Volume 29 • April/June 2023 • Number 2 • ISSN (print) 1512-5866
ISSN (online) 2232-8

MEDICAL JOURNAL
MEDICINSKI ŽURNAL

Journal of the Discipline for Research and Development
Clinical Center University of Sarajevo
Online first - www.kcus.ba

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Novi Evropski vodič za prevenciju tromboembolizma kod A Fib

CHA_2DS_2-VASc skor za procjenu rizika od tromboembolizma kod A Fib!

Risk factor-based point-based scoring system - CHA_2DS_2 -VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.

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Major i non-major riziko fakori za procjenu tromboembolizma kod A Fib!

Risk factors for stroke and thrombo-embolism in non-valvular AF

Major risk factors	Clinically relevant non-major risk factors
Previous stroke	CHF or moderate to severe LV systolic dysfunction [e.g. LV EF ☒ 40%]
TIA or systemic embolism	Hypertension
Age ☒75 years	Diabetes mellitus
	Age 65-74 years
	Female sex
	Vascular disease

AF = atrial fibrilation; EF = ejection fraction (as documented by echocardiography, radio nudide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left venticular; TIA = trasient ischaemic attack.

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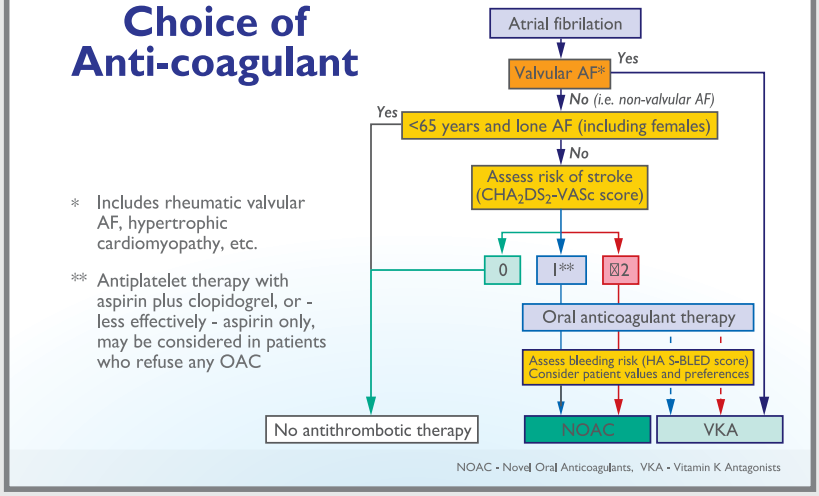
Algoritam antikoagulantne terapije nakon procjene CHA_2DS_2VASc i major risk faktora!

Choice of Anti-coagulant



* Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.

** Antiplatelet therapy with aspirin plus clopidogrel, or - less effectively - aspirin only, may be considered in patients who refuse any OAC

NOAC - Novel Oral Anticoagulants, VKA - Vitamin K Antagonists

PUBLISHER:
Discipline for Research and Development
Clinical Center University of Sarajevo
71000 Sarajevo, Bolnička 25
Bosnia and Herzegovina

For publisher:
Sebija Izetbegović, MD, PhD
General Manager
CCUS

Publishing editor:
Mirza Dilić, MD, PhD

AIMS AND SCOPE

The Medical Journal is the official quarterly journal of the Discipline for Research and Development of the Clinical Center University of Sarajevo and has been published regularly since 1994. It is published in the languages of the people of Bosnia and Herzegovina i.e. Bosnian, Croatian and Serbian as well as in English.

The Medical Journal aims to publish the highest quality materials, both clinical and scientific, on all aspects of clinical medicine. It offers the reader a collection of contemporary, original, peer-reviewed papers, professional articles, review articles, editorials, along with special articles and case reports.

EDITORIAL OFFICE

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Medical Journal, Discipline for Research and Development
Clinical Center University of Sarajevo,
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SUBSCRIPTION

Annual subscription rates: Bosnia and Herzegovina € 50; Europe € 80; and other € 100.

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Email: institutnir@bih.net.ba

PRINT

KOPIKOMERC, East Sarajevo
Printed on acid-free paper.

TECHNICAL DIRECTOR

KOPIKOMERC, East Sarajevo

CIRCULATION

500 copies

Medical Journal is Indexed in

EBSCO publishing
USA
www.ebscohost.com

Member of National Journals Networks of the European Society of Cardiology

Original articles

Review articles

Maternal cigarette smoking associated with decreased rates of placental expulsion in the study of the efficacy of intra-umbilical vein administration of carboprost versus oxytocin in the management of retained placenta

Konzumacija cigareta kod trudnica asocirana sa manjom stopom ekspulzije posteljice u studiji intra-umbilikalne venske aplikacije karboprosta i oksitocina u tretmanu zaostale posteljice

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ABSTRACT

Introduction: maternal cigarette smoking is an important public health issue recognized by the World Health Organization (WHO) as one of the most serious, preventable risk factors for developing a series of pregnancy pathologies. Aim: to determinate association between maternal cigarette smoking and rates of placental expulsion in the study of the efficacy of intra - umbilical vein administration of carboprost versus oxytocin in the management of retained placenta. Materials and methods: this prospective clinical study was conducted at the Clinic of Obstetrics and Gynecology of the Clinical Center University of Sarajevo, in the period from 2013 to 2015 and it included 200 pregnant women. Examinees were randomized in subgroups, by risk factors and interventions. The main outcome variable was expulsion of retained placenta and second outcome variables were: duration of time from intra-umbilical vein administration of drug to expulsion of RP, cord diameter, manual removal of placenta, the numbe r of cases who required blood transfusion, anesthetics and antibiotics, by smoking status. Results: history of cigarette smoking was more likely in pregnant women with high school diploma (81.6% vs. 66.7%; p<0.05). The pregnant women with positive history of cigarette smoking had statistically significant lower rates of placental expulsion compared with non-smokers (64.6% vs. 80.7%, respectively; *p*=0.013). The cord diameter <2.0 cm was more frequently in the pregnant women with positive history of cigarette smoking, compared with non-smokers, but there was not statistically significant differences (10.8% vs. 5.9%, respectively, p>0.05). Conclusion: cigarette smoking among women of reproductive age is associated with lower rates of placental expulsion.

Keywords: tobacco smoking, placenta

SAŽETAK

Uvod: konzumacija cigareta u fertilnoj dobi kod žena, predstavlja značajan javno-zdravstveni problem koji je prepoznat od strane Svjetske zdravstvene organizacije (SZO) kao jedan od najozbiljinih riziko-faktora za nastanak različitih patoloških stanja u trudnoći, koji se mogu prevenirati. Cilj: ispitati povezanost između konzumacije cigareta kod trudnica i stope ekspulzije placente u studiji intra - umbilikalne venske aplikacije karboprosta i oksitocina u tretmanu zaostale posteljice. Materijali i metode: sprovedena je prospektivna klinička studija na Klinici za ginekologiju i porodiljstvo Kliničkog centra Univerziteta u Sarajevu u periodu od 2013. do 2015. godine, koja je uključila 200 trudnica. Ispitanice su randomizirane u subgrupe, prema riziko-faktorima i intervenciji. Glavna mjera ishoda je bila ekspulzija zaostale posteljice, te su praćene i zamjenske mjere ishoda: vrijeme od intra-umbilikalne venske aplikacije lijeka do ekspulzije posteljice, prečnik pupčane vrpce, potreba za manualnom lizom, te učestalost transfuzije krvi i aplikacije anestetika i antibiotika, prema pušačkom statusu. Rezultati: historija konzumacije cigareta bila je učestalija kod trudnica sa završenom srednjom školom, kao najvišim nivoom obrazovanja (81,% naspram 66,7%; zaredom *p<0,05*). Trudnice koje su konzumirale cigarete su imale statistički značajno manje stope ekspulzije placente u poređenju sa nepušačima. (64,6% naspram 80,7%, zaredom; *p*=0,013). Prečnik pupčane vrpce <2,0 cm je bio učestaliji kod trudnica sa pozitivnom istorijom konzumacije cigareta u poređenju sa nepušačima, ali nije dostignut prag statističke značajnosti (10,8% naspram 5,9%, zaredom, *p>0,05*). Zaključak: konzumacija cigareta u rerpoduktivnoj dobi je povezana sa nižom stopom ekspulzije posteljice kod trudnica.

Ključne riječi: konzumacija cigareta, placenta

INTRODUCTION

Tobacco smoking is an important public health issue recognized by the world health organization as one of the most serious, preventable risk factors for developing a series of pregnancy pathologies (1). A national report, representing 95% of all births in the United States for 2003, shows that the smoking rate at any time during pregnancy was 8.4%, with 20.6% of women who smoked in the first or second trimesters quitting by the third trimester (2). In the U.S., one in 14 women smoked during pregnancy in 2016 (3). In the longitudinal, nationally representative study of the U.S. non-institutionalized population that is designed to measure prevalence and correlates of tobacco use from September 2013 through December 2014 (n=12.848), 20.1% of women of reproductive age (18-44 years) are cigarette smokers, 5.9% current e-cigarette users, 4.9% current cigar smokers, and 6.5% current hookah users (4). Socio-economic status influences prenatal smoking habits. In general, the lower the socio-economic status the more likely the probability of prenatal smoking (5). Lower education level, early age at smoking initiation, increased parity and marital status (unmarried more likely than married), are factors associated with an increased likelihood of smoking during pregnancy (5,6).

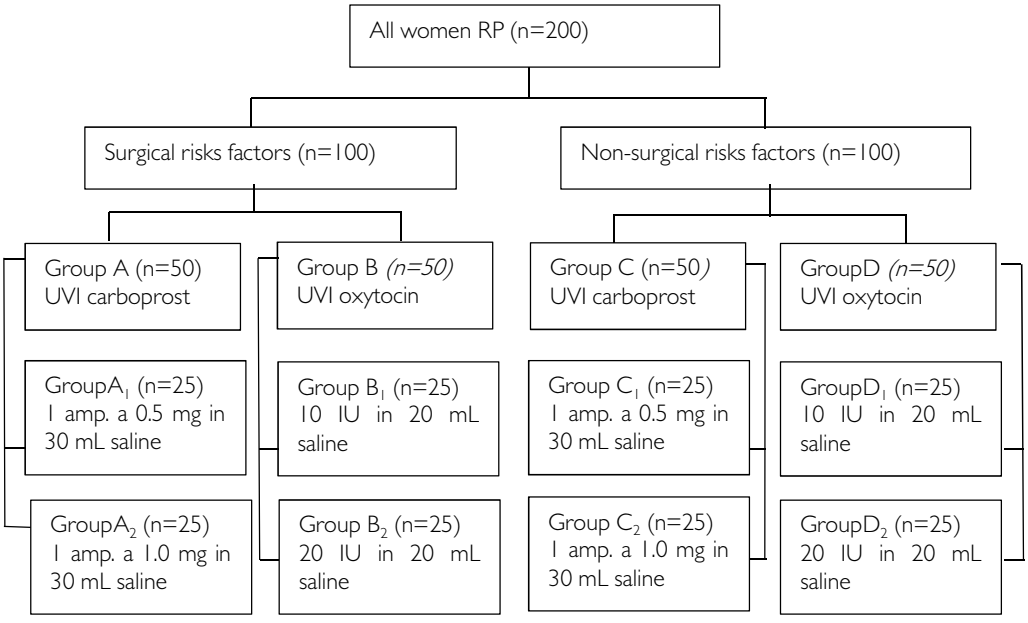
Cigarette smoke constitutes a mixture of over 7000 chemical products and most of the investigations are focused on nicotine which has a vasoconstriction effect on the uterus circulation in smoking women during pregnancy (1,7). Smoking during pregnancy has been associated with reduced vascularization of the placenta, increases in fetal and maternal heart rate are seen immediately following smoking (8). Maternal cigarette smoking in early pregnancy may be associated with villus hypoxia, which may influence angiogenesis and apoptosis (9). Newest insights indicate also faulty placentation caused by abnormal trophoblast and endothelial function or that the placenta is otherwise functionally altered when developing under the influence of tobacco (1).

Retained placenta (RP) is one of the major causes of primary and secondary post-partum hemorrhage (PPH), associated with increased risk of maternal morbidity and mortality (10). Retained placenta is caused by abnormal placental separation, representing the placenta has not been delivered within one hour after the birth of the baby (11). PPH accounts for nearly one quarter of all maternal deaths world-wide with an estimated 125,000 deaths per year (12).

Therefore, this study examined the association between maternal cigarette use and expulsion rates of placenta in active management of retained placenta.

MATERIALS AND METHODS

This prospective clinical study was conducted at the Clinic of Obstetrics and Gynecology of the Clinical Center University of Sarajevo in in the period from 2013 to 2015 and it included 200 pregnant women. Informed consent was obtained in all cases and risk factors were identified, via a questionnaire, additionally. We studied all examinees prospectively and by computerized randomization. All examinees underwent a gynecological sonography with Voluson E6 Ultrasound (General Electric), upon admission to the clinic. Patients were randomized in 2 groups by surgical risks factors and 8 subgroups by medication and doses.



Study flowchart. Abbreviations: *RP* retained placenta, *UVI* umbilical vein injection, *IU* international unit

The exclusion criteria were uterine atony and bleeding > 500 ml; maternal hemodynamic instability (pulse ≥ 120 b.p.m., or a decrease in diastolic blood pressure of more than 20mm Hg after delivery, associated medical disorders (e.g., cardiac disease, anemia, hypertension and diabetes), multiple pregnancy. The main outcome variable was expulsion of retained placenta and second outcome

variables were: duration of time from intra-umbilical vein administration of drug to expulsion of RP, cord diameter, manual removal of placenta, the number of cases who required blood transfusion, anesthetics and antibiotics, by smoking status.

The included pregnant women were with a singleton living fetus, achieved vaginal delivery, and failed to deliver the placenta after 30 minutes of active management of the third stage of labor (intravenous administration of 5 IU of Syntocinon in the presence of an intact umbilical cord, fundal pressure and controlled cord traction after 5, 10 and 15 minutes) in all examinees. A retained placenta was diagnosed when separation did not occur 30 minutes after delivery and UVI is followed. The appropriate solution was injected into the umbilical vein for 15 seconds by type of treatment and the umbilical cord was clamped again. At 5 and 10 minutes after administration of the medication, or in the case of clinical signs of placental separation, an attempt to deliver the placenta was made. If the final attempt to deliver the placenta failed, manual removal was performed by the usual maneuver under general anesthesia. Standard management of the third stage of labor was continued, including blood transfusion and uterotonic agents for continued bleeding.

Statistical analysis

The results are presented as the median (25th to 75th percentile) for numerical variables and as numbers and percentages for categorical variables. Statistical significance for differences was analyzed with Chi Square test, One-Way ANCOVA and Independent Samples T tests. Stratification analysis is used both to evaluate and control for confounding factor by subgroups (Mantel-Haenszel test). Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS Release 19.0; SPSS Inc., Chicago, Illinois, United States of America) software. Statistical significance was accepted for p-values< 0.05.

RESULTS

The demographic and obstetric data of examinees by smoking status were comparable, except for the level of education. History of cigarette smoking was more likely in pregnant women with high school diploma (p<0.05) (Table 1).

Table 1 **Socio-demographic and clinical characteristics among pregnant women by smoking status (n=200).**

	Smokers (n=65)		Non - smokers *(n=135)*		p-value
Maternal age (y)[a]	27 (24 to 32)		27 (24 to 30)		*>0.05*
Gestational age (weeks)[a]	39 (38 to 40)		39 (39 to 40)		*>0.05*
Birth length (cm)[a]	52 (50 to 53)		52 (51 to 53)		*>0.05*
Birth weight (grams)[a]	3450 (2925 to 3950)		3550 (3200 to 3900)		*>0.05*
Level of education[b]					
Elementary school	6	*(9.2)*	13	*(9.6)*	
High school	53	*(81.6)*	90	*(66.7)*	*0.045*
Higher education	6	*(9.2)*	32	*(23.7)*	
Delivery [b]					
Term	*59*	*(90.8)*	130	*(96.3)*	*>0.05*
Preterm	*6*	*(9.2)*	5	*(3.7)*	
Smoking duration (y)[a] *examination*	5 (3 to 7)		-		-

Data are presented as: [a] median (IQR), [b] number or percentage (%)

There was not statistically significant difference between A, B, C and D groups and subgroups in the success rates of the total expulsion of placenta (70% vs. 82% vs. 72% vs. 78%, respectively, p=0.483). The frequency of RP expulsion was higher in subgroups B_2 and D_2 (88.0% and 80.0%, respectively) compared with subgroups A_1 and A_2 (68.0% and 72.0%, respectively) and C_1 and C_2 (68.0% and 76.0%, respectively) (p=0.770). The group B_2 (UVI oxytocin 20 IU in 20 mL saline, surgical risk factors) and the group D2 (UVI oxytocin 20 IU in 20 mL saline, non-surgical risk factors) had shorter expulsion time (minutes) (Me=5; IQR=4 to 5; Me=5; IQR=4.3 to 6, respectively) compared with other groups (p<0.001).

The results of secondary outcomes and the success rate are presented in Table 2. The pregnant women with positive history of cigarette smoking overall had statistically significant lower rates of placental expulsion compared with non-smokers (64.6% vs. 80.7%, respectively; p=0.013). The manual removal of placenta was statistically significant likely in smokers compared with non-smokers (35.3% vs. 19.3% respectively; p=0.007). There was statistically significant difference between groups by smoking status in frequency of anesthetics application (p=0.030) and there was not statistically significant difference in the number of cases who required blood transfusion (p>0.05) and antibiotics application (p>0.05). The cord diameter <2.0 cm was more frequently in the pregnant women with positive history of cigarette smoking, compared with non-smokers, but there was not statistically significant differences (10.8% vs. 5.9%, respectively, p>0.05).

Table 2 **The outcome of the third stage of labor by smoking status (n=200).**

	Smokers (n=65)	Non - smokers *(n=135)*	p-value
Placental expulsion (min)[a]	7 (5 to 9)	7 (5 to 9)	*>0.05*
Placenta expelled spontaneously[b]	42 (64.6)	109 (80.7)	*0.013*
Manual removal of placenta[b]	23 (35.3)	26 (19.3)	*0.007*
Cord diameter < 2.0 cm[b]	7 (10.8)	8 (5.9)	*>0.05*
Blood transfusion[b]	5 (7.7)	12 (8.9)	*>0.05*
Anesthetics[b]	21 (32.3)	25 (18,.5)	*0.030*
Antibiotics[b]	33 (50.8)	56 (41.5)	*>0.05*

Data are presented as: [a] median (IQR), [b] number or percentage (%).

The pregnant women with positive history of cigarette smoking in group A (8/15 or 53.3%) had non-significant lower rates of placental expulsion compared with non-smokers (27/35 or 77.1%) [Mantel-Haenszel χ^2=2.778, p=0.09; RR=2.042; (95% CI=0.904; 4.609); OR=2.953; (95% CI=0.093; 1.224)]. The pregnant women with positive history of cigarette smoking in group B (14/18 or 77.8%) had non-significant lower rates of placental expulsion compared with non-smokers (27/32 or 84.4%) [Mantel-Haenszel χ^2=0.333, p=0.564; RR=1.422; (95% CI=0.436; 4.634); OR=1.543; (95% CI 0.357; 6.674)]. The pregnant women with positive history of cigarette smoking in group C (9/17 or 52.9%) had statistically significant lower rates of placental expulsion compared with non-smokers (27/33 or 81.8%) [Mantel-Haenszel χ^2=4.548, p=0.033; RR=2.588; (95% CI=1.071; 6.253); OR=4.0; (95% CI=1.09; 14.67)]. The pregnant women with positive history of cigarette smoking in group D (11/15 or 73.3%) had non-significant lower rates of placental expulsion compared with non-smokers (28/35 or 88.0%) [Mantel-Haenszel χ^2=0.266, p=0.606; RR=1.333; (95% CI=0.458; 3.884); OR=1.455; (95% CI=0.354; 5.973)] (Table 3).

Table 3 **Cigarette smoking and placental expulsion rate by study groups (n=200).**

Group				Placental expulsion		Total
				no	yes	
A	Smoking	no	N	8	27	35
			%	22.9%	77.1%	100.0%
		yes	N	7	8	15
			%	46.7%	53.3%	100.0%
	Total		N	15	15	35
			%	30.0%	30,0%	70,0%
B	Smoking	no	N	5	27	32
			%	15.6%	84.4%	100.0%
		yes	N	4	14	18
			%	22.2%	77.8%	100.0%
	Total		N	9	9	41
			%	18.0%	18.0%	82.0%
C	Smoking	no	N	6	27	33
			%	18.2%	81.8%	100.0%
		yes	N	8	9	17
			%	47.1%	52.9%	100.0%
	Total		N	14	14	36
			%	28.0%	28.0%	72.0%
D	Smoking	no	N	7	28	35
			%	20.0%	80.0%	100.0%
		yes	N	4	11	15
			%	26.7%	73.3%	100.0%
	Total		N	11	39	50
			%	22.0%	78.0%	100.0%

DISCUSSION

In this study we examined the association between maternal cigarette use and expulsion rates of placenta in active management of retained placenta. Smoking during pregnancy has been associated with socioeconomic determinants and it is recognized as the most important preventable risk factor for an unsuccessful pregnancy outcome. In this study, history of cigarette smoking was more likely in pregnant women with high school diploma. Other studies represented that women with lower education level are at increased risk for smoking during pregnancy (5,6,13).

Cigarette smoking disrupts placental development, and impairs fetal health and maternal fertility, however, the underlying mechanisms remain unclear (14). Maternal smoking during the first trimester is associated with a decreased risk of preeclampsia and an increased risk of having an infant small-for-gestational-age, therefore smoking might alter the placental expression of genes related to the pathogenesis of preeclampsia and small-for-gestational-age (9). In the study of Mitsuda N, et al., placental weight was greater and placental weight/birthweight ratio was higher among smokers compared with non-smokers (15). In vivo and in vitro studies have shown that nicotine acts directly on the placenta, being involved in the alteration of maternal-fetal circulation by influencing the mechanisms of trophoblastic invasion

(16). Maternal smoking, like maternal obesity and preeclampsia, causes oxidative stress, by disrupting the production of reactive oxygen species (ROS). These maternal factors have been associated with aberrant angiogenesis and placental dysfunction, leading to unwanted pregnancy outcomes (17,18). In this study, there was not statistically significant difference between A, B, C and D groups and subgroups in the success rates of the total expulsion of placenta (70% vs. 82% vs. 72% vs. 78%). The pregnant women with positive history of cigarette smoking had overall statistically significant lower rates of placental expulsion compared with non-smokers (64,6% vs. 80,7%). Stratification analysis represented that smokers in group C (9/17 or 52.9%) had statistically significant lower rates of placental expulsion compared with non-smokers (27/33 or 81,8%). In the study of Jenabi E, et al., results suggested that maternal smoking is a risk factor for the placenta accreta spectrum (19).

In this study, the cord diameter <2.0 cm was more frequently in the pregnant women with positive history of cigarette smoking, compared with non-smokers, but there was not statistically significant differences (10,8% vs. 5,9%). In the study of Ismail KI, et al, represented that umbilical cord morphometry is associated with small for gestational age (SGA) infants (20). In the systematic review of Pintican D, et al, reductions of blood flow velocity waveforms in the uterine, umbilical and fetal middle cerebral arteries are confirmed by morphometric measurements of fetal capillaries in villi that were shown to be smaller in smoke exposure groups (18).

Smoking is a well-known risk factor during pregnancy for preeclamsia, placenta abruption, small for gestational age, preterm birth, low-birth weight and perinatal death (21,22). Cigarette smoke components can influence both the maternal side as well as the embryonic side of the placenta. Disruption of fundamental processes (e.g., proliferation, apoptosis and invasion) during placental development may result in adverse pregnancy outcome (1).

A limitation of our study is that it is done at single center (n=200), thus, results may not be applicable to other populations.

CONCLUSION

Cigarette smoking among women of reproductive age is associated with lower rates of placental expulsion. Because, cigarette smoking, e-cigarettes, and other tobacco/nicotine/hookah products have the potential serious adverse effects on mother and fetus, further research is needed.

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Declaration of patient consent: the authors certify that they have obtained all appropriate patient consent forms. In the form, patients have given their consent for their images and other clinical information to be reported in the journal.

Authors' Contributions: MAEl-A and SI gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author had role in article drafting and in process of revision. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial support and sponsorship: nil.

Conflict of interest: there are no conflicts of interest.

Comparison of the functional outcome of the surgically treated unstable intertrochanteric fractures with internal osteosynthesis

Komparacija funkcionalnog ishoda operativnog liječenja nestabilnih intertrohanternih prijeloma internom osteosintezom

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ABSTRACT

Introduction: the incidence of patients with fractures of the proximal end of the femur increases every year. Intertrochanteric fractures account for about 50% of all hip fractures, and the one-year mortality of patients with this type of injury is about 15-20%. Given that hip fractures in elderly patients are usually accompanied by comorbidities such as hypertension, osteoporosis, or diabetes, such patients are usually of poorer general condition and poorer operative tolerance. The biggest dilemma with these types of fractures is which type of osteosynthesis to use - intra or extramedullary fixation?! Treatment of osteoporotic intertrochanteric fractures in the elderly is a challenge due to the anatomical region and problems associated with decreased bone density and poor quality. Aim: to determine which operative method has a better functional outcome by comparing two operative methods in unstable intertrochanteric hip fractures in elderly patients. The study was designed as an retrospective, clinically controlled study. Materials and methods: the research was conducted at the Clinic for Orthopedics and Traumatology of the Clinical Center University of Sarajevo and it included 96 elderly patients with X-ray defined unstable intertrochanteric fractures of the femur, surgically treated at the Clinic of Orthopedics and Traumatology. Results: the study included 60 female patients, with 62.5% of the sample, and 36 male patients, with 37.5% of the patients. The analysis revealed that the average age of all patients was 77.38±5.20 years. On the first postoperative day, the value of the HHS in Group I patients had an average value of 38.40, while in Group 2 score values averaged 43.04. On the twelfth postoperative day, the value of the HHS, in Group I patients had an average value of 66.44 while in Group 2 score values averaged 66.17. After I month from the procedure, the value of the HHS in group I had an average value of 68.64. In Group 2 patients score values averaged 79.13. Three months after the procedure, the value of the HHS in Group I had an average value of 79.40 while in Group 2 score values averaged 86.43. Conclusion: it is still not clearly defined in the literature which type of implant to use in the stabilization of unstable intertrochanteric fractures of the proximal end of the femur. Intramedullar osteosynthesis still represent the golden standard for the treatment because of the early mobilization, full weight bearing, better range of motions and less pain.

Keywords: intertrochanteric fracture, surgical procedure, functional outcome

SAŽETAK

Uvod: incidenca pacijenata sa prijelomima proksimalnog okrajka femura raste svake godine. Intertrohanterni prijelomi podrazumijevaju oko 50% svih prijeloma kuka, a jednogodišnji mortalitet pacijenata sa ovakvom vrstom povrede iznosi oko 15-20% . Obzirom da su prijelomi kuka kod pacijenata treće životne dobi obično praćeni komorbiditetima kao što je hipertenzija, osteoporoza ili dijabetes, ovakvi pacijenti su obično slabijeg općeg stanja i slabije operativne tolerancije. Najveća dilema kod ovakvih vrsta prijeloma jeste koju vrstu osteosinteze koristiti - intra ili ekstramedularnu fiksaciju?! Liječenje osteoporotičnih intertrohanternih fraktura kod starijih je izazov zbog anatomske regije i problema vezanih sa smanjenjem gustine i lošeg kvaliteta kostiju. Cilj: komparirajući dvije operativne metode kod nestabilnih intertrohanternih prijeloma kuka kod pacijenata treće životne dobi, utvrditi koja operativna metoda ima bolji funkcionalni ishod. Materijal i metode: studija je dizajnirana kao retrospektivna, klinički kontrolisana studija. Istraživanje je provedeno na Klinici za ortopediju i traumatologiju Kliničkog centra Univerziteta u Sarajevu. U studiju je uključeno 96 pacijenata treće životne dobi sa rtg verificiranim nestabilnim intertrohanternim prijelomima femura, operisanih na Klinici za ortopediju i traumatologiju. Rezultati:

istraživanjem je obuhvaćeno 60 pacijenata ženskog pola (62,5% uzorka) i 36 pacijenata muškog pola (37,5% pacijenata). Analiza je pokazala da je prosječna starost svih pacijenata bila 77,38±5,20 godina. Prvog postoperativnog dana vrijednost HHS kod pacijenata grupe I imala je prosječnu vrijednost 38,40, dok su vrijednosti skora u grupi 2 u prosjeku bile 43,04. Dvanaestog postoperativnog dana, vrijednost HHS kod pacijenata u grupi I imala je prosječnu vrijednost 66,44 dok su u grupi 2 skor u prosjeku iznosile 66,17. Nakon mjesec dana od zahvata, vrijednost HHS u grupi I imala je prosječnu vrijednost 68,64. U 2. grupi pacijenata, prosječne vrijednosti skora iznosile su 79,13. Tri mjeseca nakon zahvata, vrijednost HHS-a u Grupi I imala je prosječnu vrijednost od 79,40 dok su u Grupi 2 u prosjeku bile 86,43. Zaključak: u literaturi još uvijek nije jasno definirano koji tip implantata koristiti u stabilizaciji nestabilnih intertrohanternih prijeloma proksimalnog kraja femura. Intramedularna osteosinteza i dalje predstavlja zlatni standard za liječenje zbog rane mobilizacije, oslonca punom težinom, boljeg obima pokreta i manje boli.

Ključne riječi: intertrohanterni prijelom, operativni zahvat, funkcionalni ishod

INTRODUCTION

The incidence of patients with fractures of the proximal end of the femur is increasing every year. Hip fractures in the third age represent an increasing preventive problem worldwide (1,2). The complexity of intertrochanteric fractures in elderly patients presents a challenge due to the increased risk for morbidity and mortality (3). Most hip fractures in the third age occur as a result of osteoporosis and falls during activities of daily living with a gender incidence of 1:4 in favor of the female population (4,5). There are many classifications of hip fractures. The simplest division is intracapsular and extracapsular fractures. Inside the capsule, above its attachment to the femur, there is the neck and head of the femur, and extracapsular fractures include fractures of the trochanteric mass and the part of the femur that is located directly below it, and extends to about 5 cm distal to the lesser trochanter and consists of two groups fractures: intertrochanteric and subtrochanteric (6).

Extracapsular fractures of the proximal edge of the femur represent a break in the continuity of the bone in the region between the greater and lesser trochanters and are designated as intertrochanteric fractures (7). Intertrochanteric fractures comprise about 50% of all hip fractures, and the one-year mortality of patients with this type of injury is about 15-20% (8,9). The intertrochanteric region is made of dense trabecular bone and in this area is the calcar femorale, which is a vertical wall of bone that extends from the posteromedial aspect of the proximal third of the femoral diaphysis to the posterior wall of the femoral neck. This anatomical feature is extremely important because of the assessment of the type of intertrochanteric fractures as stable and unstable (10). Unstable intertrochanteric fractures are most often presented with posteromedial comminution and fracture of the greater trochanter - the classic four-part intertrochanteric fracture (11). Pathophysiologically, there is rupture of the anterior cortex under tension, which causes a fracture line along the intertrochanteric region, while the posterior wall ruptures due to compression and is very often comminuted (12). The primary goal of treatment is stable fixation and immediately after that, mobilization of the patient.

AIM

The aim of the research was to compare two operative methods of internal osteosynthesis (implantation of Dynamic Hip Screw or Gamma-Nail) in unstable intertrochanteric hip fractures in patients of the third age and to determine which operative method had better functional outcome.

MATERIALS AND METHODS

The study assessed 96 patients of the third age with X-ray verified unstable intertrochanteric fractures of femur surgically treated at the Clinic of Orthopedics and Traumatology of the Clinical Center University of Sarajevo, in the period from January to September 2022. Patients were divided into two groups depending on the type of the internal osteosynthesis implanted during the surgery. For the assessment of the surgery results Harris Hip Score and VAS pain score were used. The study assesed patients through 4 regular check-ups: 1st postoperative day, 12th postoperative day and 1 and 3 months after the surgery. The Harris Hip Scale (HHS) was developed for the assessment of the results of hip surgery, and is intended to evaluate various hip disabilities and methods of treatment in an adult population. The HHS is divided into three sections. The first sections are questions about pain and its impact which are answered by the patient. The second and third sections require the clinician to assess hip joint and function. There are ten items covering four domains. The domains are pain, function, absence of deformity, and range of motion. The pain domain measures pain severity and its effect on activities and need for pain medication. The function domain is divided into daily activities and gait. The deformity domains observe hip flexion; adduction, internal rotation, and extremity length discrepancy while the range of motion domain assess hip range of motion. VAS pain scale represents fast and widely used test for evaluation of the pain. It is used for measuring the subjective feeling of the pain from worst to best. Statistical data processing was done through IBM SPSS Version 20.0 for Windows. Analysis of categorical variables was performed using Pearson's χ^2-test or Fisher's exact probability test. Spearman rank correlation coefficients were used to examine the linear correlation. Statistical significance was set at the conventional level ($\alpha = 0.05$). The results were shown in the graph and contingency tables (numbers with three decimal places). The level of significance was $p< 0.0$.

The study inclusion criteria: patients older than 65 years of age, patients with X-ray verified unstable intertrochanteric fractures of the proximal femur. The study exclusion criteria were: patients younger than 65 years of age, pathological fractures, patients with X-ray verified stable, subtrochanteric, pertrochanteric, subcapital ol fractures of the femoral neck.

RESULTS

The study included 60 female patients, 62.5% of the sample, and 36 male patients, 37.5% of the sample. The analysis revealed that the average age of all patients was 77.38±5.20 years. The

average age of female patients was 77.42±5.41 years, and the average age of male subjects was 77.31±4.90. No significant statistical difference was found in relation to gender (p=0.920).

Table I **Age difference among two groups of patients.**

Group	N	Mean	Std. Dev.	Std. Error	t	p
Group I	48	79.16	5.96	1.19	0.019	0.985
Group II	48	79.13	4.48	0.93		

On the first postoperative day, the value of the HHS in Group I patients had an average value of 38.40 with a median value of 38 and an interquartile range of 36 to 40. In Group 2 score values averaged 43.04, with a median value of 43 and an interquartile range of 39 to 46. A significant statistical difference was found between the two analyzed groups (F=410,429, p<0.001). Subsequent Post-Hoc analyzes revealed that there is a significant difference in the value of the HHS between the two methods of internal osteosynthesis (p=0.002). On the twelfth postoperative day, the value of the HHS, in patients in group I had an average value of 66.44 with a median value of 68 and an interquartile range of 62 to 70. In patients in group 2 score values averaged 66.17, with a median value of 66 and an interquartile range of 61 to 71. A significant statistical difference was found between the two analyzed groups (F=88.533, p<0.001). Subsequent Post-Hoc analyzes revealed that there is no significant diffe rence in the value of the Harris Hip score (p=0.959). After 1 month from the procedure, the value of the HHS in group I had an average value of 68.64 with a median value of 70 and an interquartile range of 64 to 71. In Group 2 patients score values averaged 79.13, with a median value of 79 and an interquartile range of 77 to 82. A significant statistical difference was found between the two analyzed groups (F=159.08, p<0.001). Subsequent Post-Hoc analyzes revealed that there is a significant difference in t he value of the HHS between the two methods of internal osteosynthesis (p<0.001) Three months after the procedure, the value of the HHS in Group I had an average value of 79.40 with a median value of 80 and an interquartile range of 77 to 82. In patients in Group 2 score values averaged 86.43, with a median value of 88 and an interquartile range of 84 to 90. A significant statistical difference was found between the two analyzed groups (F=38.208, p<0.001). Subsequent Post-Hoc analyzes revealed that there is a significant difference in the value of the Harris Hip score between the two methods of internal osteosynthesis (p<0.001). On the first postoperative day, the value of the VAS pain scale, in patients in group I had an average value of 6.92 with a median value of 7 and an interquartile range of 6 to 8. In patients in group 2 the values the average score was 6.78, with a median value of 7 and an interquartile range of 6 to 8. No significant statistical difference was found between the two analyzed groups (K ruskal Wallis H=4.221, p=0.121). On the twelfth postoperative day, the value of the VAS pain scale, in group I had an average value of 6.40 with a median value of 6 and an interquartile range of 6 to 7. In patients in group 2 the values average scores were 5.35, with a median value of 5 and an interquartile range of 5 to 6. A significant statistical difference was found between the two analyzed groups (Kruskal Wallis H=12.928, p=0.002). It was observed that patients treated with internal osteosynthesis in group I had significantly stronger pain compared to the other group. After 1 month from the procedure, the value of the subjective pain scale, in patients in group I, had an average value of 3.88 with a median value of 4 and an interquartile range of 4 to 4. In patients in group 2, score values averaged 3.91, with a median value of 4 and an interquartile range of 3 to 5. No significant statistical differences were found between the two groups (Kruskal Wallis H=1.941, p=0.379). After 3 months from the procedure, the value of the VAS pain scale, in patients in group I, had an average value of 2.40 with a median value of 2 and an interquartile range of 2 to 3. In patients in group 2 score values averaged 2.70, with a median value of 3 and an interquartile range of 2 to 3. A significant statistical difference was found between the two analyzed groups (Kruskal Wallis H=8.720, p=0.013). It was found that after three months, patients treated with internal osteosynthesis with DHS have less pain compared to the group of patients who were treated with intramedular osteosynthesis (p=0.005).

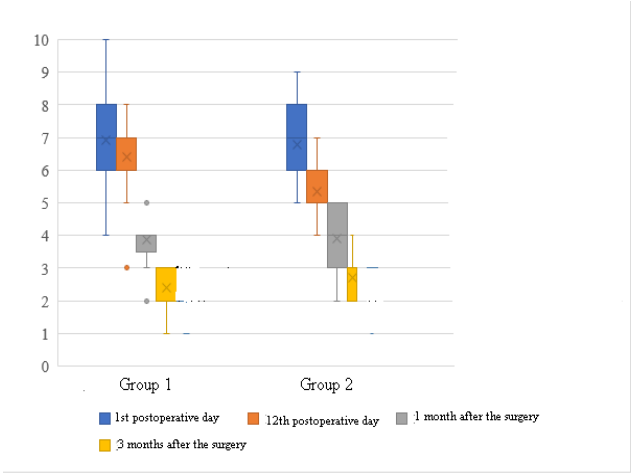

Figure I **Analysis of the VAS scale of pain between the two groups of patients.**

DISCUSSION

The available research still raises the question as to which is the optimal implant for fixation of unstable intertrochanteric fractures. Dynamic hip screw (DHS), the most representative implant of extramedullary fixation, is considered the gold standard for the treatment of intertrochanteric fractures. Follow-up studies of internal fixation of such fractures with the DHS system show a high failure rate, such as bending of the implants and their fracture. DHS often does not give good results in unstable fractures, which limits its clinical use (13). The proximal femoral nail (PFN) has been widely used for many years due to its excellent clinical results. Long-term studies, however, have shown that PFN can cause major intraoperative and late operative complications that often require revision surgery (14). The nail was designed to reduce the risk of these implant-related complications, and available research suggests that this goal may have been achieved. PFN provides angular and rotational stability, which is especially important in severe osteoporosis, and enables verticalization with full body weight on the operated extremity (15). Intramedullary implants have shown a reduced tendency to cut-out in osteoporotic bone and have better

results in cases of unstable intertrochanteric fractures. However, the role of intramedullary fixation in osteoporosis and severe comminuted intertrochanteric fractures is still undefined. A retrospective study conducted by Kregor PJ, et al. in 2014, on the topic of operative results and the need for reoperation in unstable intertrochanteric fractures, showed that the installation of DHS results in a 56% need for reoperation compared to other osteosynthesis (16).

In a meta-analysis conducted by Ma HH, et al. in 2014, the effect of internal osteosynthesis implantation in intertrochanteric hip fractures was monitored. Thus, it was concluded that the proximal femoral nail should be the osteosynthesis treatment for this type of fracture due to the low failure rate of the operative procedure, less blood loss and shorter hospitalization. The dynamic hip screw (DHS) has the advantage of being implanted in this type of fracture due to the low rate of postoperative and implant-related complications (17).

In their research, Palm et al showed that the need for reoperation was lower when installing intramedullary fixation compared to DHS in unstable intertrochanteric fractures in which the greater trochanter was also fractured, and as a result of screw slippage and a larger cut-out in the group with built-in DHS (18). In the research conducted by Memon K, et al in two regional orthopedic centers and published in 2021, a comparison of HHS for operatively treated unstable intertrochanteric fractures was made in a 2-year follow-up period. Namely, in the mentioned research, the average HHS for the DHS internal osteosynthesis group was 69.28 +/- 9.99, while in the intramedullary osteosynthesis group it was 72.12 +/- 9.71 (19). If the average of the HHS scores obtained through regular controls was made, the HHS value during the follow-up period in Group 1 was 66.75, while in Group 2 it was 72.46, which corresponded to the values obtained in the before mentioned published research. In our research the higher HHS values were recorded in Group 2 patients most probably at the expense of immediate verticalization with full weight bearing, while in Group 1 verticalization with full weight bearing was achieved gradually, rotatory movements awere limited, patients slowly returned to independent daily activities and long after the surgery were tied to the use of one of the orthopedic aids (forearm crutches or walkers).

In a study published in 2022, Chen WH, et al. monitored the VAS pain scale and HHS in operatively treated unstable intertrochanteric fractures of the geriatric population for one year. In the group of internal osteosynthesis the VAS pain scale preoperatively was 7.4, and it was significantly reduced to 2.4 at the follow-up one month after the operation, while in the intramedullar osteosynthesis group, the VAS pain scale after the treatment was an average of 1.7 (20). Comparing the results with our study, the average score of VAS pain scale is lower in the group 2 that can be accounted for the early virtualization and previous return in the regular daily activities.

CONCLUSION

It is still not clearly defined in the literature which type of implant to use in the stabilization of unstable intertrochanteric fractures of the proximal end of the femur. Internal osteosynthesis has its advantages, but in the long term, conducted studies have shown that internal osteosynthesis can cause greater intraoperative and late operative complications that often require revision surgery. Intramedullar osteosynthesis still represent the golden standard for the treatment because of the early mobilisation, full weight bearing, better range of motions and less pain.

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Declaration of patient consent: the authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal.
Authors contributions: AP, FL, ĐO, AH, BK, MS and MO gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author had role in article drafting and in process of revision. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Financial support and sponsorship: nil.
Conflict of interest: there are no conflict

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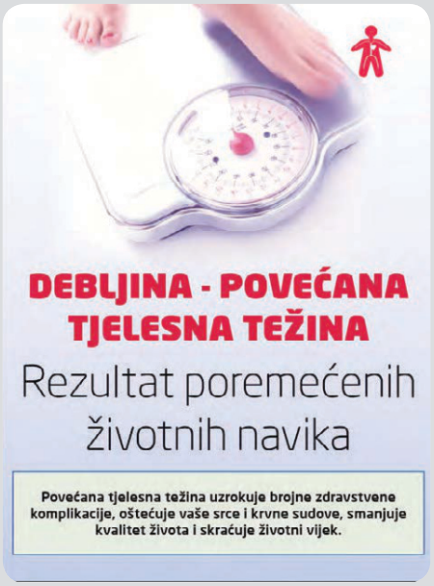

MR characterisation of the most common cystic masses of the neck

Karakterizacija cističnih masa vrata magnetnom rezonancom

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ABSTRACT

Introduction: cystic masses of the neck are uncommon and many of them have characteristic locations and imaging findings. They are divided into two groups, medial and lateral cystic masses. Some of them are acquired nature, while others are congenital. Aim: to illustrate the MR findigs of most common cystic masses of the neck. Materials and methods: this was a retrospective analysis of 67 adult patients who underwent MR imaging of the neck in the period from March 2021 to May 2022 at the Clinical Center University of Sarajevo. MR examination was made native in the T1-weighted, T2-weighted and fat-suppressed T2 scans, and with the application of intravenous contrast media in the amount of 0.1-0.2 ml/kg of their body weight. Results: cystic masses of the neck were present in 7 patients (10.5%), out of which thyroglossal duct cyst was found in 3 patients (4.5%), ranula in 2 patients (3,0%), and branchial cleft cyst and dermoid cyst were found in 1 patient (1.5%). The thyroglossal duct cyst is the most common cystic mass of the neck with a percentage frequency of 43% of all cystic neck lesions. Medial cystic masses of the neck were present at 6 patients (9.0%), while lateral cystic mass was present at just 1 patient (1.5%). Congenital cystic masses of the neck were found in 5 patients (7.5%), and acquired cystic masses in 2 patients (3.0%). Conclusion: MRI is an excellent tool for diagnosing the cystic masses of the neck. The clinical presentation in combination with a knowledge of the various compartment of the head and neck helps to establish the diagnosis or limit the diferential diagnosis.

Keywords: cystic mass, neck, medial, lateral, congenital, acquired

SAŽETAK

Uvod: cistične mase vrata su rijetke i mnoge imaju karakterističnu lokalizaciju i radiološke karakteristike. Podjeljene su u dvije grupe, medijalne i lateralne cistične mase vrata. Neke od njih su po prirodi stečene dok su druge kongenitalne. Cilj: prikazati karakteristike najčešćih cističnih lezija na vratu pomoću magnetne rezonance. Materijali i metode: retrospektivna studija obuhvata 67 odraslih pacijenata kod kojih je rađen pregled magnetnom rezonancom u periodu mart 2021. - maj 2022. godine na Klinici za radiologiju Kliničkog centra Univerziteta u Sarajevu. Pregled magnetnom rezonancom radjen je nativno u T1W, T2W i sekvencama sa supresijom masti u T2 W, te nakon intravenske aplikacije kontrastnog sredstva u količini 0,1 do 0,2 ml po kilogramu tjelesne težine. Rezultati: cistične mase vrata su detektovane kod sedam pacijenata (10,5%) od kojih je cista duktus tireoglosusa verificirana kod tri pacijenta (4,5%), ranula kod dva pacijenta (3%), a lateralna cista vrata i dermoidna cista kod jednog pacijenta (1,5%). Cista duktus tireoglotusa je najčešća cistična masa vrata sa učestalošću 43% od svih cističnih masa vrata. Medijalne ciste vrata su prezentirane kod 6 pacijenata (9%), dok su lateralne cistične mase prezentirane samo kod jednog pacijenta (1,5%). Kongenitalne cistične lezije vrata detektovane su kod pet pacijenata (7,5%), a stečene cistične mase kod dva pacijenta (3%). Zaključak: magnetna rezonanca predstavlja izuzetan dijagnostički modalitet u detekciji cističnih masa vrata. Klinička prezentacija u kombinaciji sa anatomskim poznavanjem regija glave i vrata pomaže u postavljanju definitivne dijagnoze.

Ključne riječi: cistične mase, vrat, medijalno, lateralno, urodjene, stečene

INTRODUCTION

Cystic masses of the neck are uncommon and can present in any age group. Many of these have characteristic locations and imaging findings. Cystic masses of the neck are divided into two groups: medial cystic masses (thyroglossal duct cyst, dermoid cyst and ranula) and lateral cystic masses (branchial cleft cysts). Among the aforementioned cystic lesions just ranula is acquired nature, while the others are congenital (1).

Thyroglossal duct cyst

The thyroid gland develops in the region of foramen cecum of the tongue during the third gestation week. The thyroid anlage descends down to reach the thyroid bed anterior laryngeal cartilages through the thyroglossal duct by the seventh week of gestation, and thyroglossal duct begins to involute by 8-10 weeks of gestation. If any segment of the thyroglossal duct fails to involute, then the persistent secretory activity from the epithelial lining owing to repeated infection or inflammation would give rise to thyroglossal cyst (1,2).

Most thyroglossal duct cysts are located at or below the level of the hyoid bone, at hyoid bone, in suprahyoid neck, or in the infrahyoid neck. It is commonly presented as a painless, enlarging mass and it characteristically moves upward with tongue prostrusion. Most of the times the thyroglossal duct cyst comes to

notice owing to repeated infection. Another rare but worrisome complication of the thyroglossal cyst is its association with thyroid cancer (3,4).

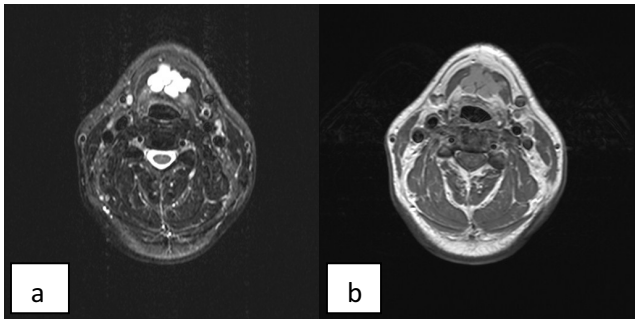

Figure 1 **Thyroglossal duct cyst on a fat-suppressed T2 axial scan *(a)* and without postcontrast enhancement *(b).***

Branchial cleft cysts

Branchial apparatus include 6 arches (mesoderm) interfaced by 4 clefts (ectoderm) and pouches (endoderm) on each side at the end of fourth week of embryonic life. The fifth arch is rudimentary and does not contribute to formation of any of the adult structure. Incomplete obliteration of I, II, III, or IV branchial apparatus can lead to respective branchial remnants like isolated cyst, fistula, or sinus (2,5).

A *first branchial cleft cyst* arises along the residual embryologic tract of the first branchial cleft or arch extending from the external auditory canal through the parotid gland to the submandibular triangle. Cysts of the first branchial cleft usually manifest as recurrent abscesses or other inflammation either around the ear or at the angle of the mandible. These cystic anomalies often mimic the clinical characteristics of parotid neoplasm (6).

Bailey classified the *second branchial cleft cysts* into four types. The Bailey typ I cyst ist the most superficial and lies along the anterior surface of the sternocleidomastoid muscle, just deep to the platysma muscle. The typ II cyst is the most common and found in the „classic" location for these cysts: along the anterior surface of the sternocleidomastoid muscle, lateral to the carotid space, and posterior to the submandibular gland. A typ III cyst extends medially between the bifurcation of the internal and external carotid arteries to the lateral pharyngeal wall. The typ IV cyst lies in the pharyngeal mucosal space and is lined with columnar epithelium (7).

Cysts arising from the third and fourth branchial cleft are extremely rare. Most of the third branchial cleft cysts are located in the posterior cervical space posterior to the sternocleidomastoid muscle. Anomalies of the fourth branchial cleft usually manifest as a sinus tract rather than a cyst or fistula. A fourth branchial cleft sinus tract arises from the pyriform sinus, pierces the thyrohyoid membrane, and begins a descent into the mediastinum, following the path of the tracheoesophageal groove (8).

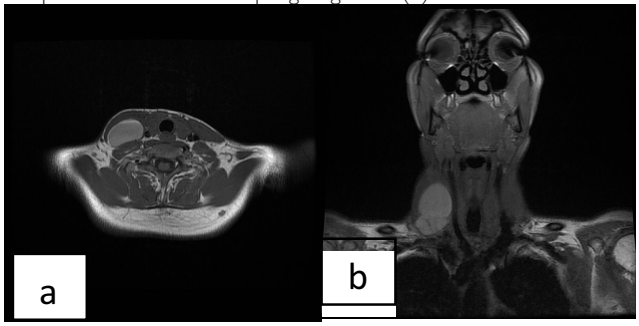

Figure 2 **Branchial cleft cyst on T1-weighted axial scan *(a)* and without postcontrast enhancement on coronal scan *(b).***

Dermoid cyst

The dermoid cyst typically occurs along embryonic lines of fusion suggesting that they exist because of entrapment of epithelial elements during development. They contain ectodermal and endodermal elements. Teratomas differ from dermoid cysts in that they contain all three germ layers. Lateral eyebrow is the most common location for head and neck, and the floor of the mouth is the second most common location. The most common clinical appearance of a dermoid cyst in the neck is a slow-growing, painless, midline subcutaneous or submucosal suprahyoid neck mass. Other rare presentations include dysphagia and airway encroachment owing to large size. Approximately 5% of dermoid cysts undergo malignant degeneration into squamos cell carcinoma (9,10).

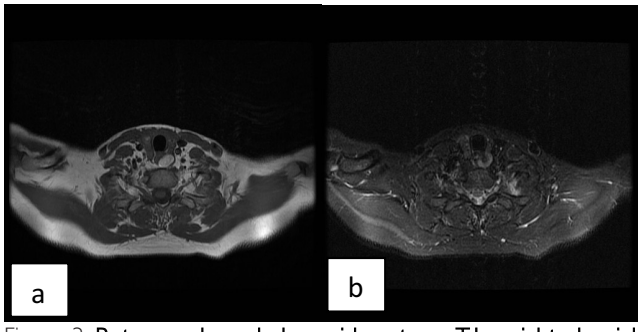

Figure 3 **Retroesophageal dermoid cyst on T1-weighted axial scan *(a)* and fat-suppressed T2 axial scan *(b).***

Ranula

Ranulas are mucoceles that occur in the floor of the mouth and usually involve the major salivary gland, specifically the sublingual gland. These lesions are divided into 2 types: oral ranulas and plunging ranulas. Oral ranulas are secondary to mucus extravasation that pools superior to the mylohyoid muscle, whereas cervical ranulas are associated with mucus extravasation along the fascial planes of the neck. Rarely, the mucocele arises within the submandibular gland and presents as a plunging ranula. Ranulas occur as the result of trauma or obstruction to the salivary gland excretory duct and spillage of mucin into the surrounding soft tissues (11).

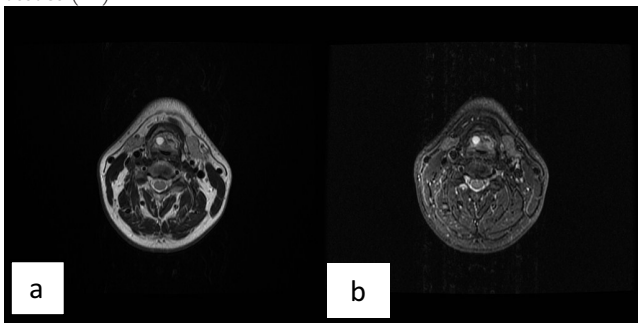

Figure 4 **Ranula on T2-weighted axial scan *(a)* and fat-suppressed T2 axial scan *(b).***

AIM

The aim of this study was to illustrate the MR findigs of most common cystic masses of the neck. These masses are interesting because they are uncommon and they can mimic other lesions.

MATERIALS AND METHODS

The study was a retrospective analysis of 67 adult patients who underwent MR imaging of the neck in the period from March 2021 to May 2022 at the Clinical Center University of Sarajevo. MR examination was made native in the T1-weighted, T2-weighted and fat-suppressed T2 scans, and with the application of intravenous contrast media in the amount of 0.1-0.2 ml/kg of their body weight.

RESULTS

The total number of patients was 67. The frequency of cystic masses of the neck is shown in Table 1. Figure 5 shows the most common cystic masses of the neck. The ratio between medial and lateral cystic masses of the neck is shown in Figure 6, while the ratio between congenital and acquired cystic masses is shown in Figure 7. MR characteristics of the most common cystic neck masses are seen in Table 2.

Table 1 **Frequency of cystic masses of the neck.**

MR findings	Number of cases	%
Thyroid disease	17	25.5
Normal findings	13	19.5
Nasopharyngeal Cancer	11	16.5
Cystic neck masses	7	10.5
Thyroid Cancer	4	6.0
Parotid disease	4	6.0
Soft tissue tumor	3	4.5
Parathyroid adenoma	2	3.0
Laryngeal Cancer	2	3.0
Glomustumor	1	1.5
Laryngeal polyp	1	1.5
Proximal esohpageal haemangioma	1	1.5
Hard palate Cancer	1	1.5

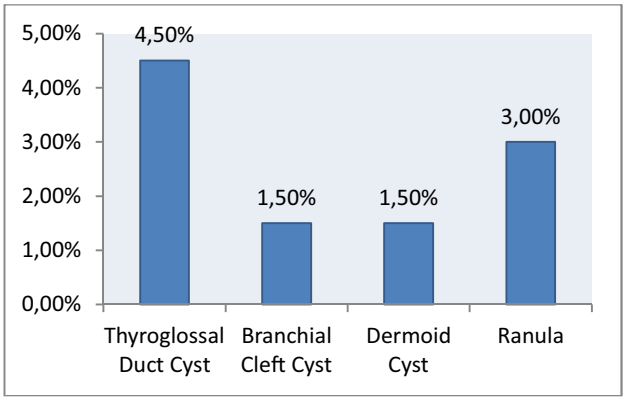

Figure 5 **Most common cystic masses of the neck.**

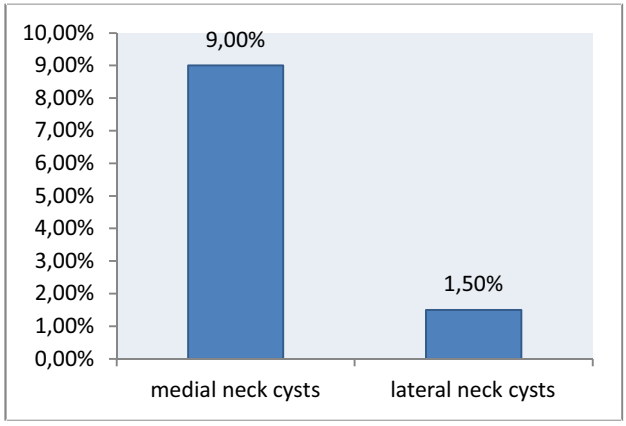

Figure 6 **Ratio between medial and lateral cystic masses of the neck.**

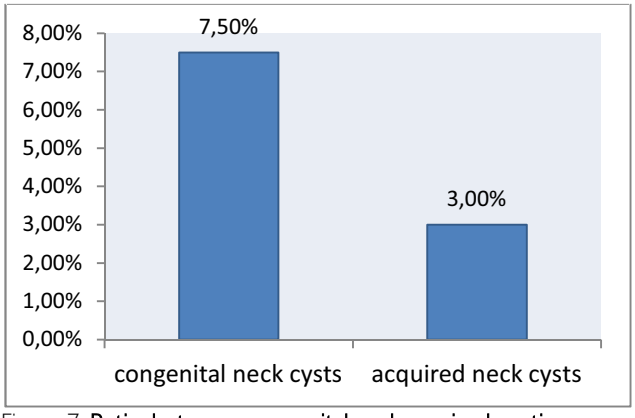

Figure 7 **Ratio between congenital and acquired cystic masses of the neck.**

Table 2 **MR characterisation of the most common cystic masses of the neck.**

Cystic neck mass	MR findings			
	T1-weighted	T2-weighted	T2 FS	T1 postcontrast
Thyroglossal duct cyst	dark	bright	bright	dark
Branchial cleft cyst	bright	bright	bright	bright, like T1-weighted
Dermoid cyst	bright	bright	partially dark (fatty parts)	bright, like T1-weighted
Ranula	dark	bright	bright	dark

DISCUSSION

In our retrospective study of 67 adult patients who underwent MR examination of the neck in the period from March 2016 to May 2017, we found that cystic masses of the neck were present in 7 patients (10.5%), out of which thyroglossal duct cyst was found in 3 patients (4.5%), ranula in 2 patients (3.0%), and second branchial cleft cyst and dermoid cyst were found in 1 patient (1.5%). All patients with cystic neck masses were presented with symptoms of a painless mass in the neck, except that one with dermoid cyst which was presented with dysphagia. The thyroglossal duct cyst is the most common cystic mass of the neck with a percentage frequency of 43% of all cystic neck lesions. The literature data show also that the thyroglossal duct cyst is the most common cystic mass of the neck which is present in about 70% of all cystic neck lesions (12,13). The second branchial cleft cyst is the most common cyst of all branchial cleft anomalies comprising up to 95% of them (5). Of all dermoid cysts, 7% are located in the region head and neck, out of which 11.5% are in the floor of the mouth (14). The literature data also show that the prevalence of ranulas is 2.0% which coincides whit our results (11).

According to our results, medial cystic masses of the neck were present at 6 patients (9.0%), while lateral cystic mass was present at just 1 patient (1.5%). Congenital cystic masses of the neck were found and 5 patients (7.5%), and acquired cystic masses were found at 2 patients (3.0%).

On MRI, an uncomplicated thyroglossal duct cyst has low signal intensity on T1-weighted images, but high signal intensity on T2-weighted and fat-suppressed T2 images, without postcontrast enhancement. The typical picture reflects its fluid content. T1-weighted images sometimes can be isointense to hyperintense related to proteinaceous contents of the cyst. In case of infection or hemorrhage, a tkick irregular rim may be visualized (15). In branch cleft cysts the cyst fluid varies from hypointense to slightly hyperintense relative to muscle on T1-weighted images and is usually hyperintense on T2-weighted images. Mural thichness and enhancement vary, depending of the presence and severity of any associated inflammatory process (12). Dermoid cyst has more complex signal on T1-weighted and heterogenous hyperintense signal on T2-weighted images. Fat-suppression T2 shows low signal in the dermoid cyst because of fat content in it. Postcontrast administration may show peripheral enhancement (16). Ranula shows the same MR characteristics as the thyroglossal duct cyst, the difference is just in the location of the cyst. Ranula is located mostly in the sublingual space, but can also be seen in the submandibular space as the plunging ranula.

CONCLUSION

MRI is an excellent tool for diagnosis of cystic masses of the neck. The clinical presentation in combination with a knowledge of the various compartment of the head and neck helps to establish the diagnosis or limit the diferential diagnosis.

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Declaration of patient consent: the author certifies that he has obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal.
Authors contributions: FZ gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work.
Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

Comparison of positive IgG index and oligoclonal bands in patients with suspected Multiple Sclerosis

Usporedba pozitivnog IgG indeksa i oligoklonalnih traka kod pacijenata sa sumnjom na multiplu sklerozu

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ABSTRACT

Introduction: Multiple sclerosis (MS) is often a progressive neurological disease of the central nervous system. Elevated levels of immunoglobulins and the presence of oligoclonal bands (OCBs) suggest localized B cell expansion within the brain. The hyperbolic formula developed by Reiber is widely recognized as the most commonly employed method for quantitatively measuring intrathecal synthesis. The IgG index is calculated as the ratio of cerebrospinal fluid IgG to serum IgG divided by the ratio of albumin CSF to serum albumin. The analysis of oligoclonal IgG by isoelectric focusing (IEF) and immunofixation (IF) represents the most frequently used complementary method to detect inflammatory processes with intrathecal IgG synthesis. It is rare for the quantitative value (IgG index) to be elevated in the absence of OCBs detected by IEF, whereas the opposite situation (positive OCBs and negative intrathecal synthesis) occurs much more frequently. Aim: to assess quantitative IgG synthesis using Reiber's formula and to compare its presence with the detection of oligoclonal bands on gel electrophoresis, which provides a qualitative assessment of intrathecal synthesis in patients with suspected multiple sclerosis (MS). Materials and methods: we applied Reiber's formula to a cohort of 99 patients who underwent diagnostic evaluation for suspected central nervous system (CNS) demyelination and lumbar puncture for oligoclonal bands detection. Results: all patients without bands present on the gel (Type 1, indicating a normal finding) had a negative result for quantitative synthesis, and consequently a negative IgG index. Among the group of 49 patients with Type 2 bands present on the gel, the intrathecal synthesis, as determined by the Reiber formula, was positive in 61.22% of cases. Conclusion: this finding is consistent with previous research and confirms that the quantitative synthesis alone cannot replace the qualitative findings observed on the bands.

Keywords: intrathecal synthesis, oligoclonal bands, IgG index

SAŽETAK

Uvod: multipla skleroza (MS) često je progresivna neurološka bolest centralnog nervnog sistema. Povišeni nivoi imunoglobulina i prisustvo oligoklonskih traka (O GT) ukazuju na lokalizirano B ćelijsko prisustvo unutar mozga. Hiperbolična formula koju je razvio Reiber poznata je kao najčešće korištena metoda za kvantitativno mjerenje intratekalne sinteze. IgG indeks se izračunava kao omjer IgG cerebrospinalne tečnosti prema IgG u serumu, podijeljen omjerom albumina u CSF-u prema albuminu seruma. Analiza oligoklonalnog IgG metodom izoelektričnog fokusiranja (IEF) i imunofiksacija (IF) predstavlja najčešće korištenu komplementarnu metodu za otkrivanje upalnih procesa sa intratekalnom IgG sintezom. Rijetko je da kvantitativna vrijednost (IgG indeks) bude povišena u odsustvu OCB-a detektiranih pomoću IEF-a, dok se obrnuta situacija (pozitivni OCB-ovi i negativna intratekalna sinteza) mnogo češće javlja Cilj: procjena kvantitativne sinteze IgG kod pacijenata sa sumnjom na multiplu sklerozu (MS) i uporedba iste sa prisustvom oligoklonalnih traka na gel elektroforezi, koja pruža kvalitativnu procjenu intratekalne sinteze. Materijali i metode: primijenili smo Reiberovu formulu na grupi od 99 pacijenata koji su bili podvrgnuti dijagnostičkoj evaluaciji zbog sumnje na demijelinizaciju centralnog nervnog sistema (CNS) i kojima je urađena lumbalna punkcija u svrhu detekcije oligoklonalnih traka. Rezultati: svi pacijenti koji nisu imali trake na gelu (Tip 1 što ukazuje na uredan nalaz) imali su negativan rezultat kvantitativne sinteze. U grupi 49 pacijenata koji su imali prisutne trake tipa 2 IgG indeks je bio prisutan u 61,22% slučajeva. Zaključak: ovaj nalaz je u skladu sa prethodnim istraživanjima i potvrđuje da IgG indeks sam po sebi ne može zamijeniti kvalitativni nalaz na trakama.

Ključne riječi: intratekalna sinteza, oligoklone trake , IgG indeks

INTRODUCTION

The immune privilege of the central nervous system (CNS) typically means the absence of B cells and plasma cells, resulting in limited immunoglobulin (Ig) synthesis within the CNS. During CNS pathologies, the permeability of the BBB (blood brain barrier) commonly increases, leading to elevated concentrations of blood borne proteins and Igs in the CSF (cerebrospinal fluid) (1).

Elevated levels of immunoglobulins and the presence of oligoclonal bands (OCBs) suggest localized B cell expansion within the brain. Analysis of the immunoglobulin heavy chain repertoire in B cells derived from CSF has revealed both clonal expansion and evidence of somatic hypermutation (2).

The hyperbolic formula developed by Reiber is widely recognized as the most commonly employed method for quantitatively measuring intrathecal synthesis. It has consistently demonstrated highly favorable outcomes in various studies (3).

In this context, it is essential to evaluate the integrity of the BBB by utilizing the albumin index (AI). The AI is a valuable tool that involves comparing the levels of albumin in both the serum and CSF. By assessing the discrepancy in albumin concentrations between these two compartments, we can determine whether there is a disruption in the BBB (4).

The IgG index is calculated as the ratio of cerebrospinal fluid IgG to serum IgG divided by the ratio of albumin CSF to serum albumin. It provides a quantitative measure of the relationship between CSF IgG and serum IgG, taking into account the same relationship for albumin. In inflammatory CNS conditions, such as multiple sclerosis (MS), the IgG index is elevated (5).

IgG oligoclonal bands (OCBs) are commonly used in the diagnostic evaluation of multiple sclerosis (MS) as they are specific to the cerebrospinal fluid (CSF). Although OCBs can be detected in other inflammatory and infectious diseases of the CNS, distinguishing them from multiple sclerosis (MS) can be achieved through additional CSF analysis and clinical assessment (6).

A number of techniques have been developed to detect CSF OCBs. The gold standard is isoelectric focusing (IEF) on agarose gel followed by immunoblotting or immunofixation for IgG2 with paired CSF and serum. The sensitivity for detection of OCBs is over 95% using this technique (7).

The analysis of oligoclonal IgG by isoelectric focusing (IEF) and i mmunofixation (IF) represents the most frequently used, complem entary method to detect inflammatory processes with

intrathecal IgG synthesis (8).

The location and number of bands generally have no importanc e for interpretation. Of most interest for neurological diagnosis are Types 2 and 3 (9).

OCBs were included in the 2017 McDonald diagnostic criteria for MS, and a positive finding of OCBs exclusively in the CSF (Type 2), or a higher number of bands in CSF compared to serum (type 3), supports the diagnosis of a pathological process (10).

Although the origin and role of oligoclonal bands (OCBs) remain unclear, their presence is closely linked to the development of MS and can provide additional support for diagnosis. It is rare for the quantitative value (IgG index) to be elevated in the absence of OCBs detected by IEF, whereas the opposite situation (positive OCBs and negative intrathecal synthesis) occurs much more frequently (11).

There is complete agreement that isoelectric focusing (IEF) on agarose gels followed by immunoblotting should be the "gold standard" for detecting the presence of oligoclonal bands (12).

AIM

The aim of this study was to assess quantitative IgG synthesis using Reiber's formula in patients with suspected multiple sclerosis (MS) and to compare its presence with the detection of oligoclonal bands on gel electrophoresis, which provides a qualitative assessment of intrathecal synthesis.

MATERIALS AND METHODS

A total of 99 patients were included in this study. All patients were hospitalized at the Neurology Clinics and samples (sera and CSF) were referred to the Department of Biochemistry and Clinical Immunology (Clinical Center University of Sarajevo) for further diagnostics, through January-December 2022. The patients were older than 18 years, and younger than 50, separated into two groups: reference group (RG) and study group (SG).

RG included 50 patients who were examined because of the neurological symptoms and differential diagnosis of MS. However, these individuals did not meet the diagnostic criteria for MS and had type 1 OCBs. The SG consisted of 49 patients with a clinically defined MS or CIS (clinical isolated syndrome). The study was approved by the Ethical Committee of the Clinical Center University of Sarajevo.

Total albumin and IgG concentrations in serum were determined using fully automated nephelometric analyzer (Siemens BN II System, Munich, Germany) according to the standard protocol.

The serum and CSF IgG concentrations of the individual patient were adjusted to each other by making an adequate dilution. Then, the procedure of OCBs detection, based on isoelectric focusing on agarose gel (9 or 3 places, where appropriate), was done using semi-automatic Hydrasys system and accompanying original kit (Sebia, Evry Cedex, France). At the end of procedure, the gel was dried and evaluated by two independent experts who compared the pattern revealed in serum with CSF pattern, thus categorizing each OCBs into one of the five OCBs types (I-V). Type II and type III patterns were considered as positive for intrathecal IgG synthesis.

After obtaining the results of the aforementioned biochemical analysis, calculations were made using the following formula:

- IgG index = (IgGcsf / IgGs) / (Albcsf / Albs)

Where:

- IgGcsf represents the concentration of IgG in the CSF
- IgGs represents the concentration of IgG in the serum
- Albcsf represents the concentration of albumin in the CSF
- Albs represent the concentration of albumin in the serum

A statistical analysis was performed using Stat Soft Statistica 13.2. Software package. Depending on the variable type and underlying distribution for metric variables, the data were expressed as the frequencies, mean ± standard deviation (SD) or median with range. The results are shown in the tables.

RESULTS

The study included a total 99 subjects; 50 health controls and 49 MS. 72% of patients were female and 28% male. The average age in the group of patients with MS was 32.4 +/-9.3 years, and in the group of healthy controls 37.6 +/-5.8 years. There is a

significant difference in the average age of the subjects between patients with MS and healthy ones, p=0.012. The average age of MS patients is lower than healthy controls.

Between the group of patients with MS and healthy controls, there is no significant difference in the gender structure of the group, p=0.129. In both groups there was a higher proportion of female respondents (Table 1).

Table 1 **Demographic characteristic of the patients.**

Group		Gender		Total	Pearson Chi-Square	p value
		Male	Female			
MS patients	N	10	39	49	2.305[a]	0.129
	%	20.4%	79.6%	100.0%		
Healthy controls	N	17	33	50		
	%	34.0%	66.0%	100.0%		

N=number of subjects; MS=multiple sclerosis, p= statistical significance

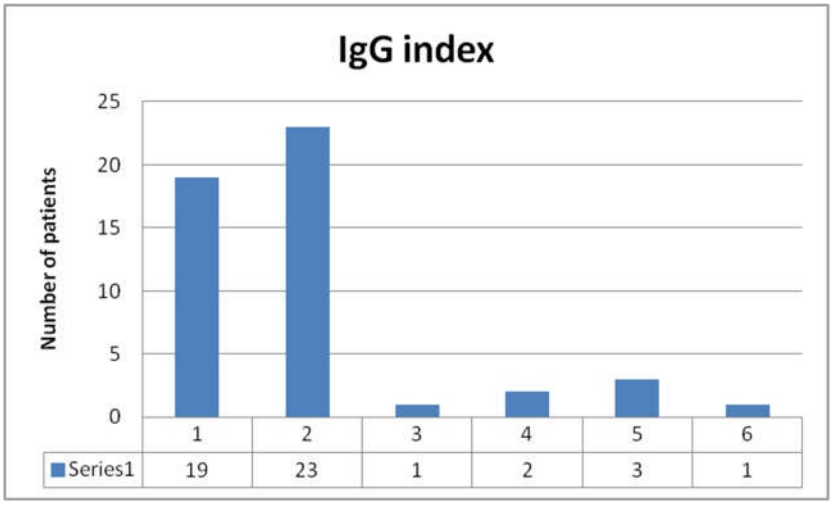
All the patients in the RG group had negative qualitative and quantitative parameters of intrathecal immunoglobulin synthesis along with preserved BBB, based on the type 1 OCBs and zero albumin and IgG index (Table 2). Contrary, in the SG group, type 2 and type 3 OCBs patterns were described with the type 2 being the most prevalent finding (93.88%). Interestingly, in the SG group, we found that 38.78% patients with type 2 and 3 OCBs had negative IgG index while the rest (61.22%) had an expected matching of these two parameters (Table 2).

Table 2 **Qualitative and quantitative parameters of the intrathecal protein synthesis for both patient groups.**

	Albumin index		IgG index		OCB				
	neg	pos	neg	poz	Type 1	Type 2	Type 3	Type 4	Type 5
RG	50 (100%)	-	50 (100%)	-	50 (100%)	-	-	-	-
SG	44 (89.79%)	5 (10.20%)	19 (38.78%)	30 (61.22%)	-	46 (93.88%)	3 (6.12%)	-	-

RG= reference group; SG=study group; OCB=oligoclonal bands;

We divided the total sample into six groups 1 based on the level of intrathecal synthesis. The majority of patients (46.94%) with a positive IgG index, exhibited value between 0 and 10. Distribution of the IgG values in SG group is presented in Figure 1.



SG= study group; IgG values (series 1 =0%; series 2= 0-10%; series 3=10-20%, series 4=20-30%; series 5=30- 40%; series 6= 40-50%)

Figure 1 **Distribution of the IgG values in SG group.**

Out of 49 patients with MS, 19 (38.8%) did not show quantitative intrathecal synthesis. In other MS patients 30 (61.2%) the average value of intrathecal synthesis was 36.2+/-21.9% (Table 3).

Table 3 **Average values of intrathecal synthesis.**

Gender	N	Mean	SD	Median	IQR		Mann-Whitney U test	p value
Male	4	22.83	28.73	11.40	4.08	53.00	29.000	0.161
Female	26	38.29	20.64	35.50	24.10	50.60		

N = number; SD = standard deviation; IQR = Interquartile range, p = statistical significance

The diagnosis of MS was present in 49 patients. The albumin quotient was positive in 5/49, the sensitivity of this test is 10.2% and the specificity is 100%. Intrathecal synthesis was positive in 30/49 patients, the test has a sensitivity of 61.2% and a specificity of 100%. In the group of patients with MS, the intrathecal synthesis test shows statistically significantly more positive results than the albumin quotient test, p<0.001 (Table 4). In the group of healthy controls, not a single case of intrathecal synthesis, as well as a disturbed albumin quotient, was recorded.

Table 4 **Sensitivity and specificity of albumin quotient and percentage of intrathecal synthesis.**

		Albumin quotient			Presence of intrathecal synthesis			Pearson Chi-Square	p value
		Pathological values	Normal values	Total	Intrathecal synthesis	Without synthesis	Total		
MS patients	N	5	44	49	30	19	49	27.778	<0.001
	%	10.2%	89.8%	100.0%	61.2%	38.8%	100.0%		
Healty controls	N	0	50	50	0	50	50	-	-
	%	0.0%	100.0%	100.0%	0.0%	100.0%	100.0%		

N=number of subjects; MS=multiple sclerosis, p= statistical significance

DISCUSSION

Reiber's formula, along with the identification of oligoclonal bands (OCBs) in cerebrospinal fluid (CSF), is an essential aspect of the typical diagnostic assessment for suspected central nervous system (CNS) disorders, notably in cases related to multiple sclerosis (MS) and demyelization.

According to age and gender characteristics, the examined groups were similar based on statistical analysis. In this study, the dominant gender was women, which is the expected data. In the literature, it is reported that MS affects women more often (distribution between women and men almost 3:1) (13).

Based on the findings of Mclean BN, et al., among the 1007 patients included in the study, 206 individuals were diagnosed with multiple sclerosis (MS). Isoelectric focusing analysis demonstrated local synthesis in 95% of cases with clinically confirmed MS, resulting in an overall detection rate of 90%. On the other hand, the Log IgG-Index yielded a positive result in only 67% of clinically definite cases, resulting in an overall detection rate of 59% (6). This study has demonstrated similar results to ours (7).

In their study, Freedman MS, et al. attempted to explain the aforementioned differences. They state that in quantitative analysis, each patient is compared to a large population, resulting in a broad reference range of blood-derived proteins in the cerebrospinal fluid (CSF). On the other hand, in qualitative analysis, the CSF IgG pattern of each patient is compared to their own parallel serum sample (12).

In their study, Lunding J, et al. highlight that the sensitivity of OCB detection through isoelectric focusing (IEF) surpasses that of other methods. They emphasize that IEF has the capability to detect OCB even in cases where IgG levels in the cerebrospinal fluid (CSF) are not elevated according to the IgG index (14).

The diagnosis of MS was confirmed by a specialist neurologist based on the clinical picture, imaging technologies and results of immunofixation of IgG proteins in the cerebrospinal fluid. The diagnosis of MS was present in 49 patients. Intrathecal synthesis was positive in 30 patients, the test has a sensitivity of 61.22% and a specificity of 100%.

In the literature, they emphasize the importance of Oligoclonal immunoglobulin G (IgG) bands (OCBs) as a useful diagnostic tool for multiple sclerosis (MS). This method depends on the individual interpretation of the observer. The objectification of this test is achieved by introducing additional tests such as intrathecal synthesis (IgG index), light kappa chains in the cerebrospinal fluid, which can replace the synthesis on the gel (15).

In line with our research, we observed positive results in approximately 61.2% of patients. This suggests that our findings agree with the previous research and reinforce the notion that the quantitative IgG index may not capture the full extent of intrathecal antibody synthesis in CNS disorders such as multiple sclerosis (MS).

It is important to note that the lower sensitivity of the IgG index implies that relying solely on quantitative measurements may lead to underestimation of intrathecal synthesis and some missed diagnoses. Therefore, incorporating qualitative techniques, such as isoelectric focusing and the detection of CSF-specific bands, is s crucial for a comprehensive assessment of CNS intrathecal antibody synthesis (16).

CONCLUSION

Overall, the combined assessment of intrathecal synthesis using Reiber's formula and the detection of oligoclonal bands plays a critical role in the diagnosis and evaluation of CNS disorders. While

quantitative measurements provide useful information, the qualitative demonstration of CSF-specific bands through isoelectric focusing offers enhanced sensitivity and specificity, enabling a deeper understanding of the localized immune processes within the CNS.

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Declaration of patient consent: the authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given their consent for their images and other clinical information to be reported in the journal.
Authors contributions: NDž, LZ-P, ST-K, AM and VM gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author had role in article drafting and in process of revision. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

Visual field evaluation in establishing affiliated diagnose of myopic glaucoma

Evaluacija vidnog polja u postavljanju asocirane dijagnoze miopije i glaukoma

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ABSTRACT

Introduction: diagnosing and managing highly myopic patients who might have or will develop glaucoma still appears to be challenging and genuine diagnostic dilemma. This is due to the fact that high myopia is associated with elongation of the eye and resulting in tilting and torsion of the optic disc, causing visual filed defects that may resemble glaucomatous damage. This is why we are constantly asking ourselves is it glaucoma or just myopia? Or even both. All ophthalmologists assessing high myopic patients often encounter this dilemma. By 2050, about half the world's population will have myopia and in some parts of the world, these rates are already approaching 90%. Aim: early diagnosis assessment in myopic patients with changes in the visual field that might indicate glaucoma is the main goal of our research. Structural and functional defects in myopic eyes are difficult to distinguish from those caused by glaucoma. Materials and methods: this was prospective-retrospective randomized, clinical research. In order to make a scientifically valuable statistical comparison, a total of 300 eyes has been examined, i.e. 100 eyes in 3 groups of respondents of both gender: I group - patients with glaucoma, II group - patients with myopia and glaucoma, III group - patients only with myopia. Each group was also divided regarding the size of the optic disc diameter into 3 categories: small (<1.30 mm), medium (1.31-2.09 mm) and large (>2.10 mm). The following ophthalmological examinations were performed on all patients: natural visual acuity and best-corrected visual acuity, Goldman applanation tonometry, biomicroscopic examination, autorefractometry, gonioscopy, fundus examination - direct ophthalmoscopy (Volk lens +90D), spectral three-dimensional optical coherence tomography (SOCT 3D), static computerized perimetry. Results: our research results showed that respondents with progressive visual field loss have accordingly a higher numeric value of Disc Damage Likelihood Scale (DDLS). There is a statistically significant difference in the quality of the visual field in relation to the size of the disc in respondents diagnosed with glaucoma with and without the associated diagnosis of myopia. Conclusion: analyzing the comorbidity of glaucoma and myopia, it is possible to create a diagnostic algorithm technique and procedure with emphasis and aim in early detection of glaucoma.

Keywords: myopia, glaucoma, diagnostic dilemma, visual field changes

SAŽETAK

Uvod: dijagnosticiranje i liječenje visoko kratkovidnih pacijenata koji bi mogli imati glaukom ili će razviti glaukom i dalje predstvlja dijagnostički izazov i istinsku dilemu. To je zbog činjenice da je visoka miopija povezana sa elongacijom oka što za posljedicu ima nagib i torziju optičkog diska, uzrokujući defekte polja vida koji mogu nalikovati glaukomskom oštećenju. Zbog toga su oftalmolozi u stalnoj dilemi pitajući se da li je u pitanju samo miopija ili glaukom? Ili čak oboje. Svi oftalmolozi koji liječe pacijente s visokom miopijom često se susreću s ovom dilemom. Do 2050. godine gotovo polovina svjetske populacije imat će miopiju, a u nekim dijelovima svijeta te se stope već približavaju 90%. Cilj: rano postavljanje dijagnoze glaukoma kod miopskih pacijenata sa promjenama u vidnom polju koje mogu ukazivati na glaukom osnovni je cilj našeg istraživanja. Strukturna i funkcionalna oštećenja optičkog diska vidnog živca koja se javljaju kod miopije teško je razlikovati od onih uzrokovanih glaukomom. Materijali i metode: Ovo je prospektivno-retrospektivno randomizirano kliničko ispitivanje. U svrhu naučno vrijedne statističke komparacije pregledano je ukupno 300 očiju, odnosno 100 očiju u 3 grupe ispitanika oba pola: I grupa - pacijenti s glaukomom, II grupa - bolesnici s miopijom i glaukomom, III grupa - pacijenti samo s miopijom. Svaka grupa je podijeljena prema veličini dijametra optičkog diska u 3 kategorije: mali (<1,30 mm), srednji (1,31-2,09 mm) i veliki (>2,10 mm). Kod svih pacijenata obavljeni su sljedeći oftalmološke pretrage: naturalna vidna oštrina i najbolje korigovana vidna oštrina, Goldmanova aplanaciona tonometrija, biomikroskopski pregled, autorefraktometrija, gonioskopija, pregled fundusa - direktna oftalmoskopija (Volk leća +90D), spektralna trodimenzionalna optička koherentna tomografija (SOCT 3D), statička kompjuterizirana perimetrija. Rezultati: utvrđeno je da ispitanici s progresivnim gubitkom vidnog polja imaju shodno tome višu numeričku vrijednost ljestvice vjerojatnosti oštećenja diska (DDLS). Postoji statistički značajna razlika u kvaliteti vidnog polja u odnosu na veličinu diska kod ispitanika s dijagnosticiranim glaukomom sa i bez pridružene dijagnoze miopije. Zaključak: analizom komorbiditeta glaukoma i miopije, moguće je izraditi dijagnostički algoritam tehnika i postupaka sa ciljem ranog otkrivanja glaukoma.

Ključne riječi: miopija, glaukom, dijagnostička dilema, promjene u vidnom polju

INTRODUCTION

Myopia or nearsightedness is a refractive error caused by excessive axial elongation. It has become increasingly concerning public health issue (1). Though it is an area of active research, it has not been established one uniform solid explanation of relation between myopia and glaucoma. This connection is still a matter of discussion as of as many already conducted and ongoing studies (2,3). It is believed that the myopic eye's structural abnormalities, mainly those related to laminar collagen fibers, increase the risk of developing glaucoma. The axial eye length can provide a simple and reasonable explanation. In myopia axial eye length is greater than in normal eyes. This elongation specifically causes stretching and thinning of the lamina cribrosa and thinning and weakening of the sclera. These structural changes, combined with morphological changes of the optic nerve, make these patients' optic nerves more susceptible to damage related to increasing intraocular pressure. Interpreting glaucomatous changes in highly myopic eyes is particularly difficult, especially in those with pathologic myopia (4).

Previous research on the relationship between myopia and glaucoma is based on the results of observational studies. However, according to recent knowledge, and based on the available studies, a systematic approach to assessing the connection between myopia and glaucoma does not exist. Knowing the real values and correct assessment of the optic disc and retinal nerve fiber layer in myopes is of inestimable importance in establishing the correct diagnosis of glaucoma (5,6). Not only when it comes to atypical forms of the optic disc (tilted optic disc), but also in other forms of the optic nerve head (7). By 2050, about half the world's population will have myopia and in some parts of the world, these rates are already approaching 90% (8). This lends urgency to the task of identifying myopic patients who are most at risk for developing glaucoma, but there isn't a simple solution for doing so. The structural and functional defects in myopic eyes are difficult to distinguish from those caused by glaucoma.

Glaucoma affects more than 70 million people worldwide with approximately 10% being bilaterally blind, making it the leading cause of irreversible blindness in the world (9). Glaucoma can remain asymptomatic until it is severe, resulting in a high likelihood that the number of affected individuals is much higher than the number known to have it (10,11).

Functional damage to the eye in glaucoma is most often evaluated by monitoring the visual field, while structural damage to the optic nerve caused by glaucoma is verified by optical coherence tomography analysis. Early detection, monitoring and understanding of changes in the retina are central to the diagnosis of glaucomatous optic neuropathy, and vital to reduce visual loss from this progressive condition (12,13).

It is an imperative to overcome the current shortcomings of optical coherence tomography regardless of the highly sophisticated examination technique. Furthermore, this is why we should rely more on other diagnostic features and experience. We should focus to longitudinally follow up these patients also as committing to determine various risk factors for glaucoma and perform cross examine visual field analysis (14).

Differentiating myopia-related optic neuropathy and normal tension glaucoma (NTG) can be very challenging due to the constellation of clinical findings particularly associated with high myopia. It has been well recognized that myopic patients with normal intraocular pressures (IOPs) can present with glaucomatous visual field defects, which can be attributed to myopia rather than to glaucoma (15).

Defects described included glaucoma-like (paracentral defects, nasal step, paracentral arcuate and arcuate), myopia-like (enlarged blind spot, vertical step, partial peripheral rim and non-specific) and combined, with approximately 10% of eyes demonstrating the glaucoma-like defects which tended to be associated with longer axial length (16,17). Progression over time and age at progression both represent important factors in differentiating glaucoma-like visual field defects from true glaucoma (18).

MATERIALS AND METHODS

This was a randomized, prospective-retrospective, descriptive-analytical clinical study conducted at the Eye Clinic "Dr Sefić" in Sarajevo. In order to make a scientifically valuable statistical comparison, a total of 300 eyes has been examined, i.e. 100 eyes in 3 groups of respondents of both gender: I group - patients with glaucoma, II group - patients with myopia and glaucoma, III group - patients only with myopia.

Each group was divided by the size of the optic disc diameter into three categories:

small optic disc (<1.30mm), medium optic disc (between 1.31 mm-2.09 mm), large optic disc (> 2.10 mm).

The following ophthalmological examinations were performed on all patients: natural visual acuity and best-corrected visual acuity, Goldman applanation tonometry, biomicroscopic examination, autorefractometry, gonioscopy, fundus examination - direct ophthalmoscopy (Volk lens +90D), spectral three-dimensional optical coherence tomography (SOCT 3D), static computerized perimetry (KOWA). ANOVA test was used in analysis. For qualitative variables, we used the chi-square test (X2-test).

Glaucoma visual field changes were defined as the existence of: 1) depression in 3 consecutive points by 5 dB, one of which is at least 10 dB, 2) depression in 2 consecutive points by 10 dB, 3) a difference of 10 dB in the nasal horizontal meridian in 2 adjacent points, which must not be edge points unless they are immediately above or below the nasal horizontal meridian.

A reliable finding was the finding of visual fields where the percentage of false positive and false negative findings was less than 30% and the loss of fixation was less than 20%.

RESULTS

This study included 300 eyes of respondents who were classified into three equal groups according to the criteria for inclusion in the study.

There was a statistically significant difference in the quality of the visual field in relation to the size of the disc in respondents diagnosed with glaucoma with and without the associated diagnosis of myopia.

Table I **Assessment of visual field changes in relation to the optic disc size.**

GROUP			Optic disc size			Total
			Small	Medium	Large	
Glaucoma	Arcuate scotoma	Amount	4	27	7	38
		%	10.5%	71.1%	18.4%	100.0%
	Paracentral scotoma	Amount	4	0	0	4
		%	100.0%	0.0%	0.0%	100.0%
	Biarcuate scotoma	Amount	3	19	8	30
		%	10.0%	63.3%	26.7%	100.0%
	Nasal step scotoma	Amount	1	9	1	11
		%	9.1%	81.8%	9.1%	100.0%
	Tunnel vision	Amount	4	9	4	17
		%	23.5%	52.9%	23.5%	100.0%
						P=0,001
Glaucoma and myopia	Arcuate scotoma	Amount	4	29	12	45
		%	8.9%	64.4%	26.7%	100.0%
	Paracentral scotoma	Amount	2	5	10	17
		%	11.8%	29.4%	58.8%	100.0%
	Biarcuate scotoma	Amount	4	12	6	22
		%	18.2%	54.5%	27.3%	100.0%
	Nasal step scotoma	Amount	0	4	1	5
		%	0.0%	80.0%	20.0%	100.0%
	Tunnel vision	Amount	0	2	9	11
		%	0.0%	18.2%	81.8%	100.0%
						P=0,043
Myopia	No significant VF loss	Amount	10	67	23	100
		%	10.0%	67.0%	23.0%	100.0%

It was found that respondents with progressive visual field loss had accordingly a higher numeric value of Disc Damage Likelihood Scale (DDLS scale - Optical Coherent Tomography). It is important to note that the subjects with the terminal stage of the visual field loss were from the group with diagnosis of glaucoma and had a DDLS value of 7.11, and subjects with the combined diagnosis of myopic glaucoma had 8.75.

Table 2 **Average DDLS values in relation to visual field changes in all examined groups.**

DDLS		N	X	SD	SEM	Minimum	Maximum
Glaucoma	Paracentral scotoma	4	6.80	1.50	0.75	7.0	10.0
	Arcuate scotoma	38	6.90	1.75	0.28	4.0	10.0
	Biarcuate scotoma	30	6.93	1.68	0.30	5.0	10.0
	Tunnel vision	17	7.11	1.97	0.47	4.0	10.0
	Nasal step scotoma	11	4.50	1.81	0.54	4.0	9.0
							F=4.150; p=0.037
Glaucoma and myopia	Paracentral scotoma	17	7.00	2.26	0.54	3.0	10.0
	Arcuate scotoma	45	7.16	1.94	0.29	3.0	10.0
	Biarcuate scotoma	22	7.17	1.87	0.39	3.0	10.0
	Tunnel vision	11	8.75	1.64	0.49	4.0	9.0
	Nasal step scotoma	5	4.90	2.16	0.96	5.0	10.0
							F=6.668; p=0.021

By analyzing the average value of the diopter height in respondents with myopia and respondents with myopia associated with glaucoma, a statistically significant difference was presented. Average height diopters in respondents with glaucoma and myopia was -3.77±1.55, while of respondents with only myopia it was -2.49±1.25, F=40.940; p<0.05.

Table 3 **Average height of myopia in relation to the examined group.**

	N	X	SD	SEM	95% CI		Minimum	Maximum
					Lower	Upper		
Glaucoma	100							
Glaucoma and myopia	100	-3.77	1.55	.156	-4.08	-3.46	-8	-1
Myopia	100	-2.49	1.25	.126	-2.74	-2.24	-6	-1
								F=40.940; p<0.05

DISSCUSION

Previous research on the relationship between myopia and open-angle glaucoma is based on the results observational studies. However, according to recent knowledge and based on available studies, a systematic approach to assessing the relationship between myopia and glaucoma does not exist. Experimental models of myopia and epidemiological data have shown that myopia is most often the result of disproportionate elongation of the last segment of the eye, which is physically limited by the fibrous sclera. It is not known with complete certainty what causes myopia, but they have been noticed certain links between the occurrence of myopia and distinguished factors that are reasonably suspected to have significant role in its development. Some of the potential risk factors are: race, ethnicity, industrial development of the country, heredity, education, profession, environment, gender, nutrition, stress etc.

In their study, Allison K, et al. tried to create a model of diagnostic procedures that will have the ability to predict the appearance and progression of glaucomatous changes. The ability to predict progression of glaucomatous damage can significantly affect clinical treatment. In this study Allison K, et al. examined the ability of structural information to predict upcoming events functional progression and impairment. Selected parameters from stereophotography of the optic nerve head, OCT and assessment of C/D ratio as well as excavation depth showed statistically significant ability predictions of visual field progression. Using a model made up of the best parameters of all of existing devices proved that only the thickness of the RNFL in the upper quadrant can be used for predicting the progression of glaucomatous damage (19).

A graphical representation of the probability that a person will develop visual field loss in association with various risk factors is the best indicator. It is important to emphasize that this is not a disability, but only a loss visual field. The probability of developing disability is much lower. It should be kept in mind that even when patients have a central corneal thickness of less than 550 microns and an IOP above 27 mmHg, as many as two-thirds of patients will not develop any visual loss fields within seven years (20). On the other hand, if the DDLS is 5 or more, 95% patients will develop visual field deterioration.

Rabiolo A, et al. analyzed the data from the AGIS study. On that occasion, it was established that they were in charge risk

factors for deterioration of the visual field were the rate of change of the visual field and the age of the patients (21).

Almost non-existent predictive value of the intraocular pressure (IOP) of an individual when assessing who will become a person with disability; we know that it is possible to prevent loss of visual field in patients with glaucoma, but many patients with glaucoma still develop a progressive loss of the visual field; changes in the visual field are often misleading; the significance of glaucoma is a function presented through the severity of the disease as such and the duration of the disease; and the likelihood that the patient will become disabled due to glaucoma is a combination of the severity and duration of the disease; the patient's ability to takes care of himself independently; skill of the ophthalmologist and adaptability of the patient (22).

Visual field is, of course, important in assessing the condition and treatment of glaucoma patients. However, trying to decide which visual fields will actually lead to deterioration or whether they represent glaucoma is far more complex than previously thought. In 2002, Weinreb wrote that specific methods for identifying true glaucomatous damage and progression have yet to be developed. It is still current and unchanged (23).

The disc damage likelihood scale (DDLS) is a tool for classifying glaucomatous structural changes to the optic disc based on the radial width of the neuroretinal rim at its thinnest location, or if no rim is present, the extent of absence of the rim. Unlike cup disc ratio (CDR), the DDLS also considers disc size. It represents a grading system based on the radial width of the Retinal Nerve Fiber Layer (RNFL) circumference measured at the thinnest point. The unit of measurement is the circumference/diameter of the disc, that is, the radial width edge versus diameter (24). Therefore, the DDLS estimates the glaucomatous damage of the optic disc more precisely than the other used method. Although this grading system is more complicated to use in clinical practice, the interobserver setting assessment of DDLS in our study was very reliable.

Bayer A, et al. conducted a study that included the examination of 141 patients, i.e. 282 eyes. The following results were obtained: there is a strong positive correlation of DDLS with visual field changes in glaucoma patients with reference to MD (Pearson r= -0.695, P<.001) and PSD (Pearson r=0.703, P<.001). With this study, they proved the connection of the staging system of the visual field with DDLS, that is, that every progression of glaucoma, which records through the finding of the field of vision in terms of its greater deterioration, correlates with adequate number on the DDLS scale (Spearman r=0.711, P<.001) (25).

CONCLUSION

Modern ophthalmology sets new requirements and goals. One of them is to detect changes related to glaucoma earlier, preferably before glaucomatous changes appear in the visual field. Progressive development of diagnostic procedures such as Spectral Domain OCT provides insight into the structural changes of the optic nerve head that they detect long before the outage in the visual field, which is of great importance in planning a timely effective treatment of glaucoma, prevention of low vision and reduction of the number of people blind from this disease. Disc Damage Likelihood Scale (DDLS) is a system for evaluation of glaucomatous damage of the optic disc, which strongly correlates with the degree of visual field loss. Furthermore, eventually it will help proper assessment in distinguishing myopic from glaucomatous changes. Analyzing the comorbidity of glaucoma and myopia, it is possible to create a diagnostic algorithm technique and procedure with emphasis and aim in early detection of glaucoma. Assessment of the structural-topographic characteristics of the optic nerve head, can lead to establishing differential-diagnostic criteria, based on which clinical and functional criteria will determine relationship between visual function and condition of the optic nerve in myopic glaucoma by comparative comorbidity analysis.

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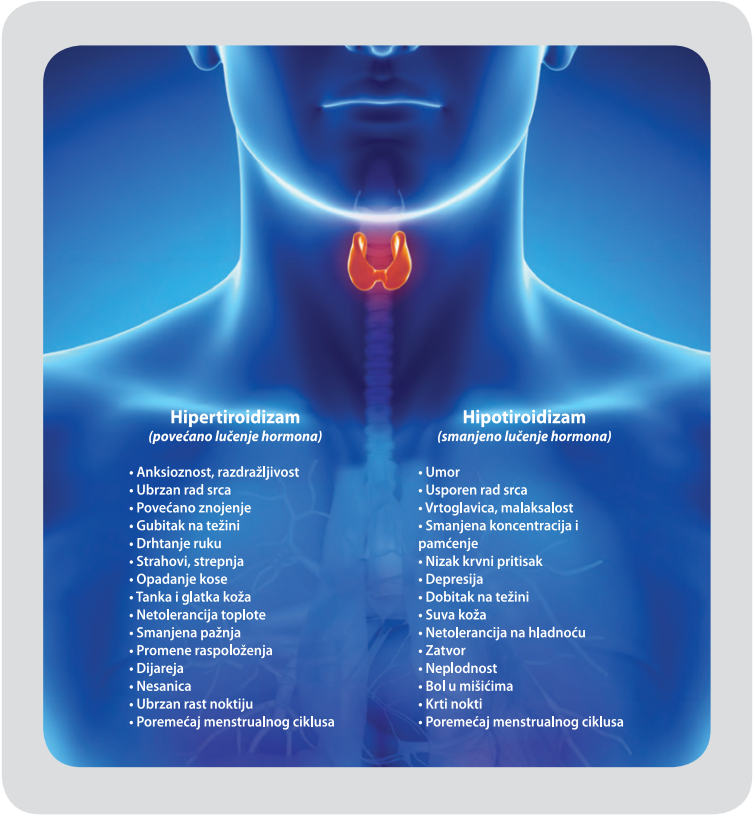
Declaration of patient consent: the author certifies that she has obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal.
Authors contributions: ED gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work.
Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.



Acute kidney injury after open surgical treatment of ruptured aortic aneurysm

Akutni poremećaj bubrežne funkcije nakon otvorenog hirurškog tretmana ruptirurane aneurizne abdominalne aorte

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ABSTRACT

Introduction: the research is concerned with acute renal insufficiency (AKI) occurring after the rupture of an abdominal aortic aneurysm. Aim: to determine the incidence rate of AKI in the total sample, and the two groups comparatively, and to determine independent predictors of AKI. Materials and methods: the sample consisted of 43 patients surgically treated at the Clinic of Cardiovascular Surgery of the Clinical Center University of Sarajevo in the period from 1 January 2021 to 31 March 2023, due to an abdominal aortic aneurysm rupture. The research was designed as an observational prospective analysis modeled on a typical cohort study. The sample was divided into two groups by the criterion determining the degree of hemorrhagic shock. Results: the incidence of survival after aortic trunk reconstruction due to abdominal aortic aneurysm rupture was 67.4%. In the total sample, 79.16% of patients had at least one form of AKI. A statistically significant disproportion between the groups is evident for AKI stage 0, as there were no patients without renal symptoms in Group 2 (p=0.004). Patients with hypertension more often showed severe types of hemorrhagic shock and consequent AKI (p<0.001). Preoperatively elevated values of serum creatinine denote a significant predictor of the occurrence of AKI (p<0.046). Conclusion: the occurrence of AKI after urgent surgical reconstruction of the aorta due to aneurysm rupture is a significantly frequent problem. The research determined intraoperative hemodynamic instability, blood loss exceeding 1500ml, and preoperative elevated serum creatinine levels as risk factors for postoperative AKI. Preoperatively elevated serum creatinine level is also a safe independent predictor of acute kidney function disorder in the postoperative period.

Keywords: acute kidney injury, aortic aneurysm, rupture

SAŽETAK

Uvod: istraživanje je posvećeno akutnoj bubrežnoj insuficijenciji (AKI) nastaloj nakon rupture aneurizme abdominalne aorte. Cilj istraživanja: odrediti incidencu AKI u ukupnom uzorku, uporediti zastupljenost ove pojave u grupama, te odrediti nezavisne prediktore AKI u uzorku. Materijali i metode: uzorak čini 43 pacijenta koji su, zbog rupture aneurizme abdominalne aorte, operisani na Klinici za kardiovaskularnu hirurgiju Kliničkog Centra Univerziteta Sarajevo u periodu 1. januar 2021. do 31. marta 2023. Istraživanje je dizajnirano kao opservaciona prospektivna analiza po uzoru na tipičnu kohortnu studiju. Uzorak je podijeljen na dvije grupe prema kriteriju koji je odredio stepen hemoragičnog šoka. Rezultati: incidenca preživljavanja nakon rekonstrukcije aortnog stablazbog rupture aneurizme abdominalne aorte je iznosila 67,4%. U ukupnom uzorku je 79,16% pacijenata imalo barem jedan oblik AKI. Prezentirana je statistički značajna razlika u grupama kada je u pitanju AKI stadij 0, jer u grupi 2 nije bilo pacijenata bez bubrežne simptomatologije (p=0,004). Pacijenti sa hipertenzijom češće su prezentirali teže oblike hemoragičnog šoka i posljedične AKI (p<0,001). Preoperativno povišene vrijednosti serumskog kreatinina predstavljaju značajan prediktor nastanka AKI (p<0,046). Zaključak: problem pojave AKI nakon urgentne hirurške rekonstrukcije aorte učinjene zbog rupture aneurizme ima značajnu učestalost. Istraživanje je istaklo intraoperativnu hemodinamsku nestabilnost sa gubitkom krvi većim od 1500ml, te preoperativno povišene vrijednosti serumskog kreatinina kao rizikofaktore za postoperativni nastanak AKI. Preoperativno povišen nivo serumskog kreatinina je ujedno i siguran nezavisni prediktor nastanka akutnog poremećaja bubrežne funkcije u postoperativnom periodu.

Ključne riječi: akutno bubrežno zatajenje, aneurizma aorte, ruptura

INTRODUCTION

Acute renal failure, or acute kidney injury (AKI) is a syndrome of sudden loss of filtration and excretory function of the kidneys, followed by oliguria up to anuria and a sudden increase of nitrogenous substances in the serum. This phenomenon arises as part of various primary clinical conditions having a rapidly progressive course and an uncertain prognosis. The causes can be prerenal - such as cardiac failure or volume loss, renal - such as an inflammatory or toxic nephron lesion, and post-renal - such as all

forms of obstructive uropathy. AKI resulting from an aneurysm rupture of the abdominal aorta belongs to the prerenal type. The pathophysiological course is clear; a hemorrhage causes a drop in systemic pressure and the opening of the juxtaglomerular connection between the vas afferens and the vas efferens, which results in bypassing the glomeruli and functional reduction of renal perfusion. Renal perfusion is calculated as the difference between systemic and mean arterial pressure minus the value of central venous pressure. Due to hypoperfusion within each nephron, there is a drop in the pressure gradient between the glomerulus and Bowman's capsule, which causes an immediate decrease in the production of primary and, consequently, definitive urine. If it is taken into account that the time during which the renal cortex tolerates ischemia is estimated at around 30-60 minutes, it is clear that, in cases of hemorrhage due to the rupture of an abdominal aortic aneurysm during the preoperative and intraoperative period, this time will certainly be exceeded, i.e. that a large percentage of the renal parenchyma suffers a significant ischemic lesion. This is also influenced by the value of the systemic, and especially the mean perfusion pressure, which should not drop below 60 mmHg (1).

The pathogenesis of this syndrome is rooted in another mechanism that follows the establishment of hemostasis and reconstruction of the aortic trunk. Namely, immediately after hemodynamic stabilization begins the reperfusion phase, in which the interaction between oxygenated blood and ischemic tissue occurs. Due to the toxic action of free oxygen radicals and other harmful metabolites, a new attack will follow on the damaged kidney cells and their function. Therefore, this type of renal failure is called an ischemia-reperfusion lesion (2,3).

Severe forms of hemorrhagic shock leave different consequences at the nephron level. The number of injured nephrons is directly proportional to the intensity and development of hemorrhagic shock, and the number of preserved nephrons correspondingly maintains the remaining renal function. The distribution of dead and preserved nephrons in the renal parenchyma is uneven. Ischemia leads to necrosis of the cells of the tubular system while the glomeruli, as a rule, remain intact. The rectus tubules and the ascending branches of Henle's loop are most often affected. Due to necrosis, the cell mass of cells breaks away from the basement membrane, so devitalized cells, leukocytes, myoglobin, hyaline cylinders, and various forms of detritus accumulate in the tubule lumen. This kind of plug forms an obturation of the tubule so that the pressure increases in the Bowman's capsule and interferes with the remaining glomerular filtration. Granular and hyaline cylinders, myoglobin, hemoglobin cylinders, and leukocytes also accumulate in the lumen of the distal and collecting tubules, which can be demonstrated in scanty urine sediment before anuria occurs. Recovery ensues through three stages and can begin only after reaching proper hemodynamic parameters. However, complete kidney recovery may fall through, depending on the intensity of the lesion, duration of ischemia, iatrogenic factors (contrast, toxic effects of antibiotics, etc.), preexisting changes, and previous latent insufficiency (4).

Regarding the clinical presentation, acute renal failure can range from mild to severe. Numerical score systems of the RIFLE system stratify renal lesions into the following levels: Risk, Injury, Failure, Loss, and End-stage kidney disease. The classification is established according to the level increase of serum creatinine, a decrease in the glomerular filtration ability, and a decrease in the excreted urine amount. This classification system precisely determines the condition of a kidney suffering from an ischemic or hypoperfusional lesion (5).

Based on the experience and through the cooperation of specialized centers that used this classification system, a network system was created, and within it, a modified and simplified classification of acute kidney injury called AKIN (Acute Kidney Injury Network) was formed. It defines AKI as a sudden reduction in kidney function, occurring within 48 hours, which is manifested by an increase in serum creatinine of 0.3 mg/dL or more (≥26.4 μmol/L), or a percentage increase in serum creatinine of 50% or more (1.5 times the initial value), and by decreasing urine output, defined as less than 0.5 mL/kg/h during a period longer than 6 hours. AKIN classification recognizes three stages of acute renal failure (6).

AIM

The aim of the research was to present the incidence, determine independent predictors, and analyze additional etiological factors of the occurrence of AKI in the early postoperative course in patients operated due to an abdominal aortic aneurysm rupture.

MATERIALS AND METHODS

The data of 52 patients who, due to the rupture of an abdominal aortic aneurysm, were surgically treated at the Clinic of Cardiovascular Surgery of the Clinical Center University of Sarajevo in the period from 1 January 2021 to 31 March 2023, was entered prospectively. From the total sample, 43 patients were taken into account who, despite bleeding, maintained a mean systolic pressure higher than 60 mmHg on admission. Of these, 35 (81.4%) were male patients, and 8 (18.6%) were female. The oldest patient was 80 years old, and the youngest was 62. The average age was 70.98 +/-7.52.

Cases that previously had a terminal form of chronic renal insufficiency, patients who had intraoperative suprarenal clamping, and those who died during the operation were excluded from the study.

The research was designed as an observational prospective analysis modeled on a typical cohort study. The protocol includes admission under emergency conditions, emergency surgery, postoperative treatment in the intensive care unit, and ambulatory supervision for a month after discharge. The study considered demographic data and all parameters related to the clinical course, objective calculation of the loss of circulating volume due to bleeding, degree of development of hemorrhagic shock, and duration of acute preoperative symptomatology. Additionally acknowledged were the relevant laboratory analyses related to the degree of renal function impairment. All data excluded from medical documentation was stored in a unique database that represents research material and the basis for statistical processing.

The research sample was divided into two groups. The first group consisted of patients with a volume loss of up to 1500ml and the second with a volume loss of over 1500ml of blood.

By applying the criteria determined by clinical and laboratory parameters, patients were classified according to the overall outcome of treatment, occurrence of postoperative complications, duration of preoperative symptomatology, amount of

intraoperative bleeding, intraoperative hemodynamic stability, and in accordance with the "AKIN" classification system.
The complete research was carried out under the provisions of the Declaration of Helsinki.

During the statistical processing of the collected data, the basic properties were presented by the number of cases and percentage representation. Categorical values were analyzed with the $\chi 2$ test and Fisher's test.

Student's T-test and Mann-Whitney U test were used to analyze quantitative values. The relationship between individual factors and renal function was assessed employing multivariate logistic regression. Statistical hypotheses were tested at the α=0.05 level, i.e. any differences between samples were considered significant if p<0.05. Statistical analyses were performed using IBM SPSS Statistics ver. 21.0.

RESULTS

In the total sample (N=43), the respondents' age ranged from 59 to 87. In the patient group with blood loss up to 1500 ml (Group 1), the age range was from 60 to 83, while in the second one, with blood loss over 1500 ml (Group 2), it was from 59 to 87.

Table 1 **Sample classification according to the criteria for AKI**

Stage	Serum creatinin (SCr)	Urin output – UO)	Group 1 N=21 (48,8%)	Group 2 N=22(51,2%)	Total N=43	p
AKI 0	Normal	0,5-1ml/kg/h	7 (33.3%)	0 (0%)	7 (16.3%)	**0.004***
AKI 1	SCr≥ 150-200%	<0,5mL/kg/h > 6 h	3 (14.3%)	7 (31.8%)	15 (34.9%)	0.911
AKI 2	SCr≥ 200-300%	<0,5mL/kg/h > 12 h	3 (14.3%)	9 (40.9%)	12 (27.9%)	0.108
AKI 3	SCr>300%	<0,3mL/kg/h/24h or anuria 12h	3 (14.3%)	6 (27.3%)	9 (20.9%)	0.475

As can be observed from Table 1, 79.16% of patients from the total sample had at least one form of AKI during the postoperative course, while moderate and severe types of AKI developed in 43.75% of patients. Regarding AKI stage 0, the presented disproportion between the groups was statistically significant given that there were no patients without renal symptoms (p=0.004) in Group 2.

Table 2 **Demographic data and risk factors for postoperative AKI after surgical reconstruction of ruptured abdominal aortic aneurysm.**

Variable	**Total** (N=43)	**Group1** Haemorrh. shock: gr.1 &2 (N=21; 48.8%)	**Group 2** Haemorrhag. shock: gr.3&4 (N=22; 51.2%)	P
Age	70.98 (±7.52)	69.95(±7.33)	71.95(±7.74)	0.389
Gender M F	35 (81.4%) 8 (18.6%)	18 (85.7%) 3 (14.3%)	17 (77.3%) 5 (22.7%)	
Hypertension	24 (55.8%)	6 (28.6%)	18 (81.8%)	**0.001***
Renal insuff.	6 (14%)	2 (9.5%)	4 (18.2%)	0.664
Symptoms <6h	21 (48.8%)	8 (38.1%)	13 (59.1%)	0.284
Symptoms >6h	22 (51.2%)	9 (42.8%)	13 (59.1%)	0.283
Haemodynamic instability	25 (58.1%)	11 (52.4%)	14 (63.6%)	0.661
Postoperative SCr max.	245.86 (±165.32)	196.19 (±167.25)	293.24 (±152.31)	**0.004***
Diabetes mellitus	6 (14%)	1 (4.8%)	5 (22.7%)	0.185
Postop.complications	19 (44.2%)	7 (33.3%)	12 (54.5%)	0.274
Outcome Cured Death	**29 (67.4%)** **14 (32.6%)**	17 (81%) 4 (19%)	12 (54.5%) 10 (45.5%)	0.128
Blood loos	1654.42 (±757.14)	959.05 (±323.83)	2318.18 (±318.68)	**0.0001***

The incidence of survival after aortic trunk reconstruction due to abdominal aortic aneurysm rupture was 67.4%. In Group 1, that percentage was a high 81%, while in Group 2, the survival percentage was 54%. The comparison of the examined groups according to this parameter did not indicate a statistically significant difference, but the result was illustrative even on a global scale.

Analyzing the preoperative anamnestic data on hypertension, it was evident that the variable was significantly more prevalent in Group 2, i.e., patients with hypertension more often presented more severe forms of hemorrhagic shock and consequent AKI (p<0.001).

Perioperative blood loss included assessment of the loss and amount of intraoperative bleeding. Although this cannot be considered a significant predictor, the loss correlates with the intensity of hemorrhagic shock and shows a substantial difference between the groups (p<0.0001).

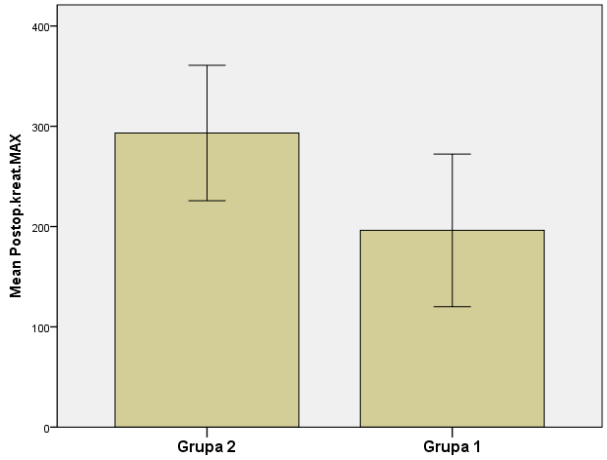

Figure 1 **Maximum values of serum creatinine in relation to the examined groups.**

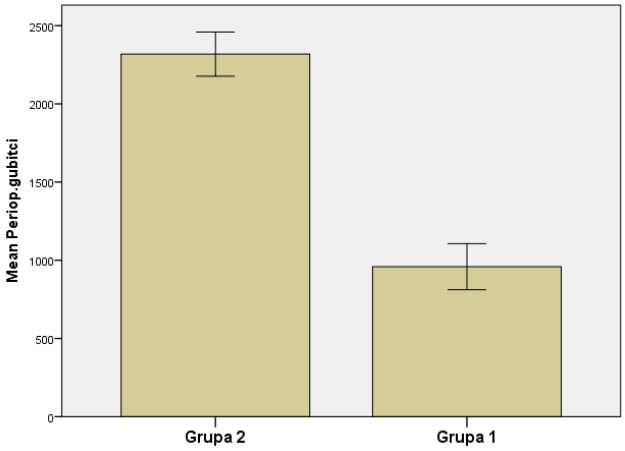

Figure 2 **Perioperative losses in relation to the examined groups.**

Table 3 **Predictors for AKI after surgical treatment of ruptured AAA.**

	OR	95% CI	P
Gender	0.567	0.060 - 5.319	0.619
Age	0.999	0.897 - 1.113	0.992
Hypertension	0.762	0.099 - 5.893	0.795
Renal insuff.	0.210	0.004 - 9.835	0.426
Vasoactive medications	1.144	0.207 - 6.329	0.877
Perioperative losses	1.001	1.000 - 1.003	0.076
Preoperative sCr	1.026	1.000 - 1.032	**0.046***
DM	2.774	0.270 - 28.537	0.394
Symptoms >or< 6h	0.901	0.167 - 4.858	0.904

As observable in Table 3, which exhibits the analyzed parameters treated as independent predictors of AKI, elevated preoperative serum creatinine levels represented the only significant factor regarding the occurrence of this complication.

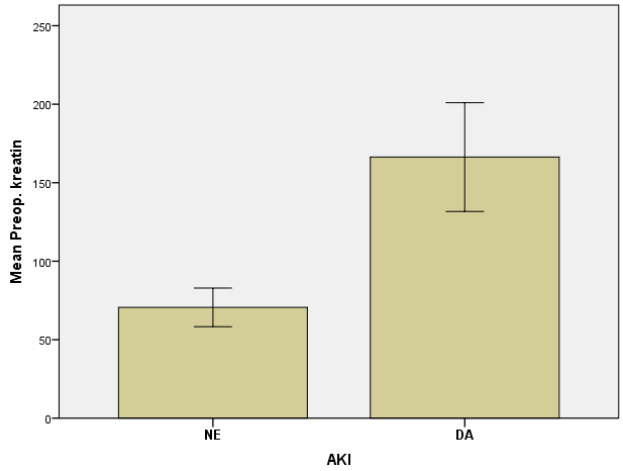

Figure 3 **Predictor of AKI development in relation to preoperative serum creatinine levels (sCr).**

DISCUSSION

AKI occurring in the postoperative period is a relatively common clinical problem across all fields of surgery. Unfortunately, however, it is frequently overshadowed by the operative procedure itself and unjustifiably neglected even in aortic surgery, where this issue is most likely to occur. The earliest major research reports on the correlation between AKI and surgical procedures were precisely in vascular surgery. Even then, it was stressed that AKI developing after surgical treatment of a ruptured abdominal aortic aneurysm increases the postoperative mortality rate to 90%. Despite progress in surgical technique, the incidence of AKI continues to grow proportionally to the number of performed surgeries. It is considered that the emergent reconstruction of a ruptured aneurysm carries the highest risk of AKI, and in some series, it reaches a rate of 75% (7,8).

The issue remains relevant to the present day, and almost all large centers, immediately upon admission of a patient with a ruptured aneurysm, consider a highly likely occurrence of postoperative AKI. For instance, the Amsterdam Acute Aneurysm Trial highlights that all centers dealing with aortic surgery must be equipped to provide temporary or even permanent dialysis treatment for operated patients. This study indicates that such probability is higher in patients treated with an open surgical approach.

Noteworthy is another study that views this issue from the same angle. Covering the period from 2003-2017, experts from the University Medical Centers in Baltimore and Honolulu

examined the frequency of acute renal failure in 80-year-old patients who underwent elective surgery on an abdominal aortic aneurysm. As expected, the research results indicated that the frequency of AKI is higher in patients who underwent open surgical reconstruction of the aorta (10.6%), and the overall frequency was more pronounced in patients over 80 years of age (15.1%).

In 2017, it was regulated by the East-Asian protocol that patients who develop a clinical presentation of AKI in the postoperative period should receive treatment in the nephrology department. While the aforementioned study presents realistic results with a total incidence of AKI of 29.9%, it is still pertinent to note that the rupture incidence rate increases to 48.1% in open surgical repair. Hence, age and the surgical approach in itself are identified as risk factors for the occurrence of AKI (9, 10, 11).

The present research reveals that, during the postoperative course, as many as 79.16% of patients had at least one type of AKI, while moderate and severe types of AKI developed in 43.75%.

The Department of Vascular Surgery of Cambridge University Hospitals in the UK published a report on a research study that also explored the association between ruptured abdominal aortic aneurysm and acute renal failure. The research lasted more than nine years and involved a sample of 205 patients who underwent aortic reconstruction due to aneurysm rupture. Among these 205, 125 patients underwent an open surgical method, while 80 received endovascular treatment. The total incidence rate of acute renal failure in that series was 36%. In patients undergoing open aortic repair, the occurrence rate of AKI was 43%. The here-mentioned report confirmed our present research results, referring to the distinct connection between preoperative elevated serum creatinine level and a severe type of acute renal failure in the postoperative period. Simultaneously, this also denoted the third important risk factor for the occurrence of AKI in the postoperative period in patients undergoing aortic surgery (12).

Data included in the analysis relates to the period elapsed from the moment of rupture to entering the operating room. Although there was no statistically relevant difference between the examined groups, it is evident that in cases where more than 6 hours passed from the moment of acute symptomatology to the start of surgery, signs of acute renal insufficiency were by 20% more frequently developed than in those patients who reached the operating table sooner. The reasons are to be found in the untimely recognition of symptoms, prolonged transportation to the place of standard treatment, diagnostic wandering, and other factors.

Having considered this pathophysiological phenomenon, and in line with the reviewed literature, it is clear that the disorder has a multifactorial genesis. Likewise, the results related to the occurrence rate of this postoperative phenomenon reveal a noticeable divergence. By presenting such data, this discussion aims to illustrate the complexity of the conditions impacting the development of acute renal failure in the treatment of more severe types of acute aortic syndrome. It is certain that hemorrhagic shock, which is further subclassified depending on its estimated severity, plays a crucial and leading role in the development of AKI, as supported by numerous empirical data and scientific evidence. Nearly all surgical fields encountering the burden of difficult-to-control bleeding bear a certain percentage of patients with postoperative AKI. This primarily refers to cardiovascular surgery, traumatology, and transplant surgery. Certain surgical specialties report that, even with well-performed bleeding control, a considerable number of patients develop postoperative AKI, largely due to transfusion complications (13).

Thus, for example, trauma patients with hemorrhagic shock have an incidence of AKI that runs up to 42.5%. It is interesting to note that in these cases, the onset of AKI is slower than in acute aortic syndrome. Namely, in 96% of trauma cases, AKI occurs within the first five postoperative days, while, according to our data, in cardiovascular patients, AKI occurs within the first three postoperative days (14).

The incidence of hospital survival in our patients who underwent emergency surgery for aneurysm rupture in this series is 67.4%. Globally, the hospital survival rate ranges from 50-77% (15,16,17).

Many factors affect overall survival, but acute renal failure is undoubtedly one of the most important. All further research, it seems, will have the task of convincing the profession that improving results of immediate survival in open surgical treatment of abdominal aortic aneurysm rupture does not mean that the list of accompanying postoperative issues loses its significance. This article can, then, hopefully serve as a cue to interested readers.

CONCLUSION

The appearance of acute kidney function disorder after urgent surgical reconstruction of the aortic trunk due to aneurysm rupture has a significant frequency, but the issue is unjustifiably underemphasized in practice. Risk factors for the occurrence of AKI are advanced stages of hemorrhagic shock, intraoperative hemodynamic instability, intraoperative blood loss over 1500ml, and elevated preoperative serum creatinine values. Preoperatively elevated serum creatinine level is also a safe independent predictor of acute kidney function disorder in the postoperative period.

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Declaration of patient consent: the authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal.
Authors' Contributions: AH, MD, EK, BB, IH-K and SŠ gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author had role in article drafting and in process of revision. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

Challenges in the management of non-tuberculous mycobacterial lung diseases

Izazovi u liječenju netuberkuloznih mikobakterijskih plućnih bolesti

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ABSTRACT

Introduction: the frequency of non-tuberculous mycobacterial lung diseases (NTM) has recently increased. The reasons for this increase can be multiple, such as better recognition of the pathology, increase in the number of patients at risk and lifestyle modification. Aim: to present the clinical and radiological characteristics as well as treatment options of NTM. Materials and methods: Data were sourced from a medical literature review on non-tuberculous mycobacterial lung diseases, the author's personal literature collection, and by checking reference lists of sourced articles. Results: the main pulmonary clinical and radiological features are the fibrocavitary form that mimics tuberculosis, then the form of both nodule and bronchiectasis and sometimes multiple nodules can be seen. A rare presentation is a unique nodular form that presents a problem of differential diagnosis with a tumor lesion and additionaly the patient is often asymptomatic and the diagnosis is established after biopsy due to negativity of bronchial samples on microbiology. Some general predisposing factors are alcoholism, diabetes, chronic liver disease and imunocompromised patients. Isolation of NTM in respiratory samples does not add to the certainty of pulmonary infection with NTM. Some species are almost exclusively pollutants. The response to treatment is quite slow, either radiologically or microbiologically. Conclusion: proper and timely diagnosing and treating NTM is very important, and thus more because the treatment of these infections differs from those caused by Mycobacterium tuberculosis complex. Systemic treatment of NTM is long-term and requires a combination of multiple antibiotics. Relapses and re-infections are not uncommon as well.

Keywords: nontuberculous mycobacteria (NTM), clinical and radiological features, diagnosis, treatment

SAŽETAK

Uvod: učestalost netuberkuloznih mikobakterijskih plućnih bolesti (NTM) je povećana u posljednje vrijeme. Razlozi za ovo povećanje su višestruki, kao što je bolje prepoznavanje patologije, povećanje broja rizičnih pacijenata i promjene načina života. Cilj: predstaviti kliničke i radiološke karakteristike, kao i opcije liječenja NTM. Materijal i metode: Podaci su skupljeni iz pregleda medicinske literature o netuberkuloznim mikobakterijskim plućnim bolestima, autorove osobne kolekcije literature, kao i pregledom listi referenci izvornih članaka. Rezultati: glavne kliničke i radiološke karakteristike oboljenja pluća su fibrokavernozna forma koja imitira tuberkulozu, zatim oblik kod kojeg su prisutni noduli i bronhiektazije, a ponekad se mogu vidjeti multipli noduli. Rijetka prezentacija je pojedinačni nodularni oblik koji predstavlja dijagnostički problem u diferencijalnoj dijagnozi sa tumorskom lezijom, a dodatno pacijent je često asimptomatičan i dijagnoza se uspostavlja nakon biopsije zbog mikrobiološke negativnosti bronhijalnih uzoraka. Neki opšti predisponirajući faktori su alkoholizam, dijabetes, hronična oboljenja jetre i imunokompromitovani pacijenti. Izolacija NTM u respiratornim uzorcima ne doprinosi sigurnosti da zaista postoji plućna infekcija uzrokovana NTM-om. Izolacija nekih vrsta se gotovo isključivo smatra kontaminacijom. Odgovor na liječenje je prilično spor, bilo radiološki ili mikrobiološki. Zaključak: Pravilno i pravovremeno dijagnosticiranje i liječenje NTM je veoma važno, a time i više, jer se liječenje ovih infekcija razlikuje od onih uzrokovanih sa Mycobacterium tuberculosis complex. Sistemsko liječenje NTM je dugotrajno i zahtijeva kombinaciju više antibiotika. Relapsi i ponovne infekcije također nisu neuob ičajeni.

Ključne riječi: netuberkulozne mikobakterije (NTM), kliničke i radiološke karakteristike, dijagnoza, liječenje

INTRODUCTION

The frequency of non-tuberculous mycobacterial lung disease (NTM) has recently increased. The reasons for this increase can be multiple, such as better recognition of the pathology, increase in the number of patients at risk and lifestyle modification (1).

Nontuberculous mycobacteria (NTM) are a diverse Nontuberculous mycobacteria group of bacteria with a wide spectrum of virulence (2). They are microaerobic, non-motile organisms that have a lipid-rich, hydrophobic cell wall that is

substantially thicker compared with most other bacteria (3). NTM are associated with biofilm formation, which contributes to disinfectant- and antibiotic-resistance (4).

Many of these organisms are also resistant to high temperature and low pH (5). Ubiquitous in the environment, NTM are found with the greatest concentrations in water sources, both natural and treated, and in soil sources (6). There are currently over 170 species of mycobacteria and more are likely to be discovered in the future owing to improved culturing techniques and molecular technology advances (7).

The majority of NTM-pulmonary disease (NTM-PD) infections are caused by the slow growing Mycobacterium avium complex (MAC) that includes Mycobacterium avium and Mycobacterium intracellulare. Other species including M. abscessus, M. xenopi, M. malmoense and M. kansasi can also cause lung disease (8).

NTM lung diseases are charasterised by clinical, microbiological and radiological criteria.

AIM

The aim of this study was to present the clinical and radiological characteristics, predisposing factors, diagnosis and treatment options of NTM.

MATERIALS AND METHODS

Data were sourced from a medical literature review on non-tuberculous mycobacterial lung diseases, the author's personal literature collection, and by checking reference lists of sourced articles.

RESULTS

Clinical and radiological features of NTM

The main pulmonary clinical and radiological features are the *fibrocavitary form* (Figure 1,2) that mimics tuberculosis which is the usual form of infections with Mycobacterium kansasii (M. kansasii), Mycobacterium xenopi (M. xenopi), Mycobacterium malmoense, then the form of both *nodule and bronchiectasis* as the prerogative of Mycobacterium avium complex (MAC) (Figure 4). Sometimes *multiple nodules* (Figure 3) can be seen, especially in pulmonary infections with M. xenopi. A rare presentation is a *unique nodular form* that presents a problem of differential diagnosis with a tumoral lesion and additionaly the patient is often asymptomatic and the diagnosis is established after biopsy due to negativity of bronchial samples on microbiology.

Clinical symptoms

The clinical symptoms are comparable. The delay between the onset of symptoms and diagnosis is long, from several months to sometimes several years (9,10).

The symptoms primarily associate productive cough (78-96%) in 67 to 87% of cases. Hemoptysis is found in 29 to 36%, dyspnea in 22 to 65%. General signs are inconsistent: fever in 10 to 58%, night sweats in 10 to 54%, weight loss in 26 to 43%. Asthenia, not very specific, is found in more than 80% of patients (10).

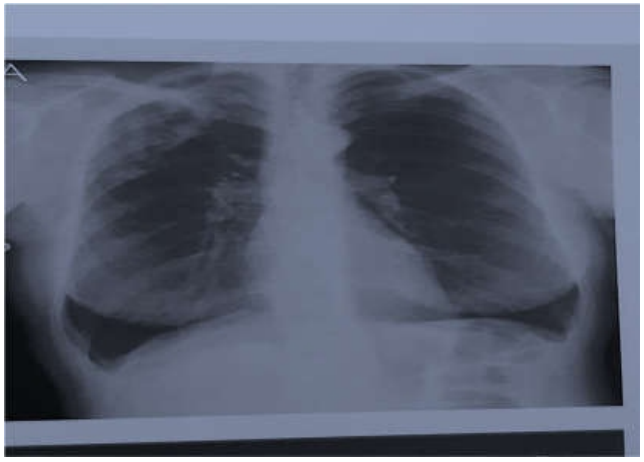

Figure 1 **Right apical lung excavated opacity patient due to M. xenopi lung infection.**

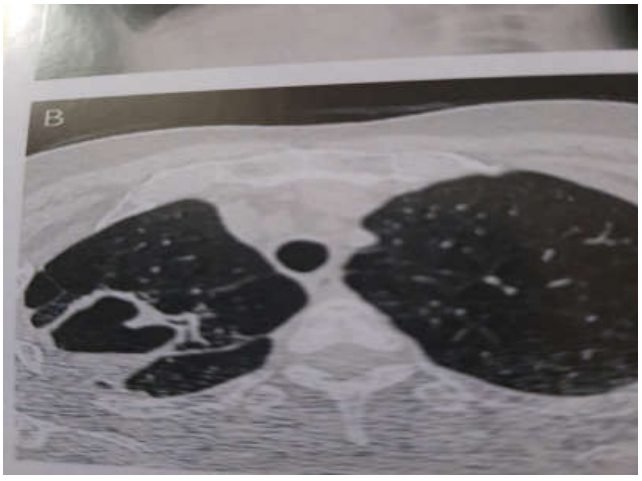

Figure 2 **Chest CT scan of the same.**

(Source: E. Catherinot, Pr O. Lortholary, N. Veziris, 2017)

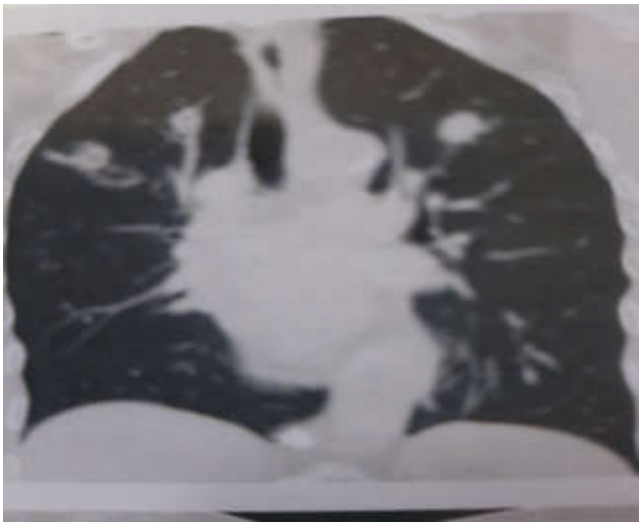

Figure 3. **Multiple pulmonary nodules as a consequence of M. xenopi lung infection.**

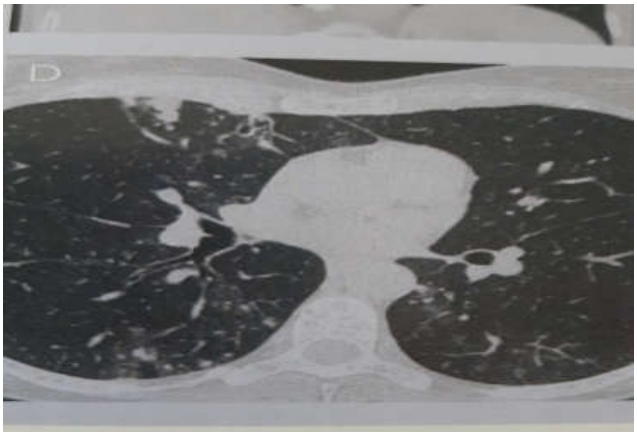

Figure 4. **Pulmonary infection with M. avium with associated multiple bilateral bronchiolar pulmonary micronodules, bronchiectasis and middle lobe nodule.**

(Source: E. Catherinot, Pr O. Lortholary, N. Veziris, 2017)

A rare presentation (less than 10% of cases) is a unique nodular form that presents a problem of differential diagnosis with a tumour lesion. The patient is often asymptomatic, and the diagnosis is established after biopsy or surgical resection due to the negativity of bronchial samples on microbiology (11).

Chest radiograph (Figure 1) and chest CT scans of the patient 1 (treated in the Clinic of Lung Diseases and TB-Clinical Centre of University Sarajevo) (Figure 6,7,8) are presented. Collapsed lung parenchyma on the left side with diffuse bronchiectasis, larger bullous formation on the left apically, displacement of mediastinal structures to the left as well as panlobar emphysema of the lung parenchyma on the right with multiple subpleural micronodules could be seen.

Figure 5 **Patient 1 (chest radiograph).**

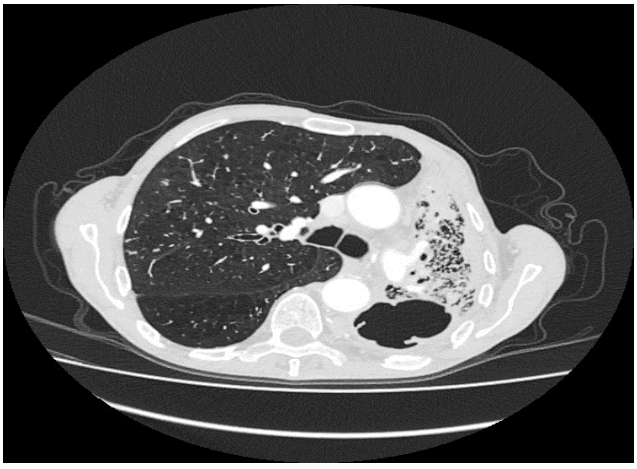

Figure 6 **Patient 1 (chest CT scan).**

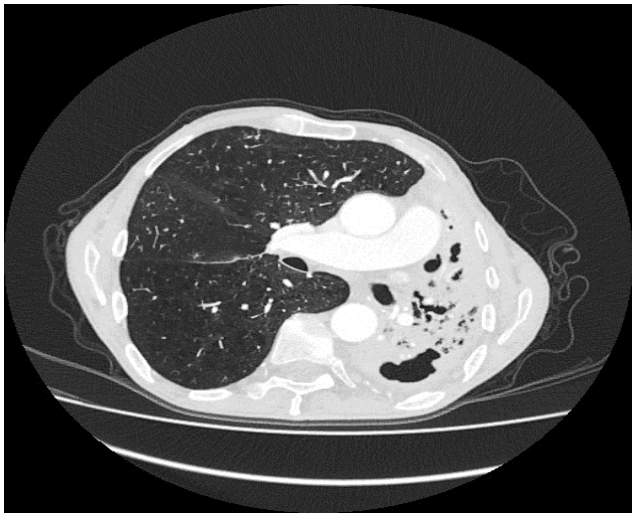

Figure 7 **Patient 1 (chest CT scan).**

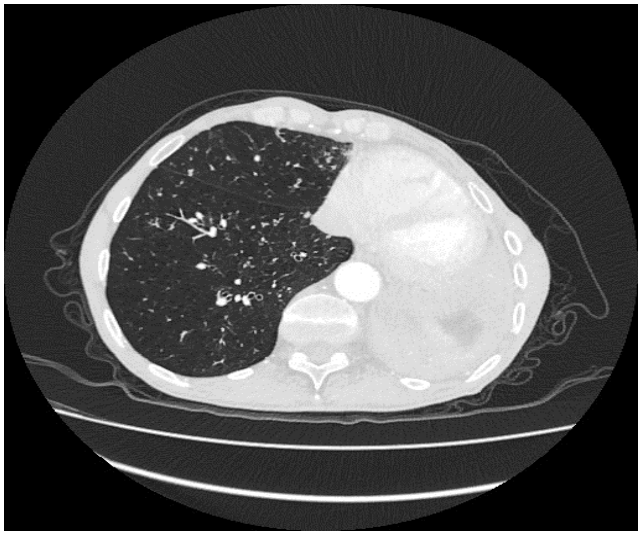

Figure 8 **Patient 1 (chest CT scan).**

Chest radiograph of the patient 2 (admitted in the Clinic of Lung Diseases and TB-Clinical Centre of University Sarajevo) showed fibroulcerous and cavitary changes bilaterally in the infraclavicular regions at admission (Figure 9). Discrete radiological regression was seen in the same patient at discharge (Figure 9). Multiple micronodules in the lung parenchyma on both sides, and in the upper lung lobes on both sides consolidation of the lung parenchyma with excavations within them were seen on chest CT scans of the patient 2 (Figures 11-15).

Figure 9 **Patient 2 (chest radiograph At admission**).

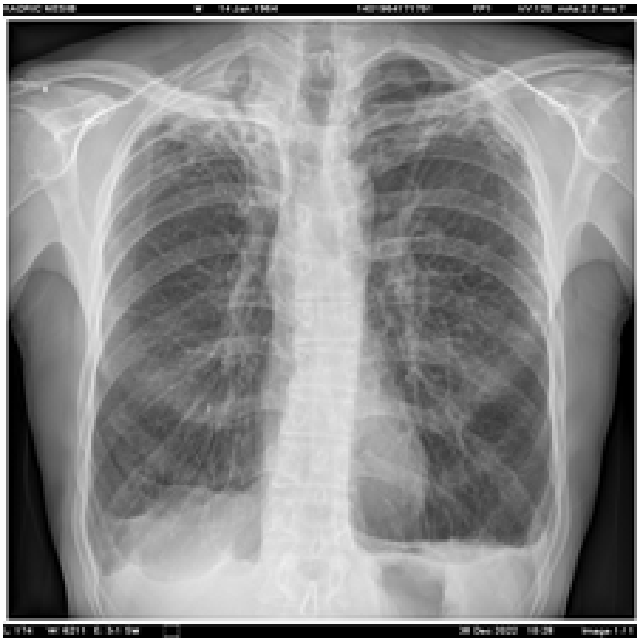

Figure 10 **Patient 2 (chest radiograph). At discharge**

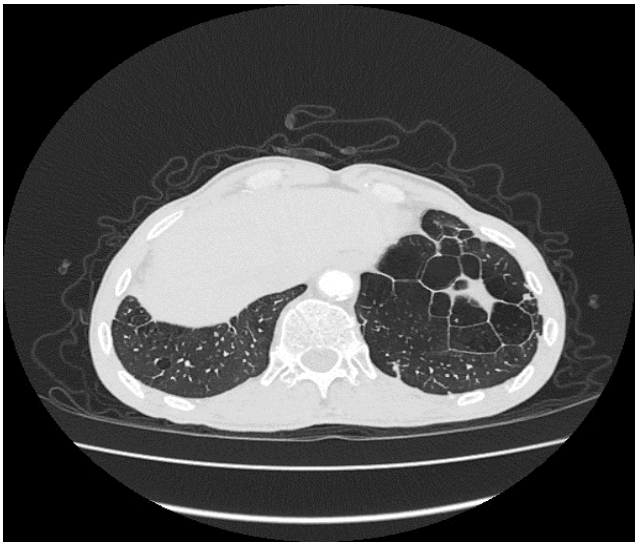

Figure 11 **Patient 2 (chest CT scan).**

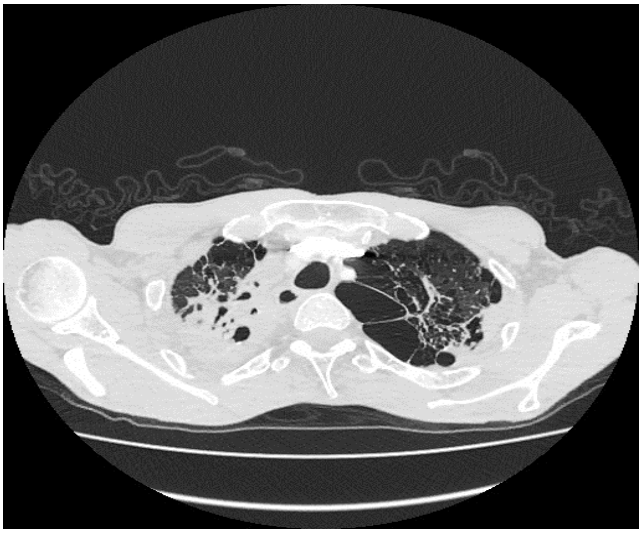

Figure 12 **Patient 2 (chest CT scan).**

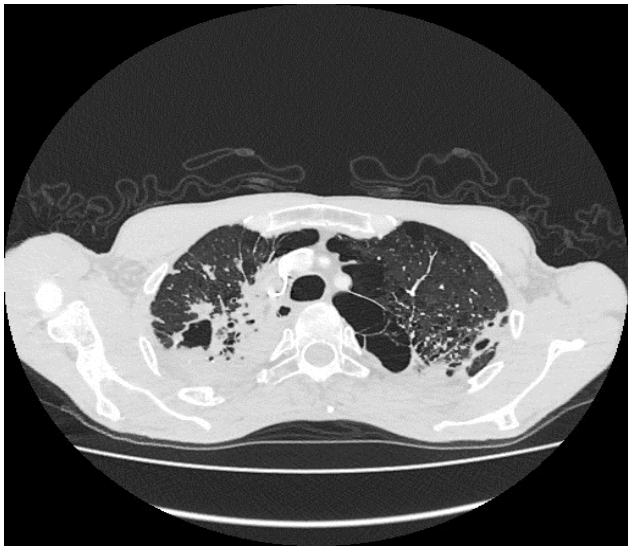

Figure 13 **Patient 2 (chest CT scan).**

Figure 14 **Patient 2 (chest CT scan).**

Figure 15 **Patient 2 (chest CT scan.)**

Predisposing factors

Some general predisposing factors reported in the studies are alcoholism, diabetes, chronic liver disease, immunocompromised patients due to HIV infection, immunosuppressive treatment for transplantation. In immunocompromised patients, the presentation may be more severe and more rapidly progressive in the form of a diffuse infiltrate with micronodules and consolidations (12). Patients with cystic fibrosis are particularly at risk of pulmonary NTM infection with a prevalence of positive respiratory isolates of 6.6 to 13% (13). The overall prevalence of NTM infection in cystic fibrosis is 7.9% (14). Patients with non-cystic fibrosis bronchiectasis (BDD) are also at high risk, with prevalence data being difficult to collect due to the fact that mycobacteria alone can cause bronchiectasis. In primary ciliary dyskinesia and in the English BDD cohort, the prevalence of MNT-positive samples was found to be 10%, comparable to that described in cystic fibrosis (15). Adult patients without local or general predisposing factors now represent a significant proportion of patients, 25 to 59% of pulmonary MAC infections (10). They are usually middle-aged women in their 60s with the associated morphological characteristics: they are usually slim and considerably taller than the control population, with an abnormal frequency of pectus excavatum, scoliosis and/or mitral valve prolapse. These 3 morphological abnormalities are genetically linked, resembling the marfanoid phenotype (16). Difficulties lay both in knowing the different steps that can lead to the diagnosis of infection and the application of treatment, and in the wide spectrum of NTM types, some of which are almost never associated with the risk of infections.

Diagnosis

NTM are ubiquitous in the environment and isolation from sputum does not always signify disease. The American Thoracic Society (ATS) and the Infectious Disease Society of American (IDSA) jointly published guidelines on diagnosis of NTM infections in 2007. (2). An early differential diagnosis of NTM lung disease from pulmonary tuberculosis is important because the therapeutic regimen differs from that of pulmonary tuberculosis and it is not necessary to track the contacts of patients with nontuberculous pulmonary disease (NTM-PD) (17). Symptoms are variable although chronic cough with or without sputum production or haemoptysis, is common. Other symptoms include fatigue, malaise, dyspnoea, fever, chest pain and weight loss. The evaluation of NTMs is often complicated by coexisting lung diseases including cystic fibrosis, bronchiectasis and pneumoconiosis.

Why is the diagnosis so complicated? How to confirm or deny the diagnosis?

Acquisition of NTM is believed to be from the environment, however, emerging literature, using sequencing of NTM isolates, suggest that indirect cross infection of M. abscessus is possible in patients with cystic fibrosis (18). This has led to changes in infection control standards in these patients groups (19,20). *Isolation of NTM in respiratory samples does not add to the certainty of pulmonary infection with NTM.* Some species are almost exclusively pollutants (M. gordonae, M. terrae complex, M. mucogenicum, M. nonchromogenicum) (9).

Summary of the American Thoracic Society diagnostic criteria for pulmonary nontuberculous mycobacterial infection (Source: Adapted from Griffth DE, Aksamit T, Brown-Elliott BA, et al, 2007).

Clinical

1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomographic scan that shows multifocal bronchiectasis with multiple small nodules: and

2. Appropriate exclusion of other diagnoses.

Microbiologic

1. Positive culture results from at least two separate expectorated sputum samples (if the results from the initial sputum samples are nondiagnostic, consider repeat sputum AFB smears and cultures); Or

2. Positive culture results from at least one bronchial wash or lavage; Or

3. Transbronchial or other lung biopsy with mycobacterial histopathological features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathological features (granulomatous inflammation or AFB) and one or more sputum or bronchial washing that are culture positive for NTM

4. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination

5. Patients who are suspected of having NTM lung disease but who do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded

6. Making the diagnosis of NTM lung disease does not, per se, necessitate the institution of therapy, which is a desicion based on potential risks and benefits of therapy for individual patients.

In patients who do not meet the diagnostic criteria because only one sputum is positive for culture, longitudinal follow-up by repeating the sputum several times over the next 12-24 months is recommended to distinguish true infection from contamination. Regarding the re-evaluation of imaging, it has been shown that the bronchiectasis score worsens after 12-24 months in most patients, but stability after 6 months does not exclude the diagnosis due to the slow development of the infection. On the other hand, the sensitivity of samples for looking for NTM is not 100%, especially in forms of nodule + bronchiectasis. Often patients have little or no sputum. In case of suspicion of infection and negative sputum, it is necessary to repeat them over time and/or perform bronchoscopy (10,21).

Treatment

Similar combinations of drugs have also been suggested for other NTM that commonly cause NTM-PD such as M. kansasii, M. malmoense and M. xenopi (2). No established regimens of proven efficacy exist for M. abscessus; although standard treatment based on case series consists of an induction phase of intravenous therapy including medications such as amikacin, carbapenem, tigecycline or cefoxitim, followed by a continuation phase of oral antibiotics (22). A macrolide-based regimen is often used and surgical debridement may also be important. However, macrolide resistance is common in M. abscessus because the organism possesses an inducible macrolide-resistance gene (23, 24). In some instances more than one NTM species is present and there are no data available to guide the clinician in these cases so they need to be evaluated and treated on an individual basis (25).

The 2007 ATS/IDSA guidelines are the most commonly followed worldwide. They recommend that treatment for most patients with nodular/bronchiectatic MAC disease involves a three-times-weekly regimen of clarithromycin (1000 mg) or azithromycin (500 mg), rifampin (600 mg) and ethambutol (25mg/kg), although in many cases daily treatment may be appropriate (27). For patients with fibrocavitary MAC lung disease or severe nodular/bronchiectatic disease, a daily regimen of clarithromycin (1000 mg) or azithromycin (250 mg), rifampin (600 mg) or rifabutin (150-300 mg) and ethambutol (15 mg/kg) with consideration of three-times-weekly amikacin or streptomycin early in therapy is recommended. Patients should be treated until culture negative for 1 year while receiving antibacterial therapy (2).

In some patients, clinical improvement and culture conversion will be the aim, however, for others, stability will be a more realistic target. The potential toxicity of anti-mycobacterial therapy must be balanced against a sometimes indolent course. A patient's comorbidities and quality-of-life issues are also important to take into account. There are currently insufficient data on the natural history of untreated infections to guide clinical decision-making in this respect. Even if NTM is diagnosed, lung disease treatment may not not always be needed. For patients with indolent NTM lung disease there is usually enough time for careful consideration of the optimal management**.** Once a risk-benefit decision has been made to begin NTM therapy, the choice of agents and duration of treatment is based on the specific organism and extent of disease (2).

Limitations of current treatment

The long duration of treatment often leads to adverse drug reactions, increased potential for drug-drug interactions and nonadherence to treatment or treatment discontinuaton (27). NTM infections are commom in elderly people and age-related changes in drug absorption, metabolism and excretion may lead to a decline in efficacy and increase toxicity (28).

What is the prognosis depending on the type of NTM? Are they all equally weighted?

While some patients with MAC associated with *nodules and bronchiectasis* have few symptoms and develop very slowly on imaging (radiological picture) without treatment over several years. *Fibro-cavitary forms* can evolve into extensive parenchymal involvement with respiratory failure and impaired general condition, which results in patient death in 1 to 2 years if treatment fails (29). On the other hand, it is clear that there is heterogeneity of virulence between mycobacterial species. M. kansasii is the cause of more symptomatic and more rapidly progressive forms of the disease. M. abscessus infections have a worse prognosis, probably partly related to the fact that their intrinsic resistance to many antibiotics leads to frequent treatment failure (30).

What explains the high frequency of relapse? How to prevent them?

Mycobacteria are naturally not very sensitive to antibiotics.This natural resistance to antibiotics arises from several mechanisms that can be excluded (impermeability due to the wax-rich wall, presence of efflux pumps, enzymatic degradation, inducible resistance) (31). Treatment aims to optimize the first line of treatment to reduce the risk of failure and the selection of resistant mutants by suggesting the best combination of antibiotics (least 3) for a longer duration (2). Failures and relapses are common, especially for MAC and at macrolide-resistant strains of MABSC. In addition, simultaneous or consecutive infections with several NTMs or several strains within the same species are not uncommon, reflecting the patient's susceptibility to this type of infection (32). In the absence of immune reconstitution in the host, relapses may occur, and subsequently by the acquisition of different resistance mechanisms (33).

CONCLUSION

Due to the frequent side effects and the frequency of failure and recurrence of this type of infection, it is possible to suggest therapeutic abstinence when the pulmonary infection is not very symptomatic, not very progressive and when the prognosis of NTM infection is secondary due to the extreme age of the patient and/or comorbidities. Standard treatment of MAC infections is based on the use of macrolides (clarithromycin or azithromycin) plus accompanying molecules that are mainly intended to avoid the appearance of resistance to macrolides (rifampicin in the first instance due to better tolerability in often elderly patients or rifabutin) + ethambutol, which act synergistically (2). The recommended duration of treatment is 18 to 24 months with the triple combination, at least 12 months after culture conversion. Intermittent treatment (3 days a week) can be offered in the form of nodule + bronchiectasis. An initial combination with an aminoglycoside (aminoside) 3 days a week during the first 3 months is recommended in extensive fibro-cavitary forms. Standard treatment of M. kansasii infections is simpler and relapses are rare. The recommended duration is 12 months after negative cultures of the combination of rifampicin, isoniazid and ethambutol (2,34). Proper and timely diagnosing and treating NTM is very important, and thus more because the treatment of these infections differs from those caused by Mycobacterium tuberculosis complex.

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Declaration of patient consent: the author certifies that he has obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal.
Authors contributions: BP gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work.
Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

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Uvod je kratak, koncizan dio rada i u njemu se navodi svrha rada u odnosu na druge objavljene radove sa istom tematikom. Potrebno je navesti glavni problem, cilj istraživanja i/ili glavnu hipotezu koja se provjerava.

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