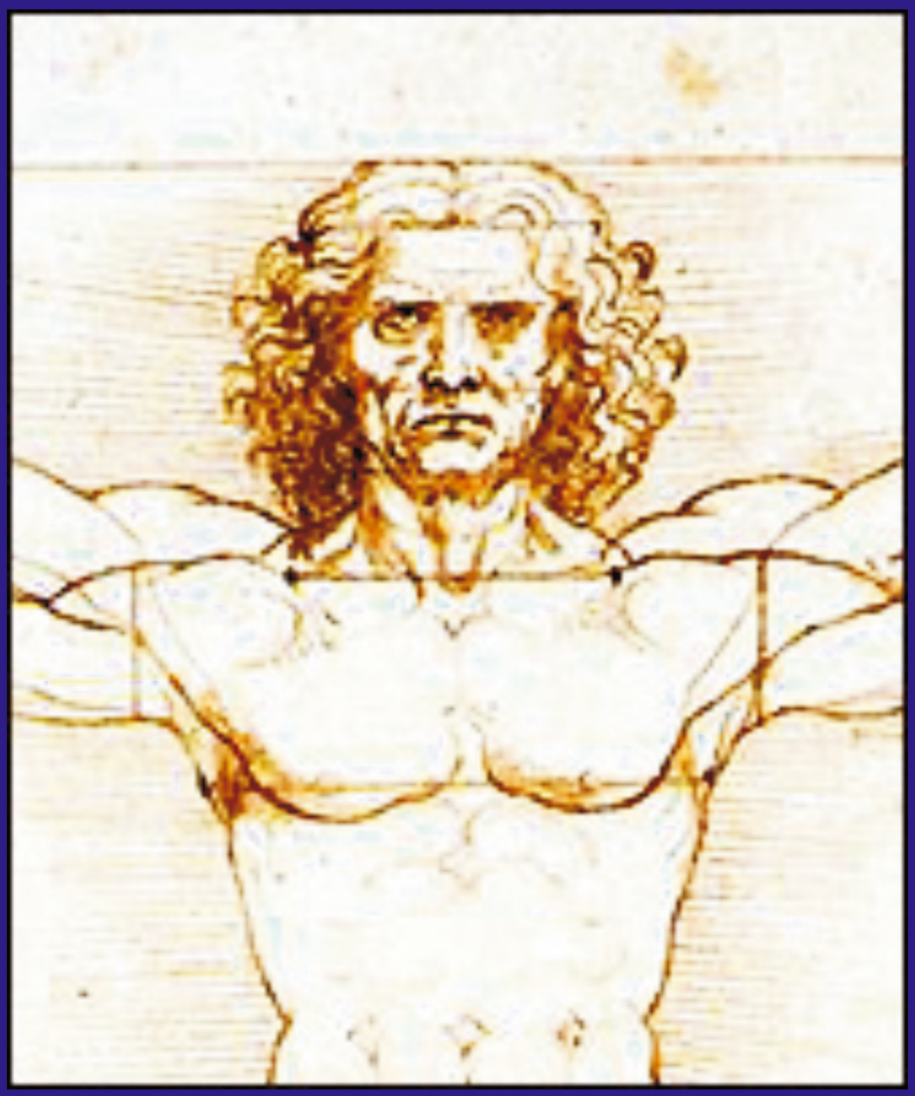
SANAMED

ISSN-1452-662X



Vol 12 (1) 2017.

MEDICINSKI ČASOPIS LEKARA

NOVI PAZAR

SANAMED

ISSN-1452-662X

Izdavač

Udruženje lekara Sanamed, Novi Pazar

ČASOPIS IZLAZI TRI PUTA GODIŠNJE

Adresa uredništva

„SANAMED“, Ul. Palih boraca 52, 36300 Novi Pazar, Srbija
email: sanamednp2006@gmail.com, www.sanamed.rs

Štampa

„ProGraphico“, Novi Pazar

Tiraž

500

Pretplata

Godišnja pretplata: 4500 din. za domaće ustanove; 1500 din. za pojedince; za inostranstvo 75 eura (u dinarskoj protivrednosti po kursu na dan uplate). Pretplatu vršiti na račun 205-185654-03, Komercijalna banka. Za sve dodatne informacije kontaktirati Uredništvo.

SANAMED

ISSN-1452-662X

Publisher
Association of medical doctors “Sanamed”, Novi Pazar

ISSUED THREE TIMES A YEAR

Editorial address
“SANAMED”, St. Palih boraca 52, 36300 Novi Pazar, Serbia
email: sanamednp@gmail.com, www.sanamed.rs

Print
“ProGraphico”, Novi Pazar

Circulation
500

Subscription
Annual subscriptions: 4500 RSD for domestic institutions and 1500 RSD for individuals. For readers abroad, annual subscription is 75 Euro (in Dinar equivalent at the exchange rate on the day of payment). For further instructions and informations, contact Editorial Board.

SANAMED

Number 12(1)/2017

CONTENTS

SANAMED

Number 12(1)/2017

SADRŽAJ

- **REVIJALNI RAD**

Editor-in-Chief / Glavni i odgovorni urednik

Prim. dr Avdo Ćeranić

Guest editors in this issue/Gostujući urednici u ovom broju

Prof. dr Milanka Tatić

Oncology Institute of Vojvodina in Sremska Kamenica, Serbia

Assoc. Professor of Anesthesiology, Faculty of medicine Novi Sad, Serbia

Member of: Association of Anesthesiologists and Intensivists of Serbia, Anesthesia section of Society of Physicians of Vojvodina of Medical Society of Serbia, Association of Intensivists of Serbia, European Society of Anesthesiologists (ESA), European Association of the Intensive Care Medicine (ESICM).

Author and co-author of about 70 scientific papers and chapters in professional monographies.

Prof. dr Nebojša Stojanović

Professor of Surgery, Faculty of Medicine, University of Nis, Serbia

Director of Neurosurgery Clinic in Nis, Clinical center Nis, Serbia

Member of Executive Board of Serbian neurosurgical society

Member of Coordinating Team for development of neurosurgery in Serbia

Awarded by the Serbian Medical Society for implementation of new diagnostic and therapeutic procedures

Prof. dr Milan Đukić

Professor of Pediatrics, School of Medicine, University of Belgrade, Serbia

Head of catheterization laboratory, University children's hospital Tirsova, Belgrade, Serbia

Member of: Association of European Pediatric cardiologist (AEPC), Cardiology Society of Serbia, Echocardiographic Society of Serbia (ECHOS)

SANAMED
2017; 12(1): 11–14
ISSN-1452-662X

DOI: 10.24125/sanamed.v1i1.162
UDK: 616-001.8-053.31; 616.61-008.6-053.31
ID: 231321868
Original article

ACUTE RENAL FAILURE IN TERM NEWBORN FOLLOWING PERINATAL ASPHYXIA

Hadzimuratovic Emina,[1] Skokic Fahrija,[2] Hadzimuratovic Adnan,[1]
Hadzipasic Nazdrajic Amra,[3] Mujic Midhat,[1] Hadzimuratovic Admir[1]

[1] Univerity Medical Center Sarajevo, Bosnia and Herzegovina
[2] University Medical Center Tuzla, Bosnia and Herzegovina
[3] Public Institution Health Centre of Sarajevo Canton, Sarajevo, Bosnia and Herzegovina

Primljen/Received 01. 12. 2016. god.
Prihvaćen/Accepted 27. 02. 2017. god.

Abstract: **Introduction:** Perinatal asphyxia (PA) results in hypoxic damage to almost all organs, kidneys being most frequently (40%) affected.

Objectives: was to determine the incidence of acute renal failure (ARF) in term neonates with PA and to correlate it with severity of hypoxic ischemic encephalopathy (HIE).

Materials and methods: This prospective study of 54 term neonates with PA was performed in tertiary level neonatal intensive care unit at Pediatric Clinic Sarajevo from June 2014 to June 2016. The severe PA was defined as 5. minute Apgar score < 3 and moderate PA as 5. minute Apgar score 4-6. Criteria adopted for ARF were serum creatinine > 1.5 mg/dl (> 133 micromol/L) on 3rd day of life or urine output < 0.5 ml/kg/hr for > 6 hrs beyond 24 hrs of life.

Results. Out of 54 neonates with PA, 22 (40.74%) had ARF. Most of them (63.6%) had non-oliguric ARF with mean renal output of 2.2 ± 0.5 ml/kg/h. Eight neonates (36.4%) had oliguric ARF with mean renal output of 0.35 ± 0.6 ml/kg/h. Most of the neonates with oliguric ARF (63.4%) had severe PA while in those with non-oliguric ARF moderate PA was predominant. ARF was highest in the neonates with HIE III (85.71 %) (Figure 1). This showed that as HIE stage progressed, more renal dysfunction was seen in asphyxiated babies and this difference in incidence was found statistically significant ($p < 0.05$).

Conclusions. Neonates with severe PA had more frequent ARF and the predominant type of renal involvement was non oliguric. Neonates with HIE stage II and III had significantly higher incidence of ARF.

Keywords: perinatal asphyxia, acute renal failure, HIE staging, oliguria.

INTRODUCTION

Perinatal asphyxia (PA) is the major cause of neonatal mortality and long term neurological morbidity with an estimated incidence of 1-10/1000 live births (1). It results in hypoxic damage to almost all organs of the neonate; with kidneys being most frequently (40%) involved (1). The neonatal kidney is anatomically and functionally immature. Renal insufficiency manifests as early as 24 hours of life leading to irreversible cortical necrosis when prolonged. Detection of renal failure is vital in neonates with hypoxic ischemic encephalopathy (HIE) to sustain a stable biochemical milieu and initiate appropriate treatment (2). Neonatal acute renal failure (ARF) is a diagnostic and therapeutic challenge as clinical and laboratory parameters are not strictly defined yet (2). PA and birth injuries together contribute to almost 29% of neonatal deaths. World Health Organisation (WHO) defined birth asphyxia as "failure to initiate and sustain breathing at birth" with Apgar score of < 7 at 1. minute of life (1, 3). American College of Obstetrics and Gynecologists (ACOG) and American Academy of Pediatrics (AAP) have laid down essential criteria to diagnose PA which include, prolonged metabolic or mixed acidemia (pH < 7.0 on cord arterial blood sample), persistence of an Apgar score of < 3 for 5 min or longer, clinical neurologic manifestation as seizures, hypotonia, coma or HIE in the immediate neonatal period coupled with multiorgan dysfunction (1, 3).

METHODS

This prospective study was conducted in a tertiary level neonatal intensive care unit at Pediatric Clinic Sarajevo from June 2014. to June 2016. Consecutive 54 term (37-42 weeks) neonates with perinatal asphyxia

(PA) (5. minutes Apgar score (AS) < 7) were enrolled in the study. Neonates with factors that can alter renal function such as septicemia, respiratory distress syndrome, necrotizing enterocolitis or major congenital anomalies were excluded from the study. Neurological status was assessed using Sarnat and Sarnat staging (4). All the neonates were evaluated clinically and their renal functions were assessed on 3rd day. Renal profile was done by estimation of serum creatinine, urea, sodium and potassium. Assessment of fractional excretion of sodium was done to differ intrinsic from extrinsic renal failure. Criteria adopted for ARF were serum creatinine > 1.5 mg/dl (> 133 micromol/lit) on 3rd day of life or urine output < 0.5 ml/kg/hr for > 6 hrs beyond 24 hours of life. Statistical analysis was conducted using statistical products and services solutions (SPSS) software version 17.0.

RESULTS

The mean birth weight in studied neonates was 3352 g (SD = 427.3), length 51,3 cm (SD = 2.1), clinical gestation 38,9 weeks (SD = 0.87) and head circumference 34,4 cm (SD = 1.6). Most of the neonates were delivered by the vaginal route (59%), 39% via caesarian section and 2% via vacuum extraction. Only 11,1 % (6/54) of the neonates had a very low 5. minutes Apgar score of 0–3, while 88,9% (48/54) had a moderate 5. minute Apgar score of 4–6. Nine neonates (16.6%) were intubated and mechanically ventilated, 5 of them during primary resuscitation and others later within first three days of life (Table 1).

Staging of hypoxic ischemic encephalopathy (HIE) by Sarnat and Sarnat system was done on admission. Nineteen neonates (19/54; 35.19%) had HIE I, twenty-eight (28/54; 51.85%) had HIE II and 7 (7/54; 12.96%) HIE III. Out of 54 neonates with PA, 22 (22/54; 40.74%) had ARF. Most of neonates with ARF (14/22; 63.64%) had non-oliguric ARF with mean renal output of 2.2 ± 0.5 ml/kg/h. In those neonates with oliguric ARF (8/22; 36.36%) the mean renal output was 0.35 ± 0.6 ml/kg/h. Out of eight neonates with oliguric ARF, five (5/8; 62.5%) had severe PA while in those with non-oliguric ARF moderate PA was predominant and present in 8 out of fourteen neonates (8/14; 57.14%). This difference in a type of ARF (non-oliguric/oliguric) in a correlation with a degree of PA was found statistically significant ($p < 0.05$), with oliguric type more frequent in neonates with more severe PA. Sixteen out of twenty-eight neonates (16/28; 57.14%) with HIE II and five out of seven neonates (5/7; 71.43%) with stage III had ARF. Only one out of nineteen neonates (1/19; 5.26%) with HIE I had ARF.

Table 1. *Basic characteristics of neonates included in our study*

Subjects	Value
Gender (male)	35 (54.7%)
Birth weight < 2,5 kg (LBW)	15 (27.8%)
Mean birth weight (kg)	3,35 ± 0.42
Positive CPR	13 (24.1%)
Ventilator requirement	9 (16.6%)
Acute renal failure present	22 (40.74%)

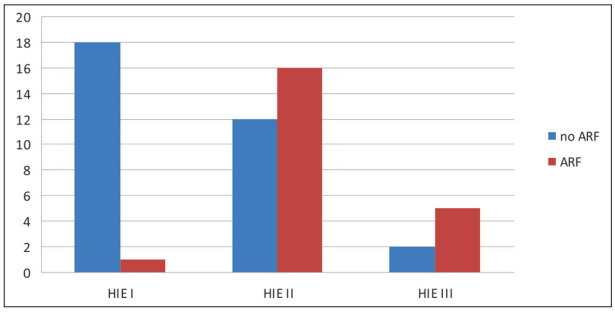


Figure 1. *Incidence of ARF in correlation to a degree of HIE*

ARF was highest in the neonates with HIE III (85.71%). (Figure 1). This showed that as HIE stage progressed, more renal dysfunction was seen in asphyxiated babies and this difference in incidence was found statistically significant ($p < 0.05$). The mean values of serum values of urea, creatinine, Na and K are shown in Table 2.

Table 2. *Urea, creatinine, Na and K levels correlated with HIE staging*

HIE staging	N	Blood urea (mg/dl) Mean SD	P value (between stage I, II, III by Anova test)	Serum creatinine (mg/dl) Mean SD	P value (between stage I, II, III by Anova test)	Serum Na (mmol/l) Mean SD	P value (between stage I, II, III by Anova test)	Serum K (mmol/l) Mean SD	P value (between stage I, II, III by Anova test)
I	19	27.4 ± 19.2	P < 0.05	10.10 ± 0.25	P < 0.05	131.65 ± 2.15	P < 0.05	4.4 ± 0.23	P < 0.05
II	28	46 ± 19.1		1.55 ± 0.24		132.45 ± 2.35		5.8 ± 0.36	
III	7	67.3 ± 22.1		2.17 ± 0.36		136.65 ± 1.72		6.2 ± 0.43	
Total	54	41.7 ± 22.8		1.52 ± 0.46		132.65 ± 2.25		4.5 ± 0.4	

FeNa (fractional excretion of sodium) >2.5% was considered as an indicator of intrinsic renal failure.

$$\text{Fractional Excretion of Na} = \frac{\text{Urinary Na x Plasma Creatinine}}{\text{Plasma Na x Urinary Creatinine}}$$

Incidence of pre-renal renal failure was 13/22 (59.09%) while of intrinsic renal failure was 9/22 (40.91%).

DISCUSSION

PA is an insult during the intrauterine or immediate extrauterine period to the fetus or the newborn due to hypoxic and/or ischemic damage to various organs of greater magnitude which leads to transitory or permanent functional and biochemical changes. Hypoxia and ischemia can result in impairment of every tissue and organ of the body, kidneys are extremely sensitive to oxygen deprivation. Neonates are more susceptible to acute kidney injury because they have low glomerular filtration rate, high renal vascular resistance, high plasma renin activity and decreased reabsorption of sodium in the proximal tubules. Renal insufficiency can manifest within 24 hours of a hypoxic ischemic episode, and if prolonged, may even lead to irreversible cortical necrosis (4). Difficulties in serum creatinine interpretation make it more difficult to achieve a consensus regarding ARF definition (3, 5). Recent studies recognize that even small increments in serum creatinine levels increase morbidity and mortality (6, 7, 8). Studies by Jayshree (9), Nouri (10) and Gupta (2) chose the cut-off level of 90 ìmol / l for serum creatinine at 48 hours of life. We took the cut-off of 133 ìmol / l for creatinine at 72 hours of life.

In our study, incidence of ARF was 40.74% in asphyxiated babies. This is well matched with earlier studies (2, 9, 10).

The presence of PA and its severity significantly correlated with increasing incidence of ARF (4.5). Our study noted a 13.5 fold increase risk of developing ARF in HIE III compared to HIE I. ARF was the highest in the neonates with HIE III (71.43%) and the lowest in the neonates with HIE I (5.26%). The higher degree of HIE was also statistically significantly associated with oliguric type of ARF in comparison to non-oliguric type of ARF. This is also concordant to earlier studies (2, 9, 10).

CONCLUSION

Neonates with severe PA had more frequent ARF. The predominant type of renal involvement was non oliguric. Neonates with HIE stage II and III had significantly higher incidence of ARF. The most of the neonates with oliguric ARF had severe PA.

Abbreviations

ARF — acute renal failure
HIE — hypoxic-ischaemic encelopathy
PA — perinatal asphyxia
SD — standard deviation

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Sažetak

AKUTNA BUBREŽNA INSUFICIJENCIJA KOD NOVOROĐENČADI KAO POSLEDICA PERINATALNE ASFIKSIJE

Hadžimuratović Emina,[1] Skokić Fahrija,[2] Hadžimuratović Adnan,[1]
Hadžipašić Nazdrajić Amra,[3] Mujić Midhat,[1] Hadžimuratović Admir[1]

[1] Univerity Medical Center Sarajevo, Bosnia and Herzegovina
[2] University Medical Center Tuzla, Bosnia and Herzegovina
[3] Public Institution Health Centre of Sarajevo Canton, Sarajevo, Bosnia and Herzegovina

Uvod: Perinatalna asfiksija (PA) rezultuje hipoksičkim ostećenjima skoro svih organa, među kojima je bubreg najčešće zahvaćen (40%).

Cilj: Cilj rada je da se utvrdi incidenca akutne bubrežne insuficijencije (ARF) kod donešenih neonatusa sa PA i da se napravi korelacija sperinatalne asfiksije i težine hipoksično ishemijske encefalopatije (HIE9).

Materijal i metode: Ova prospektivna studija obuhvatila je 44 donešena neonatusa sa PA i izvedena je u tercijarnoj ustanovi neonatalne intenzivne nege na Pedijatrijskoj klinici u Sarajevu od juna 2014. do juna 2016. godine. Težina PA je definisiana kao 5.ominutni Apgar skor; 3 i umereni PA kao 5.ominutni Apgar skor 4-6. Kriterijumi koji su uzeti u obzi za ARF su bili se-

rumski kreatinin: 1.5 mg/dl (:133 mikromol/lL) trećeg dana života ili uzlučivanje urina; 0.5 ml/kg/sat na preko 6 sati u okviru prvih 24 sata života.

Rezultati: Od 54 neonatusa sa PA, 22 (40,74%) su imali ARF. Većina njih (63,6%) su imali neoliguričan oblik ARF sa srednjim bubrežnim izlučivajem u vrednosti od 2.2 ± 0.5 ml/kg/h. 8 neonatusa (36,4%) je imalo oliguričan oblik ARF sa srednjim bubrežnim izlučivanjem 0.35 ± 0.6 ml/kg/h. Većina neonatusa oliguričnog oblikom ARF (63,4%) je imala ozbiljnu PA, dok kod onih sa neoliguričnim oblikom ARF, umerena PA je bila predominantna. ARF je bio najviši kod neonatusa sa HIE III (85.71%) (Fig. 1). Možemo zaključiti da HIE progredira, više je zahvaćena renalna disfunkcija, koja je bila zabeležena kod beba sa asfiksijom i ova razlika u incidenci je bila statistički značajna.

Zaključak: Neonatusi sa ozbiljnim PA su imali češće izraženu ARF i to neoligurični tip. Neonatusi sa HIE stadijuma II i III su imali visoko značajnu incidencu ARF.

Ključne reči: perinatalna asfiksija, akutna bubrežna insuficijencija, HIE gradiranje, oliguria.

REFERENCES

1. American College of Obstetrics and Gynecology, Task Force on Neonatal Encephalopathy and Cerebral Palsy, American Academy of Pediatrics. Neonatal Encephalopathy and Cerebral Palsy: Defining the Pathogenesis and Pathophysiology. Edited by Washington, DC, American College of Obstetricians and Gynecologists, 2003.

2. Gupta BD, Sharma P, Bagla J, Parakh M, Soni JP. Renal failure in asphyxiated neonates. Indian pediatr. 2005; 42(9): 928–34.

3. Bhatnagar A, Bairwa AL, Meena KC. Incidence of acute kidney injury in perinatal asphyxia and its correlation with hypoxic ischemic encephalopathy (HIE) staging. Paripex Indian Journal of Research. 2014; 3(3): 12–3.

4. John P. Cloherty ECE, Ann R. Stark. Manual of neonatal care. 6th edition. Phildelphia: Lippincott Williams & Wilkinsn; 2007.

5. Gopal G. Acute kidney injury (AKI) in perinatal asphyxia. Indian J Pharm Biol Res. 2014; 2(2): 60–5.

6. Mohan PV, Pai PM. Renal insult in asphyxia neonatorum. Indian Pediatr. 2000; 37(10): 1102–6.

7. Karlowicz MG, Adelman RD. Non oliguric and oliguric acute renal failure in asphyxiated term neonates. Pediatr Nephrol. 1995;9(6):718-22. 8. Pejovic B, Peco-Antic A, Dunjic R. Acute oliguric renal failure in hypoxic neonates born at full term. Srp Arh Celok Lek. 2002; 130(11–12): 367–70.

9. Jayashree G, Dutta AK, Sarna MS, Saili A. Acute renal failure in asphyxiated newborns.Indian Pediatr. 2011; 28(1): 19–23.

10. Nouri S, Mahdhaoui N, Beizig S, Zakhama R, Salem N, Ben Dhafer S, et al. Acute renal failure in full term neonates with perinatal asphyxia. Prospective study of 87 cases. Arch Pediatr. 2008; 15(3): 229–35.

Correspondence to / Autor za korespondenciju
Emina Hadžimuratović
Klinički centar Univerziteta u Sarajevu, Pedijatrijska klinika
Patriotske lige 81, 71 000 Sarajevo, Bosna i Hercegovina
email: eminahadzimuratovic@yahoo.com,
tel. + 387 33 566 438
fax. + 387 33 566 525

SANAMED
2017; 12(1): 15–19
ISSN-1452-662X

DOI: 10.24125/sanamed.v1i1.174
UDK: 616.1-02-053.6; 613.25-053.6
ID: 231307788
Original article

PREDICTORS OF CAROTID INTIMA MEDIA THICKNESS IN OBESE ADOLESCENTS

Paripović Dušan,[1] Vukomanović Goran,[2] Čivčić Milorad,[3] Peco-Antić Amira[1, 4]

[1] Nephrology Department, University Children's Hospital, Belgrade, Serbia
[2] Cardiology Department, University Children's Hospital, Belgrade, Serbia
[3] Clinic for Endocrinology, Diabetes and Metabolic Disorders, Clinical Centre of Serbia, Belgrade, Serbia
[4] School of Medicine, University of Belgrade, Belgrade, Serbia

Primljen/Received 31. 01. 2017. god. Prihvaćen/Accepted 20. 03. 2017. god.

Abstract: Our aim was to assess cardiovascular risk factors that may predict increased carotid intima media thickness (cIMT) in obese children and adolescents. Children and adolescents were included in the cross-sectional study if they were aged 9-19 years and had primary obesity. Besides anthropometric and biochemical measurements, ambulatory blood pressure monitoring, measurement of carotid intima media thickness and exercise stress test were performed. We included 103 obese patients and divided them according to the ambulatory blood pressure findings in two groups: obese patients with and without ambulatory hypertension. There were 49 obese patients with and 54 without ambulatory hypertension Univariate analysis showed that there was a significant positive correlation of cIMT with age (r = 0.334, p= 0.001), body mass index (r = 0.288, p = 0.004), waist circumference (r = 0.352, p = 0.000), hip circumference (r = 0.288, p = 0.004), night-time systolic blood pressure (r = 0.226, p = 0.027), and peak diastolic blood pressure on exercise test (r = 0.241, p = 0.018). In a stepwise model, age, waist circumference and peak diastolic blood pressure on exercise test were independent predictors of cIMT.

Key words: Ambulatory blood pressure monitoring, Hypertension, Obesity, Intima media thickness, Exercise stress test.

INTRODUCTION

Epidemy of obesity lead to rise in prevalence of arterial hypertension (1). Rise in the number of children with hypertension will lead to increased number of complications. Clinical significance of hypertension is in effect of blood pressure on cardiovascular systemleading to left ventricular hypertrophy and increased carotid intima media thickness (cIMT). Long term effect of elevated blood pressure results in pathologic remodeling of arterial blood vessels with increased cIMT (2). Increased cIMT can predict increased risk of stroke and myocardial infarction in adults (3).

Our aim was to ascertain cardiovascular risk factors that may predict increased cIMT in obese children and adolescents.

PATIENTS AND METHODS

Cross-sectional study was performed at University Children's Hospital between October 2008. and June 2014. Children and adolescents were included in the study if they were aged 9-19 years and had primary obesity. Exclusion criteria was secondary hypertension, which was diagnosed according to recomended investigations of hypertension in children (4).

The study was approved by the hospital Ethics committee. Written informed consent from parents and written assent from subjects were obtained.

Office blood pressure (BP)

The average of three office BP measurements using a mercury sphygmomanometer was used for analysis. Measurements were taken after at least 5 minutes of rest with an appropriate cuff size. To control for the differences in age and body size, BP index was calculated for each patient as mean office BP divided with 95th percentile for age, gender and height (4). Office hypertension was determined when indexed office systolic and/or diastolic BP was ≥ 1.

Ambulatory blood pressure monitoring (ABPM)

All ABPM measurements were obtained on an outpatient basis using an oscillometric device (Space-

Lab 90217, Seattle, WA, USA). BP index was calculated (mean BP > 95th percentile for gender and height) for 24-hour, daytime and night-time BP according to the data from the European multicenter study (5). Ambulatory hypertension was defined as mean day-time systolic or diastolic BP index ≥ 1 or BP load above 25%.

Measurement of carotid intima media thickness

Measurement of carotid intima media thickness was performed according to standardiyed protocol on ultrasound device Simens Acuson x300 Ultrasound System (Siemens Medical Solutions, Mountain View, CA, USA). Radiologist was not aware of the blood pressure status of the patient. Patients were seating 10 minutes prior to measurement. Longitudinal view in B mode of distal carotid artery was scanned with linear probe. cIMT was measured at 1 cm proximal to bifurcation. Mean value of six measurements was used for further analysis. We used reference values of cIMT acquired in a study of 247 healthy children (6).

Exercise stress test

Exercise stress test was performed on a Schiller Cardiovit Ergo-Spiro CS-200 treadmill (Schiller AG, Baar, Switzerland) according to the modified Bruce protocol (7). Blood pressure and heart rate were measured before test, during maximal exercise, and after the test. The test was stopped when the subjects refused to continue despite encouragement.

Data analysis

Descriptive statistics are expressed as percentages or means ± SD. Continuous variables were tested for normal distribution by the Shapiro-Wilk test. Chi-square test was used to compare dichotomous variables between groups. Univariate regression analysis was used to investigate the relationships between cIMT and anthropometric, biochemical, and BP-related parameters among obese subjects. All parameters that had significant correlation with cIMT were included in stepwise multiple linear regression model. Stepwise multiple linear regression analysis was used to determine independent predictors of cIMT. Statistical significance was assumed at $p < 0.05$. Data were analyzed using SPSS version 13 (SPSS, Chicago, IL).

RESULTS

We included 103 obese patients referred for ambulatory blood pressure monitoring (ABPM) in the study. Patients were divided according to the ABPM findings in two groups: obese patients with and without ambulatory hypertension. The anthropometric and blood pressure characteristics of 103 obese patients classified according to ambulatory BP levels are described in Table 1. Age and gender were not significantly different between the two groups. There were no significant differences in anthropometric characteristics, exercise stress test, cIMT or biochemical results between the groups (Table 1 and 2).

Stepwise multiple regression analysis was performed to investigate the independent predictors of cIMT

Table 1. *Anthropometric characteristics, exercise stress test and intima media thickness*

	Obese with hypertension (n = 49)	Obese without hypertension (n = 54)
Gender (male %)	67.3	72.2
Age (years)	14.1 ± 2.0	14.1 ± 2.3
BMI (kg/m^2)	29.4 ± 3.2	30.0 ± 3.8
Waist circumference (cm)	95.5 ± 8.8	98.1 ± 10.3
Hip circumference (cm)	99.4 ± 9.5	102.6 ± 10.6
Resting heart rate (bpm)	86 ± 10	89 ± 14
Systolic BP at maximum exercise (mmHg)	187 ± 19	183 ± 16
Diastolic BP at maximum exercise (mmHg)	57 ± 10	56 ± 8
Heart rate at maximum exercise (bpm)	187 ± 7	187 ± 7
Intima media thickness	0.43 ± 0.05	0.44 ± 0.05

[a] $p < 0.05$ between obese with hypertension (OHT) and obese without hypertension (ONT)
BMI, body mass index; BP, blood pressure

Table 2. *Biochemical results of the study groups*

	Obese with hypertension	Obese without hypertension
Urea (mmol/L)	4.1 ± 0.9	4.2 ± 1.0
Creatinine (ìmol/L)	75.7 ± 14.7	77.8 ± 16.4
Ac. uricum (mmol/L)	328.8 ± 61.6	360.6 ± 89.6
Sodium (mmol/L)	140.0 ± 1.8	140.3 ± 1.6
Potassium (mmol/L)	4.4 ± 0.3	4.3 ± 0.3
CRP (mg/L)	2.9 ± 2.2	4.8 ± 9.2
HOMA-IR	3.6 ± 2.0	3.9 ± 1.8
Triglyceride (mmol/L)	1.2 ± 0.6	1.1 ± 0.6
Total cholesterol (mmol/L)	4.3 ± 1.1	4.3 ± 0.9
HDL cholesterol (mmol/L)	1.1 ± 0.2	1.1 ± 0.3
LDL cholesterol (mmol/L)	2.6 ± 1.1	2.7 ± 0.8

[a] $p < 0.05$ between obese with hypertension (OHT) and obese without hypertension (ONT)
CRP, C reactive protein
HOMA-IR, homeostasis model assessment of insulin resistance

Table 3. *Best model for determining independent predictors of cIMT in obese children and adolescents (adjusted $R^2 = 0.192$, $p < 0.001$)*

Independent variable	ß	95% CI	p
Waist circumference (cm)	0.223	0.007-0.237	0.038
Peak diastolic blood pressure on exercise test (mmHg)	0.241	0.033-0.241	0.011
Age (years)	0.243	0.079-1.142	0.025

in obese subjects. Univariate analysis showed that there was a significant positive correlation of cIMT with age (r = 0.334, p= 0.001), body mass index (r = 0.288, p = 0.004), waist circumference (r = 0.352, p = 0.000), hip circumference (r = 0.288, p = 0.004), night-time systolic blood pressure (r = 0.226, p = 0.027), and peak diastolic blood pressure on exercise test (r = 0.241, p = 0.018). Hence, these variables were included as potential predictors of cIMT in a stepwise multiple regression analysis. In a stepwise model, age, waist circumference and peak diastolic blood pressure on exercise test were independent predictors of cIMT (Table 3). Carotid IMT was not correlated with casual BP or with any of the ABPM parameters.

DISCUSSION

Arterial hypertension is one of the most important cardiovascular risk factors. It is observed that even slight changes in blood pressure levels might cause significant change in hypertension-induced morbidity (8). Consequently, additional survey of blood pressure status in childhood could improve future cardiovascular health of adults. Hence, blood pressure measurement is recommended as essential part of pediatric exam (4). ABPM is considered as superior method in comparison to casual blood pressure measurement as it can better predict hypertension induced target organ damage (9).

Primary hypertension has become the dominant form of hypertension in adolescents due to escalation of obesity. Hypertension is also the most important modifiable risk factor for atherosclerosis. Therefore, a notion that pediatric hypertension often remains undiagnosed deserves closer attention (10).

Our study did not find significant differences in exercise stress test results between obese subjects with and without hypertension. This could be explained with early stopping of exercise stress test in obese subjects.

Obesity is well established independent predictor of cardiovascular diseases in adults (11). In addition to effect via metabolic, endocrine and inflammatory parameters known to increase risk of cardiovascular diseases, obesity also has a direct influence on alterations in structure and function of blood vessels (12).

Previously it was considered that obese children and adolescents are population less prone to cardiovascular diseases. However, a recent report declared that cardiovascular damage associated with obesity occurs even in childhood (13). In comparison with children who lived between 1986. and 1989, modern youth has increased cardiovascular risk (14). Given the increased prevalence of obesity in XXI century this seems to be common issue of health care systems around the world.

Carotid IMT measurement allows noninvasive detection of early arteriosclerotic changes (15). Preclinic form of cardiovascular diseases may last for decades, hence detection of disease in presymptomatic phase during childhood allows timely management (16). The most important predictive risk factors of cIMT in children with primary hypertension were systolic and pulse pressure (17, 18).

Previous investigations performed in children with primary hypertension did not find correlation of office blood pressure measurement and cIMT, but there was a significant correlation between cIMT and several parameters of ABPM (19), such as day-time systolic blood pressure load and day-time systolic blood pressure index, which are parameters of hypertension severity. Our results revealed correlation of cIMT and night-time systolic blood pressure.

Sorof showed that cIMT was directly correlated with BMI and left ventricular mass index in children with primary hypertension (2). Since obesity may occur prior to overt hypertension (20), obese children have increased risk for future cardiovascular complications. In obese children cIMT was associated with BMI, systolic blood pressure, fasting glucose level, HOMA resistance index, basal insulin, resistin and decrease of adiponectin level. When adjusted for gender and BMI, only adiponectin level remained as independent predictor of cIMT (21).

In contrast to previous studies in children and adults (22, 23), our findings revealed correlation of cIMT in obese children with with age, body mass index, waist circumference, hip circumference, night-time systolic blood pressure, and peak diastolic blood pressure on exercise test.

According to literature review, association of cIMT with blood pressure parameters during exercise test was not investigated. Our findings indicate that peak diastolic blood pressure on exercise test, in addition to age and waist circumference, is predictor of cIMT.

Previous research established association of obesity and cIMT (24,25,26). Obese children have increased cIMT compared with normal weight children independent of blood pressure influence (27). Correlation between cIMT and waist circumference is in concert with previous results, which noted the importance of

central obesity in children as an independent cardiovascular risk factor.

It is still not clear how structural changes of blood vessel evolve with aging of obese adolescents. Future longitudinal investigations should analyze progression of cardiovascular disorders, their influence on health and future structure and function of blood vessels.

CONCLUSION

In conclusion, age, waist circumference, and peak diastolic blood pressure on exercise test may predict cIMT in obese children and adolescents.

Abbrevations

cIMT — carotid intima media thickness
BP — blood pressure
ABPM — Ambulatory blood pressure monitoring
BMI — body mass index

ACKNOWLEDGEMENT

The study was supported by the Ministry of Science and Environmental Protection, Government of Serbia, Grants no. 175079.

Conflict of interest

The authors declare that there are no conflicts of interest.

Sažetak

PREDIKTORI DEBLJINE INTIME I MEDIJE KAROTIDNIH ARTERIJA KOD GOJAZNIH ADOLESCENATA

Paripović Dušan,[1] Vukomanović Goran,[2] Čivčić Milorad,[3] Peco-Antić Amira[1, 4]

[1] Odeljenje za nefrologiju, Univerzitetska dečija klinika, Beograd, Srbija
[2] Odeljenje za kardiologiju, Univerzitetska dečija klinika, Beograd, Srbija
[3] Klinika za endokrinologiju, dijabetes i bolesti metabolizma, Klinički centar Srbije, Beograd, Srbija
[4] Medicinski fakultet Univerziteta u Beogradu, Beograd, Srbija

Cilj rada je ispitati faktore rizika kardiovaskularnih oboljenja (biohemijski parametri, vrednost krvnog pritiska) koji utiču na povećanje debljine intime i medije karotidnih arterija (cIMT) kod gojazne dece i adolescenata. U studiju preseka su uključeni deca i adolescenti koji su ispunjavali kriterijume za ulazak ispitanika u studiju: uzrast od 9 do 19 godina i primarna gojaznost. Pored antropometrijskih i biohemijskih merenja učinjena su sledeća ispitivanja: merenje krvnog pritiska 24-časovnim ambulatornim merenjem, ultrasonografsko određivanje debljine intime i medije karotidnih arterija, i test opterećenja fizičkim naporom. U ispitivanje je uključeno 103 gojazna pacijenta koji su prema vrednostima krvnog pritiska pri ambulatornom monitoringu podeljeni u 2 grupe – gojazni pacijenti sa hipertenzijom i gojazni pacijenti bez hipertenzije. Grupu gojaznih pacijenta sa hipertenzijom činilo je 49 ispitanika, dok je u grupi gojaznih pacijenata bez hipertenzije bilo 54 ispitanika. Pronađena je statistički značajna korelacija cIMT sa uzrastom (r = 0,334, p= 0,001), indeksom telesne mase (r = 0,283, p = 0,005), obimom struka (r = 0,352, p = 0,000), obimom kukova (r = 0,288, p = 0,004), noćnim sistolnim krvnim pritiskom (r = 0,226, p = 0,027), i dijastolnim krvnim pritiskom pri maksimalnom opterećenju pri testu opterećenja fizičkim naporom (r = 0,241, p = 0,018). Multipla linearna regresija je pokazala da su uzrast, obim struka, i dijastolni krvni pritisak pri maksimalnom opterećenju nezavisni prediktori cIMT.

REFERENCES

1. Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ. Overweight, ethnicity, and the prevalence of hypertension in school-aged children. Pediatrics. 2004; 113(3 Pt1): 475–82.

2. Sorof JM, Alexandrov AV, Cardwell NG, Portman RJ. Carotid intima-media thickness and left ventricular hypertrophy in children with elevated blood pressure. Pediatrics.2003; 111(1): 61–6.

3. Zielinski T, Dzielinska A, Januszewicz A, Rynkun D, Makowiecka Ciesla M, Tyczynski P, et al. Carotid intima-media thickness as a marker of cardiovascular risk in hypertensive patients with coronary disease. Am J Hypertens. 2007; 20(10): 1058–64.

4. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004; 114 (2 Suppl 4th Report): 555–76.

5. Soergel M, Kirschstein M, Busch C, Danne T, Gellermann J, Holl R, et al. Oscillometric twenty-four-hour ambulatory blood pressure values in healthy children and adolescents: a

multicenter trial including 1141 subjects. J Pediatr. 1997; 130(2): 178–84.

6. Jourdan C, Wuehl E, Litwin M, Fahr K, Trelewicz J, Jobs K, et al. Normative values of intima-media thickness and distensibility of large arteries in healthy adolescents. J Hypertens.. 2005; 23(9): 1707–15.

7. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J. 1973; 85(4): 546–62.

8. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med. 1998; 338(23): 1650–6.

9. Maggio AB, Aggoun Y, Marchand LM, Martin XE, Herrmann F, Beghetti M, et al. Associations among obesity, blood pressure, and left ventricular mass. J Pediatr. 2008; 152(4): 489–93.

10. Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of hypertension in children and adolescents. JAMA. 2007; 298(8): 874–9.

11. Hubert HB, FeinIeib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular diseases: a 26-year of follow-up of participants in the Framingham Heart Study. Circulation. 1983; 67(5): 968–77.

12. Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Mäki-Torkko N, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA. 2003; 290(17): 2277–83.

13. Cote AT, Harris KC, Panagiotopoulos C, Sandor GG, Devlin AM. Childhood obesity and cardiovascular dysfunction. J Am Coll Cardiol. 2013; 62(15): 1309–19.

14. Crowley DI, Khoury PR, Urbina EM, Ippisch HM, Kimball TR. Cardiovascular impact of the pediatric obesity epidemic: higher left ventricular mass is related to higher body mass index. J Pediatr. 2011; 158(5): 709–14.

15. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation. 1997; 96(5): 1432–7.

16. Urbina EM, Williams RV, Alpert BS, Collins RT, Daniels SR, Hayman L, et al. Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American Heart Association. Hypertension. 2009; 54(5): 919–50.

17. Sorof JM, Alexandrov AV, Garami Z, Turner JL, Grafe RE, Lai D, et al. Carotid ultrasonography for detection of vascular abnormalities in hypertensive children. Pediatr Nephrol. 2003; 18(10): 1020–4.

18. Litwin M, Niemirska A, Sladowska J, , Antoniewicz J, Daszkowska J, Wierzbicka A, et al. Left ventricular hypertrophy and arterial wall thickening in children with essential hypertension. Pediatr Nephrol. 2006; 21(6): 811–9.

19. Lande MB, Carson NL, Roy J, Meagher CC. Effects of childhood primary hypertension on carotid intima media thickness: a matched controlled study. Hypertension. 2006; 48(1): 40–4.

20. Sakarcan A, Jerrell J. Population-based examination of the interaction of primary hypertension and obesity in South Carolina. Am J Hypertens. 2007; 20(1): 6–10.

21. Pilz S, Horejsi R, Moller R, Almer G, Scharnagl H, Stojakovic T, et al. Early atherosclerosis in obese juveniles is associated with low serum levels of adiponectin. J Clin Endocrinol Metab. 2005; 90(8): 4792–6.

22. Martino F, Loffredo L, Carnevale R, Sanguigni V, Martino E, Catasca E, et al. Oxidative stress is associated with arterial dysfunction and enhanced intima-media thickness in children with hypercholesterolemia: the potential role of nicotinamide-adenine dinucleotide phosphate oxidase. Pediatrics. 2008; 122(3): e648–55.

23. Ashfaq S, Abramson JL, Jones DP, Rhodes SD, Weintraub WS, Hooper WC, et al. The relationship between plasma levels of oxidized and reduced thiols and early atherosclerosis in healthy adults. J Am Coll Cardiol. 2006; 47(5): 1005–11.

24. Reinehr T, Kiess W, de Sousa G, Stoffel-Wagner B, Wunsch R. Intima media thickness in childhood obesity: relations to inflammatory marker, glucose metabolism, and blood pressure. Metabolism. 2006; 55(1): 113–8.

25. Retnakaran R, Zinman B, Connelly PA, Harris SB, Hanley AJ. Non-traditional cardiovascular risk factors in pediatric metabolic syndrome. J Pediatr. 2006; 148(2): 176–82.

26. Meyer AA, Kundt G, Steiner M, Schuff-Werner P, Kienast W. Impaired flow-mediated vasodilation, carotid intimamedia thickening and elevated endothelial plasma markers in obese children: the impact of cardiovascular risk factors. Pediatrics. 2006; 117(5): 1560–7.

27. Stabouli S, Kotsis V, Karagianni C, Zakopoulos N, Konstantopoulos A. Blood pressure and carotid artery intima-media thickness in children and adolescents: the role of obesity. Hellenic J Cardiol. 2012; 53(1): 41–7.

Correspondence to / Autor za korespondenciju
Dušan Paripović
Nephrology Department, University Children's Hospital,
Tiršova 10, 11 000 Belgrade, Serbia
e-mail: dusanparipovic73@gmail.com
Phone: 011 2060705

SANAMED
2017; 12(1): 21–25
ISSN-1452-662X

DOI: 10.24125/sanamed.v1i1.178
UDK: 616.858:616.89-008.454; 616.858:616.892.3
ID: 231291916
Original article

DEPRESSION IN PATIENTS WITH PARKINSON'S DISEASE WITH DEMENTIA

Perovic Zlatana,[1] Cukic Mirjana[2]

[1] Neurology department, General Hospital Niksic, Montenegro
[2] Department of Neurology, University Clinical Center of Montenegro, Podgorica, Montenegro

Primljen/Received 10. 02. 2017. god.

Prihvaćen/Accepted 24. 03. 2017. god.

Abstract: **Introduction:** Parkinson's disease is a multisystem disorder which is characterized by a combination of motor and non-motor symptoms. Non-motor symptoms include: depression, cognitive impairment, autonomic and sensor symptoms. It is difficult to detect and treat depression symptoms in patients with Parkinson's disease with dementia. Early identification and treatment of depression symptoms can greatly improve the quality of life in these patients, as well as facilitate the quality of caregivers' lives.

Goal of the paper: The aim of our research was to evaluate frequency of depression occurrence in patients with Parkinson's disease with cognitive impairment.

Patients and methods: We did a prospective study which included 59 PD patients, who came for a regular check-up to Neurological infirmary of the General Hospital in Niksic, in the interval from 1st January 2016to 31st December 2016, all of whom were previously diagnosed with Parkinson's disease. We tested their cognitive status using the Mini Mental State Examination scale. Out of 59 patients, 32 displayed cognitive deficit and were included in further research. We gave directions about testing to guardians or caregivers of the patients who displayed moderate or distinct cognitive impairment. The testing was done on the next check-up, with Cornell's depression scale.

Results: Research showed that out of 32 patients, 5 (15.6%) didn't suffer from depression, 8 (25%) probably suffered from major depression, while 19 (59.4%) definitely suffered from major depression. On the cognitive scale, 6 (18.8%) patients had mild, 11 (34.4%) moderate and 15 (46.9%) distinct cognitive deficit. Out of 8 patients with probable depression 3 (9.4%) had mild, 3 (9.4%) had moderate and 2 (6.2%) distinct cognitive deficit. We can also: conclude that out of 19 (59.4%) with certain depression, 1 (3.1%) had mild, 5 (15.6%) had medium severe, and 13 (40.6%) had severe cognitive deficit.

Conclusion: Prevalence of depression and dementia in Parkinson's diseasepatients is high. Our patients have moderate cognitive deficit in 34.4% of the cases, and distinct cognitive deficit in 46.9% of the cases; while 59.4% definitely suffers from major depression at some point of their illness. Their early detection is of great importance for treatment and quality of life of these patients.

Keywords: depression, dementia, Parkinson disease.

INTRODUCTION

Parkinson's disease (PD) is a multisystem degenerative disorder which is characterized by a combination of motor and non-motor symptoms (1, 2). Non-motor symptoms include: depression, cognitive impairment, autonomic and sensor symptoms (2, 3). It can be very complicated to identify depression in PD patients who have cognitive impairment, for known depression scales are not reliable markers to evaluate depression (4). Dementia is present in more than 30% of PD patients, especially in those over 70 years old (5, 6). Depression and dementia are often connected comorbidities; however, depression can be considered a risk factor for dementia development in PD (7). Early depression identification and treatment can significantly improve the quality of life in PD patients, as well as facilitate the quality of caregivers' lives (7-10). Depression may appear as one of the first symptoms of PD, but it can appear many years before the beginning of motor symptoms of the illness. Dementia in PD implies impairment of executive function, attention, slow cognitive speed, recalling learned information, and visuospatial problem (11). Dementia is also a part of neurodegenerative illnesses, including PD (12-14). Prevalence of major depression in PD patients is from 2.7% to 8.2% and from 13% to 34.5% in case of minor de-

pression (14-16). Prevalence of mild cognitive impairment in PD patients is from 18.9% to 55% (17-19). PD patients with distinct cognitive deficit, who need a caregiver, form a special group. Mild cognitive deficit is present in about 35% of the patients at the beginning of motor symptoms and in about 50% of the patients after 5 years of being ill (20).

Depression is a very common in dementia as part of PD. Therefore, its early identification is of the essence in order to begin early medicament therapy, which will in the long-run improve the quality of life both of the patient and the caregiver (11, 16, 21).

PATIENTS AND METHODS

We researched presence and degree of depression in patients with Parkinson's disease with cognitive impairment.

Patients that were tested are those who came for a regular check-up to Neurological infirmary of the General Hospital in Niksic, Montenegro, in the interval from 1st January to 31st December 2016, all previously diagnosed with idiopathic Parkinson's disease.

We tested cognitive status in 59 patients with idiopathic Parkinson's disease, using the MMSE scale. Out of the 59 patients, 32 were included in the research, all of whom tested less than 23 points on the Mini Mental State Examination (MMSE). They were divided to three groups: with mild (20-23), moderate (11-19), and severe cognitive deficit (0-10 points). After the applied MMSE testing, patients or caregivers of the patients received instructions about observing the patient in the next 7 days, when the testing with the Cornell's scale for depression would be applied (13). Cornell's scale for depression was applied on patients with dementia in order to achieve a more objective assessment. The scale consists of 19 parameters which are grouped into 5 groups: mood-related signs, behavioral disturbances, physical signs, cyclic functions and ideational disturbances. Each item is rated on a scale of 0-2 (0- absent, 1- mild or intermittent, 2- severe). Score above 10 indicates probable major depression; score above 18 indicates definite major depression; score below 6 as a rule is associated with absence of significant depressive symptoms (22).

Scores are presented tabularly and in percentage. We used the Chi-square test to connect depression and cognitive impairment.

We researched the significance of the Cornell scale in detecting depression in PD patients.

Ethics Statement: The paper was approved by the Ethical committee of the hospital where we did the research, and all the patients signed the informational consent before the beginning of research.

RESULTS

Out of 32 patients with cognitive deficit, 17 (53.1%) were men and 15 (46.9%) were women (Table 1), average age of 73.03 years old (Table 2), average illness duration being 8.175 years (Table 3). Out of 32 patients included in the study, 5 (15.6%) didn't suffer from depression, 8 (25%) probably suffered from depression, while 19 (59.4%) definitely suffered from major depression. On the MMSE scale, 6 (18.8%) patients had mild, 11 (34.4%) moderate and 15 (46.9%) distinct cognitive deficit (Table 3).

Table 1. *Distribution of patients with PD and cognitive impairment in relation to gender*

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Male	17	53.1	53.1	53.1
	Female	15	46.9	46.9	100.0
	Total	32	100.0	100.0	

Table 2. *Average agepatients with PD and cognitive impairment*

The mean age was 73.03 years

Statistics		
Age		
N	Valid	32
	Missing	0
Mean		73.03

Table 3. *The average length of the disease*

Statistics		
Duration of illness		
N	Valid	32
	Missing	0
Mean		8.175

Out of 8 patients with probable depression 3 (9.4%) had mild, 3 (9.4%) had moderate and 2 (6.2%) distinct cognitive deficit. We can also conclude that out of 19 (59.4%) with certain depression, 1 (3.1%) had mild, 5 (15.6%) had moderate, and 13 (40.6%) had severe cognitive deficit (Table 4).There is a significant correlation between depression and cognitive impairment (Table 5). The size of the impact of depression on cognitive impairment is a high (Table 6).

We feel that the Cornell Scale is greatly significant in identifying depression in these patients (Table 7).

Table 4. *The incidence of depression compared to the weight of dementia:*

Analysis of the data by χ^2- test we got the results:cognitive impairment

Depression * Cognitive impairmentCrosstabulation						
			Cognitive impairment			Total
			mild	medium	severe	
Depression	no	Count	2	3	0	5
		% within depression	40.0%	60.0%	0.0%	100.0%
		% within cognitive impairment	33.3%	27.3%	0.0%	15.6%
		% of Total	6.2%	9.4%	0.0%	15.6%
	probably	Count	3	3	2	8
		% within depression	37.5%	37.5%	25.0%	100.0%
		% within cognitive impairment	50.0%	27.3%	13.3%	25.0%
		% of Total	9.4%	9.4%	6.2%	25.0%
	certainly	Count	1	5	13	19
		% within depression	5.3%	26.3%	68.4%	100.0%
		% within Cognitive impairment	16.7%	45.5%	86.7%	59.4%
		% of Total	3.1%	15.6%	40.6%	59.4%
Total		Count	6	11	15	32
		% within depression	18.8%	34.4%	46.9%	100.0%
		% within Cognitive impairment	100.0%	100.0%	100.0%	100.0%
		% of Total	18.8%	34.4%	46.9%	100.0%

Cornel scale: score > 10 probable depression, score > 18 certainly depression
MMSE scale cognitive impairment: (20-23) mild, (11-19) medium, (0-10)severe

Table 5. *The correlation between depression and cognitive impairment*

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	10.926[a]	4	.027
Likelihood Ratio	13.160	4	.011
Linear-by-Linear Association	9.508	1	.002
N of Valid Cases	32		
a. 7 cells (77.8%) have expected count less than 5. The minimum expected count is .94.			

Sig. 0027, indicating that significant correlation Yeats

Table 6. *The size of the impact of depression on cognitive impairment*

Symmetric Measures			
		Value	Approx. Sig.
Nominal by Nominal	Phi	.584	.027
	Cramer's V	.413	.027
N of Valid Cases		32	
a. Not assuming the null hypothesis.			
b. Using the asymptotic standard error assuming the null hypothesis.			

The size of the impact of the 0,413 high.

Table 7. *Cornel scale in detecting depression*

Tests of Normality						
	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Cornel scale	.100	32	.200*	.983	32	.884
Depression	.364	32	.000	.707	32	.000
*. This is a lower bound of the true significance.						
a. Lilliefors Significance Correction						

DISCUSSION

Patients with Parkinson's disease, in over 50% of the cases, suffer from significant cognitive impairment at a certain stage of the illness, which is in accordance with many previous studies (17-20). In case of our PD patients, with cognitive impairment, at a certain point of the illness, 25% probably suffer from major depression, and 59.4% definitely suffer from depression, which is more than in previously shown results in other studies (14-16).

Cornell's scale may help us in our daily work to early diagnose depression in PD patients with dementia, which is a prerequisite for early treatment of depression of these patients (22).

Minimizing the disability includes treating not just motor symptoms, but treating also dementia, depression and psychosis. Therefore, identification of clinically relevant screening and diagnostic tools for depression and cognitive impairment are necessary in PD patients (22-23).

CONCLUSION

Depression and dementia are a common problem in PD patients. Their detection is highly significant to clinical practice. PD patients with cognitive impairment present a special difficulty in identifying depression.

Abbreviations

MMSE — Mini Mental State Examination
PD — Parkinson's disease

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Licensing

Sažetak

DEPRESIJA KOD PACIJENATA SA PARKINSONOVOM BOLEŠĆU SA DEMENCIJOM

Perovic Zlatana,[1] Cukic Mirjana[2]

[1] Neurology department, General Hospital Niksic, Montenegro
[2] Department of Neurology, University Clinical Center of Montenegro, Podgorica, Montenegro

Uvod: Parkinsonova bolest je multisistemski poremećaj koji se karakteriše kombinacijom motornih i nemotornih simptoma. Nemotorni simptomi su depresija, kognitivno oštećenje, autonomni i senzorni simptomi. Otkrivanje i lečenje depresije je otežavajuće kod pacijenata sa Parkinsonovom bolešću i demencijom. Rano prepoznavanje i lečenje simptoma depresije može značajno poboljšati kvalitet života ovih pacijenata, ali i olakšati kvalitet života i negovatelja.

Cilj rada: Cilj našeg istraživanja bio je da se proceni učestalost depresije kod pacijenata sa Parkinsonovom bolešću sa kognitivnim oštećenjem.

Metod rada: Sproveli smo prospektivnu studiju koja je uključila 59 pacijenata sa PB koji su se javili na redovni pregled u Neurološku ambulantu Opšte bolnice Nikšić u Crnoj Gori, u periodu od 01. 01. 2016. do 31. 12. 2016. g, kod kojih je ranije postavljena dijagnoza Parkinsonove bolesti. Kognitivni status pacijenata smo testirali pomoću Minimental skale. Od ukupno 59 pacijenata, 32 su na ovoj skali pokazali kognitivni deficit i uključeni su u dalje istaživanje. Kod pacijanata koji su pokazali umereno ili izraženo kognitivno oštećenje dali smo uputstva o testiranju starateljima ili negovateljima pacijenata. Na narednoj kontroli, je testiranje urađeno Korlenovom skalom za depresiju.

Rezultati: Od 32 pacijenta sa kognitivnim deficitom, 17 (53,1%) su bili muškarcii 15 (46,9%) žene, prosečne starosti 73,03 godina, sa prosečnom dužinom trajanja bolesti od 8,175 godina. Istraživanje je pokazalo da od 32 pacijenta 5 (15,6%) nema depresiju, 8 (25%) verovatno ima veliku depresiju, dok 19 (59,4%) sigurno ima veliku depresiju. Na MMSE skali 6 (18,8%) pacijenata su imali blagi, 11 (34,4%) umereni i 15 (46,9%) izraženi kognitivni deficit. Od 8 pacijenata sa verovatnom depresijom 3 (9,4%) ima blagi, 3 (9,4%) srednjii 2 (6,2%) izraženi kognitivni deficit. Takođe se može zaključiti da od 19 (59,4%) sa sigurnom depresijom 1 (3,1%) ima blagi, 5 (15,6%) ima srednje teškii 13 (40,6%) teški kognitivni deficit.

Zaključak: Učestalost depresije i demencije kod obolelih od Parkinsonove bolesti je visoka. Naši pacijenti imaju u 34,4% umereni i u 46,9% izražen kognitivni deficit, dok 59,4% ima sigurno depresiju u nekom trenutku bolesti. Njihovo rano otkrivanje je od velikog značaja za lečenje i kvalitet života ovih pacijenata.

Ključne reči: depresija, demencija, Parkinsonova bolest.

REFERENCES

1. Lang AE, Lozano AM.Parkinson's disease.First of two parts. N Engl J Med. 1998; 339 (15): 1044–53.

2. Stacy M. Nonmotor symptoms in Parkinson's disease. Int J Neurosci. 2011; 121(2): 9–17.

3. Zweig RM, Disbrow EA, Javalkar V. Cognitive and psychiatric disturbances in Parkinsoniansyndromes. Neurologic clinics. 2016; 34(1): 235–46.

4..Torbey E, Pachana NA, Dissanavaka NN. Depression rating scales in Parkinson's disease: A critical review updating recent literature. J affect disord. 2015; 184: 216–24.

5. Aarsland D, Tandberg E, Larsen JP, Cummings JL. Frequency of dementia in Parkinson disease. Arch Neurol. 1996; 53(6): 538–42.

6. Biggins CA, Boyd JL, Harrop FM, Madeley P, Mindham RH, Randall JI et al.A controlled, longitudinal study of dementia in Parkinson's disease.J NeurolNeurosurg Psychiatry. 1992; 55(7): 566–71.

7. Rickards H. Depression in neurological disorders: an update. Curr Opin Psychiatry. 2006; 19(3): 294–8.

8. Lim SY, Fox SH, Lang AE. Overview of the extranigral aspects of Parkinson disease. Arch Neurol. 2009; 66(2): 167–72.

9. Weintraub D, Stern MB.Psychiatric complications in Parkinson disease. Am J Geriatr Psychiatry. 2005; 13(10): 844–51.

10. Schrag A. Quality of life and depression in Parkinson's disease. J Neurol Sci. 2006; 248(1–2): 151–7.

11. Baquero M, Martin N.Depressive symptoms in neurodegenerative diseases. World J Clin Cases. 2015; 3(8): 682–93.

12. Caballol N, Marti MJ, Tolosa E. Cognitive dysfunction and dementia in Parkinson disease. Mov Disord. 2007; 22 (17): 358–66.

13. Hancock P, Larner AJ. Cornell Scale for Depression in Dementia: clinical utility in a memory clinic. Int J Psychiatry ClinPract. 2015; 19(1): 71–4.

14. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Recognition and treatment of depression in Parkinson's disease. J Geriatr Psychiatry Neurol. 2003; 16(3): 178–83.

15. Costa A, Peppe A, Carlesimo GA, Pasqualetti P, Caltagirone C. Alexithymia in Parkinson's disease is related to severity of depressive symptoms. Eur J Neurol. 2006; 13(8): 836–41.

16. Grover S, Somaiya M, Kumar S, Avasthi A. Psychiatric aspects of Parkinson's disease. J Neurosci Rural Pract. 2015; 6(1): 65–76.

17. Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson disease. J Neurol Sci. 2010; 289(1–2): 18–22.

18. Caviness JN, Driver-Dunckley E, Connor DJ, Sabbagh MN, Hentz JG, Noble B, et al. Defining mild cognitive impairment in Parkinson's disease. Mov.Disord.2007; 22(9): 1272–7.

19. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology. 2005; 65(8): 1239–45.

20. Broeders M, de Bie RM, Velseboer DC, Speelman JD, Muslimovic D, Schmand B. Evolution of mild cognitive impairment in Parkinson disease. Neurology. 2013; 81(4): 346–52.

21. Connolly B, Fox SH.Treatment of cognitive, psychiatric, and affective disorders associated with Parkinson's disease. Neurotherapeutics. 2014; 11(1): 78–91.

22. Williams JR, Marsh L. Validity of the Cornell scale for depression in dementia in Parkinson's disease with and without cognitive impairment. Movement Disorder. 2009; 24(3): 433–7.

23. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease. J Am GeriatrSoc. 2004; 52(5): 784–8.

Correspondence to/Autor za korespondenciju
Zlatana Perović MD
General Hosptal Niksic, Montenegro
Str Radoia Dakica bb, Niksic, Montenegro
Tel +382 69 351 378
Email: zlataperovic@gmail.com

SANAMED
2017; 12(1): 27–31
ISSN-1452-662X

DOI: 10.24125/sanamed.v1i1.170
UDK: 616.728.3-006.33
ID: 231277324
Case report

INTRACAPSULAR AND PARA-ARTICULAR CHONDROMA OF KNEE: CASE REPORTS

Temelkovski Zlatko,[1] Nanceva Jasminka,[1] Samardziski Milan,[1]
Nancheva Andrea,[2] Andonovski Alan[1]

[1] University Clinic for Orthopaedic Surgery, Skopje, Macedonia
[2] General Hospital "8mi Septemvri", Skopje, Macedonia

Primljen/Received 10. 01. 2017. god. Prihvaćen/Accepted 27. 02. 2017. god.

Abstract: **Introduction:** Intracapsular and Para-articular chondroma is a rare variant of the extraskeletal chondromas. It arises from the capsule and/or the para-articular connective tissue of the large joints (mostly the knee) and is a result of cartilaginous metaplasia. In the course of time these tumors ossify and this is where their second name comes from: Para-articular osteochondromas. **Case reports:** We report six new cases of para-articular chondroma of the knee. On physical examination there was slow-growing solid mass in the knee and moderate pain. The radiological findings and CT scan show soft-tissue mass with variable amount of ossification, and on histological examination the presence of mature hyaline and connective cartilage was confirmed in all of the cases. **Conclusion:** The diagnosis of these benign tumors is made with correlation of clinical, radiological and histological features. Treatment of choice is surgical excision.

Key words: Para-articular, Chondroma, Osteochondroma, Knee.

INTRODUCTION

Extraskeletal chondromas are benign tumors which appear in three variants: synovial chondromatosis, para -articular chondroma and soft tissue chondroma. The first type is very common, but the last two variants are quite rare and they may show atypical features (1, 2, 3).

The fibrous coat of the capsule of a joint and/or the para-articular connective tissue, very rare, can suffer cartilaginous metaplasia. As an end result of this metaplasia, intracapsular or para-articular chondromas are formed. In time, they usually ossify so they are also known as capsular and para- articular osteochondromas. Mostly seen in the large joints (the knee), they vary in size depending on the size of the joint (4, 5, 6, 7). We have found only 30 cases of para-articular chondromas in the reviewed literature (3, 5, 6). We report six new cases of capsular and para-articular chondroma of the knee with their clinical, radiological and histological features in the University Clinic for Orthopedic Surgery, Skopje, Macedonia in period 2007-2015.

CASE REPORTS

Case report 1

Male patient, 24 years old, reports with painful mass on the medial side of the right knee, with no record of trauma. He first noticed it one year prior to the examination. On physical examination the tumorous formation is movable, tender on palpation, produces pain during active motion. The profile X-ray shows para- and supra-patellar soft tissue tumorous formation (Figure 1A). On CT- scan this soft tissue mass is clearly seen, oval shaped and intracapsular (Figure 1B). The tumor was surgically excised. During the operation, the intracapsular but extrasynovial position of the tu-

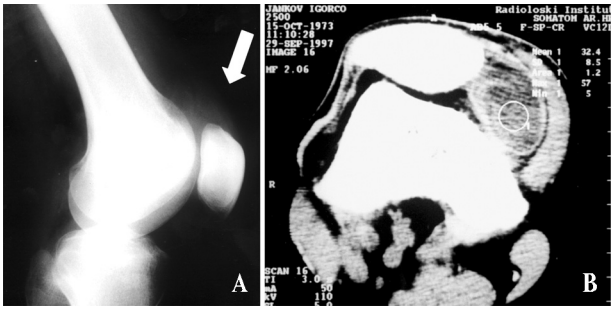


Figure 1. A. *Lateral radiograph of the right knee: the arrow points to a parapatellar soft tissue mass* ***B.*** *CT scan of the same knee: parapatelar, intracapsular soft tissue mass which has displased the patella*

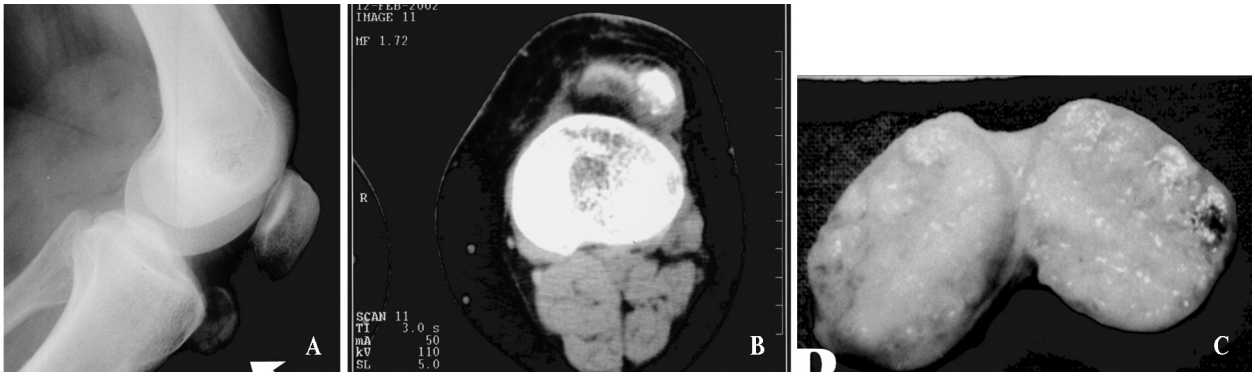


Figure 2. A*. Lateral radiograph of the right knee: large infrapatellar ossified mass.* ***B.*** *CT scan of the same knee: encapsulated ossified mass.* ***C.*** *Macroscopic appereance of the excised tumour on cross-section.*

mor was confirmed. It was oval shaped, 8 x 5 x 2.5 cm. The histological examination showed mature hyaline cartilage with foci of mixomatous tissue with benign characteristics. The diagnosis was intracapsular chondroma without ossification.

Case report 2

Female patient, age 41 complains on a solid mass on the lateral aspect of the left knee that has been slowly growing for the past two years. It caused limitation of joint movement and required surgical removal. The lateral radiograph of the left knee showed infrapatellar ossified mass (Figure 2A), whilst the CT- scan showed mostly ossified, encapsulated tumor just beneath the lateral border of the patella, but not attached to it (Figure 2B). The surgically excised mass was oval, 3 x 3.5 x 2.5 cm (Figure 2C), situated in the continuity with the capsule of the joint, but extrasynovial. Macroscopically, on cross section there is a central zone of mature trabecular bone, surrounded by a hyaline cartilage cup (Figure 2C). On histological examination there was mature trabecular bone surrounded by hyaline cartilage with endochondral ossification. The diagnosis was intracapsular chondroma with high rate of ossification.

Case report 3

A female patient aged 72 was admitted after a mild trauma of the left knee. Physical exam showed painful mass under the patella and limited flexion and extension of the knee which were present for more than 10 years. The recent trauma of the left knee caused pain and swelling of the knee. The lateral radiograph of the knee showed subpatellar, partly ossified mass and the transverse section on CT-Scan showed posttraumatic hematoma in the knee joint, as well as soft tissue tumor with ossification beneath the patella, situated in the para-articular connective tissue (Figure 3.A and B). The

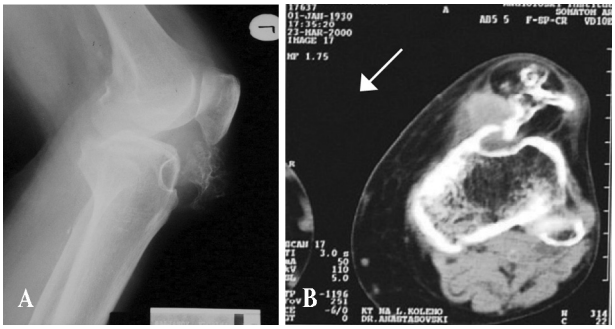


Figure 3. A. *Lateral X-ray of the knee shows the localization of the chondroma.* ***B.*** *Transverse section on computer tomography of the knee shows proximal tibia, chondroma and posttraumatic hematoma (arrow)*

diagnosis was para-articular chondroma of the knee with ossification.

Case report 4

Female patient aged 56 complained on the intense pain and lack of extension in her right knee. There was no history of trauma, but she could remember heavy activities after which progressive restriction of the extension and pain started. History of the patient showed that she had slightly painful, slowly growing lump seated beneath and laterally of the patella for more than 30

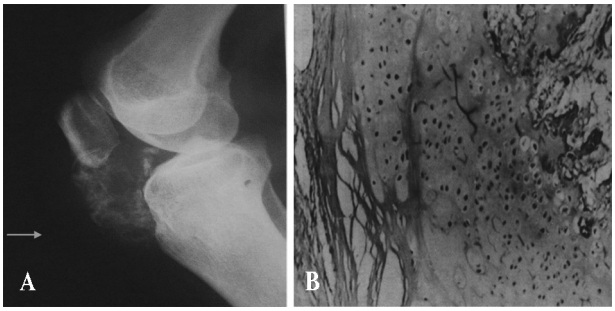


Figure 4. A. *Lateral x-ray of the right knee, showing infrapatellar chondroma (arrow)* ***B.*** *histopathology of the chondroma (HE x600)*

years (Figure 4A and B). After the surgical extirpation of the para-articular chondroma, full range of painless motion was regained.

Case report 5

Female patient aged 62 with long history of pain. Anterior knee pain, swelling of the joint, loss of function (flexion and full extension) (Figure 5A and B, Figure 6 A and B).

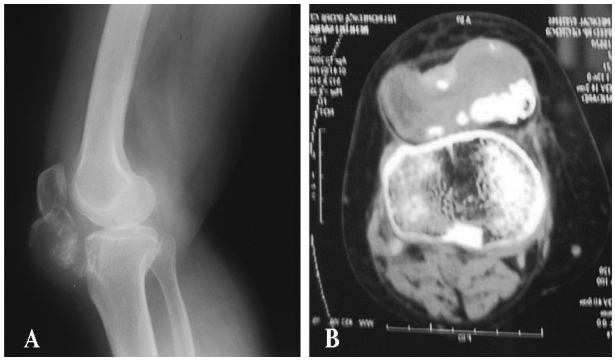


Figure 5. A. *Lateral x-ray of the right knee, showing large infrapatellar chondroma* ***B.*** *Size and position of the chondroma*

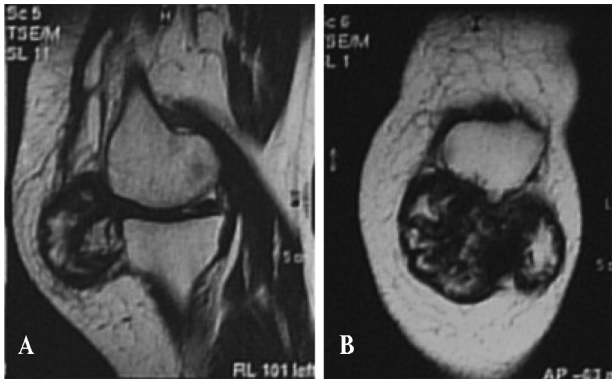


Figure 6. A. *MRI investigation – lateral view, big tumor in anterior part of the knee and compression of the cartilage of knee condyles.* ***B.*** *Correlation with patella, the tumor volume displaced the patella and make pressure in his inferior part*

Case report 6

Female patient aged 53 with local discomfort of the right knee, long history of pain, swelling, painful function and feeling of free body in his knee joint. Clinically moving tissue in his joint, pseudo blockage in her knee joint (Figure 7, 8).

DISCUSSION AND CONCLUSION

Para-articular and intracapsular chondromas are rare benign tumors mostly seen in the vicinity of the

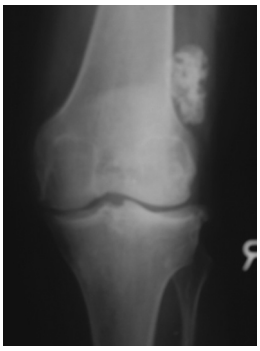


Figure 7. *Large Chondroma in the lateral recessus of the Knee*

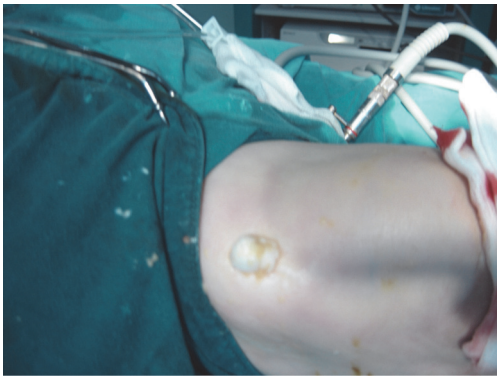


Figure 8. *Arthroscopic procedure in tumor extirpation*

large joints. They were often named capsular osteoma, osteochondroma or chondroma depending on the proportion of bone and cartilage (8). According to Jaffe, there is only one single lesion in question regardless of the ossification, and in 1958 he classified all these terms under one entity: intracapsular and para-articular chondroma (5). The Pathogenesis of these tumors is also controversial. They most likely originate from the connective tissue in the vicinity of the capsule of a joint or from the outer coat of the capsule as a result of cartilaginous metaplasia. Prior trauma is unlikely to play any significant role in the pathogenesis of these tumors. In the beginning comprising exclusively of cartilaginous tissue, in the course of time they usually ossify (3, 4). That is why their "second name" used in the literature comes from osteochondroma.

From the relatively small number of reported cases we can conclude that, although there have been cases in the ankle, elbow and the hip joint (3, 9), they are mostly seen in the knee joint (4, 6, 8). The location is para-articular and intracapsular, mostly infrapatellar or medial to the patella. The reported age varies from 12 to 75 years. The clinical complaints are of some month to several years of local discomfort, moderate pain, slow growing mass and some degree of limited motion in the joint. Radiologically, there is a soft tissue mass with a different degree of central radiodensity due to

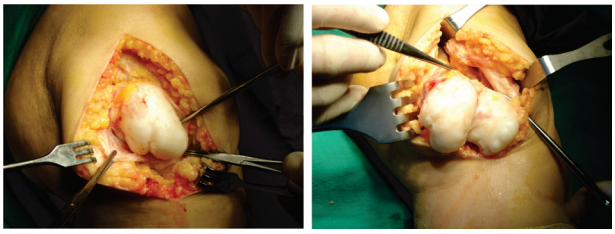


Figure 9. *Operative procedure in case 5*

ossification. Macroscopically their size varies, depending on the size of the involved joint, from 2 to 10 cm (Figure 9).

The six cases we report have all the features of the previously reported chondroma found in the literature. Clinically they present with moderate pain and restricted range of motion in the involved knee joint. On plain radiographs, there was a soft tissue mass with a different degree of ossification while the CT- scan has enabled us to make a more detailed analysis as to the exact position of the tumor (intracapsular or extracapsular) (8), its relationship with the adjacent structures, it's size and structure (7). In all of our cases, the tumors were intracapsular, but with no direct contact with the joint. Grossly, they were large, and the pathological analysis confirmed the presence of hyaline cartilage with variable amounts of mature trabecular bone (10, 11). Using the definition of Jaffe, the diagnosis in all of the six cases was: para-articular chondroma. The treatment in all of the cases was surgical excision.

The diagnosis of these benign tumors is made with clinical and radiological correlation with the pathological features (8, 9). Although rarely seen, they should be considered in the differential diagnosis of soft tissue masses around the joints: hematoma, bursitis, periosteal chondroma, synovial sarcoma, and synovial chondrosarcoma. The treatment of choice for these tumors is surgical excision, while being careful not to injure the joint integrity. Malignant transformation has never been reported. With correct diagnosis unnecessary aggressive surgical treatment will be avoided.

Conflict of interest

The authors declare that there is no conflict of interest.

Licensing

Sažetak

INTRAKAPSULARNI I PARAARTIKULARNI HONDROMI KOLENA: PRIKAZI SLUČAJA

Temelkovski Zlatko,[1] Nanceva Jasminka,[1] Samardziski Milan,[1]
Nancheva Andrea,[2] Andonovski Alan[1]

[1] University Clinic for Orthopaedic Surgery, Skopje, Macedonia
[2] General Hospital "8mi Septemvri", Skopje, Macedonia

Uvod: Intrakapsularni i paraartikularni hondromi su retke varijante ekstraskeletalnih hondroma. Nastaju od kapsule i/ili paraartikularnog vezivnog tkiva velikih zglobova (najčešće kolena) i rezultat su kartilaginozne metaplazije. Tokom vremena ovi tumori osifikuju i otuda proističe njihov drugi naziv: paraartikularni osteohondromi.

Prikazi slučaja: Prikazujemo 6 novih slučajeva paraartikularnih hondroma kolena. Na fizikalnom pregledu uočava se spororastuća, tvrda masa u kolenu i bol umerenog intenziteta. Radiološki nalazi i CT pokazuju mekotkivnu promenu sa varijabilnim procentom osifikacije, a na histološkom pregledu primećuje se prisustvo zrele hijaline hrskavice, kao i vezivne hrskavice u svih 6 slučaja.

Zaključak: Dijagnoza ovih benignih tumora je postavljena u korelaciji sa kliničkom slikom, radiološkim i histološkim promenama. Lečenje je hirurška ekscizija.

REFERENCES

1. Chung EB, Enzinger FM. Chondroma of soft parts. Cancer. 1978; 41(4): 1414–24.

2. Hagan RF, Schoneker PL. Para-articular osteochondroma. Am J Orthop. 1995; 24(1): 65–7.

3. Gayle EL, Morrison WB, Carino JA, Parsons TW, Liang CY, Stevenson A. Extrasceletal osteochondroma of the foot. Skeletal Radiol. 1999; 28(10): 594–8.

4. Gonzales Lois C, Garcia de la Torre JP, Santos Briz Terron A, Vila J, Manrique Chico J, Martinez Tello FJ. Intracapsular and para-articular chondroma adjacent to large joints: report of three cases and review of the literature. Skeletal Radiol. 2001; 30(12): 672–6.

5. Jaffe HL. Intracapsular and Para-articular Chondroma. In: Henry L. Jaffe: Tumors and Tumorous Conditions of the Bones and Joints. Philadelphia: Lea & Febiger, 1958: 567–9.

6. Reith JD, Bauer TW, Joyce MJ. Para-articular osteochondromas of the knee: report of two cases and review of the literature, Clin Orthop. 1997; 334: 225–32.

7. Singh R, Jain M, Siwach R, Rohilla S, Sen R, Kaur K. Large para-articular osteochondroma of the knee joint: a case report. Acta Orthop Traumatol Turc. 2012; 46 (2): 139–43.

8. Džoleva-Tolevska R, Poposka A, Georgieva D, Božinovski Z, Nanceva J, Gjoshev S. Comparative analyses of diagnostic methods in knee injuries. Sanamed. 2016; 11(1): 39–45.

9. Steiner GC, Meushar N, Norman A, Present D. Intracapsular and para-articular chondromas. Clin Orthop. 1994; 303: 231–6.

10. Sakai H, Tamai K, Iwamoto A, Saotome K. Para-articular chondroma and osteochondroma of the infrapatellar fat pad: a report of three cases. Int Orthop. 1999; 23(2): 114–7.

11. Dhanda S, Quek ST, Bathla G, Jagmohan t.Intra-articular and Peri-articular Tumors and umour mimics- what a clinician and onco-imaging radiologist should know. Malays J Med Sci. 2014; 21(2): 4–19.

Correspondence to / Autor za korespondenciju
Zlatko Temelkovski, MD, Ph.D
Clinic for Orthopaedic Surgery, Vodnjanska 17, 1000 Skopje, Macedonia.
Tel.: ++389 70 245 818, fax: ++389 02 3165 137
E-mail: ztemelkovski2002@yahoo.com

SANAMED
2017; 12(1): 33–36
ISSN-1452-662X

DOI: 10.24125/sanamed.v1i1.171
UDK: 616.37-007.41
ID: 231311372
Case report

ECTOPIC PANCREATIC TISSUE IN THE STOMACH: CASE REPORT

Lukić Dejan,[1, 2] Tatić Milanka,[1, 2] Radovanović Zoran,[1, 2] Ranisavljević Milan,[1, 2] Kresoja Milana,[1] Đurić Mladen[1]

[1] Department of Surgical Oncology, Oncology Institute of Vojvodina, Sremska Kamenica, Serbia
[2] University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

Primljen/Received 18. 01. 2017. god. Prihvaćen/Accepted 20. 02. 2017. god.

Abstract: **Introduction:** Ectopic pancreas is a rare developmental anomaly. It is a presence of pancreatic tissue without anatomic or vascular continuity with the normally developed pancreas. The most common heterotopic site is the stomach commonly involving antrum and prepyloric region on the greater curvature or posterior wall. Ectopic pancreas is diagnosed by endoscopic ultrasound, gastroscopy and biopsy, CT scan and MRI of the abdomen, a definitive diagnosis is verified by histopathological examination. Treatment is surgical.

Case report: A 56-year-old woman presented with epigastric pain, nausea and fatigue. Esophagogastroduodenoscopy showed submucosal mass in the prepyloric region, biopsy was performed. Histopathological findings described normal gastric mucosa. Endoscopic ultrasonography and CT of the abdomen showed submucosal tumor, 18 mm in diameter, located in the prepyloric region. Surgical treatment was indicated. Gastrotomy with total extraction of tumor was performed. Histopathology findings showed ectopic pancreatic tissue in the submucosal and muscular layer of the stomach. Postoperatively patient fully recovered, and in the 2 year folow-up did not develop any symptoms related to gastrointestinal tract.

Conclusion: Although presentation of ectopic pancreatic tissue in stomach is a very rare condition, it should be considered during gastroitestinal diagnostic in patients with nonspecific gastrointestinal symptomatology. In most of cases, for this patients, surgery is curative and definitive solution.

Key words: Ectopic pancreas, stomach, surgery, heterotopic pancreas.

INTRODUCTION

Ectopic pancreas (EP) is a rare congenital anomaly that involves the presence of pancreatic tissue outside the normal anatomical location (1). It is a rare developmental anomaly with a reported incidence of 0.55–14% at autopsy (2, 3, 4), in approximately one in every 500 upper gastrointestinal surgical specimens and in 0.6–13% of necropsies (5-9). It was the first described in 1727 by Schultz in an ileal diverticulum, and the first histological diagnostic confirmation was described by Klob (10, 11) in 1859. Ectopic pancreas in the stomach also known as myoepithelial hamartoma, heterotopic pancreas or aberant pancreas, is described as presense of pancreatic tissue outside its normal anatomical location. It is the presence of pancreatic tissue without anatomic or vascular continuity with the normally developed pancreas. Although it is common to occur intra abdominally from anywhere along distal end of the oesophagus to the colon, it has been reported very rarely in extra abdominal sites such as mediastinal cysts, bronchi, lung, umbilicus and brain (12, 13, 14). Out of gastrointestinal lesions, the commonest area is the upper gastrointestinal tract i.e. stomach (30%), duodenum (25%) and jejunum (15%). At rare instances it can also occur in association with hepatobiliary organs such as liver, gallbladder, common bile duct, cystic duct (2, 15). Heterotopic pancreas is usually found incidentally and is generally asymptomatic. However it may become symptomatic when complicated by inflammation, bleeding, obstruction or malignant transformation (16, 17). The most common heterotopic site is the stomach commonly involving antrum and prepyloric region on the greater curvature or posterior wall (18). Gastric EP is found in the submucosal layer of the gastric wall, usually localized prepyloric and pyloric. Symptoms can occur if there is inflammation, bleeding, gastric obstruction and malignant transformation. The most common symptoms are: nausea, vomiting, epigastric pain, melena (3).

Ectopic pancreas is diagnosed by endoscopic ultrasound, oesophagoduodenogastroscopy and biopsy, CT scan and MRI of the abdomen, a definitive diagno-

sis is verified by histopathological examination. Diagnosing of the EP in the stomach is very difficult due to the similarity with gastrointestinal stromal tumor (GIST), gastrointestinal autonomic nerve tumor (GANT), carcinoid, lymphoma and gastric cancer (4).

CASE REPORT

A 56 years old woman was admitted in hospital due to melena, severe abdominal pain and fatigue. She reported that symptoms involving black stools occurred in the last three days following the nausea, stabbing pain in the upper abdomen and left hypochondrium. She also complained about weakness, fatigue and sweating. Ten years ago patient had similar symptoms. Therefore, she underwent the oesophagoduodenogastroscopy and the submucosal tumor in the prepyloric region of the stomach was diagnosed, which did not act malignantly. Symptoms retreated, so the surgical treatment was not indicated, but during all these years patient was followed by the surgeon and gastroenterologist.

Clinical examination showed diffuse abdominal tenderness. Hematological and biochemical parameters were in the reference range, except mild sideropenic anemia. Native X-ray and ultrasound of the upper abdomen did not provide the significant data. The abdominal CT scan showed submucosal mass in the prepyloric region of the stomach (Figure 1).

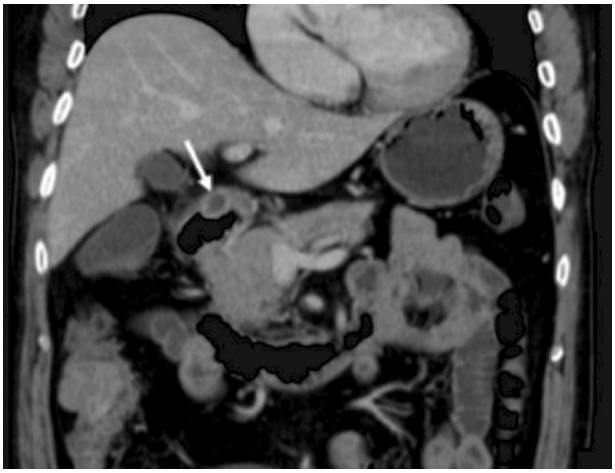


Figure 1. *Submucosal mass of the stomach (CT)*

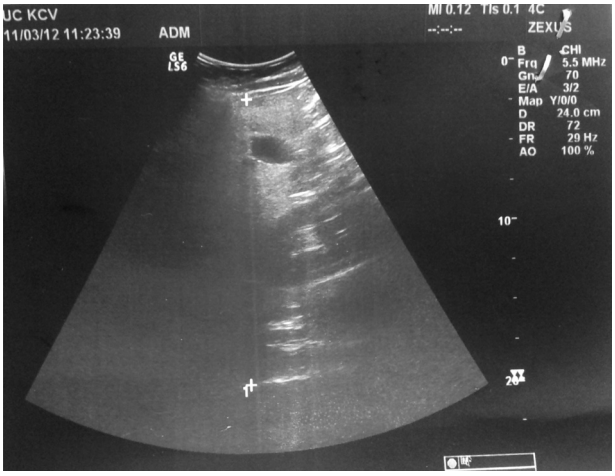


Figure 2. *Hypoechogenic mass in the antral region of the stomach*

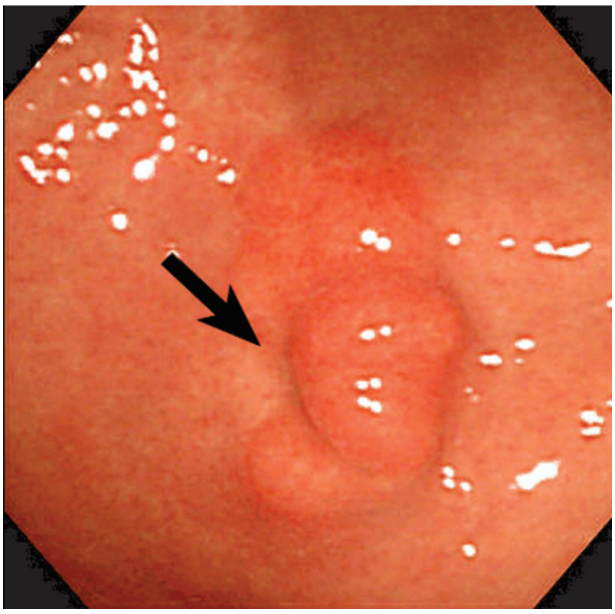


Figure 3. *Gastroscopy, submucosal mass*

Endoscopic ultrasound of the stomach discovered 18 mm submucosal gastric lesion in the prepyloric region of the stomach. The first assumption was GIST (Figure 2).

Oesophagoduodenogastroscopy confirmed the existence of submucosal tumor in the prepyloric region of the gastric mucosa (Figure 3). Biopsy was performed and specimen was sent to histopathology (HP) examination. HP findings had showed normal gastric mucosa.

Given the patient constant symptoms and results of CT, endoscopic ultrasonography and patohistological results, surgical treatment was indicated. After a usual preoperative preparation, surgery was performed in the general anesthesia. We used the upper medial laparotomy to access the stomach. Through palpation lesion was identified, about 5 cm from the pylorus, at the large curvature of the stomach, measuring about 20 mm, elastic consistency, clearly limited by the surrounding structures. Gastrotomy was done, mucosa above the tumor was intact. The tumor was completely removed and sent to HP analysis. The stomach was closed with continuous stitches in two layers. The postoperative course was uneventful, with no postoperative complications. The patient was discharged on the seventh postoperative day.

Histopathology findings showed the ectopic pancreatic tissue in the submucosal and muscular layer of the stomach. Ectopic pancreatic lobular structure, lobules, is located in the gastric submucosal layer. Lobules

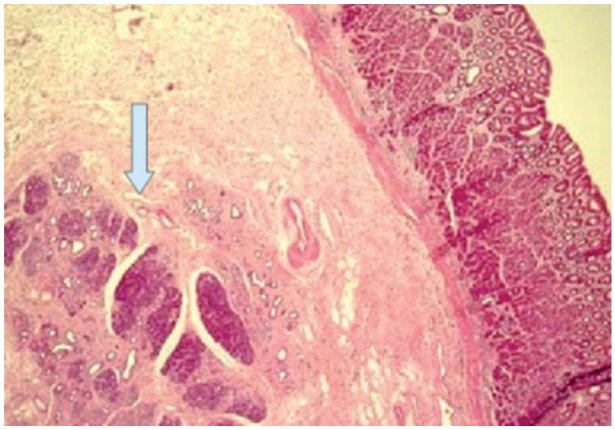


Figure 4. *Pancreatic acini with ductal structures and islets of Langerhans*

contain pancreatic acini with ductal structures, and islets of Langerhans, the mucosa above is intact (Figure 4).

DISCUSSION

The etiology of ectopic pancreas is unknown. It is believed that early, in fetal development, during the rotation of the digestive tube and connection of dorsal and ventral part of the pancreas, small parts remain separate and continue to develop at the atypical location (5). Ectopic pancreatic tissue is rare, with a reported incidence of 0.55 4% at autopsy (1, 7), in approximately one in every 500 upper gastrointestinal surgical specimens and in 0.6 3% of necropsies (8, 9). Gastric antrum is the commonest site for heterotopic pancreatic tissues in stomach which accounts about 85–95%, being more common along the greater curvature. Our patient had the lesion at the large curvature of stomach. The most common symptoms are: nausea, vomiting, epigastric pain, melena (3), which is consistent with our findings.

Diagnosing EP in the stomach is difficult. Although the EP of the stomach is rare, in cases with submucosal tumor in the gastrointestinal tract, it is necessary to consider the differential diagnosis of ectopic pancreas. Endoscopic examination has become useful adjunct in the evaluation of submucosal lesions. Despite the wide range of diagnostic possibilities, EP presents a diagnostic challenge. Although positive biopsy establishes the diagnosis, in most cases, biopsies are superficial and therefore non-diagnostic. Ultrasound of upper abdomen, CT, MRI an X-ray often provide poor results due to great similarities with GIST and GANT tumors, as well as carcinoid, lymphoma and gastric cancer. Definitive HP findings on operatively removed tumor provide helpful data for diagnosis (7, 9).

CONCLUSION

Although, presentation of ectopic pancreatic tissue in stomach is very rare condition, it should be considered during gastroitestinal diagnosing in patients with nonspecific gastrointestinal symptomatology. In the most cases, for these patients, surgery is curative and definitive solution.

Abbrevations

EP — Ectopic pancreas
CT — Computed Tomography
MRI — Magnetic resonance imaging
GIST — Gastrointestinal stromal tumor
GANT — Gastrointestinal autonomic nerve tumor
HP — Histopathology

All co-authors were actively involved in the collection and processing of data.

Conflict of interest

The authors declare that there is no conflict of interest.

Sažetak

EKTOPIČNO TKIVO PANKREASA U ŽELUCU: PRIKAZ SLUČAJA

Lukić Dejan,[1, 2] Tatić Milanka,[1, 2] Radovanović Zoran,[1, 2] Ranisavljević Milan,[1, 2] Kresoja Milana,[1] Đurić Mladen[1]

[1] Klinika za operativnu onkologiju, Institut za onkologiju Vojvodine, Sremska Kamenica, Srbija
[2] Medicinski fakultet Univerziteta u Novom Sadu, Novi Sad, Srbija

Uvod: Ektopični pankreas je retka razvojna anomalija koja podrazumeva prisustvo pankreasnog tkiva van uobičajene anatomske lokacije. Najčešće se nalazi na želucu antralno ili prepiloričnо na velikoj krivini zadnjeg zida. Ektopični pankreas se dijagnostikuje endoskopskom ultrasonografijom, gastroskopijom i biopsijom, CT-om i MR-om abdomena, a definitivnu potvrdu dijagnoze daje PH nalaz. Terapija je hirurška.

Prikaz slučaja: Žena stara 56 godina se žalila na bolove u želucu, mučninu i slabost. Ezofagogastroduo-

denoskopijom je uočena submukozna tumorska masa koja je bioptirana. Patohistološki nalaz opisuje normalnu gastričnu mukozu. Endoskopskim ultrazvukom i CT-om abdomena, je uočen submukozni tumor prečnika 18 mm, lokalizovan u prepiloričnoj regiji želuca. Indikovana je i urađena operacija, gastrotomija i ekstrakcija tumora. Patohistološki nalaz je verifikovao ektopični pancreas u submukozi i muskularnom sloju želuca. Pacijentkinja se potpuno oporavila, tokom dvogodišnjeg praćenja nije imala simptoma vezanih za gastrointestinalni trakt.

Zaključak: Iako je ektopični pankreas na želucu retka pojava, u slučajevima dijagnostikovanja submukoznih tumora, potrebno je diferencijalno dijagnostički razmotriti i ektopični pankreas. Operativno lečenje je indikovano samo u slučajevima pojave simptoma.

Ključne reči: Ektopični pankreas, želudac, hirurgija, heterotopični pankreas.

REFERENCES

1. Ormarsson OT, Gudmundsdottir I, Marvik R. Diagnosis and treatment of gastric heterotopic pancreas. World J Surg. 2006; 30(9): 1682–9.

2. Christodoulidis G, Zacharoulis D, Barbanis S, Katsogridakis E, Hatzitheofilou K. Heterotopic pancreas in the stomach: a case report and literature review. World J Gastroenterol. 2007; 13(45): 6098–100.

3. Chandan VS, Wang W. Pancreatic heterotopia in the gastric antrum. Arch Pathol Lab Med. 2004; 128(1): 111–2.

4. Eisenberger CF, Gocht A, Knoefel WT, Busch CB, Peiper M, Kutup A, et al. Heterotopic pancreas-clinical presentation and pathology with review of the literature. Hepatogastroenterology. 2003; 51(57): 854–8.

5. Pang LC. Pancreatic heterotopia: a reappraisal and clinicopathologic analysis of 32 cases. South Med J. 1988; 81(10): 1264–75.

6. Matsushita M, Hajiro K, Okazaki K, Takakuwa H. Gastric aberrant pancreas: EUS analysis in comparison with the histology. Gastrointest Endosc. 1999; 49(4Pt1): 493–7.

7. Low G, Panu A, Millo N, Leen E. Multimodality imaging of neoplastic and nonneoplastic solid lesions of the pancreas. Radiographics. 2011; 31(4): 993–1015. Shetty A, Paramesh AS, Dwivedi AJ, et al. Symptomatic ectopic pancreas. Clinical. Review. 2002; 58: 203–207.

8. Tanaka K, Tsunoda T, Eto T, Yamada M, Tajima Y, Shimogama H, et al. Diagnosis and management of heterotopic pancreas. Int Surg. 1993; 78(1): 32–5.

9. Klob L. Pancreas accesorium. Zeitschrift der Kaiserl. Konigl. Gesellschaft der Aerzte zu Wien. 1859; 15:732.

10. Caberwal D, Kogan SJ, Levitt SB. Ectopic pancreas presenting as an umbilical mass. J Pediatr Surg. 1977; 12(4): 593–9.

11. Heller RS, Tsugu H, Nabeshima K, Madsen OD. Intracranial ectopic pancreatic tissue. Islets. 2010; 2(2): 65–71.

12. Jaschke W, Aleksic M, Aleksic D. Heterotopic pancreatic tissue in a bronchogenic cyst-diagnosis and therapy. Thorac Cardiovasc Surg. 1982; 30(1): 58–60.

13. Szabados S, Lenard L, Tornoczky T, Varady E, Verzar Z. Ectopic pancreas tissue appearing in a mediastinal cyst. J Cardiothorac Surg. 2012; 7:22.

14. Hsia CY, Wu CW, Lui WY. Heterotopic pancreas: a difficult diagnosis. J Clin Gastroenterol. 1999; 28(2): 144–7.

15. Emerson L, Layfield Lj, Rohr LR, Dayton MT. Adenocarcinoma arising in association with gastric heterotopic pancreas: a case report and review of the literature. J Surg Oncol. 2004; 87(1): 53–7.

16. Papaziogas B, Koutelidakis I, Tsiaousis P, Panagiotopoulou K, Paraskevas G, Argiriadou H, et al. Carcinoma developing in ectopic pancreatic tissue in the stomach: a case report. Cases J. 2008; 1(1): 249.

17. Galatioto C, Goletti O, Franceschi M, Buccianti P, Neri E, Amillota N, et al. Laparoendoscopic treatment of gastric ectopic pancreas. Surg Laparosc Endosc Percutan Tech. 1999; 9: 160–4.

18. Christodoulidis G, Zacharoulis D, Barbanis S, Katsogridakis E, Hatzitheofilou K. Heterotopic pancreas in the stomach: a case report and literature review. World J Gastroenterol. 2007; 13(45): 6098–100.

Correspondence to / Autor za korespondenciju
Dejan Lukić
Oncology Institute of Vojvodina
Put dr Goldmana 4, Sremska Kamenica, Serbia
Phone: 021/480 5500
e-mail: dejan.lukic f.uns.ac.rs

SANAMED
2017; 12(1): 37–40
ISSN-1452-662X

DOI: 10.24125/sanamed.v1i1.172
UDK: 618.19-006.6-089.168; 615.8
ID: 231288332
Case report

FUNCTIONAL COMPLICATIONS FOLLOWING BREAST CANCER THERAPY AND THE ROLE OF REHABILITATION IN RECOVERY OF FUNCTIONAL STATUS — A CASE REPORT

Popović-Petrović Svetlana,[1, 2] Kovač Aleksandra,[1] Novakov Ivana,[1] Tatić Milanka[1, 2]

[1] Oncology Institute of Vojvodina, Sremska Kamenica, Serbia
[2] Faculty of Medicine, University of Novi Sad, Serbia

Primljen/Received 23. 01. 2017. god. Prihvaćen/Accepted 15. 03. 2017. god.

Abstract: **Introduction.** The most common functional complications after the treatment of breast cancer are reduction of range of motion in the shoulder joint (incidence of 10 to 73%), lymphedema of the arm (10-30%) and nerve damage of the arm or damage of brachial plexus (1.8-4.9%). Multiple complications rarely occur and they are usually of mild to moderate forms.

Case report. VV (woman), born in 1965 was exposed to quadrantectomy of the left breast with axillary dissection in 2003 (histopathology: ductal carcinoma; 4 removed lymph nodes, 1 of which with a secondary deposit). After the surgical intervention, the patient underwent chemotherapy (CMF protocol VI cycles) and radiation therapy (50 Gy/12 cycles). Four months after the therapy completion, lymphedema of the left arm was developed, and few months later brachial plexus injury as well. First visit to physiatrist was five years later, with a significant reduction of range of motion in the left arm and severe lymphedema (maximum difference to 7.5 cm). EMNG trial indicated a moderate lesion of left median nerve and ulnar nerve and mild to moderate lesion of left radial nerve injury; DASH score was 107. After repeated physical treatments (since 2009), the last control in October 2016 showed that the functional status was significantly improved: reduction of range of motion was present in flexion and abduction only, lymphedema was reduced (maximum difference of 5.5 cm); DASH score was 48, while EMNG indicated a lesion of the median nerve and ulnar nerve in lower level, with signs of recovery.

Conclusion. The implementation of an early rehabilitation program for the patients who were surgically treated for breast cancer is necessary in order to prevent functional complications and to enable continuous monitoring of the patients, while in the case with already developed complications, physical therapy should be initiated regardless of the period in which the functional limitations occurred.

Key words: breast cancer, functional complications, physical treatment.

INTRODUCTION

Functional complications in breast cancer may occur as a consequence of therapy (surgery with or without axillary dissection, radiotherapy, chemotherapy) (1-4), absence of the early rehabilitation program and influence of natural factors (trauma, physical overload) (4-6). The most common are: reduction in range of motion in the shoulder joint of ipsilateral arm, with an estimated incidence of 10-73% (7, 8), secondary lymphedema of the arm (average incidence 20-30%) (9, 10), nerve damage of the arm or brachial plexus, which is reported in 1.8-4.9% of patients with breast cancer (11). Those complications are mostly individual and in most cases mild, while their persistence leads to permanent dysfunction of the ipsilateral arm (5, 6).

The main aim of this case report is to show the effect of rehabilitation interventions in improving the functional state in conditions of chronic and permanent damage caused by the treatment of breast cancer.

CASE REPORT

VV (woman), born in 1965 underwent surgery on 1st Ferbuary 2003. Quadrantectomia mammae lateris sinistri (histopathological findings: Carcinoma ductale infiltrativum; HG2; tumor size 30 x 26 x 18 mm; localization: upper lateral quadrant; 4 removed lymph nodes, 1of which includes a secondary deposit. After the

surgical intervention, the patient underwent therapy prescribed by the breast cancer multidisciplinary team: CMF chemotherapy, VI cycles (March 2003). Radiotherapy conducted during May and June, 2003: TD 50 Gy/12 fractions on the second day (area of the rest of the breast tissue, axilla and supraclavicular region).

Swelling of the left hand appeared four months after the completion of radiotherapy. The patient did not receive a treatment of lymphedema. In May 2004, she began to feel numbness of the left hand and the inability to raise her left arm. A few weeks later, she complained of pain in her left hand, with the inability to perform daily activities with her left hand.

During the first visit to the Oncology Institute of Vojvodina (IOV), Department of Rehabilitation, on 25 May 2009, the patient complained of pain (Visual Analogue Scale – VAS = 5) and a feel of „weight“ of the left arm.

Reports: Disease free according to medical oncologist (12 May 2009). Laboratory findings and breast tumor marker (CA 15-3) were within normal ranges. Abdominal ultrasound examination: nothing abnormal detected. Computed tomography of the chest (17 January 2008): postradiation fibrotic changes apically and in the upper lobe of the lungs leftward, with no secondary deposits. The old fractures of III and IV ribs with marginal sclerosis and the development of pseudoarthrosis were observed. Those fractures were a consequence of severe postradiation osteoporosis, with no signs of bone dissemination of the disease.

Objective findings: pronounced, fibrotic, reddish-livid colour changes in skin of the left hemithorax, axillary and supraclavicular region (Figure 1). Mild flexion contracture in the left elbow joint and radial deviation in the left radiocarpal (RC) joint. Edema of the left forearm as a whole (without hand) and lower 2/3 of the upper arm with unchanged skin colour.

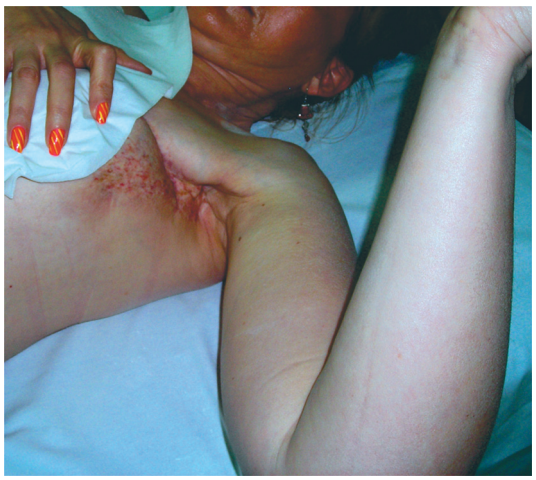


Figure 1. *Postradiation fibrotic changes in skin of the chest and axillary region*

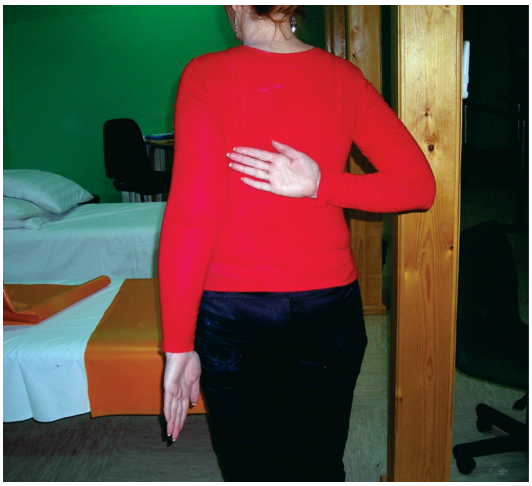


Figure 2. *The internal rotation in both shoulder joints - before starting treatment*

Palpatory: edema of firmer consistency, with palpatory zone of fibrosis (junction of the upper and middle thirds of the upper arm). Range of motion in the shoulder joint: abduction (abd) 80°; flexion (fl) 80°, extension (ext) 30°, external rotation (SR) 10°, internal rotation (UR) 0° (Figure 2). The range of the extremities (edematous/contralateral hand difference): over the metacarpophalangeal joint (MCP) - there is no difference; over the RC joint - difference is 1cm; 10 cm below the olecranon - difference is 7.5 cm; over the olecranon - difference is 6 cm; 10-15 cm above the olecranon - difference is 7.5 cm. Manual muscle testing (MMT): except the flexor carpi ulnaris muscle (2+), scores for all the other muscles of the left shoulder-scapular area and segments of the left arm range from 3- to 3+. The Disabilities of the Arm, Shoulder and Hand score (DASH) is 107. Electromyoneurography (EMNG): chronic lesions of the left median and ulnar nerve to moderate degree and left radial nerve from mild to moderate degree.

Physical therapy was performed at the Department of rehabilitation of IOV since 2009, 2-3 times per year, 10-15 treatments each time. The therapy included kinesiotherapy, manual lymphatic drainage and education (risk factors, protective factors and kinesiotherapy at home).

The last check-up with a physiatrist was in October 2016. Patient subjectively rated herself as mostly pain-free. Periodically, “when she works too much”, there is a pain of mild intensity (Visual Analogue Scale - VAS = 1-2) and the inability to raise her left arm above her shoulder. Functional status: range of motion in the left shoulder joint: abd 90°; fl 110°; ext 30°; SR 40°; UR 80° (Figure 3). The scope of the extremities (edematous/contralateral arm difference): over MCP 1 cm; over RC joint 1 cm; 10 cm below the olecranon 5.5 cm; over the olecranon 5.5 cm; 10-15 cm above the olecranon, range difference is 4.5 cm. MMT: scores 4

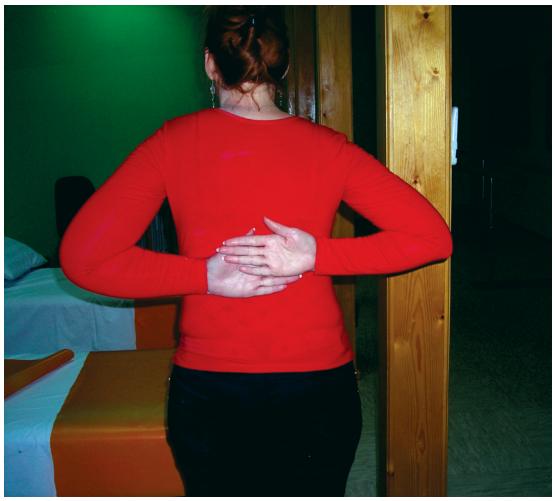


Figure 3. *The internal rotation in both shoulder joints – the last check-up*

for all muscles of the left arm's segments and shoulder-scapular area, except for the muscles of the left thumb (score 4-). DASH score was 48. EMNG - control: lesion of the left median and ulnar nerve is now quite mild - improvement, reporting signs of recovery.

DISCUSSION

This case is interesting for several reasons:

1. The literature has shown incidences of separate functional post-therapeutic complications in breast cancer in the form of contractures in the segments of the ipsilateral arm (7, 8), lymphedema of the arm (9, 10) and brachial plexus lesions (11). We did not find any representation of multiple functional post-therapeutic complications in existing literature, as we have described it in our case.

2. In addition, the findings of CT of the thorax which describes expressed postradiation sequel to the lung parenchyma, with the consequent osteoporosis and fracture of III and IV ribs and formation of pseudoarthrosis, is an additional adverse factor, which prevents further increase of range of motion in the left shoulder joint. Maximum increase of range of motion abd to 90° and fl to 110°, below the threshold of pain is safe in relation to the possibility of re-fracture of the ribs.

3. Lack of early rehabilitation – the patient was not operated in IOV and since 1996, IOV has implemented the program of early rehabilitation of patients surgically treated for breast cancer, according to a constructed algorithm of early rehabilitation (12), therefore multiple functional complications and individual complications of severe degree have not been reported.

4. Lack of rehabilitation programs (for unknown reasons) immediately after the occurrence of lymphedema or later, after the development of plexopathy and consequently significantly reduced abilities to perform daily activities, greatly reduced the possibility of full restitution of resulting functional limitations.

5. Inclusion in a rehabilitation program 6 years after completion of therapy, and 5 years after developed post-therapeutic complications, and significant functional recovery are confirmation that the rehabilitation interventions should be carried out regardless of the temporal distance from the occurrence of functional complications.

6. Finally, the patient's subjective perception of quality of life has improved significantly, she carries out daily activities, which is best illustrated by the words of the patient "now I can put on my bra and belt by myself."

CONCLUSION

The introduction of an early rehabilitation program in patients who underwent breast cancer surgery, continuous monitoring and rehabilitation program immediately after the diagnosis of functional complications is necessary for good quality of life of patients with breast cancer, while in the case with already developed complications, physical therapy should be initiated regardless of the period in which the functional limitations occured.

Abbreviations

DASH score — The Disabilities of the Arm, Shoulder and Hand score
CMF — Cyclophosphamide, Methotrexate, Fluorouracil
EMNG — Electromyoneurography
IOV — Oncology Institute of Vojvodina
MMT — Manual muscle testing
MCP — Metacarpophalangeal joint
RC — Radiocarpal joint
VAS — Visual Analogue Scale

Conflict of interest

The authors declare that there is no conflict of interest.

Sažetak

POSTTERAPIJSKE KOMPLIKACIJE KOD KARCINOMA DOJKE I ULOGA REHABILITACIJE U FUNKCIONALNOM OPORAVKU — PRIKAZ SLUČAJA

Uvod. Najčešće funkcionalne komplikacije nakon terapije karcinoma dojke su kontraktura u ramenom zglobu (incidencija 10%-73%), limfedem ruke (10-30%) i oštećenje nerava ruke ili brahijalnog pleksusa (1,8-4,9%). Retko se javljaju udružene komplikacije i uglavnom su blažeg ili umerenog oblika.

Prikaz slučaja. V. V. 1965, kvadrantektomija leve dojke sa disekcijom aksile rađena 2003. godine (patohistološki nalaz: duktalni karcinom; 4 izvađene limfne žlezde od kojih je 1 sa sekundarnim depozitom). Potom je primila hemioterapiju (protokol CMF VI ciklusa) i zračnu terapiju (50 Gy/12 ciklusa). Četitri meseca nakon završene terapije, razvija se limfedem leve ruke, a nekoliko meseci kasnije i oštećenje brahijalnog pleksusa. Prvi put se javlja kod fizijatra nakon pet godina, sa značajnom redukcijom obima pokreta u segmentima leve ruke, izraženim limfedemom (najveća razlika do 7,5 cm). EMNG ispitivanje je ukazalo na umerenu leziju levog n.medianus-a i levog n.ulnaris-a i lako do umerenu leziju levog n.radialis-a; DASH skor je bio 107. Nakon ponavljanih fizikalnih tretmana (od 2009), na poslednjoj kontroli oktobra 2016. funkcionalni status je značajno poboljšan: redukcija pokreta samo u fleksiji i abdukciji, limfedem redukovan (najveća razlika 5,5 cm); DASH skor je 48, a EMNG ukazuje na leziju n.medianus sinistri i n.ulnaris sinistri lakšeg stepena, uz znake oporavka.

Zaključak. Neophodno je uvođenje programa rane rehabilitacije kod operisanih od karcinoma dojke radi prevencije funkcionalnih komplikacija, kontinuirano praćenje pacijenata, a kod razvijenih komplikacija, fizikalni tretman započeti bez obzira na vremenski period od nastanka funkcionalnih ograničenja.

Ključne reči: karcinom dojke, funkcionalne komplikacije, fizikalni tretman.

REFERENCES

1. Armer JM, Fu MR, Wainstock JM, Zagar E, Jacobs LK. Lymphedema following breast cancer treatment, including sentinel lymph node biopsy. Lymphology. 2004; 37(2): 73–91.

2. Stubblefield DM. Radiation fibrosis syndrome: neuromuscular and musculosceletal complications in cancer survivors. PM R. 2011; 3(11): 1041–54.

3. Hojan K, Milecki P. Opportunities for rehabilitation of patients with radiation fibrosis syndrome. Rep Pract Oncol Radiother. 2013; 19(1): 1–6.

4. Hack FT, Kwan BW, Tomas-Macklean LR, Towers A, Miedema B, Tilley A, et al. Predictors of arm morbiity following breast cancer surgery. Psychooncology. 2010; 19(11): 1205–12.

5. Cinar N, Seckin U, Keskin D, Bodur H, Bozkurt B, Cengiz O. The effectiveness of early rehabilitation in patients with modified radical mastectomy. Cancer Nurs. 2008; 31(2): 160–5.

6. Chan DN, So KW. Developing an evidence-based exercise guideline on improving shoulder motion and lessening the severity of lymphedema for breast cancer patients after axillary lymph-node dissection. Clin Oncol Cancer Res. 2010; 7(3): 169–74.

7. Chun MS, Moon SM, Lee HJ, Lee EH, Song YS, Chung YS, et al. Arm morbidity after breast cancer treatments and analysis of related factors. J Korean Soc Ther Radiol Oncol. 2005; 23(1): 32–42.

8. Thomas-Macklaen RL, Hack T, Kwan W, Towers A, Miedema B, Tilley A. Arm morbidity and disability after breast cancer: new directions for care. Oncol Nurs Forum. 2008; 35(1): 65–71.

9. Deo SVS, Ray S, Rath GK, Shukla NK, Kar M, Asthana S, et al. Prevalence and risk factors for development of lymphedema following breast cancer treatment. Indian J Cancer. 2004; 41(1): 8–12.

10. Popovic-Petrovic S, Nedeljkovic M, Popovic L, Petrovic V. Secondary lymphedema of the arm in breast carcinoma at the Încology Institute of Vojvodina: 2001- 2006. HealthMED 2011; 5(6): 1719–24.

11. Topkan E, Onal C, Yavuz N, Yavuz A. Pathophysiology and treatment of radiation induced brachial plexopathy. Int J Hematol Oncol. 2008; 3(18): 180–5.

12. Popović-Petrović S, Tomić S, Nedeljković M, Popović L, Matovina G. Early rehabilitation in patients operated for breast carcinoma. Vojnosanit Pregl. 2013; 70(4): 407–10.

Correspondence to / Autor za korespondenciju
Popović-Petrović Svetlana
Oncology Institute of Vojvodina
21204 Sremska Kamenica, Put dr Goldmana 4
E mail: petrovic.svetlana@onk.ns.ac.rs
Phone: + 381 21 4805489
Fax: + 381 21 661 3741

SANAMED
2017; 12(1): 41–44
ISSN-1452-662X

DOI: 10.24125/sanamed.v1i1.175
UDK: 616.831-006.328-089
ID: 231316748
Case report

ENDOVASCULAR PRELUDE FOR DELICATE MENINGEOMA OPERATION: A CASE REPORT

Kostic Aleksandar,[1] Ristic Saša,[2] Nikolov Vesna,[1] Stefanović Ivan,[1] Dzelebdzic Zvonimir,[1] Berilazic Luka[1]

[1] Clinic of Neurosurgery, Clinical Center Nis, Serbia
[2] Institute of Radiology, Clinical Center Nis, Serbia

Primljen/Received 02. 02. 2017. god. Prihvaćen/Accepted 05. 03. 2017. god.

Abstract: **Introduction:** Embolization prior to surgery can make tumor resection less complicated by reducing blood loss during surgery and shortening the time of the operation.

Case report: In this paper, we presented a case of a sixty-three-year-old woman who was admitted to the Clinic of Neurosurgery, Clinical Center Niš, Serbia, at November 2016, after she underwent a CT brain scan that showed a large tumor of the left cerebellopontile angle. Digital subtraction angiography presented a large, highly vascularized tumor lesion that compressed the brain stem. The patient underwent endovascular procedure, and complete embolization of the tumor vessels was established. The radiologist delivered embolization material via the left ascending pharyngeal artery. In the next 24 hours, an operation was performed i.e.radical extirpation surgery (Simpson grade I). Postoperatively, the patient's GCS was 15, with no new neurological deficit. Postoperative brain CT scan showed neither rest tumor nor blood clot inside the tumor bed. Pathohistological finding revealed atypical meningioma grade II.

Conclusion: Despite some clinicians' dilemma considering the utility of preoperative embolization of meningioma vessels, we believe that a team of educated and dedicated radiologist and neurosurgeon could achieve great results in resection of large and inaccessible cranial tumors.

Key words: embolization, meningioma, highly vascularized tumor.

INTRODUCTION

Many cranial tumors have dense three-dimensional vessel net and strong blood influx to a tumor lesion, and that can complicate or even make impossible complete tumor removal. Tumors like meningiomas, hemangiopericitomas, glomus tumors and paragangaliomas or some spinal tumors tend to bleed intensively, making the surgery a dramatic and risky event. Tumor embolization may help treating such tumors by blocking the blood vessels that supply them. Embolization prior to surgery can make tumor resection less complicated by reducing blood loss during surgery and by shortening the time of the operation. In some cases, it can be a tumor therapy *per se* (1), where indicated intra-arterial embolization can provide palliative therapy. There are a lot of different kinds of embolization materials available for this procedure, depending on the tumor size, type, location, and the diameter and convolution of the blood vessels. Some of them are polyvinyl alcohol (PVA) particles of different sizes, pledges of gelatin sponge and microfibrillar collagen. Liquid embolization agents are Onyx, n-butylcyanoacrylate, and ethanol. Occlusion of large vessels (diameter > 1,5 mm) may require the use of detachable coils, where only tumor supplying feeders are embolized without the occlusion of the tumor vasculature. Complex anatomy of cranial vasculature should always be kept in radiologist's mind as many vascular anastomoses can make intervention uncertain and lead to an unexpected neurological deficit (2).

Time to operation after embolization may vary depending on tumor characteristics, embolization technique, and degree of devascularization. Embolization is usually performed within the first day or two of expected surgical resection, while some new embolization materials allow up to seven-day period between embolization and operation (3).

Embolization can be performed trans-arterially or by direct puncture in order to achieve occlusion of the small tumor vessels, sparing the normal brain vessels.

Trans-venous embolizations are rare, and they are not considered for tumor embolization but for arteriovenous malformations (4).

CASE REPORT

A sixty-three-year-old woman was admitted to the Clinic of Neurosurgery, Clinical Center Niš, Serbia, at November 2016. after she underwent a CT brain scan that showed a large tumor of the left cerebellopontile angle (Figure 1).

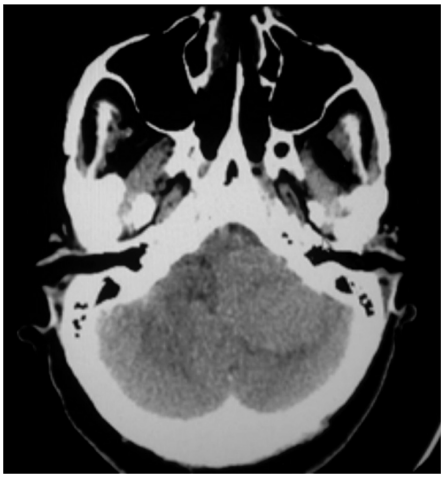


Figure 1. *Preoperative CT scan - large tumor of the left cerebellopontile angle*

Except for extreme vertigo, horizontal nystagmus and walking instability, neurological examination showed no other pathological findings. Digital subtraction angiography presented a large, highly vascularized tumor lesion that compressed the brain stem (Figure 2).

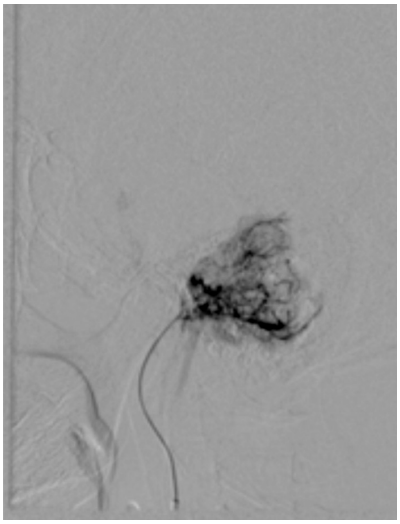


Figure 2. *Digital subtractionon angiography - highly vascularized tumor lesion*

The patient underwent endovascular procedure, and complete embolization of the tumor vessels was established (Figure 3). ASAHI Masters PARKWAY HF KIT guide wire preloaded micro-catheter was used for the application of embolization material: Bead-Block 500–700 μm compressible polyvinyl-alcohol microspheres in the quantity of 1 ml. The radiologist delivered embolization material via the left ascending pharyngeal artery.

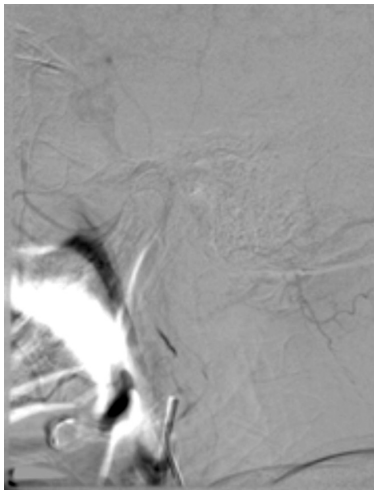


Figure 3. *Post-embolization finding – complete obliterated tumor vessels*

In the next 24 hours, an operation was performed. The patient was operated in the sitting position, using all the necessary monitoring equipment. Surgery lasted for 9 hours, and the patient lost 320 ml of blood. Radical extirpation surgery (Simpson grade I) was performed. Postoperatively, the patient's GCS was 15, with no new neurological deficit. Postoperative brain CT scan showed neither rest tumor nor blood inside the tumor bed (Figure 4).

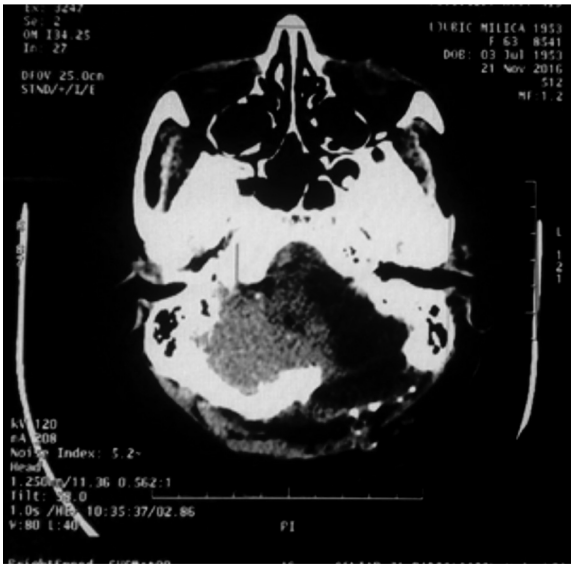


Figure 4. *Control brain CT scan – favorable finding*

Ten days after admission and 7 days after the operation, the patient was discharged from the hospital. The pathohistological finding reveled atypical meningioma grade II.

DISCUSSION

The two main problems concerning surgery are bleeding and infection. Postoperatively, infection of CNS could be fatal in a significant percentage, especially if bacterial meningitis occurs. Intra-operatively, bleeding could be an urgent problem, and any method that reduces it is of essential importance for surgery. Tumor embolization is one such method. Ideal tumor embolization can be achieved by the occlusion of the small vessels within a tumor, while preserving supply to the surrounding neural tissue. Sometimes, this golden standard of embolization can be outflanked (5).

Due to the lack of randomized controlled clinical trials, it is difficult to assess the usefulness of preoperative embolization of meningioma vessels to consider it a standard practice (6). Nevertheless, if there is an opportunity of reducing intraoperative bleeding and therefore decreasing surgical morbidity by reducing blood loss, shortening operative procedure time, allowing better visualization of surgical filed, and therefore increasing the chances of complete surgical resection and reducing the possibility of damaging the surrounding normal tissue, then there is hardly any surgeon who would not embrace it.

Tumor derives its vascular supply from a dominant vessel, and is visualized as a "blush" after applying a contrast injection. In the region of the anterior and temporal skull base, meningiomas are vascularized via the middle meningeal and accessory meningeal arteries arising from the internal maxillary artery. Olfactory groove meningioma usually has blood influx from the ethmoidal arteries. In this case report, meningeal tumor was usually vascularized from the anterior and posterior branches of the left or right VA, with the support of meningeal branches via the ascending pharyngeal and occipital arteries. In this case, the radiologist used endovascular approach via ascending pharyngeal artery and completely obliterated tumor vasculature.

Few decades ago, materials like gel foam, lyophilized duramater and several kinds of catheters were available (7, 8) for tumor embolization. Nowadays, new materials and techniques make tumor vessels' embolization relatively safe and reliable option in preoperative treatment (9, 10, 11, 12). Intra-arterial perfusion MRI and a new imaging modality for identifying biomarkers can reveal perfusion status and extent of ischemia in embolized meningiomas, thus becoming new, very useful diagnostic tool in meningioma patients (13).

We used asimilar therapeutic approachas some authors (14) and achieved complete tumor mass embolization. In the study of Gruber et al. (9), the total or subtotal angiographic devascularization of the tumor parenchyma was accomplished in more than 60% of cases of intracranial meningiomas (9). Our patient had no post-embolization complications, which is similar to some studies that have shown low to moderate percentage of post-embolized complication in patients with cranial meningioma, ranging from 5% to 17% (6, 9). Blood loss during our operation of embolized large tumor was less than 500 ml, similarly to data published in Sigla's (6) paper where average blood loss was 574 ml.

In the same study, an average time of surgery was 4 hours and 18 minutes, while our operation lasted much longer. Location of the tumor adherent to the brain stem, which demands a careful microscopic arachnolisis, with the preservation of all cranial nerves and vessels contained inside the pontocerebellar angle, is a reason for prolonged duration of surgery. Using CUSA could have expedited the operation, but technical reasons prevented us from using it.

Atypical meningiomas are difficult to treat as they have high recurrence and low survival rates. In the series of Jo et al. (15), complete resection of the tumor was a key determinant for a preferable outcome. Adjuvant radiation therapy is recommended if incomplete surgical resection was performed.

CONCLUSION

Despite some clinicians' dilemma considering the utility of preoperative embolization of meningioma vessels, we believe that a team of educated and dedicated radiologist and neurosurgeon could achieve great results in resection of large and inaccessible cranial tumors.

Acknowledgements

We are grateful to the patient for giving her permission for the publication of this paper.

Abbreviations

CT — computed tomography,
GCS — Glasgow Coma Score,
CNS — central nervous system,
VA — vertebral artery,
MRI — magnetic resonance imaging,
CUSA — Cavitron Ultrasound Surgical Aspirator

Conflict of interest

Authors confirmed that no actual or potential conflict of interest exists in relation to this article.

Source of Funding

There were no external funding sources for this study.

Sažetak

ENDOVASKULARNA PRIPREMA ZA DELIKATNU OPERACIJU MENINGEOMA — PRIKAZ SLUČAJA

Kostić Aleksandar,[1] Ristić Saša,[2] Nikolov Vesna,[1] Stefanović Ivan,[1]
Dželebdžić Zvonimir,[1] Berilažić Luka[1]

[1] Klinika za neurohirurgiju, Klinički centar Niš, Srbija
[2] Institut za radiologiju, Klinički centar Niš, Srbija

Uvod: Preoperativna embolizacija može učiniti resekciju tumora manje komplikovanom tako što skraćuje vreme operacije i smanjuje intraoperativni gubitak krvi.

Prikaz slučaja: U ovom prikazu slučaja, prikazali smo bolesnicu staru 63 godina, koja je primljena na Kliniku za neurohirurgiju Kliničkog Centra u Nišu, novembra 2016, nakon urađenog CT-a mozga koji je pokazao postojanje velikog tumora pontocerebelarnog ugla. Panangiografija krvnih sudova mozga je pokazala da je tumor koji vrši kompresiju na moždano stablo, dobro prokrvljen. Kod bolesnice je preduzeta endovaskularna procedura, kompletna embolizacija tumorskih krvnih sudova. Interventni radiolog je embolzacioni material isporučio u tumorsku masu preko a. pharingicae ascedens. Resekcija tumora je izvršena u sledećih 24 sata, po tipu kompletnog odstranjenja, (Simpson gradus I). Postoperativno, bolesnica je bila potpuno svesna, bez novonastalih neuroloških deficita. Postoperativni CT mozga je pokazao da nema ostataka tumora, niti krvarenja u loži. Patohistološki nalaz je ukazao na atipični meningeom, gradus II.

Zaključak: Uprkos dilemi nekih kliničara oko upotrebne vrednosti preoperativne embolizacije, mišljenja smo da edukovani i posvećeni tim radiologa i neurohirurga može postići velike rezultate u operacijama velikih i teško pristupačnih tumora.

Ključne reči: embolizacija, meningeom, vaskularizovani tumori.

REFERENCES

1. Lazzaro MA, Badruddin A, Zaidat OZ, Darkhabani Z, Pandya DJ, Lynch JR. Endovascular embolization of head and neck tumors. Front Neurol. 2011; 2: 64.

2. Becker H. Complication following embolization of a meningioma. ClinNeuroradiol. 2010; 20(4): 237–41.

3. Shimoda Y, Osanai T, Terasaka S, Kobayashi H, Yamaguchi S, Endo S, et al. Efficiency of embosphere in the preoperative embolization of meningioma: clinical experience No ShinkeiGeka. 2016; 44(7): 555–60.

4. He HW, Jiang CH, Wu ZX, Li YX, Lü XL, Wang ZC. Transvenous embolization with a combination of detachable coils and Onyx for a complicated cavernous duralarteriovenous fistula. Chin Med J (Engl). 2008; 121(17): 1651–5.

5. Minakawa T, Koike T, Tanaka R, Ito J. Disappearance of a tumor shadow fed by the tentorial artery after embolization of the external carotid artery. Surg Neurol. 1987; 28(3): 208–10.

6. Singla A, Deshaies EM, Melnyk V, Toshkezi G, Swarnkar A, Choi H, et al. Controversies in the role of preoperative embolization in meningioma management. Neurosurg Focus. 2013; 35(6): E17.

7. Richter HP, Schachenmayr W. Preoperative embolization of intracranial meningiomas. Neurosurgery. 1983; 13(3): 261–8.

8. Berenstein A, Kricheff II. Catheter and material selection for transarterial embolization: technical considerations. II. Materials. Radiology. 1979; 132(3): 631–9.

9. Gruber A, Killer M, Mazal P, Bavinzski G, Richling B. Preoperative embolization of intracranial meningiomas: a 17-years single center experience. Minim Invasive Neurosurg. 2000; 43(1): 18–29.

10. Kusaka N, Tamiya T, Sugiu K, Tokunaga K, Nishiguchi M, Takayama K, et al. Combined use of TruFill DCS detachable coil system and Guglielmi detachable coil for embolization of meningioma fed by branches of the cavernous internal carotid artery. Neurol Med Chir (Tokyo). 2007; 47(1): 29–31.

11. Esquembre V, Cabanes J, Vazquez-AZón V, Chirivella M, Giner R, Gutiérrez A, et al. Preoperative embolization of a ponto-cerebellar meningioma. Advantages and indications. Neurocirugía. 2001; 12(4): 342–7.

12. Felbaum DR, Mueller K, Liu AH, Armonda RA. Onyx embolization of a meningioma with a dysplastic aneurysmal anterior cerebral artery vessel. Cureus. 2016; 11; 8(9): e776.

13. Shah A, Choudhri O, Jung H, Li G. Preoperative endovascular embolization of meningiomas: update on therapeutic options. Neurosurg Focus. 2015; 38(3): E7.

14. Fang QR, He XY, Li XF, Zhang X, Chen M, Li H, et al. Comparative efficacy of Glubran and polyvinyl-alcohol particles in the embolization of meningiomas. Int J Neurosci. 2016; 126(12): 1112–9.

15. Jo K, Park HJ, Nam DH, Lee JI, Kong DS, Park K, et al. Treatment of atypical meningioma. J ClinNeurosci. 2010; 17(11): 1362–6.

Correspondence to/Autor za korespondenciju
Aleksandar Kostić
Clinical center Niš,
Bld. Zorana Đinđića 48
18000 Niš, Serbia
Email: aleko018@yahoo.co.uk
tel: +381631094208

SANAMED
2017; 12(1): 45–50
ISSN-1452-662X

DOI: 10.24125/sanamed.v1i1.158
UDK: 606:615.3
ID: 231281932
Review article

REGULATORY CONSIDERATIONS OF BIOSIMILARS AND CLINICAL DILEMA OF THEIR USE

Stavrik Genadieva Sonja,[1] Grozdanova Aleksandra,[2] Netkovska Ancevska Katerina,[2] Dimitrova Genadieva Magdalena,[3] Dimitrov Gligor[4]

[1] University "Ss. Cyril and Methodius", Medical faculty Skopje, University hematology clinic, Skopje, R. Macedonia
[2] University "Ss. Cyril and Methodius", Faculty of Pharmacy Skopje, R. Macedonia
[3] University "Ss. Cyril and Methodius", Medical faculty Skopje, University gastroenetrology clinic, Skopje, R. Macedonia
[4] University "Goce Delcev", Medical faculty Stip, R. Macedonia

Primljen/Received 19. 10. 2016. god. Prihvaćen/Accepted 20. 01. 2017. god.

Abstract: Biomedical products are complex molecules, produced by living cells. More accurately, they are molecules that are naturally produced in the human body, like hormones or growth factors, monoclonal antibodies, blood products, immunological medicinal products, sera and vaccines, allergens, and advanced technology products such as gene and cell therapy products. Copies of these drugs, known as biosimilars, are comparable but not identical and are not generic version of innovator biological products. Specific regulatory requirements and abbreviated registration process apply in the case of biosimilars, in order to demonstrate efficacy and safety profile and to prove that product is similar to the original biomedical product.

Like all medicines, biological medicines work by interacting with the body to produce a therapeutic outcome, but the mechanisms by which they do this may vary from product to product and through indications. Therefore the role of the physicians in treatment of patients with these complex medicinal products is particularly important.

Regulatory issues, manufacturing, safety, physicians have part in develop use of biosimilars as much as generic drugs. Even though, the most important factor for market of biosimilar are commercial factor, still, real clinical dilemma of use are present, so it is necessary to have clear regulatory framework and postmarketing data on the use of biosimilars.

Keywords: biosimilars, innovate product, monoclonal antibodies, regulatory.

INTRODUCTION

Biomedical products are drugs whose active substance is made by living systems (plant or animal cells, bacteria, viruses and yeast) and biological medicines are used to treat diseases and genetic disorders in humans. Biological drugs are well established in the treatment of many conditions with increasing use in future years. Many, but not all biological medicines, are made using genetically-modified cells. The global biologic industry has come a long way since its first drug Humulin, that has been awarded US Food and Drug Administration (FDA) approval in 1982 (1). Biological sales now account for about US$92 billion and are expected to worth more than US$176 billion by 2015 (2). Biosimilars are biological products that are similar, but not identical, to an innovator product that is already on market and its patent has expired (3).

Biosimilars is a drug that is designed to be similar to the existing biological reference drug. Due to the complex of biological products and manufacturing process, there will always be small differences in molecular structure, more than reference one. Each manufacturer has its own unique cell lines and develops its own proprietary (unique) manufacturing processes. It is noted that some biological medicines are produced by non-Biotechnology methods and are therefore not necessarily authorized through the centralized procedure. The production of biological medicines involves processes such as fermentation and purification. The manufacturing processes for biological medicines are very sensitive and it is vital that these are precisely controlled in order to obtain consistent results and to guarantee the safety and efficacy of the final product.

When all intellectual property protection and marketing exclusivity for the references drugs have expi-

red, copying can be offered by other biotech company. The patent expire of many biological drugs will open the door for numbers of biosimilars to enter the market. Marketing approval legal regulation is much more complex issue than generic equivalents of reference drugs.

In order to innovating product enter the clinical use, clinicans should be aware of use biosimilars of some of the issues that have emerged during the development and approval of these products (4).

The aim of this article is to introduce and describe specific perplexities regarding the regulatory considerations of biosimilars and the clinical dilemma of their use, that often occurs in clinicians.

CLINICAL DILEMMA OF USE

From clinical point of view it is always interesting to share your experience with other clinicians and pharmacists, because there is no universal rule.

Monoclonal antibody was one of the biggest advancement in treating the hematologic malignant diseases. In November, 1999 in Journal of Clinical Oncology Ronald Levy published Karnofsky lecture: Immunotherapy of Lymphoma. He claimed "Monoclonal antibodies are the first example of the payoff for cancer treatment that comes from our knowledge of the immune system. Monoclonal antibodies were the product of a fundamental discovery and they are now changing the paradigm of how disease are diagnosed and treated"(5).

The goal of CD 20 targeted therapy is to kill B lymphocytes by the use of monoclonal antibodies (MoAbs) against the B cell specific human CD 20 molecule. As a clinicians we are aware that rituximab is a human-to-mouse chimeric monoclonal antiCD20 antibody. Rituximab acts via three different mechanisms: complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), induction of apoptosis and complexity of interaction between these mechanisms. Today, rituximab is a mainstay in the therapy of a broad variety of B-cell malignancies, but we still do not understand the exact mechanism of action responsible for rituximab's anti-tumor effects (6).

In 1997 the first MoAb called rituximab was approved by US Food and Drug Administration, specifically for the treatment of patients with relapsed/refractory CD20 positive low-grade/follicular lymphoma (7). Today, nearly over two decades later, rituximab has become a benchmark of a target therapy and one of the biggest treatment successes in B-cell lymphoid malignances. So, today the standard of care for a vast majority of B-cell lymphoid malignant hematologic disease include rituximab as single agent or in combination with chemotherapy. Rituximab has enhanced the outcome of patients with B cell hematologic malignancies by the great deal and has become a part of a therapy for newly diagnosed patients with B-cell Non-Hodgkin lymphoma at the stage of diagnosis as well as for relapsed patients. The improvement in response rate, progression free survival and overall survival in patients treated with immunochemotherapy makes rituximab the standard for care of the patients with indolent B-cell lymphoma as well as for the B cell high grade lymphoma. Rituximab has greatly changed the manner in which B-cell NHL are treated. (8). After long term follow up data had been available to be analyzed and introduction of rituximab combined with chemotherapy translated into improved survival in patients with B-cell indolent and aggressive lymphoma. A combination of rituximab and an antracyline-based chemotherapy has been accepted as the standard of treatment for patients with any stage diffuse large B-cell lymphoma. Patients with follicular B-cell lymphoma, as the most frequent low-grade lymphoma, after induction therapy, should be treated with maintenance program after immunochemotherapy for two years with rituximab as a single agent.

So, there is no dough, that a huge cohort of patients has been successfully treated with rituximab. Rituximab has been recognized as well-tolerated, relatively safe and very important often less invasive alternative in comparison with traditional mostly chemotherapy based therapies for those conditions. We must emphasize that these conclusions are based on a results gathered from multicenter randomized studies and the measuring of the efficacy of rituximab has been estimated through response rate, progression free survival and overall survival (9).

From clinical point of view, doctors can assess response rate of the treatment very early but there is a high risk of relapse, so response rate is not firm surrogate for estimating the therapeutically results. Progression free survival may not correlate to the overall survival. So, overall survival is the hardest to achieve but is the safest in order to estimate the effect of treatment of these patients. Sometimes we need follow-up of the lymphoma patients treated with rituximab for a long period of time, even a decade to clearly estimate the benefit of treatment. Every clinician will agree that only survival data will safely demonstrate equivalence (10).

Rituximab biosimilars are at an advanced stage of development and pharmacokinetic data seems identical. Having in mind that every monoclonal antibody is unique, meaning that only small structural change can have significant consequence in terms of efficacy, safety and immunogenicity. Moreover, much of the development and clinical experience gained from the generation and optimization of antibody clearly emphasized

that assays might not be able to discriminate differences and safety may differ with impurity profile, so efficacy might not be transferable (11).

Many questions are waited to be answered. Do we have firm evidence or are we still in need of the robust clinical trials to ensure comfort among hematologist who treat malignant hematologic diseases. Based on the definition, that biosimilars are the agents that are similar but not identical to the reference biopharmaceutical monoclonal antibody-biosimilar have been introduced and described as products with well-established manufacture and structural characterization, with available potency assays, well established function, well known safety profile and well established efficacy profile (12).

From the practice points of view, legislative battles are still going on, so clinicians need to be active participants in such a debate. At the present moment there are no dilemmas whether clinicians have a huge clinical experience, but in some points still a limited understanding of the biosimilars, due to the fact of its origin, that is quite distinct from traditional generics. Clinical potential of monoclonal antibodies have to be increased by improving existing properties as a key strength of antibodies as therapeutic and it is still unmet need. A clinical imperative is to achieve a better outcome for patients and to target malignant cell with more potent and effective monoclonal antibody.

REGULATORY CONSIDERATIONS OF BIOSIMILARS

A generic drug is a less expensive copy of an innovator drug product. Generic can be produced when the patent on a drug has expired, for drugs which have never held patent, in countries where patent is not in force, so generic company can certify that the branded company patent is invalid or unenforceable. Generic drug applications are generally not required to include preclinical and clinical data to prove safety and effectiveness. The generic manufacture demonstrates only pharmaceutical equivalence and bioequivalence between generic and innovator products.

However, this approach cannot be applied to biosimilars, because the active substance of biological products is a collection of large protein isoforms and not a single molecular entity, as is generally true for conventional small- molecule drugs. Thus the active substances in two products are highly unlikely to be identical and, therefore, unlike generics, biosimilars are only similar and not identical to the innovator products. These differences imply that biosimilars should not be approved and regulated in the same way as conventional generic drugs.

The regulatory process for approval of biosimilars is more complex than for the generic innovator product because the design of a scientifically valid study to demonstrate the similarity of a highly process-dependent product is not easy. Further, the analytical tests currently available are not sophisticated enough to detect the slight but important structural differences between innovator and biosimilar products. Modest differences may have clinical implications and pose a significant risk to patient safety. Therefore, it is considered necessary that biosimilars must be assessed for clinical efficacy and safety by valid preclinical and clinical studies before marketing approval (13, 14, 15, 16).

The European Union (EU) has established a regulatory framework for the marketing authorization of biosimilars, based on comparative quality and clinical pharmacokinetic studies, nonclinical studies, clinical pharmacodynamic studies, and limited toxicology studies, as well as comparative clinical efficacy and tolerability studies. In the USA, a regulatory framework was established in 2010 (17). The market accessibility of biosimilars may reduce costs to patients and social security systems. In general, the literature expects biosimilar medicines to be around 15% to 30% cheaper. For instance, a European analysis observed that in 2009, the percentage price difference between reference biopharmaceuticals and biosimilar medicines amounted to 14% for somatropin, 17% for erythropoietin, and 35% for filgrastim. The market accessibility of biosimilars is also motivated by key government objectives related to, for instance, building manufacturing capabilities within a country than reference biopharmaceutical medicines (18). In this respect, some European countries have implemented industrial policies to encourage the development of biological products (19). For example, even though Croatian guidelines do not permit the substitution of originator with biosimilars, data collected from Clinical Hospital Centre Rijeka, in the period 2014-2016, showed increased trend of infliximab biosimilars prescribing, while the market share for erythropoietin's and filgrastim's is more stable. That means that although procurement for some of the biosimilar medicines is regulated at the hospital level, still there is difference within market dynamic and different biosimilar therapy areas (20). Another study done to project drug cost savings from the introduction of biosimilar trastuzumab showed that savings and price discount only for this biosimilar medicine can be between 15% (0.26 million euros) up 35 % (0.69 million Euros) (21).

Interchangeability and/or substitution of innovator drug with biosimilars is also a big clinical and regulatory challenge. Interchangeability refers to the prescription of a biosimilar in place of the reference prod-

uct by prescribers, while substitution means that pharmacists are allowed to dispense a biosimilar (22). This is due to the assumption that generic drugs and reference drugs are considered identical molecules if they have demonstrated bioequivalence. But, since biosimilar drugs are not exact copies and the generic approach cannot be applied in this case, the discussion whether they can be substitutes of original biologics is still open. Interchangeability and substitution of biosimilars is not regulated buy any EU regulatory document and EMA does not have the authority to designate a biosimilar as automatically substitutable, so it is left to each member country to decide how this process is going to be defined (23). European Consensus document released by the European Commission notes that interchangeability implies an initiative or agreement by the prescriber, patients and pharmacist about switching decisions and changing therapy from one biologic product to another (24).

Substitution and interchangeability of biosimilars are closely tied to their naming because when doctors prescribe biologics by a unique identifier, and not by their INN, the substitution of a biosimilar product when dispensed by a pharmacist would likely occur much less often. In practice, substitution by a pharmacist of a biosimilar for a reference biopharmaceutical medicine in general is not allowed in any European country (25) and is not recommended by the World Health Organization or by medical societies. The major concern about interchangeability is that repeated switches between the biosimilars and the reference biological may increase immunogenicity, leading to adverse reactions. Even during pharmacovigilance the studies are typically designed on patient population and never follow a single patient, making it very difficult to track the status of interchangeability issues. Therefore, it would be difficult for regulatory bodies to certify that the drug is truly interchangeable without adequate data. There has been considerable debate over this issue in all regulatory agencies and the EU Generics Association claims that more than 12 countries have rules against automatic substitution. However, France has now permitted the switch of biosimilars and generics with the originals as part of a new Social Security Budget Legislation (article 47), which came into practice in January 1st, 2014 (26). Still, due to the concerning health risks and differences of biosimilars in relation to the reference product, giving uncertainty for prescribers and patients, the application of interchangeability and/or substitution is limited. Nevertheless, the use of biosimilars in the clinic practice may have a positive impact in the near future, leading the way towards adequate decisions (27).

CONCLUSION

The first generation of biomedical products manufactured using recombinant technologies was in the 1980s, and they are now on the way to patent expiration. As a result research based and generic pharmaceutical companies are making effort to develop substitutes for original biologics, referred as biosimilars. Nevertheless, introducing a biosimilar to an innovator product is far more complex than introducing a generic equivalent to innovator product based on a new chemical entity. Biomedical products are produced by cells in culture which are more variable than chemical synthesis methods. However, for generic pharmaceuticals, it is impossible to generate the same or identical copy of an innovator product. The field of biosimilars presents more challenges such as: verification of similarity, compatibility of biosimilars and innovator, unique naming to various products, regulatory framework, marketing, intellectual property rights, and safety. EU countries through EMA had established a tied regulatory framework for the licensing of biosimilars, but still the questions of naming and nomenclature of biosimilars, interchangeability and substitution, pharmacovigilance and the degree of comparability between a biosimilar and the reference need to be considered. Also there is a need for more comparative studies in order to collect the data necessary to follow-up and evaluate uncertainties concerning the long term safety, effectiveness, and cost-effectiveness of a biosimilars.

Conflict of interest

The authors declare that there is no conflict of interest.

Licensing

Sažetak

RAZMATRANJE REGULATIVA BIOSIMILARA I KLINIČKE DILEME U NJIHOVOJ PRIMENI

Stavrik Genadieva Sonja,[1] Grozdanova Aleksandra,[2] Netkovska Ancevska Katerina,[2] Dimitrova Genadieva Magdalena,[3] Dimitrov Gligor[4]

[1] University "Ss. Cyril and Methodius", Medical faculty Skopje, University hematology clinic, Skopje, R. Macedonia
[2] University "Ss. Cyril and Methodius", Faculty of Pharmacy Skopje, R. Macedonia
[3] University "Ss. Cyril and Methodius", Medical faculty Skopje, University gastroenetrology clinic, Skopje, R. Macedonia
[4] University "Goce Delcev", Medical faculty Stip, R. Macedonia

Biomedicinski proizvodi su kompleksni molekuli, koje stvaraju žive ćelije. Tačnije, to su molekuli koji se prirodno stvaraju u živom organizmu, kao što su hormoni ili faktori rasta, monoklonalna antitela, produkti krvi, imunološki proizvodi, sera i vakcine, alergeni, kao i proizvodi nastali zahvaljujući naprednim tehnologijama, kao što su geni i terapija ćelijskim produktima. Kopije ovih lekova, poznatije kao biosimilarni, su komparabilni, ali ne i identični, i nisu generička verzija inovativnih bioloških produkata. Specifični regulatorni zahtevi, kao i skraćeni proces registracije se primenjuje u slučaju biosimilarnih proizvoda, u cilju pokazivanja efikasnosti i sigurnosti profila i radi dokazivanja da je proizvod sličan originalnom biomedicinskom proizvodu.

Kao i svi lekovi i biološki lekovi deluju tako što se resorbuju u organizmu i završavaju se terapeutskim ishodom, ali mehanizam delovanja zavisi od proizvoda do proizvoda. S toga, uloga kliničara u prepisivanju lekova ove vrste je od izuzetnog značaja.

Pitanja regulativa, proizvodnje, bezbednosti su pitanja koja se odnose na korišćenje biosimilara, kao i generičkih lekova. Iako su za distribuiranje biosimilara najbitniji komercijalni faktori, dileme kliničara su i dalje prisutne, tako da je neophodno da postoji tačan regulatorni okvir kao i postmarketinški podaci i instrukcije o korišćenju biosimilara.

Ključne reči: biosimilari, inovativni produkti, monoklonalna antitela, regulative.

REFERENCES

1. Gienentech Inc. Corporate Chronology. 1982. http://www.gene.com/gene/about/corporate/history/timeline.html.

2. Global Biopharmaceutical Market Report (2010-2015) IMARC October 29, 2010: 234 pages. Pub ID: IMRC2849563.

3. Mc Kinnon RA, Lu CY. Biosimilars are not (bio)generics. Aust Prescr, 2009; 32(6): 146–7.

4. Ledford H. Biosimilar drugs poised to penetrate market. Nature. 2010; 468(7320): 18–9.

5. Levy R. Karnofsky Lecture: Immunotherapy of lymphoma. J Clin Oncol 1999; 17(11 suppl): 7–12.

6. van Meerten T, Hagenbeek A. CD20 - target therapy: The next generation of antibodies. Semin Hematol. 2010; 47(2): 199–210.

7. Sousou T, Friedberg J. Rituximab in indolent lymphomas. Semin Hematol. 2010; 47(2): 133–42.

8. Zwick C, Murawski N, Pfeundshuh M, German High-Grade Non-Hodgkin Lymphoma Study Group. Rituximab in High-Grade Lymphoma. Semin Hematol. 2010; 47(2): 148–55.

9. Reichert JM, Rosenweig CJ, Faden LB , Dewitz MC. Monoclonal antibody successes in the clinic. Nat Biotechnol. 2005; 23(9): 1073–8.

10. Hirsch BR, Lyman GH. Biosimilars: A cure to the U.S. health care cost conundrum? Blood Rev. 2014; 28(6): 263–8.

11. Jahn EM, Schneider CK. How to systematically evaluate immunogenicity of theraeutic proteins- regulatory considerations. N Biotechnol. 2009; 25(5): 280–6.

12. Simoens S. Biosimilar medicines and cost-effectivness. Clinicoecon Outcomes Res. 2011; 3: 29–36.

13. Crommelin D, Bermejo T, Bissig M, et al. Pharmaceutical evaluation of biosimilars: important differences from generic low-molecular-weight pharmaceuticals. Eur J Hosp Pharm Sci. 2005; 11(1): 11–7.

14. Roger SD. Biosimilars: how similar or dissimilar are they? Nephrology (Carlton). 2006; 11(4): 341–6.

15. Roger SD, Mikhail A. Biosimilars: opportunity or cause for concern? J Pharm Pharmaceut Sci. 2007; 10(3): 405–10.

16. Schellekens H. Follow-on biologics: challenges of the žnext generation'. Nephrol Dial Transplant. 2005; 20(suppl 4): 31–6.

17. Mellstedt H. The future of biosimilars. Hosp Pharm Europe. 2010; 49: 33–4.

18. Long M, Trout J, Akpinar P. Biosimilars: HGH to TNFS, how will payers respond? ISPOR 12th Annual European Congress; October 26, 2009; Paris, France.

19. Danzon PM, Furukawa MF. Prices and availability of biopharmaceuticals: an international comparison. Health Aff (Millwood). 2006; 25(5): 1353–62.

20. Stanic Benic M, Jakovac S, Zekic T, Vlahovic-Palcevski V. Trend of Biosimilars Prescribing In A Croatian Teaching Hospital. Clin Ther. 2016; 38(10S).

21. Cesarec A, Likić R. Budget impact analysis of biosimilar Trastuzumab for the treatment of breast cancer in Croatia. Appl Health Econ Health Policy. 2016 Oct 11. [Epub ahead of print].

22. European Generic Medicines Association. Biosimilars Handbook. 2nd ed. Brussels: European Generic Medicines Association, 2011.

23. Grozdanova A, Netkovska KA, Sterjev Z, Naumovska Z, Zarevski R, Dimovski A, et al. Biosimilar medical products - licensing, pharmacovigilance and interchangeability. Pril (Makedon Akad Nauk Umet Odd Med Nauki). 2016; 37(1): 27–36.

24. Consensus Information Paper 2013. What you need to know about Biosimilar Medicinal Products. European Commission. Available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf.

25. EMA. Questions and Answers on Biosimilar Medi-cines, 2012. Available from: http://www.ema.europa.eu/docs/ en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf.

26. France to allow biosimilars substitution. 2014. Available at: http://www.gabionline.net/Policies-Legislation/France-to-allow-biosimilars-substitution/(highlight)/france%20 substitution.

27. Weise M, Kurki P, Wolff-Holz E, Bielsky MC, Schneider CK. Biosimilars: the science of extrapolation. Blood. 2014; 124(22): 3191–6.

Correspondence to / Autor za korespondenciju
Prof Dr Sonja Genadieva Stavrik
University hematology Clinic
Medical faculty Skopje, R. Macedonia
Vodnjanska 17, 1000 Skopje, R. Macedonia
email: sgenstav@yahoo.com
tel: +389 70 222 031

SANAMED
2017; 12(1): 51–56
ISSN-1452-662X

DOI: 10.24125/sanamed.v1i1.161
UDK: 617.711-002-084; 616.98:578.826
ID: 231320332
Review article

PREVENTION OF ADENOVIRAL EYE INFECTION — REVIEW

Janicijevic Katarina,[1] Kocic Sanja,[1] Radovanovic Snezana,[1] Radevic Svetlana,[1] Vasiljevic Dragan,[1] Djonovic Nela,[1] Sarenac Vulovic Tatjana[1, 2]

[1] Faculty of Medical Sciences, University of Kragujevac, Serbia
[2] Clinic of Ophthalmology, Clinical Centre of Kragujevac, Serbia

Primljen/Received 04. 11. 2016. god. Prihvaćen/Accepted 19. 12. 2016. god.

Abstract: Epidemic viral conjunctivitis caused by adenovirus is the most common infectious conjunctivitis. The exact incidence of adenoviral conjunctivitis is still poorly known, but there are two well-defined adenoviral keratoconjunctivitis clinical syndromes: epidemic keratoconjunctivitis (EKC) and pharyngoconjunctival fever (PCF). Epidemic keratoconjunctivitis is also the most severe form and presents with watery discharge, hyperemia, chemosis and ipsilateral lymphadenopathy. Diagnosis is mainly clinical, but its etiology can be confirmed using cell cultures, antigen detection, polymerase chain reaction or immune-chromatography. Multiple treatments have been tried for this disease, but none of them seem to be completely effective. Viruses are resistant to desiccation and certain common surface disinfectants. Prevention is the most reliable and recommended strategy to control this epidemic infection. Global epidemic surveillance system definitely needs to be established to monitor and analyze the epidemic conjunctivitis in the future. There is clearly a need for the national and the military public health institutions to work together on guidelines to handle future challenges.

Key words: epidemic, adenoviral, conjunctivitis, keratitis, diagnosis, therapy, prevention.

INTRODUCTION

PREVENTION OF ADENOVIRAL EYE INFECTION — REVIEW

Keratoconjunctivitis is corneal and conjunctival inflammation. Epidemic viral conjunctivitis caused by adenovirus is the most common infectious conjunctivitis and a highly contagious eye disease that occurs worldwide. Cases are more frequent during warmer months. Epidemiological analysis indicated the regional and the seasonal distribution dominated in the winter and early spring. The exact incidence of adenoviral conjunctivitis is still poorly known (1).

There are two well-defined adenoviral keratoconjunctivitis clinical features: epidemic keratoconjunctivitis and pharyngoconjunctival fever, which are caused by different serotypes. Adenoviruses are highly contagious pathogens. Pathogens commonly detected in epidemic keratoconjunctivitis outbreaks are human adenovirus serotypes 8, 19, 37, etc. Epidemic keratoconjunctivitis caused by new genomic variants of adenovirus types 8, 19 and 37 (2). Adenovirus serotype 8 represents the main agent of epidemic keratoconjunctivitis and outbreaks mainly occur in hospital wards. Adenoviruses' conjunctivitis is generally severe, lasting two to three weeks. Keratitis with persistent infiltrates may be observed for more than a year (2).

Keratoconjunctivitis caused by adenoviruses (epidemic keratoconjunctivitis, ICD10, B30) is very common. It can be severe and may cause significant morbidity. In the early stages of adenoviral infections, it is often difficult to differentiate the clinical presentation from other causes of red eye (3).

Incubation period is approximately 14 days. The modes of transmission are mainly through hand-eye contact, ocular secretions and contact with ophthalmic care providers and the medical instruments. Epidemic keratoconjunctivitis is also the most severe form and presents with irritative triade, mixed hyperemia, chemosis, conjunctival membranes and subconjunctival hemorrhage, corneal subepithelial infiltrates and ipsilateral lymphadenopathy. Pharyngoconjunctival fever is characterized by abrupt onset of high fever, pharyngitis, bilateral conjunctivitis and periauricular lymph node enlargement. Adenoviral infection typically starts with a unilateral foreign body sensation and then develops, within a few hours or days, into bilateral keratoconjunctivitis with marked chemosis, epiphora and

photophobia. Because of its highly resistant properties to desiccation and highly developed escape mechanisms which protect the virus from the host's immune response, long-term problems often remain. Remnants of viral proteins often persist on the corneal surface of Bowman's layer for a long time, and may lead to the formation of subepithelial infiltrates (4).

Epidemic keratoconjunctivitis is eye infection characterized by inflammation of the conjunctiva and cornea and can result in vision loss. Visual impairment can persist for months because of subepithelial corneal infiltrates (nummular), irregular astigmatism, etc. Several complications, such as corneal erosion and conjunctival pseudomembrane, are observed in some of the cases and corneal subepithelial opacity may bring visual impairment (5).

DIAGNOSES

Diagnosis is mainly clinical, but its etiology can be confirmed using cell cultures, antigen detection, polymerase chain reaction or immunochromatography, etc (6).

Even today the diagnosis is still mainly clinical, with laboratory tests only rarely contributing. New diagnostic tests, such as the Rapid Pathogen Detector, the AdenoPlus detection kit, that are practical, rapid and expensive to use in the general practice may obviate the problems (7).

THERAPEUTIC APPROACHES

There is no actual treatment of epidemic keratoconjunctivitis and therefore preventive measures appear as essential to avoid and/or limit such outbreaks in hospital wards. Multiple treatments have been tried for this disease, but none of them seem to be completely effective. Viruses are resistant to desiccation and certain common surface disinfectants. Contagion is possible through direct contact or fomites and the virus is extremely resistant to different physical and chemical agents. Effective antiviral treatments and vaccines are not available. Antiseptics and disinfectants are extensively used in hospitals and other health care settings for a variety of topical and hard-surface applications. A wide variety of active chemical agents (biocides) are found in these products, many of which have been used for hundreds of years, including alcohols, phenols, iodine and chlorine. Most of these active agents demonstrate broad-spectrum antimicrobial activity. However, little is known about the mode of action of these agents in comparison to antibiotics (8).

Currently, no effective, cost-efficient and tolerable virustatic is available. Treatment is symptomatic and anti-inflammatory. Late scarring may be amenable to phototherapeutic keratectomy. Cyclosporin A eye drops are a good option with a low risk profile. The use of topical steroids can possibly be disadvantageous but can be discussed at all stages of the disease. As nosocomial spread of adenoviruses is relatively common, preventive measures remain the major responsibility for ophthalmologists (9).

PREVENTION ASPECTS 1

The virus is endemic in the general population, and frequently causes severe disease in immunocompromised patients, especially the pediatric patients. Prevention is the most reliable way to control this contagious infection (10, 11).

Disinfection of semi-critical products with alcohol 70% or in an approximate concentration can not be recommended to all health care products in an unrestricted way (12).

Isopropyl alcohol, with limited activity against adenovirus in vitro, also was being used to "disinfect" pneumo-tonometer tips between uses at six other area eye clinics polled by telephone. The results demonstrate the need for changes in the design and manufacture of equipment used in the eye clinics (13).

Epidemic keratoconjunctivitis were treated with different eye drops: cortisone, antibiotics and iodine. Iodine showed that inflammatory symptoms disappeared rapidly, corneal complications however such as superficial keratitis could not be prevented. On account of the hygienic prophylactic measures further infections could be prevented at the clinics almost completely (14).

Polymerase Chain Reaction test (PCR test) is the gold standard for the detection of human adenovirus. The same is also high costs for many clinical laboratories. The combination of homogenization and heat treatment of sensitive in-house real-time PCR provides accurate results at a price comparable price as a viral culture (15).

Employees of the Johns Hopkins Hospital with signs and symptoms of adenoviral conjunctivitis were underwent rapid diagnosis in real time PCR. Prevention of infection is a useful tool, which reduces the loss of productivity in relation to clinical diagnosis, and determines prevalence of serotype adenoviruses in working populations (16).

Hospital employees with suspected adenoviral conjunctivitis underwent evaluation and testing with real-time polymerase chain reaction. Four employees had genotypes consistent with epidemic keratoconjunctivitis. This algorithm minimizes productivity loss compared with clinical diagnosis (17).

Adenovirus was the most common virus isolated from conjunctiva (60-70%). It is essential that a rapid

and specific diagnosis is offered under atypical viral presentation for the institution of specific antiviral therapy and to avoid complications that can be a result of inappropriate treatment (18).

Around a million people in Japan are suffering from adenoviral conjunctivitis every year and it is recognized as one of the major pathogens of nosocomial infection. Remarkable anti adenoviral effect was observed in zalcitabin, sanilbudine, and interferon beta and anti-osteopontin peptide. Interferon beta and antiosteopontin peptide displayed anti adenoviral effects by absorption inhibition. These agents are divided into two categories: inhibitors of adenoviral replication-zalcitabin and sanilbudine; and suppressors of adenoviral infection- interferon beta and antiosteopontin peptide. It is expected that eye drops for specific treatment of adenoviral conjunctivitis are going to be available in the near future following investigation of therapeutic effect in adenoviral infected animals and clinical trials in humans (19).

Many different germicides (antiseptics and disinfectants) were selected for many study based on their current uses in health care. These results emphasize the need for proper selection of germicides for use in disinfecting noncritical surfaces and semi critical medical devices, such as applanation tonometer, in order to prevent outbreaks of epidemic keratoconjunctivitis (20).

PREVENTION ASPECTS 2

Many ophthalmic solutions, or laser therapies were not associated with infection, and all environmental cultures were negative. This outbreak emphasizes the need for implementation of routine infection control the guidelines to prevent nosocomial transmission of epidemic keratoconjunctivitis and stresses the need for appropriate disinfection of many instruments (21).

Epidemiology encompasses identification of infectious disease, vectors of transmission, containment practices and preventative measures to stop further transmission of disease can be contracted from interpersonal exposure, contact with contaminated items or iatrogenic transmission from health-care settings and providers. The interview process and patient education are method of epidemiologic assessment that acts as the format to dealing with the epidemics (22).

This review considers what is known about the mode of action and spectrum of activity of antiseptics and disinfectants. The widespread use of these products has prompted some speculation on the development of microbial resistance, in particular whether antibiotic resistance is induced by antiseptics or/and disinfectants (23, 24).

The evaluation of patient care practices showed that common risk factors among affected cases were measurement of ocular tension with a tonometer in the Ophthalmology Clinic (without disinfection of the tonometer between patients), contamination of work surfaces (equipment, furniture), and poor compliance of hand hygiene. Control measures adopted were cleaning, disinfection of tonometer, equipment and work surfaces, and reinforcement of hand hygiene measures. With these measures, it was possible to control the nosocomial outbreak, despite the continued outpatient care of community-acquired cases (25, 26).

The Goldmann applanation tonometer presents the problem of being one of the most widely used pieces of equipment in the ophthalmic clinics and a known risk factor for the transmission of epidemic keratoconjunctivitis. There are the 3 effectiveness methods of disinfection: alcohol swabs, immersion in peroxide and the use of disposable prisms. An economic evaluation is undertaken to assess the cost-effectiveness of the 3 alternatives. The analysis was undertaken from the hospital perspective and included all equipment and labor costs. The incremental cost-effective ratios from the cost-effectiveness analysis were $12,000/case averted using peroxide and $61,000/case averted with Tonosafe as compared with alcohol (27).

Diagnosis of viral conjunctivitis is clinical accuracy rate of less than 50%. Rapid diagnostic tests are cost benefit to reduce the unnecessary use of local antibiotics. Most cases are self-curable, and the complex treatment is required in complicated cases (28).

Gottsch's study was to determine whether implementation of measures in control policies and procedures for infection can reduce number of outbreaks in epidemic keratoconjunctivitis and number nosocomial infected patients. Measures of infection control are determined in the regulations implemented in 1992 and include: management of the patient, hand washing, disinfection of instruments, distribution of medicines and personal employees. After implementation of measures there were significantly less epidemic number and affected patients of adenoviral conjunctivitis (29, 30).

The West Virginia Bureau for Public Health was notified by urban ophthalmology as epidemic keratoconjunctivitis occurs of casual interaction in health care organizations and in the community. The persistence of live virus on the surfaces for up to 30-35 days hampers outbreak prevention and control efforts (31, 32, 33, 34).

CONCLUSION

Today, deterioration of the clinical symptoms presents a new challenge for future resources. The virus is very resistant to desiccation and it is transmitted by direct contact. Immune reaction against these remnants

will lead to the formation of subepithelial infiltrates and subconjunctival haemorrhagiae. The diagnosis is mainly clinical, with laboratory tests only rarely contributing information rapidly. Diagnosis of etiology can be confirmed using cell cultures, antigen detection, polymerase chain reaction and/or immunochromatography.

Multiple treatments have been tried for epidemic disease, but none of them seem to be completely effective. There is no other treatment than symptomatic eye drops. The major sequelae are subepithelial infiltrates, which are difficult to treat. The use of topical steroids is discussed at all stages of the disease. Randomized clinical trials have not shown any clear benefit in the acute phase from any of a variety of treatments, including steroids, calcineurin inhibitors, virostatic drugs and many disinfecting agents. In the chronic phase, cyclosporin A eye drops accelerate the regression of subepithelial infiltrates. The hygienic measures, including conscientious hand and surface disinfection, can stop the spread of the contagious disease. The first priority in the treatment of patients with definite or suspected epidemic keratoconjunctivitis is the rigorous application of hygienic measures in medical facilities.

Prevention is the most reliable and recommended strategy to control the contagious infection and the most important action of the ophthalmologists. We presented and analyzed keratoconjunctival epidemic in region of Kragujevac from September 2008 to February 2009. The most common causes of our epidemic were adenovirus, herpes virus, and rarely cytomegalovirus, occurred with higher frequency as secondary infections (serological tests confirmed mixed distribution of the cause). All outpatients activities were carried out, while hospital hygienic, sanitary, intra-, extra-hospital and therapeutic procedures were undertaken (33). Based on the authors' experience, in order to eradicate epidemics as fast as possible and achieve efficient treatment, it is recommended that the epidemic should be reported, guidelines of referent institutions be obeyed, all of which diminishes the recognizable our professional risk and our decreases mistakes.

Global epidemic surveillance system definitely needs to be established to monitor and analyze the epidemic conjunctivitis in the future. There is clearly a need for the national and the military public health institutions to work together on guidelines to handle future challenges.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Abbreviations

PCR — Polymerase Chain Reaction
EKC — epidemic keratoconjunctivitis
PCF — pharyngoconjunctival fever

Sažetak

PREVECENCIJA ANENOVIRUSNOG KONJUNKTIVITISA — REVIJALNI RAD

Janicijevic Katarina,[1] Kocic Sanja,[1] Radovanovic Snezana,[1] Radevic Svetlana,[1] Vasiljevic Dragan,[1] Djonovic Nela,[1] Sarenac Vulovic Tatjana[1, 2]

[1] Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Srbija
[2] Klinika za oftalmologiju, Klinički Centar Kragujevac, Srbija

Epidemijski virusni konjunktivitis uzrokovan adenovirusima je najčešći kontagiozni konjuktivitis. Tačna učestalost adenovirusnih konjuktivitisa još uvek je slabo poznata, ali su dobro definisane forme adenovirusnih keratokonjunktivitisa kroz dva klinička sindroma: epidemijski keratokonjunktivitis (EKK) i faringokonjunktivalna groznica (FKG). Epidemijski keratokonjunktivitis je najteži oblik i predstavljen je sa kliničkom slikom epifore, hiperemije, hemoze i ipsilateralne limfadenopatije. Dijagnoza je uglavnom klinička, dok se njegova etiologija može potvrditi pomoću ćelijske kulture, detekcije antigena, lančane reakcije polimeraze ili imunohromatografije. Pokušani su mnogi tretmani ove bolesti, ali nijedan od njih izgleda da nije bio potpuno efikasan. Virusi su otporni na sušenje i većini dezinfekcionih sredstava za tretiranje raznih površina. Prevencija je najpouzdaniji postupak i preporučuje se kao strategija za kontrolu navedene epidemije. Sistematski nadzor nad globalnim epidemijama, definitivno mora da se uspostavi, da prati i analizira epidemije virusnih konjuktivitisa u budućnosti. Očigledno je da postoji jaka potreba u nacionalnim i javno-vojnim, zdravstvenim ustanovama, da zajedno rade na smernicama za upravljanje budućih izazova u ovom domenu.

Ključne reči: epidemija, adeno virusi, konjunktivitis, keratitis, dijagnostika, terapija, prevencija.

REFERENCES

1. Zhang L, Zhao N, Sha J, Wang C, Jin X, Amer S, et al. Virology and epidemiology analyses of global adenovirus-associated conjunctivitis outbreaks, 1953-2013. Epidemiol Infect. 2016; 144(8): 1661–72.

2. Chang CH, Lin KH, Sheu MM, Huang WL, Wang HZ, Chen CW. The change of etiological agents and clinical signs of epidemic viral conjunctivitis over an 18-year period in southern Taiwan. Graefes Arch Clin Exp Ophthalmol. 2003; 241(7): 554–60.

3. Pleyer U, Birnbaum F. Adenoviral keratoconjunctivitis. Ophthalmologe. 2015; 112(5): 459–69.

4. Ghebremedhin B. Human adenovirus: Viral pathogen with increasing importance. Eur J Microbiol Immunol (Bp). 2014; 4(1): 26–33.

5. González-López JJ, Morcillo-Laiz R, MuZoz-Negrete FJ. Adenoviral keratoconjunctivitis: an update. Arch Soc Esp Oftalmol. 2013; 88(3): 108–15.

6. Renard G. Adenoviral keratoconjunctivitis. J Fr Ophtalmol. 2010; 33(8): 586–92.

7. Mochizuki K, Katada T, Ohkusu K, Kaneko H. Three cases of acute conjunctivitis caused by human adenovirus in medical workers. Kansenshogaku Zasshi. 2010; 84(4): 469–73.

8. Doyle TJ, King D, Cobb J, Miller D, Johnson B. An outbreak of epidemic keratoconjunctivitis at an outpatient ophthalmology clinic. Infect Dis Rep. 2010; 2(2): e17.

9. Bialasiewicz A, Brehler R, Draeger J, Schmitz H. Mathematical modelling of epidemics under specific regard of adenoviral keratoconjunctivitis. Eur J Med Res. 2008; 13(8): 355–65.

10. Sendra-Gutiérrez JM, Martín-Rios D, Casas I, Sáez P, Tovar A, Moreno C. An outbreak of adenovirus type 8 keratoconjunctivitis in a nursing home in Madrid. Euro Surveill. 2004; 9(3): 27–30.

11. Shiota H, Ohno S, Aoki K, Azumi A, Ishiko H, Inoue Y, et al. Guideline for the nosocomial infections of adenovirus conjunctivitis. Nippon Ganka Gakkai Zasshi. 2009; 113(1): 25–46.

12. Ribeiro MM, Neumann VA, Padoveze MC, Graziano KU. Efficacy and effectiveness of alcohol in the disinfection of semi-critical materials: a systematic review. Rev Lat Am Enfermagem. 2015; 23(4): 741–52.

13. Koo D, Bouvier B, Wesley M, Courtright P, Reingold A. Epidemic keratoconjunctivitis in a university medical center ophthalmology clinic; need for re-evaluation of the design and disinfection of instruments. Infect Control Hosp Epidemiol. 1989; 10(12): 547–52.

14. Hiti H, Hanselmayer H, Hofmann H. Experience in therapy and prophylaxis of epidemic keratoconjunctivitis (author's transl). Klin Monbl Augenheilkd. 1979; 174(3): 456–61.

15. Al-Siyabi T, Binkhamis K, Wilcox M, Wong S, Pabbaraju K, Tellier R, et al. A cost effective real-time PCR for the detection of adenovirus from viral swabs. Virol J. 2013; 10: 184.

16. Kuo IC, Espinosa C, Forman M, Valsamakis A. A polymerase chain reaction-based algorithm to detect and prevent transmission of adenoviral conjunctivitis in hospital employees. Am J Ophthalmol. 2016; 163: 38–44.

17. Kuo IC, Espinosa C, Forman M, Pehar M, Maragakis LL, Valsamakis A. Detection and prevalence of adenoviral conjunctivitis among hospital employees using real-time polymerase chain reaction as an infection prevention tool. Infect Control Hosp Epidemiol. 2014; 35(6): 728–31.

18. Marangon FB, Miller D, Alfonso E. Laboratory results in ocular viral diseases: implications in clinical-laboratory correlation. Arq Bras Oftalmol. 2007; 70(2): 189–94.

19. Uchio E. New medical treatment for viral conjunctivitis. Nippon Ganka Gakkai Zasshi. 2005; 109(12): 962–84.

20. Rutala WA, Peacock JE, Gergen MF, Sobsey MD, Weber DJ. Efficacy of hospital germicides against adenovirus 8, a common cause of epidemic keratoconjunctivitis in health care facilities. Antimicrob Agents Chemother. 2006; 50(4): 1419–24.

21. Clement C, Capriotti JA, Kumar M, Hobden JA, Foster TP, Bhattacharjee PS et al. Clinical and antiviral efficacy of an ophthalmic formulation of dexamethasone povidone-Iodine in a rabbit model of adenoviral keratoconjunctivitis. Invest Ophthalmol Vis Sci. 2011; 52(1): 339–44.

22. Gleavy D. The nursing role in epidemiology, risk management, and patient-public education. J Ophthalmic Nurs Technol. 1990; 9(5): 215–9.

23. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. Clin Microbiol Rev 2001; 14(1): 227.

24. Aoki K, Benkö M, Davison AJ, Echavarria M, Erdman DD, Harrach B, et al. Members of the Adenovirus Research Community. Toward an integrated human adenovirus designation system that utilizes molecular and serological data and serves both clinical and fundamental virology. J Virol. 2011; 85(11): 5703–4.

25. Nercelles MP, Peirano NL, Herrera OR, Rivero BP, Márquez PL. A nosocomial outbreak of epidemic keratoconjunctivitis. Rev Chilena Infectol. 2010; 27(6): 534–8.

26. Meyer-Rüsenberg B, Loderstädt U, Richard G, Kaulfers PM, Gesser C. Epidemic keratoconjunctivitis: the current situation and recommendations for prevention and treatment. Dtsch Arztebl Int. 2011; 108(27): 475–80.

27. Sehulster, L., R. Y. W. Chinn. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). Morb. Mortal. Wkly. Rep. 2003; 52: 1–44.

28. Schrauder A, Altmann D, Laude G, Claus H, Wegner K, Köhler R, et al. Epidemic conjunctivitis in Germany, 2004. Euro Surveill. 2006; 11(7): 185–7.

29. Mema SC, MacDonald J, Wyse JP, Gonder T, Musto R, McIntyre L. Public Health adds value to an investigation of epidemic keratoconjunctivitis. Can J Ophthalmol. 2010; 45(5): 538.

30. Centers for Disease Control and Prevention (CDC). Adenovirus-associated epidemic keratoconjunctivitis outbreaks four states, 2008-2010. Morb Mortal Wkly Rep. 2013; 62(32): 637–41.

31. Omar Akhtar A, Singh H, Si F, Hodge WG. A systematic review and cost-effectiveness analysis of tonometer disinfection methods. Can J Ophthalmol. 2014; 49(4): 345–50.

32. Jhanji V, Chan TC, Li EY, Agarwal K, Vajpayee RB. Adenoviral keratoconjunctivitis. Surv Ophthalmol. 2015; 60(5): 435–43.

33. Janićijević Petrović M, Srećković S, Petrović N, Šarenac T. Epidemijski keratokonjunktivitis. Srp Arh Celok Lek. 2011; 139(5–6): 282–5.

34. Massey J, Henry R, Minich L, Lamson DM, St George K. Notes from the field: health care-associated outbreak of epidemic keratoconjunctivitis West Virginia, 2015. Morb Mortal Wkly Rep. 2016; 65(14): 382–3.

Correspondence to / Autor za korespondenciju
Katarina M. Janicijevic
Faculty of Medical Sciences, University of Kragujevac, Serbia
Svetozara Markovica 69, 34000 Kragujevac, Serbia
Tel: +38134/369828
Mob: +381642183797
E-mail: kaja.andreja@yahoo.com

SANAMED
2017; 12(1): 57–57
ISSN-1452-662X

RETRACTION NOTE

RETRACTED ARTICLE: COCAINE CARDIOMYOPATHY — A CASE REPORT

Georgiev Antonio,[1] Zhivadinovik Julija[2]

[1] PHO Cardiology – Prima, MIT University, R. Macedonia
[2] Institute of Anatomy, Medical Faculty, Skopje, University "Ss. Cyril and Metodius", R. Macedonia

Published in December 2014, Sanamed, Vol 9, issue 3, p. 233–237.

In Sanamed medical journal, vol. 9, issue 3, in the paper titled "COCAINE CARDIOMYOPATHY — A CASE REPORT" there was strong reason to believe that the authors have plagiarized some parts in this article.

The mistake was discovered by the Center for Evaluation in Education and Science (CEON). Authors were informed from the Editorial Board of medical journal "Sanamed" and the stated parts of the paper were timely corrected. The correction of the article COCAINE CARDIOMYOPATHY — A CASE REPORT (2014, Vol 9, issue 3, p. 233–237.) was published in December 2016. doi: 10.5937/sanamed1603255G

Nevertheless, this article has been retracted at the request of Center for Evaluation in Education and Science (CEON). and Serbian citation index, because there is still a strong reason to believe that the authors have plagiarized some parts in this article, using variety of sources.

UPUTSTVO AUTORIMA

SANAMED je medicinski časopis osnovan 2006. godine. Časopis objavljuje: originalne naučne i stručne članke, prikaze bolesnika, revijske radove, pisma uredniku, članke iz istorije medicine, prikaz objavljenih knjiga i druge medicinske informacije.

Rukopise slati na adresu:
Prim. dr Avdo Ćeranić,
(za Sanamed)
Ul. Palih boraca 52, 36300 Novi Pazar
Email: sanamednp2006@gmail.com
www.sanamed.rs

Prispeli rukopis Uređivački odbor šalje recenzentima radi stručne procene. Ukoliko recenzenti predlože izmene ili dopune, kopija recenzije se dostavlja autoru s molbom da unese tražene izmene u tekst rada ili da argumentovano obrazloži svoje neslaganje s primedbama recenzenta. Konačnu odluku o prihvatanju rada za štampu donosi glavni i odgovorni urednik.

Časopis se štampa na engleskom jeziku, sa kratkim sadržajem prevedenim na srpski jezik.

OPŠTA UPUTSTVA

Tekst rada kucati u programu za obradu teksta *Word*, latinicom, sa dvostrukim proredom, isključivo fontom *Times New Roman* i veličinom slova 12 tačaka (12 pt). Sve margine podesiti na 25 mm, a tekst kucati sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm, bez deljenja reči (hifenacije).

Rukopis mora biti organizovan na sledeći način: naslovna strana, sažetak na srpskom jeziku, sažetak na engleskom jeziku, ključne reči, uvod, cilj rada, bolesnici i metodi/materijal i metodi, rezultati, diskusija, zaključak, literatura, tabele, legende za slike i slike.

Svaki deo rukopisa (naslovna strana, itd.) mora početi na posebnoj strani. Sve strane moraju biti numerisane po redosledu, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u zagradama, i to onim redosledom kojim se pojavljuju u tekstu.

Obim rukopisa. Celokupni rukopis rada, koji čine naslovna strana, kratak sadržaj, tekst rada, spisak literature, svi prilozi, odnosno potpisi za njih i legenda (tabele, slike, grafikoni, sheme, crteži), naslovna strana i sažetak na engleskom jeziku, mora iznositi za originalni rad, saopštenje, rad iz istorije medicine i pregled literature do 5.000 reči, a za prikaz bolesnika, rad za praksu, edukativni članak do 3.000 reči; radovi za ostale rubrike moraju imati do 1.500 reči.

Provera broja reči u dokumentu može se izvršiti u programu *Word* kroz podmeni *Tools-Word Count* ili *File-Properties-Statistics*.

Sva merenja, izuzev krvnog pritiska, moraju biti izražena u internacionalnim SI jedinicama, a ako je neophodno, i u konvencionalnim jedinicama (u zagradi). Za lekove se moraju koristiti generička imena. Zaštićena imena se mogu dodati u zagradi.

Naslovna strana. Naslovna strana sadrži naslov rada, kratak naslov rada (do 50 slovnih mesta), puna prezimena i imena svih autora, naziv i mesto institucije u kojoj je rad izvršen, zahvalnost za pomoć u izvršenju rada (ako je ima), objašnjenje skraćenica koje su korišćene u tekstu (ako ih je bilo) i u donjem desnom uglu ime i adresu autora sa kojim će se obavljati korespondencija.

Naslov rada treba da bude sažet, ali informativan.

Ako je potrebno, može se dodati i podnaslov.

Kratak naslov treba da sadrži najbitnije informacije iz punog naslova rada, ali ne sme biti duži od 50 slovnih mesta.

Ako je bilo materijalne ili neke druge pomoći u izradi rada, onda se može sažeto izreći zahvalnost osobama ili institucijama koje su tu pomoć pružile.

Treba otkucati listu svih skraćenica upotrebljenih u tekstu. Lista mora biti uređena po abecednom redu pri čemu svaku skraćenicu sledi objašnjenje. Uopšte, skraćenice treba izbegavati, ako nisu neophodne.

U donjem desnom uglu naslovne strane treba otkucati ime i prezime, telefonski broj, broj faksa i tačnu adresu autora sa kojim ce se obavljati korespodencija.

Stranica sa sažetkom. Sažetak mora imati do 350 reči. Treba koncizno da iskaže cilj, rezultate i zaključak rada koji je opisan u rukopisu. Sažetak ne može sadržati skraćenice, fusnote i reference.

Ključne reči. Ispod sažetka treba navesti 3 do 8 ključnih reči koje su potrebne za indeksiranje rada. U

izboru ključnih reči koristiti Medical Subject Headings — MeSH.

Stranica sa sažetkom na engleskom jeziku. Treba da sadrži pun naslov rada na engleskom jeziku, kratak naslov rada na engleskom jeziku, naziv institucije gde je rad urađen na engleskom jeziku, tekst sažetka na engleskom jeziku i ključne reči na engleskom jeziku.

Struktura rada. Svi podnaslovi se pišu velikim slovima i boldovano.

Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

Rezultati. Rezultati treba da budu jasni i sažeti, sa minimalnim brojem tabela i slika neophodnih za dobru prezentaciju.

Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

Reference se citiraju prema tzv. Vankuverskim pravilima, koja su zasnovana na formatima koja koriste *National Library of Medicine* i *Index Medicus*.

Primeri:

1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prvih šest i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad.

Slike. Sve ilustracije (fotografije, grafici, crteži) se smatraju slikama i označavaju se arapskim brojevima u tekstu i na legendama, prema redosledu pojavljivanja. Treba koristiti minimalni broj slika koje su zaista neophodne za razumevanje rada. Slova, brojevi i simboli moraju biti jasni, proporcionalni, i dovoljno veliki da se mogu reprodukovati. Pri izboru veličine grafika treba voditi računa da prilikom njihovog smanjivanja na širinu jednog stupca teksta neće doći do gubitka čitljivosti. Legende za slike se moraju dati na posebnim listovima, nikako na samoj slici.

Ako je uveličanje značajno (fotomikrografije) ono treba da bude naznačeno kalibracionom linijom na samoj slici. Dužina kalibracione linije se unosi u legendu slike.

Uz fotografije na kojima se bolesnici mogu prepoznati treba poslati pismenu saglasnost bolesnika da se one objave.

Za slike koje su ranije već objavljivane treba navesti tačan izvor, treba se zahvaliti autoru, i treba priložiti pismeni pristanak nosioca izdavačkog prava da se slike ponovo objave.

Pisma uredniku. Mogu se publikovali pisma uredniku koja se odnose na radove koji su objavljeni u SANAMEDU, ali i druga pisma. Ona mogu sadržati i jednu tabelu ili sliku, i do pet referenci.

Propratno pismo. Uz rukopis obavezno priložiti pismo koje su potpisali svi autori, a koje treba da sadrži: izjavu da rad prethodno nije publikovan i da nije istovremeno podnet za objavljivanje u nekom drugom časopisu, te izjavu da su rukopis pročitali i odobrili svi autori koji ispunjavaju merila autorstva. Takođe je potrebno dostaviti kopije svih dozvola za: reprodukovanje prethodno objavljenog materijala, upotrebu ilustracija i objavljivanje informacija o poznatim ljudima ili imenovanje ljudi koji su doprineli izradi rada.

Troškovi pripreme rada

Svi autori radova, imaju obavezu da pre nego što dobiju potvrdu da će rad biti objavljen u Sanamedu, izvrše uplatu za pokriće dela troškova štampe koja za autora rada iznosi 2500 dinara, a za koautore po 1500 dinara, za svaki prihvaćeni rad. Za autora rada iz inostranstva naknada za štampanje iznosi 40 eura (u dinarskoj protivrednosti po kursu na dan uplate), a za koautore 20 eura. Dodatno će biti naplaćena svaka stranica na kojoj se nalaze slike u boji, po ceni od 30 eura; crno bele slike se ne naplaćuju.

Za sva dalja uputstva i informacije kontaktirajte Uredništvo.

Napomena. Rad koji ne ispunjava uslove ovog uputstva ne može biti upućen na recenziju i biće vraćen autorima da ga dopune i isprave. Pridržavanjem uputstva za pisanje rada za SANAMED znatno će se skratiti vreme celokupnog procesa do objavljivanja rada u časopisu, što će pozitivno uticati na kvalitet i redovnost izlaženja svezaka.

INSTRUCTIONS TO AUTHORS

SANAMED is a medical journal, published since 2006. The journal publishes: original papers, case reports, review articles, letters to the Editor, other articles and information concerned with practice and research in medicine.

Address manuscripts to:
Prim. dr Avdo Ćeranić,
(for Sanamed)
Ul. Palih boraca 52, 36300 Novi Pazar
Email sanamednp2006@gmail.com
www.sanamed.rs

Arrived manuscript is sent to reviewers for expert assessment by the Editorial Board. If reviewers propose changes or amendments, copies of reviews are submitted to authors with a request to enter the required changes to the text or explain its disagreement with the remarks of the reviewer. The final decision of acceptance for publishing is given by Editor in chief.

The journal is published in English, with the summary translated into Serbian.

GENERAL GUIDELINES

Text of the paper should be typed in a word processing program *Word*, written in Latin, double-spaced, only in *Times New Roman* font size 12 points. All margins should be set at 25 mm, and the text should be typed with the left alignment and paragraph indentations of 10 mm, without dividing the words.

The manuscript should be arranged as following: title page, abstract, key words, introduction, patients and methods/material and methods, results, discussion, conclusion, references, tables, figure legends and figures.

Each manuscript component (title page, etc.) begins on a separate page. All pages are numbered consecutively beginning with the title page.

References in the text are designated with Arabic numerals in parentheses, and the order in which they appear in the text.

Manuscript volume. The complete manuscript, which includes title page, short abstract, text of the article, literature, all figures and permisions for them and legends (tables, images, graphs, diagrams, drawings), title page and abstract in English, can have the length up to 5000 words for original paper, report, paper on the history of medicine and literature overview, while for patient presentation, practice paper, educative article it can be up to 3000 words, and other papers can be up to 1500 words.

The word count check in a document can be done in *Word* processor program in submenu *Tools Word Count* or *File Properties Statistics*.

All measurements, except blood pressure, are reported in the System International (SI) and, if necessary, in conventional units (in parentheses). Generic names are used for drugs. Brand names may be inserted in parentheses.

Title page. The title page contains the title, short title, full names of all the authors, names and full location of the department and institution where work was performed, acknowledgments, abbreviations used, and name of the corresponding author. The title of the article is concise but informative, and it includes animal species if appropriate. A subtitle can be added if necessary.

A short title of less than 50 spaces, for use as a running head, is included.

A brief acknowledgment of grants and other assistance, if any, is included.

A list of abbreviations used in the paper, if any, is included. List abbreviations alphabetically followed by an explanation of what they stand for. In general, the use of abbreviations is discouraged unless they are essential for improving the readabillity of the text.

The name, telephone number, fax number, and exact postal address of the author to whom communications and reprints should be sent, are typed at the lower right corner of the title page.

Abstract page. An abstract of less than 180 words concisely states the objective, findings, and conclusion of the studies described in the manuscript. The abstract does not contain abbreviations, footnotes or references.

Below the abstract, 3 to 8 keywords or short phrases are provided for indexing purposes.

The structure of work. All headings are written in capital letters and bold.

Original work should have the following headings: introduction, aim, methods, results, discussion, conclusion, references.

A case report include: introduction, case report, discussion, references.

Review of the literature include: an introduction, subheadings, conclusion, references.

Patients and methods/Material and methods. The selection of patients or experimental animals, including controls is described. Patients' names and hospital numbers are not used.

Methods are described in sufficient detail to permit evaluation and duplication of the work by other investigators.

When reporting experiments on human subjects, it should be indicated whether the procedures followed were in accordance with ethical standards of the Committee on human experimentation of the institution in which they were done and in accordance with the Declaration of Helsinki. Hazardous procedures or chemicals, if used, are described in detail, including the safety precautions observed. When appropriate, a statement is included verifying that the care of laboratory animals followed the accepted standards.

Statistical methods used, are outlined.

Results. Results are clear and concise, and include a minimum number of tables and figures necessary for proper presentation.

Discussion. An exhaustive review of literature is not necessary. The major findings should be discussed in relation to other published works. Attempts should be made to explain differences between results of the present study and those of the others. The hypothesis and speculative statements should be clearly identified. The discussion section should not be a restatement of results, and new results should not be introduced in the discussion.

References. References are identified in the text by Arabic numerals in parentheses. They are numbered consecutively in the order in which they appear in the text. Number of references should not exceed 30, except in the literature review, which is allowed to be to 50.

Avoid using abstracts as references and abstract older than two years are not cited.

References are cited by the so-called Vancouver rules, which are based on formats that use the National Library of Medicine and Index Medicus. The following are examples:

1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first six are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

Tables. Tables are typed on separate sheets with figure numbers (Arabic) and title above the table and explanatory notes, if any, below the table.

Figures and figure legends. All illustrations (photographs, graphs, diagrams) are to be considered figures, and are numbered consecutively in the text and figure legend in Arabic numerals. The number of figures included is the least required to convey the message of the paper, and no figure duplicates the data presented in the tables or text. Letters, numerals and symbols must be clear, in proportion to each other, and large enough to be readable when reduced for publication. Figures are submitted as near to their printed size as possible. Legends for figures should be given on separate pages.

If magnification is significant (photomicrographs), it is indicated by a calibration bar on the print, not by a magnification factor in the figure legend. The length of the bar is indicated on the figure or in the figure legend.

Photographs of identifiable patients are accompanied by written permission from the patient.

For figures published previously, the original source is acknowledged, and written permission from the copyright holder to reproduce it is submitted.

Letters to the Editor. Both letters concerning and those not concerning the articles that have been published in SANAMED will be considered for publication. They may contain one table or figure and up to five references.

Cover letter. The letter signed by all authors must be attached with the manuscript. The letter should consist of: the statement that the paper has not been published previously and that it is not submitted for publication to some other journal, the statement that the manuscript has been read and approved by all the authors who fulfill the authorship criteria. Furthermore, authors should attach copies of all permits: for reproduction of previously published materials, for use of illustrations and for publication of information about pub-

licly known persons or naming the people who contributed to the creation of the work.

Costs of paper preparation

All authors of papers, have obligation, before they receive confirmation that the paper will be published in Sanamed, to pay part of expenses of printing, which is 2500 RSD for author, 1500 RSD for co-authors, for each paper.

For paper author from abroad printing fees are 40 Euro (in Dinar equivalent at the exchange rate on the day of payment), and 20 Euro for co-authors. Additionally will be charged each page with pictures in color, costing 30 Euro; black and white pictures will not be charged.

For any further instructions and information, contact Editorial Board.

Note. The paper which does not fulfill the conditions set in this instruction cannot be set to reviewers and will be returned to the authors for amendments and corrections. By following the instructions for writing the papers for Medical Journal, the time needed for the process of publication of papers in the journal will be shortened, which will have positive impact on the quality and regularity of publication of volumes.

CIP — Каталогизација у публикацији
Народна библиотека Србије, Београд

61

SANAMED / glavni i odgovorni urednik Avdo Ćeranić. — God. 1, br. 1 (2006)– . — Novi Pazar : Udruženje lekara Sanamed, 2006– (Novi Pazar : ProGraphico). — 30 cm

Tri puta godišnje. — Drugo izdanje na drugom medijumu: Sanamed (Online) = ISSN 2217-8171

ISSN 1452-662X = Sanamed

COBISS.SR-ID 135154444

ISSN 1452-662X