavor to make the guests feel as comfortable as possible. They will give a scrub or a pedicure to the guests in the steam room if they ask for it. They should do everything to keep their guests satisfied. Both they and their employees should avoid unnecessary intimacy, but must strive to please the guests of the spa and to earn their satisfaction "[4]. The House Rules also emphasized that "at work, employees of the bath are forbid-

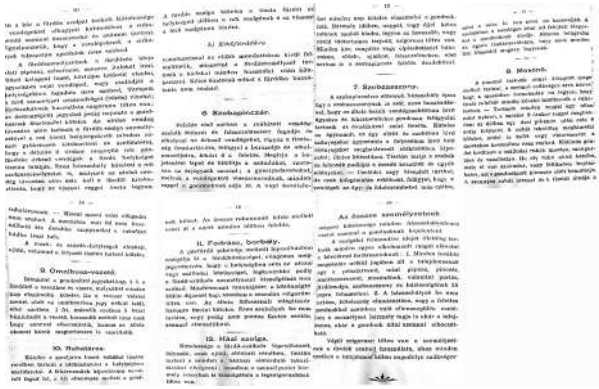


Figure 2. "House Rules of the Rimanoczy Spa-Hotel" Nagyvarad: Jozsef Lang printing shop, 1897 (continuing) [4]
Slika 2. *Kućni red Rimanoczy banje-hotela" Nagyvarad; štamparija Jožefa Langa; 1897. godine (nastavak) [4]*

den to smoke pipes and cigarettes, have alcoholic drinks, wear a hat or shoes with leather soles, and must not receive visits from their guests or family members on the spa premises" [4].

The Hose Rules also included interesting regulations on the spa dress code: "the male employees must wear red trousers and swimsuits are strictly forbidden" [4]. In the bathrooms with bathtubs, "the spa attendant is obliged to wash the bathtub after each use. Women of the streets are not allowed in the spa" [4]. A number of tasks were given to valets and maids. Thus, the maid "is obliged to take care of bedding, carpets in front of the bed and in the room, as well as of those in the corridors. They must dust or wash them at certain time intervals", as well as "keep the beds clean, without parasites" [4].

The workers' rights, working hours and responsibilities toward the employer may be analyzed from several aspects. According to the House Rules, the **laundress** was working "every morning from 5 AM until noon, when there was an one-hour pause, and continued working until 8 PM" [4]. The connection of the spa with the means of transportation of passengers is visible from the timetable of the omnibus (tram) driver, who "regularly receives the tickets for the line between the spa and the train station and back from the manager, and he must settle the bills with the manager daily. If the controller finds someone without a ticket, the driver will receive a fine of 1 forint for the first transgression, and 2 forints for the next one. For the third case, not only is the driver immediately fired, but he must also compensate the damages incurred" [4]. Hairdressers, barbers as well as cloakroom attendants, were also available to the spa guests [4]. The housekeeper (janitor) was "obliged to keep the stairs, corridors, doors and windows of the spa-hotel, as wel as to clean everything at the establishment, but he was also strictly forbidden to serve the employees in any way" [4]. At the Rimanoczi Spa Hotel, the emphasis was placed on keeping staff fully accessible to guests, while the guest's responsibilities were not so precisely stated, that is, all services were subordinated to the satisfaction of the spa guests. In the same period of time, the Lipik Iodine Spa Resort (Republic of Croatia), offered numerous additional facilities besides spa baths [8], also had Spa Regulations [9]. The Spa Regulations, as published in the book "The Lipik Iodine Bath and its Spa" in 1877, specified the responsibilities of the spa guests in eight paragraphs. For instance, regarding the time, "baths are to be used between 5 and 12 in the morning and 2 – 8 in the afternoon"; a precise separate record was kept of the order of persons who were referred to use the baths, and they were not to be used longer than exactly one hour, including undressing and dressing [10].

In the letter to the City Council of the Free Royal City of Novi Sad, ticket prices for the Rimanoczy Spa were also provided. The Pricelist of the Rimanoczy Spa Hotel shows which services were provided to guests and at what price (in crones of that time). Thus, this spa offered the following facilities: steam bath for men (price 1.30 crones), regular bath for women (1 crone), shower for men (0.90), lounge (luxury) bath (1.60), double lounge bath (3.00), use of first-class bath (0.80), and second-class bath (0.60), as well as double tubs of second class (1.20 crones). The price for baths at the hotel was 0.90 crones, while a cold bath for men was 1.40 crones. The additional offer included the use of sheets (0.20 crones), towels (0.10), soaps (0.10), while tickets for children were more affordable (0.40 crones). Civil Servants had a discount for showers (100 tickets for 64 crones), as well as for steam baths (100 tickets for 94 crones). There was also an offer for baths in cold medicinal water: 10 baths for 10.00 crones, 20 baths for 18.00 crones, and 30 baths for 26 crones. Also, showers were available (0.70 crones) and a steam baths at discount price (1 crone) [4]. Tickets at preferential, lower prices for certain categories of the population were later offered to the citizens of Novi Sad in the city bath. Thus, on December 21, 1925, the Novi Sad Iodine Medicinal Spa and Mineral Water Factory (Limited Liability Company) sent 300 half-price bath tickets for the following year (1926) to the City Council to be used by city pensioners [11].

The dedication of the City Iodine Spa employees to their guests, the variety of offerings, luxurious spa exterior and interior, all contributed to its great popularity, as stated in the contemporary press: "Last year, 15 800 people visited this Spa, most of them foreigners who had been guests for 8 – 14 days, which is a great success" [2, 12].

Conclusion

The success of Novi Sad City Artesian Spa in the late 19th and early 20th century was attributed to visionaries, architects, city authorities, doctors, as well as numerous employees, who invested their knowledge and abilities to the people's needs in order to improve the wellbeing and health of the Spa guests.

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IN MEMORIAM
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Prof. dr PETAR DRAČA
(1928–2020)

Prof. dr Petar Drača rođen je 28. januara davne 1928. godine u Jasenovcu, u Hrvatskoj. Gimnaziju je završio u Somboru gde je položio maturski ispit sa odličnim uspehom. Za vreme Drugog svetskog rata uhapšen je u Jasenovcu i potom odveden u logore Jasenovac, Stara Gradiška i Zemun – Sajmište, odakle je sa grupom maloletnika prebačen u Beograd, gde je nastavio školovanje. U Narodnooslobodilačku borbu stupio je kao bolničar u Glavnoj vojnoj bolnici u Beogradu 1944. godine.

Na Medicinski fakultet Univerziteta u Beogradu upisao se 1947. gde je i diplomirao 1954. godine. Lekarski staž obavio je u Opštoj bolnici u Somboru i potom radio kao savetnik u socijalnom osiguranju sreza Sombor. Specijalizaciju iz ginekologije i akušerstva obavio je na Ginekološko-akušerskom odeljenju glavne pokrajinske bolnice u Novom Sadu u periodu od 1956. do 1961. godine. Specijalistički ispit položio je na Ginekološko-akušerskoj klinici Medicinskog fakulteta Univerziteta u Beogradu 1961. godine sa odličnim uspehom. Habilitacioni rad pod naslovom *Forceps u uslovima savremenog akušerstva* odbranio je 1966. godine. Doktorsku disertaciju pod naslovom *Antropometrijske karakteristike karlice žena u nekim krajevima Jugoslavije sa posebnim osvrtom na uticaj socijalno-ekonomskih i klimatskih faktora na njihov razvoj* uspešno je odbranio na Medicinskom fakultetu Univerziteta u Novom Sadu 1972. godine.

U toku 1961. godine izabran je u zvanje asistenta za predmet Ginekologija i opstetricija na Medicinskom fakultetu Univerziteta u Novom Sadu, u zvanje docenta 1967, vanrednog profesora 1973. i redovnog profesora 1980. godine. U periodu 1972–1974. godine bio je prodekan za nastavu i naučni rad na Medicinskom fakultetu Univerziteta u Novom Sadu. Profesor Petar Drača svoj radni vek proveo je na Klinici za ginekologiju i akušerstvo u Novom Sadu. Njegov razvojni put tekao je postupno i sistematično od lekara na specijalizaciji, potom lekara specijaliste, šefa odseka, načelnika odeljenja i Upravnika Zavoda za ginekologiju (1981–1985, 1990–1993). U periodu 1985–1990. bio je savetnik Klinike, penzionisan je 1993. godine.

U toku svog specijalističkog staža i rada na Klinici (1961−1993.) profesor Petar Drača značajno je unapredio i modernizovao ginekološku službu uvođenjem čitavog niza različitih hirurških postupaka i dijagnostičkih metoda. Njegov doprinos posebno je značajan u oblastima ginekološke urologije i ginekološke onkologije koje su danas u Evropi, SAD i ekonomski visokorazvijenim zemljama priznate kao zasebne supspecijalističke grane medicine. U hirurškom lečenju urinarne stres-inkontinencije u rutinsku primenu uveo je različite operacije: *Colporrhaphia anterior s. Kennedy, Musculus pubococcigeus repair sec. Ingelman-Sundberg, Oxford i Aldridge sling, Colposuspensio sec Burch*. U hirurškom lečenju kompletnog spada (prolapsa) vagine posle prethodne histerektomije uveo je tzv. *abdominalni sling* (*Sling abdominalis sec. Shirodkar*) u kombinaciji sa zatvaranjem (obliteracijom) Duglasovog špaga plasiranjem cirkularnih šavova po Moskovicu (*Moschowitz*). U operativnom lečenju karcinoma grlića materice u toku radikalne histerektomije uveo je tzv. *strehicu uretera po Novaku* i *mezenterijum uretera po Stalvortiju (Stalworthy*), da bi smanjio pojavu ureterovaginalnih fistula. Kod radikalnih operacija u maloj karlici zalagao se za drenažu i uveo ekstraperitonealnu vakuum-dre-

nažu obturatornih jama posle radikalne histerektomije. Kod mladih žena koje boluju od karcinoma grlića materice uveo je originalnu metodu očuvanja (konzervacije) i podizanja (elevacije) jajnika izvan karlice u nivo bubrežne lože, obeležavajući ih metalnim klipsovima kako bi izbegao njihovo oštećenje u toku dopunske zračne terapije čime se značajno poboljšavao kvalitet života ovih mladih osoba. U rutinsku hirurško praksu uveo je i radikalnu blokdiskeciju vulve tehnikom po Veju u hirurškom lečenju invazivnog karcinoma vulve. Bio je veliki zagovornik vaginalnog hirurškog pristupa, vaginalne histerektomije i tzv. *morcellement,* odnosno intraoperativnog uklanjanja „u komadima" velike miomatozne materice u toku vaginalnog hirurškog pristupa. Tehniku vaginalne histerektomije modifikovao je fiksiranjem sakrouterinih ligamenta za zadnji gornji rub vagine, visokom peritonizacijom Duglasovog špaga i plasiranjem tri šava u predelu pubokokcigealnih mišića po Kenediju, kako bi u kasnijem periodu života sprečio nastanak recidiva i poremećaja statike karličnoga dna.

Svoje hirurško znanje i umeće nesebično je delio sa drugim lekarima specijalistima ginekolozima-akušerima a operacije je obavljao, pored matične klinike, i u Somboru, Zrenjaninu, Prištini, Podgorici, Užicu i Republici Srpskoj. U periodu postojanja Republike Srpske Krajine odlazio je u Vukovarsku bolnicu gde je vršio i veće ginekološke hirurške zahvate (1991–1997) jer bolnica nije imala finansijska sredstva da ove pacijente uputi u Novi Sad ili u druge centre. Za lekare iz Sremsko-baranjske oblasti organizovao je nekoliko zapaženih edukativnih skupova sa predavačima iz Srbije a bio je jedan od predavača u Školi operativne tehnike ginekološko-*akušerskih operacija* u Užicu 1991. godine.

Profesor Petar Drača publikovao je preko 300 stručnih i naučnih radova. Bio je autor četiri monografije: Ginekološka urologija (*Matica srpska, Novi Sad, 1983*), Ginekološka urologija, II dopunjeno izdanje (*Grafoofset, Sremska Kamenica, 1997*), Klinička ginekološka onkologija (*Matica srpska, Novi Sad, 1989*) i Razvoj ginekologije i akušerstva u Vojvodini do 2000. godine (*Medicinski fakultet, Novi Sad, 2008*). Kao saradnik učestvovao je u pisanju poglavlja u 11 različitih monografija i knjiga drugih autora kao i u pisanju interfakultetskih udžbenika iz ginekologije i akušerstva. Bio je rukovodilac i saradnik u izradi brojnih naučnih projekata (1972–1990) a njegova proučavanja virusa kao mogućih faktora u nastanku genitalnih karcinoma u zajednici sa drugim istraživačima saopštena su u Veneciji 1991. godine na 7. Internacionalnom sastanku iz ginekološke onkologije. Profesor Petar Drača održao je brojna predavanja po pozivu na domaćim i međunarodnim skupovima, među kojima se izdvajaju međunarodni naučni sastanci posvećeni uglednim ginekolozima: penzionisanje profesora J. Stalvortija (Oksford, Velika Britanija, 1973), 70-godišnjica života akademika Franca Novaka (Ljubljana, 1978), penzionisanje akademika Vojina Šulovića (SANU, Beograd, 1989), kao i Simpozijum posvećen 20-godišnjici osnivanja Medicinske akademije Srpskog lekarskog društva (Novi Sad, 1996). Držao je i predavanja po pozivu u poznatim američkim ginekološkim i onkološkim ustanovama u Filadelfiji, Hjustonu i Njujorku, ali i u drugim evropskim gradovima: Moskvi, Lenjingradu, Padovi, Skoplju, Portorožu.

Profesor Petar Drača postao je član Srpskog lekarskog društva 1954. godine, a u periodu 1976–1980. godine bio je i potpredsednik ovog udruženja. Obavljao je funkciju sekretara (1972–1976) i potom predsednika Društva lekara Vojvodine (1976–1980). Bio je član Predsedništva Ginekološko-akušerske sekcije Srpskog lekarskog društva i član Redakcionog odbora zbornika radova sa ginekoloških nedelja, sekretar i predsednik Ginekološko-akušerske sekcije Društva lekara Vojvodine, član Predsedništva i generalni sekretar Saveza lekarskih društava Jugoslavije, član Predsedništva i predsednik Udruženja ginekologa i opstetričara Jugoslavije i predsednik organizacionog odbora XI kongresa ginekologa Jugoslavije, održanog 1988. godine u Novom Sadu. U Balkanskoj medicinskoj uniji bio je sekretar Sekcije za Jugoslaviju, a u Matici srpskoj član Odbora za prirodne nauke; bio je član je Udruženja ginekologa i akušera Srbije, Crne Gore i Republike Srpske, *International College of Surgeons, European Society of Gynecological Oncology i European Society of Gynecology.* Dugi niz godina bio je aktivista Crvenog krsta Vojvodine a u Pokrajinskoj konferenciji Socijalističkog saveza Vojvodine predsednik Saveta za planiranje porodice.

Organizovao je nekoliko naučnih skupova u okviru Srpskog lekarskog društva, Udruženja ginekologa i opstetričara Jugoslavije i Saveza lekarskih društava Jugoslavije: Jugoslovenski simpozijum o stres-inkontinenciji mokraće (Novi Sad, 1979), Simpozijum 259 godina ginekologije i akušerstva na tlu Vojvodine (Novi Sad, 1981), XI Kongres ginekologa i opstetričara Jugoslavije (Novi Sad, 1988), *II Scientific meeting of Yugoslavia-United States Medical Association* (Filadelfija, SAD, 1980), IV Sovjetsko-jugoslovenski medicinski dani (Lenjingrad, 1978) i IV Jugoslovenski simpozijum za neurologiju i urodinamiku (Novi Sad, 1991).

Profesor Petar Drača izabran je za počasnog člana Udruženja ginekologa i opstetričara Jugoslavije, Udruženja za ginekološku onkologiju Srbije i Ginekološko-akušerske sekcije *na Makedonsko zdrženije za ginekolozi i akušeri* (1995), ka i *Titulaire de l'Union Medicale Balkanique* (1979), *Honorary Member, Centre Oncologique et Biologique de Recherche Appliquée Saint-Étienne* (1987) i počasni predsednik Društva lekara Vojvodine (1980). Bio je predsednik izdavačke delatnosti Društva lekara Vojvodine, član i predsednik Redakcionog odbora časopisa Medicinski pregled i urednik za ginekologiju časopisa Jugoslovenska ginekologija i perinatologija. Profesor Drača bio je član inicijativnog odbora za osnivanje Medicinske akademije Srpskog

lekarskog društva i član prvog predsedništva Akademije (1976). Učestvovao je u donošenju prvog pravilnika o radu Akademije, a potom je bio još u nekoliko mandata član Predsedništva i član Naučnog veća Akademije; organizovao je i nekoliko zapaženih naučnih skupova u okviru naučne delatnosti Akademije. Posebno treba istaći njegov rad na povezivanju ginekologa i akušera iz Srbije i susednih zemalja i organizaciju nekoliko nedavnih međunarodnih skupova ginekologa: Srpsko-slovenački naučni skup ginekologa i akušera (Beograd, 2014), Slovenačko-srpski sastanak ginekologa akušera (Dobrna, Slovenija, 2015) i Srpsko-makedonski naučni skup (Beograd, 2015).

Profesor Petar Drača je nosilac Ordena rada sa zlatnim vencem (1975), Ordena zasluga za narod sa srebrenim zracima (1981) i Zlatnog znaka Crvenog krsta Jugoslavije (1973). Dobitnik je Nagrade za organizaciju zdravstvene službe Srpskog lekarskog društva (1977), Godišnje nagrade za naučnoistraživački rad Društva lekara Vojvodine (1989), Jubilarne medalje Udruženja ginekologa Italije (1994), Medalje „Dr Milan Hadžić“ Ginekološko-akušerske sekcije Srpskog lekarskog društva, Nagrade za životno delo Srpskog lekarskog društva (2005), Nagrade „Veliki pečat“ Srpskog lekarskog društva (2009) i Diplome FIGO za naučna ostvarenja i doprinos zaštiti zdravlja žena, koja mu je dodeljena povodom 40-godišnjice udruženja FIGO na XIV Svetskom Kongresu ginekologa i akušera u Montrealu (Kanada, 1994).

Profesor Petar Drača poživeo je dugo, pune 92 godine. Svoj život posvetio je medicini, posebno ginekološkoj hirurgiji, ginekološkoj urologiji i onkologiji. Radio je i pisao puno. U svojoj poslednjoj monografiji (2008) koja je posvećena razvoju ginekologije i akušerstva u Vojvodini do 2000. godine citirao je reči čuvenog književnika Ive Andrića koje najbolje ilustruju njegovo životno delo: „*Ništa ne izdaje čoveka kao pamćenje i ništa ne vara kao re*č. *Samo ono što je zapisano ostaje*“. Aktivno je učestvovao u organizaciji i radu različitih medicinskih društava i udruženja i za života za svoj stručni i naučni rad i doprinos medicini dobio je brojne nagrade i priznanja. Bio je kompletan profesor medicine u pravom značenju te reči, stručnjak praktičar, ginekolog hirurg i naučnik. Takvih doktora medicine uvek i u svim vremenskim razdobljima bilo je malo. Njegov životni put, stručno i naučno delo, posebno u ovim bremenitim i teškim vremenima trebalo bi da predstavlja svetionik i putokaz mlađim generacijama koje polaze dugim i neizvestim putevima medicine .

Prof. dr Srđan Đurđević,
Šef Katedre za ginekologiju i akušerstvo

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

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

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

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

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

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

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

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

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

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

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

Priprema rukopisa

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

Propratno pismo:

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

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

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

Rukopis

Opšta uputstva

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

Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana

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

2. Sažetak

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

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

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

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

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

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

3. Tekst članka

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

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

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

Uvod

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

Materijal i metode

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

Rezultati

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

Diskusija

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

Zaključak

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

4. Literatura

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

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

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

∗ Organizacija kao autor

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

∗ Bez autora

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

∗ Volumen sa suplementom

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

∗ Sveska sa suplementom

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

∗ Sažetak u časopisu

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

Knjige i druge monografije

∗ Jedan ili više autora

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

∗ Urednik (urednici) kao autor (autori)

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

∗ Poglavlje u knjizi

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

∗ Zbornik radova sa kongresa

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

∗ Disertacija

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

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

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

∗ Monografija u elektronskom formatu

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

∗ Kompjuterska datoteka

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

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

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

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

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

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

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

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

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

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

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

6. Dodatne obaveze

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

INFORMATION FOR AUTHORS

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

Since January 1th, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/user/register.

Manuscript submission should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/

A SUPPLEMENTARY FILE, WITH THE STATEMENT THAT THE PAPER HAS NOT BEEN SUBMITTED OR ACCEPTED FOR PUBLICATION ELSEWHERE AND A CONSENT SIGNED BY ALL AUTHORS, HAVE TO BE ENCLOSED WITH THE MANUSCRIPT.

Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

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

All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

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

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

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

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

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

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

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

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

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

Preparation of the manuscript

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

The covering letter:

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

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

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

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

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

2. Summary.

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

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

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

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

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

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

3. The text of the paper.

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

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

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

Materials and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

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

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

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

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

Articles in journals

∗ *A standard article*

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

∗ *An organization as the author*

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

∗ *No author given*

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

∗ *A volume with supplement*

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

∗ *An issue with supplement*

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

∗ *A summary in a journal*

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

Books and other monographs

∗ *One or more authors*

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

∗ *Editor(s) as author(s)*

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

∗ *A chapter in a book*

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

∗ *A conference paper*

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

∗ *A dissertation and theses*

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

Electronic material

∗ *A journal article in electronic format*

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

∗ *Monographs in electronic format*

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

∗ *A computer file*

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

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

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

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

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

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

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

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

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

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

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

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.