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DISCIPLINA ZA NAUKU I NASTAVU


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Novi Centralni medicinski blok - Klinički centar Univerziteta u Sarajevu
New Central Medical Building - Clinical Center University of Sarajevo

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.

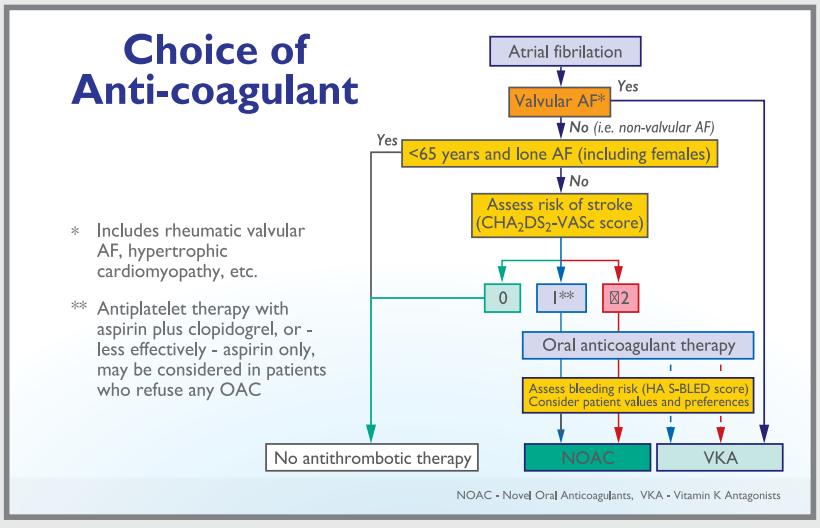
Major i non-major riziko fakori za procjenu tromboembolizma kod A Fib!

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.

Algoritam antikoagulantne terapije nakon procjene CHA_2DS_2VASc i major risk faktora!



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CCUS

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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.

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Address:
Medical Journal, Discipline for Research and Development
Clinical Center University of Sarajevo,
71000 Sarajevo,
Bolnička 25,
Bosnia and Herzegovina,
Phone: +387 33 298 514
Web. www.kcus.ba
Technical secretariat: svjetlana.barosevcic@kcus.ba

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EDITORIAL LETTER

Regarding the letter of the Director of the Discipline for Child Health, Professor Dr Edo Hasanbegović, No. 40-30-5-26257 of 22 July 2024 concerning the establishment of the factual state and correction of the name and surname of the co-author of an original article, the Editorial Board of the Medical Journal informs about the following:

In the article entitled "*Multisystem inflammatory syndrome associated with COVID-19 in previously healthy children*" published in the 2020 Medical Journal, Volume 26 No. 3-4, ISSN (print) 1512-5866, ISSN (online) 2232-8, during the technical preparation of the paper by the Discipline for Child Health, an error occurred when Dr Amra Čengić, was listed as the first co-author.

In order to establish the correct factual state, the Editorial Board of the Medical Journal agrees to correct the error in a way that the name of Amra Čengić is replaced by the name of **ADISA ČENGIĆ**, Paediatrician, Allergist, employee of the Paediatric Clinic of the Clinical Center University of Sarajevo.

Medical Journal (2020) Vol.26, No. 3,4

Multisystem inflammatory syndrome associated with COVID-19 in previously healthy children

Multisistemski inflamatorni odgovor udružen sa COVID-19 kod prethodno zdrave djece

Edo Hasanbegović*, Adisa Čengić, Aida Omerčahić-Dizdarević, Velma Selmanović

Pediatric Clinic, Clinical Center University of Sarajevo, Patriotske lige 81, 71000 Sarajevo, Bosnia and Herzegovina

Sincerely yours,

Editorial Board of the Medical Journal

DOPIS UREDNIŠTVA

U vezi sa dopisom Direktora za zdravlje djeteta, prof. dr Ede Hasanbegovića br 40-30-5-26257 od 22.07.2024. godine kojim se traži utvrđivanje činjeničnog stanja i ispravka imena i prezimena autora naučnog rada, Uredništvo Medicinskog žurnala obaviještava o sljedećem.

U radu pod nazivom "*Multisistemski inflamatorni odgovor udružen sa COVID-19 kod prethodno zdrave djece*" objavljenom u Medicinskom žurnalu Volume 26 br. 3 -4 iz 2020. godine, ISSN (print) 1512-5866, ISSN (online) 2232-8, prilikom tehničke pripreme rada od strane Discipline za zdravlje djeteta došlo je do pogreške kada je kao prvi koautor navedena dr Amra Čengić.

U cilju utvrđivanja činjeničnog stanja Uredništvo Medicinskog žurnala je saglasno da se greška ispravi na način da se u radu umjesto dr Amre Čengić, kao prvog koautora, navede ime **dr ADISE ČENGIĆ**, pedijatra alergologa imunologa, uposlenice Pedijatrijske klinike Kliničkog centra univerziteta u Sarajevu.

Medical Journal (2020) Vol.26, No. 3,4

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Pediatric Clinic, Clinical Center University of Sarajevo, Patriotske lige 81, 71000 Sarajevo, Bosnia and Herzegovina

S poštovanjem,

Uredništvo Medicinskog žurnala

The six-month outcome of hypertensive crises in relation to cardiovascular risk factors

Šestomjesečni ishod hipertenzivnih kriza u odnosu na kardiovaskularne riziko faktore

Amela Ahmić*

Clinic of Emergency Medicine, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: a hypertensive crisis is characterized by a state of acutely elevated blood pressure. It can arise as a consequence of uncontrolled chronic hypertension or manifest suddenly in previously healthy individuals. Aim: to explore the impact of cardiovascular risk factors on the type and outcome of hypertensive crises (HC). Additionally, to investigate the occurrence of new cardiovascular events in a six-month period and define possible risk factors that may influence this. Materials and methods: the data from the hospital electronic medical records of patients presented with HC at the Emergency Medicine Clinic of the Clinical Center of the University of Sarajevo over a six-month period (01.07.-31.12.2023) were retrospectively collected. Data collection encompassed blood pressure levels, age, sex, history of chronic hypertension, smoking status, and presence of diabetes mellitus and dyslipidemia as cardiovascular risk factors. Outcomes after initial admission (1. discharge, 2. hospitalization and 3. death) and after six-month follow up (1. absence of readmission, 2. readmission and 3. death) were recorded. Results: the study included 243 patients: 66 (27.2%) with hypertensive emergencies and 177 (72.8%) with hypertensive urgencies without significant difference between these groups regarding age, history of chronic hypertension, presence of dyslipidemia, smoking status, and presence of diabetes mellitus ($p>0.05$). Men were predominated in HE, while women were predominated in HU group ($p<0.05$). Diastolic blood pressure values were higher in HE patients [median (IQR) 110(20) vs. 100(10)] ($p<0.05$). After initial treatment 98.3% of HU patients were discharged, 92.4% were hospitalized and 3% of HE patients died. After a 6-month follow-up, there was no significant difference in the number of readmissions between these two groups ($p>0.05$), but mortality was significantly higher in HE (15.15% vs 6.21%) ($p<0.05$). There was no significant difference in risk factors between patients with the observed outcomes ($p>0.05$) except that the age was higher in deceased patients ($p<0.05$). Conclusion: male gender and higher DBP have been identified as risk factors for the development of HE, the need for hospital treatment, and increased in-hospital and six-month mortality. Older age represents a risk for readmissions and mortality.

Keywords: hypertensive crisis, risk factors, outcome

SAŽETAK

Uvod: hipertenzivnu krizu karakterizira stanje akutno povišenog krvnog pritiska. Može nastati kao posljedica nekontrolisane hronične hipertenzije ili se iznenada manifestuje kod inače zdravih osoba. Cilj: istražiti uticaj kardiovaskularnih riziko faktora na vrstu i ishod hipertenzivnih kriza. Dodatno istražiti učestalost novih kardiovaskularnih incidenata u šestomjesečnom periodu (01.07 – 31.12. 2023.) i definisati potencijalne riziko faktore koji mogu imati uticaj na to. Materijali i metode: retrospektivno su prikupljeni podaci iz bolničkog elektroničkog sistema o pacijentima sa hipertenzivnim krizama koji su se javili na Kliniku urgentne medicine Kliničkog centra Univerziteta u Sarajevu u šestomjesečnom periodu (01.07 – 31.12. 2023.). Prikupljeni podaci uključivali su vrijednosti krvnog pritiska, starost, spol, podatke o prisustvu ili odsustvu prethodne hronične hipertenzije, pušenju, prisustvu diabetes mellitusa i dislipidemije kao kardiovaskularnim faktorima rizika. Zabilježeni su ishodi nakon inicijalnog tretmana (1. otpuštanje, 2. hospitalizacija i 3. smrt) te nakon šestomjesečnog follow up perioda (1. odsustvo readmisija, 2. readmisije i 3. smrt) Rezultati: istraživanje je uključilo 243 pacijenta: 66 (27.2%) sa hipertenzivnim emergencijama (HE) i 177(72.8%) sa hipertenzivnim urgencijama (HU) bez signifikantne razlike između ovih grupa pacijenata po pitanju starosti, prisustva hronične hipertenzije, dislipidemije, pušačkog statusa i prisustva diabetes mellitusa ($p>0.05$). Muškarci su preovladavali u HE, a žene u HU grupi ($p<0.05$). Vrijednosti dijastolnog krvnog pritiska su bile signifikantno veće kod pacijenata sa HE [median(IQR) 110(20) vs. 100(10)] ($p<0.05$). Nakon inicijalnog tretmana 98.3% HU pacijenata je otpušteno a 92.4% HE pacijenata je hospitalizirano te 3% umrlo. Nakon šest mjeseci od inicijalnog tretmana nije bilo signifikantne razlike u broju readmisija između HE i HU grupa pacijenata ($p>0.05$) ali je mortalitet bio signifikantno veći kod HE pacijenata (15.15% vs 6.21%) ($p<0.05$). Nije bilo signifikantne razlike u ispitivanim riziko faktorima između grupa pacijenata sa ispitivanim ishodima ($p>0.05$) osim što je dob bila viša kod preminulih pacijenata ($p<0.05$). Zaključak: muški spol i viša vrijednost dijastolnog krvnog pritiska su prepoznati kao riziko faktori razvoja HE odnosno potrebe hospitalnog tretmana te većeg intrahospitalnog i šestomjesečnog mortaliteta. Viša starosna dob predstavlja rizik za pojavu readmisija i smrtni ishod.

Ključne riječi: hipertnezivna kriza, riziko faktori, ishod

INTRODUCTION

A hypertensive crisis is characterized by a state of acutely elevated blood pressure (>180 systolic/120 diastolic), necessitating prompt medical intervention to prevent serious consequences and potential death (1). It can arise as a consequence of uncontrolled chronic hypertension or manifest suddenly in previously healthy individuals (2). Hypertensive crises are classified into two types: hypertensive urgency (HU), characterized by the absence of hypertensive mediated organ damage (HMOD), and hypertensive emergency (HE), characterized by its presence. Treatment recommendations differ as HU is considered milder and less dangerous, often requiring ambulance-administered peroral drug for blood pressure reduction, whereas HE typically necessitates hospitalization and intravenous therapy. This patient categorization is a one-time assessment conducted during admission to the medical ambulance, aiming to aid physicians in decision-making. The reasons why acute hypertension leads to organ damage in some individuals and not in others remain unclear. Are there factors influencing the outcome of an acute hypertensive crisis? Moreover, it's uncertain whether the type of hypertensive crisis affects the likelihood of future cardiovascular events. Should patients with HE be more concerned than those with HU? If so, is it due to the potential risk factors they are exposed to? There is a scarcity of studies examining the impact of cardiovascular risk factors on the outcome of hypertensive crises, either immediately or after a certain follow-up period.

MATERIALS AND METHODS

This retrospective study included patients aged 18 years or older with systolic blood pressure (SBP) ≥180 mmHg and/or diastolic blood pressure (DBP) ≥120 mmHg, who were admitted to the Clinic of Emergency Medicine of the Clinical Center University of Sarajevo over a six-month period (from 01.07 to 31.12.2023). Data were collected from hospital electronic patient records, with pregnant women being excluded from the study. Patients who died before completing the diagnostic examination or determining the presence/absence of hypertensive mediated organ damage (HMOD), which distinguishes hypertensive emergency (HE) from hypertensive urgency (HU), as well as patients with incomplete data regarding risk factors or other relevant information, were also excluded.

Data collection encompassed not only blood pressure levels, diagnostic results, and outcomes but also cardiovascular risk factors such as age, sex, history of chronic hypertension, dyslipidemia, smoking status, and presence of diabetes mellitus. The outcomes after admission were categorized into 3 categories: 1. discharge after ambulance treatment, 2. discharge after hospitalization, and 3. death (either during ambulance transport or hospitalization).

A six-month follow-up involved collecting all medical records from the electronic medical registry during this period. We documented occurrences of new hypertensive crises, cardiovascular events, and cardiovascular-caused deaths, while excluding patients who died from other causes. The final six-month outcomes were classified into three categories: 1. absence of new events and emergency department (ED) or hospital readmissions, 2. readmissions caused by recurrent hypertensive crises and/or other cardiovascular events, and 3. death. As this was a retrospective non-interventional observational study, patients who died soon after the initial recorded admission (considered the primary outcome) were included in the six-month outcome analysis to present the overall outcome from the time of admission to the ED ambulance until six months afterward (considered the final outcome).

Statistical Analysis

All data were analyzed and graphically presented using the IBM SPSS 20 software. The Shapiro-Wilk test was utilized to assess the normality of distribution for continuous variables. Descriptive statistics, including counts, percentages, medians, and interquartile ranges, were employed. Categorical data were compared using the chi-square test, while non-normally distributed data were analyzed using non-parametric methods such as the Kruskal-Wallis test for multiple independent data and the Mann-Whitney test for two independent data groups. A significance level of $p > 0.05$ was considered statistically significant.

RESULTS

The study included 243 patients: 66 (27.2%) with hypertensive emergencies and 177 (72.8%) with hypertensive urgencies. Hypertensive mediated organ damage (HMOD) in hypertensive emergencies presented as ischemic/haemorrhagic stroke in 25 cases (37.8%), acute coronary syndrome in 18 cases (27.3%), acute heart failure/pulmonary edema in 15 cases (22.7%), acute aortic syndrome in 4 cases (6.1%), and other conditions in 4 cases (6.1%). The median values of systolic/diastolic pressure in the observed patients were 190 (IQR 30) / 100 (IQR 10) mm HG. Both groups had similar values except for the diastolic pressure in hypertensive emergencies, which was significantly higher with a median value of 110 mmHG (IQR 20) ($p<0.05$).

Analysis of risk factors showed non-significant difference according to sex (49.4% of men vs 50.6% of women) in the overall sample, but there was a statistically significant predominance of men (68.2%) in hypertensive emergencies and women (57.6%) in hypertensive urgencies ($p<0.05$). The median age of the overall sample was 66 (IQR 15) years, and there was no statistically significant difference in age between patients with hypertensive urgencies and emergencies ($p>0.05$). In whole sample there were 29.6% were smokers, 18.5% had diabetes mellitus, and 81.1% had a history of previous chronic hypertension. There was no statistically significant difference between patients with hypertensive urgencies and emergencies regarding the frequency of each of these three risk factors ($p>0.05$). The median blood pressure levels of the overall sample were 190 (IQR 30) / 100 (IQR 10) mmHG. Patients with hypertensive urgencies and emergencies did not statistically differ according to systolic blood pressure levels, but those with hypertensive emergencies had significantly higher diastolic blood pressure levels ($p<0.05$). Dyslipidemia was present in 39.5% of all patients without significant differences between the groups ($p>0.05$). The results are summarized in Table 1.

Table 1 **Presentation of risk factors in hypertensive crisis patients.**

	Total (N=243)	Hypertensive Emergencies (N=66)	Hypertensive Urgencies (N=177)	p-value
Male sex [N (%)]	120 (49.4)	45 (68.2)	75 (42.4)	0.000*
Female sex [N (%)]	123 (50.6)	21 (31.8)	102 (57.6)	
Age [Median (IQR)]	66 (15)	65 (12)	66 (15)	0.577**
Chronic hypertension (N)	197 (81.1)	46 (69.7)	151 (85.3)	0.006*
Systolic blood pressure [Median (IQR)]	190 (30)	190 (43)	190 (30)	0.083**
Diastolic blood pressure [Median (IQR)]	100 (10)	110 (20)	100 (10)	0.002**
Dyslipidemia [N (%)]	96 (39.5)	22 (33.3)	74 (41.8)	0.229*
History of smoking [N (%)]	72 (29.6)	15 (22.7)	57 (32.2)	0.150*
History of diabetes [N (%)]	45 (18.5)	13 (19.7)	32 (18.1)	0.773*

*Chi square test
**Mann-Whitney test

The vast majority of HU patients (98.3%) were discharged after ambulance treatment, with only 1.7% requiring hospitalization due to resistant elevated blood pressure levels without HMOD. In contrast, and understandably, the majority of HE patients (92.4%) were hospitalized and discharged after successful treatment, while 3% died during hospitalization. Although HMOD was significant for these patients, there were still 4.5% of discharged patients due to a milder form of the disease or patient refusal for hospitalization (Figure 1).

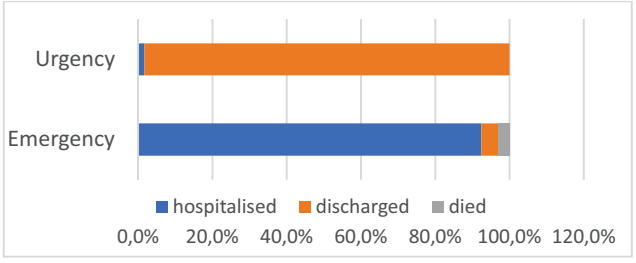

Figure 1 **Outcome of the initial admission.**

After a six-month follow-up, we discovered that 65% of patients experienced no complications. Both HU and HE patients had a similar percentage of individuals without readmission to medical services (63.3% and 69.7% respectively). In total, there were 93 recorded readmissions, with 9 patients experiencing two readmissions and 3 patients having three readmissions. Among these readmissions 30 were hypertensive crises with or without organ damage, accounting for 32.3% of all readmissions. The clinical presentation of readmissions is detailed in Table 2.

Table 2 **Clinical presentation of readmissions.**

Readmission Diagnosis	Number (N)	Percentage (%)
Hypertensive crisis with or without organ damage	30	32.3
Transitory cerebrovascular ischaemia	25	26.9
Cerebrovascular stroke	10	10.8
Myocardial infarction	4	4.3
Angina pectoris	21	22.6
Heart failure/pulmonary edema	5	5.4
Other	6	6.5

** The number of diagnoses does not match the number of patients or readmissions because some patients had two or more diagnoses at readmission. Percentages are related to the total number of readmissions (N=93).*

The HU group exhibited a 30.51% rate of non-fatal complications and a 6.21% rate of fatal complications, while the HE group had identical percentages of 15.15% each (p=0.011). These results are depicted in Figure 2, which illustrates the outcomes of patients from the initial admission to the six-month follow-up period.

The mortality rate of HE patients was 15.15%, with 3% of patients who died during the initial admission, resulting in a 12.15% mortality rate for subsequent readmissions. Conversely, all HU patients survived after the initial admission, yielding a mortality rate of 6.21% for readmissions. Figure 2. displays the outcomes of patients from the initial admission to the six-month follow-up period.

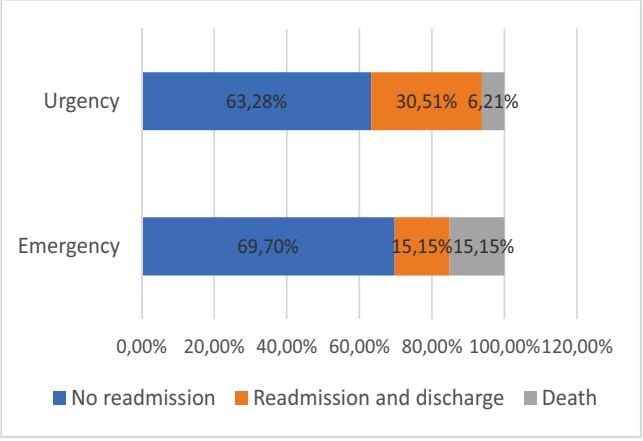

Figure 2 **Six months outcome.**

An analysis of the impact of risk factors on the six-month outcome revealed no statistically significant difference in the number of male/female patients, those with a history of chronic hypertension, smokers, and patients with diabetes mellitus between the groups of hypertensive crisis patients without complications, with non-fatal complications, and with fatal complications (p>0.05). However, age was significantly higher in patients with complications during the six-month period (p<0.05). The results are presented in Table 3.

Table 3 . **Presentation of risk factors and 6 months outcome.**

	No Readmission (N=158)	Readmission and Discharge (N=64)	Death (N=21) *	P Value
Emergency [N (%)]	46 (29.1)	10 (15.6)	10 (47.6)	0.011**
Urgency [N (%)]	112 (70.9)	54 (84.4)	11 (52.4)	
Male Sex [N (%)]	75 (47.5)	34 (53.1)	11 (52.4)	0.717**
Female Sex [N (%)]	83 (52.5)	30 (46.9)	10 (47.6)	
Age [Median (IQR)]	64 (18)	73 (13)	73 (12)	0.000***
Chronic Hypertension [N (%)]	125 (79.1)	53 (82.8)	19 (90.5)	0.421**
Dyslipidemia [N (%)]	63 (39.9)	24 (37.5)	9 (42.9)	0.898**
Smoker [N (%)]	49 (31.0)	19 (29.7)	4 (19.0)	0.529**
Diabetes [N (%)]	26 (16.5)	13 (20.3)	6 (28.6)	0.370**

**Number of deaths includes those who died at the initial admission as well as at the readmission*
**Chi square test
***Mann-Whitney test

DISCUSSION

The observed sample of patients showed a predominance of HU over HE cases (72.8% vs. 27.2%) consistent with clinical experience and other findings (4). The most common presentations of HMOD in HE patients were stroke (hemorrhagic or ischemic), followed by acute coronary syndrome and heart failure/pulmonary edema, while other presentations were rare. Discrepancies in findings across studies may be attributed to differences in lifestyle, health habits, and ethnicity in the studied populations (4,5).

The frequency of observed risk factors was compared with results from other studies. The percentage of patients with existing hypertension in our research was relatively high (81%), similar to samples from other studies. There was also a predominance of patients older than 65 years in our study and others (6,7). While we found a slight predominance of women (50.6%), some studies reported significantly higher percentages of men (7). Additionally, the number of patients with a history of diabetes varied across different studies (6,7,8), possibly due to differences in therapy, lifestyle habits, ethnicity, and sample selection. The prevalence of smokers in our sample (29.6%) fell between the percentages reported in other studies, which could reflect differences in anti-smoking campaigns and patient reporting accuracy. Our sample also had a significant proportion of patients with dyslipidemia (39.5%), which aligns with expectations given local dietary habits though it contrasts with findings from other studies conducted in Italy (5). Blood pressure values at admission were similar in our study compared to other reports (5,8).

Patients with HU and HE did not statistically differ in terms of smoking status, diabetes mellitus, or median age. However, there was a significant predominance of men and patients with previously verified hypertension in the HE group. This group also had significantly higher diastolic blood pressure levels. These results suggest that male sex, a history of hypertension, and higher diastolic blood pressure could be factors increasing the likelihood of hypertensive crisis leading to organ damage. However, Vallelonga et al. did not find any significant differences in risk factors between HU and HE groups, including those significant in our results (5).

The outcomes after admission were as expected. Most HU patients were discharged after ambulance treatment, although a small percentage (1.7%) required hospitalization due to difficulties in lowering blood pressure levels. The majority of HE patients with organ damage were hospitalized, with only a small number (4.5%) discharged. These discharged patients either refused hospitalization or had mild cerebrovascular incidents that did not require hospital treatment. Three percent of HE patients died either in the ambulance or during hospitalization. A recent meta-analysis by Shiddiqi TJ, et al. reported a higher in-hospital mortality rate for HE of 9% (9). Guiga H, et al. also found a similar mortality rate (10). A study investigating the outcome of hypertensive crisis patients admitted to the coronary care unit also found a higher hospital mortality rate in HE patients (11).

Our mortality rate would likely have been higher if we had not excluded patients who died before completing data collection or diagnostic procedures. Additionally, the number of patients who died during transport to the ambulance was unknown.

The association between risk factors and outcomes after admission was not observed because most discharged patients were HU and hospitalized patients were HE, and all deceased patients had HE. This suggests that all risk factors significantly higher in the HE group (male sex, history of hypertension, higher diastolic blood pressure) could be considered enhancers of the risk for hospitalization and mortality at admission. Furthermore, patients without previously verified chronic hypertension were more likely to have their first hypertensive crisis resolve as HU without organ damage or hospital treatment.

Although the majority of patients had no complications during the six-month period after their hypertensive crisis, the results were still concerning. More than a third of patients (35%) had readmissions to medical services due to new episodes of elevated blood pressure or other cardiovascular events, ending either in discharge or death. The main cause of readmissions was new hypertensive crises, accounting for 32.3% of all readmissions. This rate is concerning compared to the 15.3% reported in a study with a much longer follow-up period (7). Additionally, a mortality rate of 8.64% cannot be overlooked. We attempted to investigate the reasons for these results and identify possible influencing factors. Although HU and HE patients had a similar proportion of patients without readmissions to medical services, the severity of new episodes differed, as evidenced by the significantly higher mortality rate in HE compared to HU patients (12.15% vs. 6.21%, respectively). Considering that the overall mortality rate of HE patients, including those who died during the first admission, was 15.15%, we conclude that patients with HE were almost twice as likely to experience a lethal outcome. The fact that there were a similar number of HU and HE patients among the deceased, despite the HE group being much larger, further confirms this. Other studies also found higher mortality rates in HE patients (10,12,13).

Exploring the impact of risk factors on the six-month outcome, we found that only age was significantly higher in patients who had readmissions. The median age of patients without readmissions was

64, while in the other groups, it was 73 years. A trial conducted in HU patients found that age above 63 years was a risk factor for cardiovascular events (14). In another trial, age over 65 years was a risk factor for 30-day readmission in HE patients (15). Both groups of patients, those who died and those who survived after readmission, had a similar age profile. None of the other investigated factors (sex, dyslipidemia, history of diabetes, and chronic hypertension) could be considered risk factors for readmission. This also applied to the severity and outcome of events. Studies focused on sex-related outcomes of hypertensive crisis had contradictory results. Conclusions varied, with some studies suggesting that men (16) or women (14,15) had more cardiovascular events. However, these trials focused on only one type of hypertensive crisis (HE or HU, respectively) and had different follow-up periods.

CONCLUSION

Male gender and higher diastolic blood pressure have been identified as risk factors for the development of HE, the need for hospital treatment, and increased in-hospital and six-month mortality. Older age represents a risk for readmissions and mortality.

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Reprint requests and correspondence:
Amela Ahmić, MD, MSc
Clinic of Emergency Medicine
Clinical Center University of Sarajevo
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina
Email: amelatuco@gmail.com
ORCID ID: 0000-0002-7777-1204

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Significant differences in the management of the ticks bites during 2007 and 2017 - problematic use of serological tests and antibiotic therapy

Značajne razlike u menadžmentu uboda krpelja 2007. i 2017. godine - problematična upotreba seroloških testova i antibiotske terapije

Alma Sejtarija-Memišević* Rusmir Baljić

Clinic of Infectious Diseases, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: Bosnia and Herzegovina is a country with extremely rich vegetation and therefore represents a perfect place for life and development of various tick species, so the most of the human population at least once in their lifetime has experienced a tick bite. Aim: to identify differences in tick bite management in the period of 10 years, from 2007 to 2017, and to point to possible irregularities, in accordance with applicable protocols, during 2017. Materials and methods: the study included patients admitted to the Infirmary of the Clinic of Infectious Diseases of the Clinical Center University of Sarajevo due to tick bite during 2007 and 2017, respectivelly. Results: the number of patients in 2017 was higher by 58% compared to 2007. In 2007, antitetanic prophylaxis was recommended in 100% of cases, while in 2017 this practice was completely abandoned. In 2007, the notion of prophylactic dose of antibiotics was not known, so the antibiotic dosage was administered in 94.56%, and serology was recommended in 88.04% of cases, with only 11% of patients receiving adequate recommendations. In 2017, in 68.04% of cases, an antibiotic was administered, in 31.54% prophylaxis, and in 68.46% of the cases therapeutic dose. Serology was recommended in 17.81%, and 65.29% of patients were given adequate recommendations during 2017. Conclusion: during the ten-year period, there were significant differences in the management of tick bite, but a significant percentage of doctors still prescribes therapeutic doses of antibiotics and recommends serology. This practice should be abandoned as soon as possible and doctors and patients should be educated about risks of this practice and introduce good medical practice based on the protocols accepted all over the world.

Keywords: tick bite, prophylaxis of Lyme disease, Lyme disease, serology, *Ixodes ricinus*, tick bite treatment

SAŽETAK

Uvod: Bosna i Hercegovina je zemlja sa izuzetno bogatom vegetacijom i samim tim predstavlja pogodno mjesto za život i razvoj krpeljskih vrsta, tako da većina stanovništva barem jednom u životu zadobije ubod krpelja. Cilj: ustanoviti razlike u menadžmentu uboda krpelja u razmaku od deset godina, od 2007. do 2017. godine, i ukazati na eventualne nepravilnosti, shodno važećim protokolima, tokom 2017. godine. Materijali i metode: istraživanjem su obuhvaćeni pacijenti primljeni u ambulantu Klinike za infektivne bolesti Kliničkog centra Univerziteta u Sarajevu zbog uboda krpelja tijekom 2007. odnosno 2017. godine. Rezultati: broj pacijenata je za 58% bio veći u 2017. godini u odnosu na 2007. godinu. U 2007. godini antitetanična profilaksa preporučena je u 100% slučajeva, dok je u 2017. godini ovakva praksa u potpunosti napuštena. U 2007. godini nije bio poznat pojam profilaktične doze antibiotika, tako da je terapijska doza antibiotika ordinirana u 94,56 % , a serologija je preporučena u 88,04 % slučajeva, a kod svega 11 % je data adekvatna preporuka. U 2017. godini u 68,04 % slučajeva je ordiniran antibiotik i to u 31,54 % profilaksa, a u 68,46 % terapijska doza. Serologija je preporučena u 17,81 %, a 65,29 % pacijenata je data adekvatna preporuka tokom 2017. godine. Zaključak: tokom desetogodišnjeg perioda, desile su se značajne razlike u menadžmentu uboda krpelja, ali se i dalje u značajnom postotku propisuju terapijske doze antibiotika i preporučuje serologija. Ovakvu praksu treba što prije napustiti, educirati ljekare i pacijente da se ovakvim načinom nanosi šteta zdravlju, te čim prije uvesti dobru medicinsku praksu prema protokolima koji su diljem svijeta prihvaćeni.

Ključne riječi: ubod krpelja, profilaksa lajmske bolesti, lajmska bolest, serologija, *Ixodes ricinus*, tretman uboda krpelja

INTRODUCTION

Ticks are very resistant individuals surviving in the most extreme weather conditions by their ability to enter diapauses. Heat, light, humidity are activating factors that trigger the development and reproduction of ticks. In areas with four seasons, during the winter, the ticks are quiet, and at the very beginning of the spring they are activated. The basic activity of the tick is search

for the host, another animal species or the human from whom they will take their blood meal. In the selection of hosts, they are extremely uncritical, resulting in the fact of being vectors of various pathogens for humans and for other animals. In human medicine, the most important disease that can infect humans is Lyme disease. Over 30 types of ticks are choosing humans to attach on, according to their uncritical selecton of hosts, and only one species is infected with spirohetes *Borrelia burgdorferi*, causative agent of Lyme disease (1).

In Europe, *Ixodes ricinus* is the only type of tick that can carry a *Borrelia burgdorferi* species in itself (2). In the BiH region, a large number of people had tick on their skin at least once in their lives. In the Internet era and accessibility of information, most people are informed about the potential danger that ticks represent for human health, and as soon as they notice tick, seek medical help. As ticks cause fear in patients, they still present a certain challenge in the practice of medicine in terms of administering therapy and recommendations for diagnostic procedures.

The research of the tick-borne diseases in Bosnia and Herzegovina is only sporadic and mainly of a health significance (as a transmission of a large number of animal and human disease patogens). At the same time, it is important to note that there are no studies about coevolution of the ticks and the pathogens they are infested with (3).

The first written data about ticks date back to the time of ancient Egypt (4). Descriptions of ticks as parasites of dogs are found in the writings of Homer and Aristotle (5). Interest in biosystematic tick formation increased at the end of the XIX century when Smith and Kilbourne (1893) found that the species *Rhipicephalus (Boophilus) annulatus* Say, a 1822 transporter of *Babesia bigemina* Smith, the 1893 causative agent of Texas cow fever, has been proven that ticks can be tr ansponders infectious diseases (6). At the beginning of the twentieth century it was found that ticks could be vectors of the cause of bacterial diseases of humans (7). The discovery of Lyme disease, which today is considered to be the most significant vector-borne disease in Europe and North America, as well as the identification of its cause (spirohete *Borrelia burgdorferi* Swellengreber, 1907), 80s of the last century (8), research on tick-borne diseases has been intensified since a significant number of tick-borne pathogens were then registered (9). Jongejan and Uilenberg (2004) indicate that about 10% of the ticks are reservoirs and vectors of pathogens of infectious diseases of humans and animals (10). More than 30 types of ticks parasitize on humans have been described (1).

Since the discovery of Lyme disease, to this day, the cause of the disease and ticks that have transmitted it has become a very important focus of various researches. A total of 19 species of *Borrelia burgdorferi sensu lato* complex have been discovered, five of which are related to human pathology. It has been proven that certain species cause specific clinical entity of the disease. The unbroken topic of the research is the geographical distribution and degree of tick infestation, and by what type of borrelia, which greatly contributes to understanding, diagnosis and treatment of the Lyme disease itself.

Despite the diversity of *Borrelia burgdorferi sensu lato* complex species, only four types of ticks are designated as significant vectors of these pathogens: *I. ricinus* Linnaeus, 1758, *I. persulcatus* Schulze, 1930, *I. scapularis* Say, 1821 and *I. pacificus* Cooley, 1943, that suggests the evolution of a highly specific relationship between the vector and the Lyme disease pathogen (2). Despite of the great importance of Lyme disease in human and veterinary medicine, a small number of studies have contributed to understanding the mutual relationship between the pathogen and the vector of this disease. Mechanisms of trasmission, the survival of the borrelia in the tick have not been fully clarified.

Identification of the reservoir and knowledge of the complete enzootic cycle *Borrelia burgdorferi sensu lato* in nature are of exceptional importance for the understanding of the ecology of Lyme disease (11).

It is considered necessary that the tick has to be fixed to the host for at least 24 hours prior to the start of transmission of the pathogen. According to the results of the study *Borrelia burgdorferi sensu strico* Baranton, 1992 in North America, the most effective pathogen transmission is after 48 hours of tick fixation (12).

Although ticks and *Borrelia burgdorferi sensu lato* complex are an inexhaustible topic for research around the world, but no research has been carried out in the territory of Bosnia and Herzegovina to include the biological relations of the mentioned taxonomic categories. There is a great need for this "area" to be explored by the data on annually verifying an average of about 300 tick bites in the Clinic of Infectious Diseases of the Clinical Center University of Sarajevo (13).

Significant changes in the treatment of patients who received tick bite during the ten-year period, from 2007 to 2017

During the ten-year period, from 2007 to 2017, at the Clinic of Infectious Disease of the Clinical Center University of Sarajevo, three events significantly influenced the changes in the treatment of patients who received a tick bite.

For a long period of time, a protocol implying that each patient receiving tick bite was vaccinated with antitetanic prophylaxis, adult patients with Doxycyclin 2x100 mg per os for 21 days, pregnant women with Amoxicillin 4x1g per os 6 weeks and children with Amoxicillin 50mg/kg per os divided into three doses for 21 days, was applied.

The first significant changes occurred following the International Congress of Infection in 2010, in Moscow. There guidelines stated that it was unjustifiable to administer antitetanic prophylaxis for tick bite, and that antibiotics should not be administered if the tick was expertly removed within 24 hours. These guidelines largely altered the previous protocol, but it was not specified which antibiotic should be administered and for how long in the prophylaxis of Lyme disease.

Treatment of a patient who received a tick bite was re-updated at the International Congress of Infection, in 2012, in Konjic. At that time, the guidelines which the infectologists accepted in Moscow in 2010 were practically made public, but still without clear recommendations for the prophylaxis of Lyme disease.

Finally, in April 2014, at the "First School of Infection - ANTIBIOTICS IN PRACTICE" held in Sarajevo, the presentation entitled "What and how after tick bite" was prepared by doctors of the Clinic of Infectious Disease of the Clinical Center University of Sarajevo. The presentation reflected the previous practice of doctors in the period from 2006 to 2013, and for the first time, guidelines of CDC protocols were clearly outlined regarding the treatment of patients receiving tick bite. That included a 200 mg single dose of Doxycylin. These guidelines have been valid so far (according to the CDC and UPTODATE database).

Treatment for a tick bite

The most important step in treating a patient with a tick bite is timely and proper tick removal. The tick should be removed with a special shape tweezer that will not squeeze the tick body, which would be counterproductive and would expel the eventual pathogen from the gut of the tick to the host's blood. It is necessary to catch the ticks nearest to the skin of the patient, for the hard part of the individual. The tick must not be overwhelmed before, as this increases the risk of transmission of the disease. There are special twisters, cards, specialized tools for the successful removal of ticks from the skin.

After tick bite, prophylactic antibiotic therapy should be administered only to those patients who meet all the criteria listed in Table 1.

Table 1 **Criteria for antibiotic prophylaxis of Lyme disease after tick bite (16).**

Prophylactic antibiotic therapy should be prescribed only to patients who meet ALL of the stated criteria:
The tick was identified as an adult or nymph of the *Ixodes ricinus* species
The tick was attached to the skin for > = 36 hours
Prophylaxis can be started within 72 hours of tick removal
Tick infestation with the pathogen *Borrelia burgdorferi* in that region was >20%
Doxycycline was not contraindicated

If all of the criteria are fulfilled, one dose of 200 mg Doxycycline per os should be administered (single dose). If Doxycylin is contraindicated, other antibiotics (Ampicillin, Amoxicillin, etc.) have not shown efficacy and therefore prophylaxis with them is not performed.

It is important to educate patients to monitor the tick bite site for the next month and report if they notice redness.

Infestation percentage of I. ricinus with Borrelia burgdorferi sensu lato

The high prevalence of *Borrelia burgdorferi sensu lato* in *I. ricinus* ticks has been proven in countries located in the near and surrounding BiH:

- Croatia in 45% of analyzed ticks (15),
- Serbia 42.5% (18,19),
- Bulgaria in 32.7% (20),
- Germany 36.2% (21),
- and Switzerland 49% (22),

Similar studies have not been done in BiH; therefore, there are no data on the percentage of tick infestation.

According to the Rauter and Hartung classification (2005) in Europe, there are regions with:

- low,
- high, and
- extremely high (> 30%) tick infection rates (21).

Croatia and Serbia are included in the last category - extremely high infestation rates. Accordingly, there is a serious posibility of a high percentage of tick infestation on the territory of BiH with *Borrelia burgdorferi sensu lato* complex and therefore a high risk of Lyme disease.

AIM

The aim of the paper was to determine, by a retrospective analysis, whether there were significant differences in the treatment of patients admitted to the Clinic of Infectious Diseases of the Clinical Center University of Sarajevo due to tick bite in 2017 compared to 2007. Also, the aim was to determine if there were any irregularities in the management of the tick bite in 2017 based on the applicable protocols.

MATERIALS AND METHODS

The respondents of the study were patients admitted to the Infirmary of the Clinic of Infectious Diseases of the Clinical Center University of Sarajevo due to tick bite during 2007 and 2017, respectivelly. The data were obtained from the Hospital Information System, and were processed with a retrospective analysis.

The strict inclusive criteria of this work implied that only patients who did not have any redness at the site of ticks or any syptoms of a general infectious syndrome, were included.

Retrospective analysis included data on:

- whether the tick was removed from the skin within 36 hours,
- whether it was professionally removed,
- whether the patient was admited to the Clinic within 72 hours from the moment of the tick removal,
- whether the adequate recommendation for monitoring the local status at the site of the tick bite was provided,
- whether antitetanic prophylaxis was administered,
- whether antibiotic therapy was administered,
- whether a prophylactic or therapeutic dose of antibiotics was administered,
- which antibiotic was administered and for how long,
- Was serology recommended?

The data were entered and processed in Excel, and statistically processed.

RESULTS

The total number of patients admitted to the Clinic of Infectious Diseases due to tick bite, and who fulfilled the inclusive criteria of the work, was 92 in 2007 and 219 patients in 2017. The most significant difference between 2007 and 2017 was recorded in the practice of administering antitetanic prophylaxis. In 2007,

antitetanic prophylaxis was administered in 100% of cases, while this practice was completely abandoned until 2017. In 2007, the mere fact that the patient received a tick bite was sufficient to administer the therapeutic dose of antibiotic therapy. Antibiotic was not administered in only 5.44% of cases, which is statistically insignificant compared to 94.56% when it was administered. The notion of prophylaxis, single doses of Doxycycline 200 mg, was not recorded in 2007. During 2017, there was a significant increase, compared to 2007, of patients who were not treated by antibiotic, 31.96%. A novelty in 2017 was a prophylactic dose of antibiotics, a single dose of Doxycycline 200 mg per os, administered in 31.54% of cases (the percentage refers to the total number of those administered by the antibiotic), and the therapeutic dose antibiotics was administered in the remaining 68.46%. During 2007, the practice of giving adequate recommendations to the patient, monitoring the site of the tick bite for the next month and reporting a check-up in case of redness at the site of the bite, was almost nonexistent. Only 11% of doctors provided adequate or similar recommendations. In 2017, the situation on this issue was different. More than half of doctors were aware of the importance of this recommendation, specifically 65.29% of them gave adequate recommendations to the patient. During 2007, as a rule, to almost every patient, 88.04%, serology was recommended. A significant difference was recorded in 2017. Serology was recommended in 17.81% of patients (Table 2).

Table 2 **Basic parameters included in the retrospective analysis for 2007 and 2017.**

PARAMETERS			2007		2017	
Total number of patients			92		219	
Ana-Te was ordinated			92/92 100 %		0/219 0 %	
Antibiotic prescribed	YES	prophylaxis	87/92 94.56 %	0/87 0 %	149/219 68.04%	47/149 31.54 %
		therapy		87/87 100%		102/149 68.46 %
	NE		5/92 5,44 %		70/219 31.96 %	
Adequate recommendation given			10/92 11%		143/219 65.29 %	
Recommended serology			81/92 88.04 %		39/219 17.81 %	

Cases in 2017, in which the tick was timely registered and expertly removed, i.e. patients who did not have any criteria for administering prophylaxis, were particularly isolated (Table 3). A total of 40 patients who met this condition were registered. The antibiotic was administered in 37.50% of cases, at 20.00% prophylaxis, and in the 80.00% therapeutic dose of antibiotics. The most commonly administered antibiotic was Doxycyclin in adults and Amoxicillin in children.

Table 3 **Presentation of the antibiotics prescribing practice in the course of 2017, to patients who did not meet any of the criteria for prescribing a prophylactic dose of antibiotics (those patients in whom the tick definitelly stayed on the skin <36 hours and which was then professionally removed).**

PARAMETERS		2017										
Total number of patients		**40**/219 18.26 %										
Antibiotic prescribed	YES	15/40 37.50 %	Prophylaxis	3/15 20.00 %	AGE	Type of AB	Duration of therapy (days)					
							1	2	5	10	14	x*
					Adults 3/3 100 %	Doxycyclin 3/ 3 100 %	3/3 100 %					
					Children 0/3 0 %	0/3 0 %						
			Therapy	12/15 80.00 %	Adults 5/12 41.67 %	Doxycyclin 5/5 100 %			1/5 20.00 %	1/5 20.00 %	3/5 60.00 %	
					Children 7/12 58.33 %	Amoxicillin 4/7 57.14 %		1/4 25.00 %		2/4 50.00 %	1/4 25.00 %	
						Azytromicin 3/7 42.86 %			2/3 66.66 %			1/3 33.33 %
	NO	25/40 62.50 %										

* The length of therapy is not specified

Table 4 shows patients who fulfill at least one criterion for the antibiotic prophylaxis. The antibiotic was not administered in 25.14% of the case. Additionally, those 45 patients were analyzed and it was determined that 37 (82.22%) did not indicate how long the tick was on their skin, assumingly not longer than 36 hours, and 26 (57.77%) was surely expertly removed. Such an assumption would explain why the antibiotic was not administered, but we could not know for sure.

The prophylactic dose of antibiotics, Doxycyclin 200 mg per os, was administered exclusively in 32.84% of adults. The therapeutic dose was administered in 67.16% of the cases, 71.12% of which were adults, and 28.88% were children. In the case of adults, Doxycylin was dominantly administered, at 76.56%, although the proportion of Azytromzcin was significant, 12.50% compared to other antibiotics. Children were generally treated with Amoxicillin, 76.26%, while Azytromycin was twice as prescribed in relation to Ampicillin (4/2).

Table 4 **Presentation of the antibiotics prescribing practice in the course of 2017, in patients in whom the tick remained on the skin for >36 hours and/or was unprofessionally removed (all patients not included in Table 3), with a note that this Table also includes patients in whom neither was specified.**

PARAMETERS		2017						
Total number of patients		179/219 81.74 %						
Antibiotic prescribed	YES	134/179 74.86 %	Prophylaxis	44/134 32.84 %	Age	Proportion	Type of antibiotics	Proportion
					Adults	44/134 32.84 %	Doxycyclin	44/44 (100 %)
			Therapy	90/134 67.16 %	Adults	64/90 71.12%	Doxycyclin	49/64 (76.56 %)
							Amoxicillin	1/64 (1.6 %)
							Ampicillin	1/64 (1.6 %)
							Azytromicin	8/64 (12.50 %)
							Cefuroxim	3/64 (4.7 %)
							Not specified*	2/64 (3.12 %)
					Children	26/90 28.88%	Amoxicillin	20/26 (76.93 %)
							Azytromicin	4/26 (15.38 %)
							Ampicillin	2/26 (7.69 %)
	NO	45/179 25.14 %						

- The physician declared that the already prescribed therapy should continue, without specifying the therapy

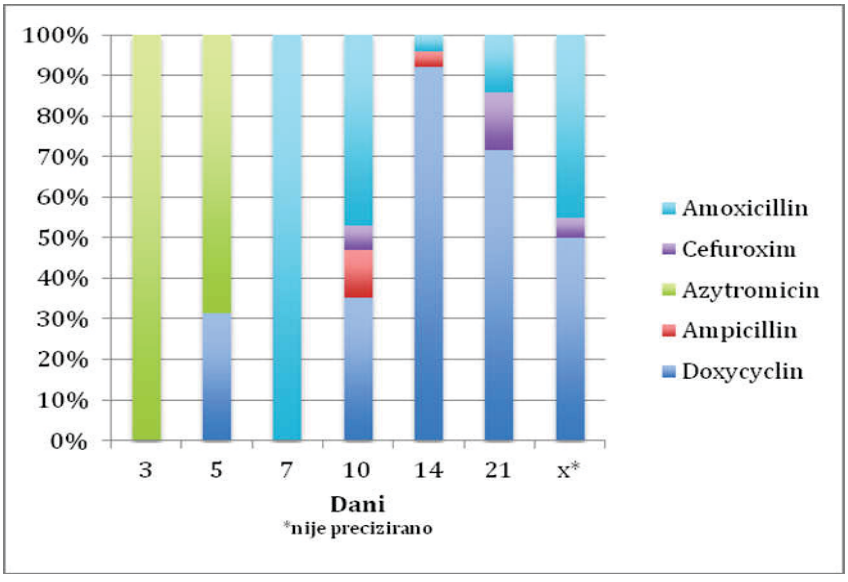

Figure 1 **Length of antibiotic therapy prescribed to patients from Table 4.**

The data in Table 5 indicate that in practically 50% of cases, even in both years, doctors did not ask and/or did not record the data on how long tick was attached on the skin.

Table 5 **Data on whether the tick was removed from the skin within 36 hours in 2007 and 2017, respectively.**

DATA	2007	2017
Total number of patients	92	219
The tick stayed on the skin <36 hours	32/92 34.78 %	64/219 29.23 %
The tick stayed on the skin >36 hours	12/92 13.04 %	22/219 10.05 %
The patient does not know when the tick got attached	4/92 4.35 %	22/219 10.05 %
Not stated in the finding, not requested	44/92 47.83 %	111/219 50.68 %

The data on whether the tick was expertly removed was mainly reported in both years, in just about 5% of patients this information was not required, i.e. not listed (Table 6).

Table 6 **Data on whether the tick was professionally removed from the skin in 2007 and 2017, respectively.**

DATA	2007	2017
Total number of patients	92	219
The tick was professionally removed	66/92 71.74 %	130/219 59.36 %
The tick was not professionally removed	22/92 23.92 %	78/219 35.62 %
Not stated in the finding, not requested	4/92 4.34 %	11/219 5.02 %

Considering the fact that most of the patients were admitted to the clinic shortly after extirpation of the tick, most patients fulfilled the requirement to prophylaxis within 72 hours, as indicated in Table 7.

Table 7 **Data on whether the patient reported within 72 hours from tick removal.**

DATA	2007	2017
Total number of patients	92	219
<= 72 hours	82 89.14 %	184 84.01 %
> 72 hours	8 8.69 %	20 9.13 %
Not stated in the finding, not requested	2 2.17 %	15 6.84 %

The administration of the antibiotics in the group of children was particularly analyzed (Table 8).

Table 8 **Presentation of the antibiotics prescribing practice in a group of children for 2017.**

PARAMETER	2017
Total number of children included in the analysis	65/219 29.68 %
Antibiotic was not prescribed	33/65 50.76 %
Antibiotic was prescribed (therapeutic dose)	32/65 49.23%

DISCUSSION

During 2017, a significantly larger number of patients was recorded, 58% more than in 2007 (Table 2). We can not for sure tell the exact reason for this difference. We assume that two key reasons are possible. The first is that in recent years a lot more media have promoted the importance of ticks in the transmission of the disease, and therefore patients are more likely to visit the doctor because of tick bites, which was not the case before when the patients themselves removed ticks and did not seek medical assistance. Other reason relates to climat conditions. During 2007, the season was quite dry and hot, resulting in reduced tick activity, while it was significantly moist in 2017, which ultimately contributed to increase in the tick activity (22). It is noted that the term season relats to periods when the ticks are active (spring peak, summer and beginning of autumn). On the other hand, the number of bites registered in 2017 corresponded to the average number of bites registered at the Clinic of Infectious Diseases of the CCUS and other infectious clinics in the region, although it was reported on numerous occasions that this number could vary significantly year after year all depending on climate conditions as previously stated (13,23,24).

The most significant difference between 2007 and 2017 was recorded in the practice of administering antitetanic prophylaxis. In 2007, antitetanic protection was administered in 100% of cases, while this practice was completely abandoned until 2017.

A large percentage of patients treated with a therapeutic dose of antibiotics during 2017 was the main issue of this paper (Table 2). Despite the fact that they were patients who did not have any signs of Lyme disease or any other sign of the general infectious syndrome, doctors administered an antibiotic in 68.04% of cases. The therapeutic dose of antibiotics was administered in 68.46% of patients, and prophylactic in the remaining 31.54%. It could be concluded with certainty that doctors have not abandoned the practice of administering antibiotics as fast as antitetanic prophylaxis. In the introduction to this paper, it was clearly specified what criteria needed to be met in order to administer the prophylactic dose of antibiotics (14). Also, these criteria were modified for our possibilities, which ultimately meant that we needed to monitor three parameters: whether the tick was removed from the skin within 36 hours, whether it was professionally removed and whether it was possible to administer prophylaxis within 72 hours of the moment of the tick removal. The therapeutic dose of the antibiotic is justified only in the case of a manifest Lyme disease, which in the narrower sense of the word implies the occurrence of Erythema migrans (25).

The question arises as to why the practice of administering the therapeutic dose of antibiotics is retained in this percentage? The analysis of the available literature showed that this practice did not exist only in Bosnia and Herzegovina, but practically all over the world. Despite the fact that there are clear guidelines for the management of tick bites, which have been practically valid for two decades and have not undergone significant changes, the treatment of a patient with a tick bite and prophylaxis of Lyme disease are often subject to various analyzes and research. One such study, in the form of a doctoral dissertation, was made in Kragujevac, Republic of Serbia, was consistant in taking a clear stand on the justification of early application of antibiotic therapy after a tick bite. The study itself states that there are contradictory views in the world.

The proposed antibiotics, doxycycline and ampicillin for seven days, as the single dose of doxycycline 200 mg, are considered insufficient in prophylaxis (26). There is an opinion, in the region and beyond, that if it is suspected that there may have been a transfer of a borrelia after a tick bite, it is justified to administer an antibiotic for up to two weeks (27,28). On the other hand, there is a much lager number of those studies whish aim was to analyze and point to the unnecessary administration of antibiotic prophylaxis for tick bite (29,30,31).

Already 20 years ago in North America, Eastern Shore of Meryland, a study was published that pointed to the problematic use of serological tests and antibiotic therapy for tick bite in endemic areas (29). Some of the conclusions of this study were that most patients underwent costly serological testing with no use, and most received an antibiotic treatment with no clear benefit, and that ultimately, it was necessary to work on the education of doctors in order to properly manage the tick bite, but also on the education of the citizens of endemic areas.

The duration of antibiotic therapy (Figure 1) varies from 3 to 21 days, which again indicates nonuniformity when prescribing a therapeutic dose of antibiotics, regarding the need to leave this practice as soon as possible.

The results shown in Table 3 show us more closely the physician's uncritic atitude in administering the therapeutic dose of antibiotics. The patients in whom the tick did not stay on the skin for more than 36 hours and were expertly removed were observed. Despite the fact that in these 40 cases none of the criteria for the administration of the prophylactic dose of antibiotics were met, the antibiotic was administered in 37.50% of cases. The prophylactic dose was administered in 20% of cases, and it was further disappointing that the therapeutic dose of antibiotics was administered in 80% of cases. Prophylaxis was administered in Doxycyclin 200 mg once per os, and in the therapeutic dose also Doxycyclin, but in a different duration (5, 10 and 14 days).

During the analysis, the impression that doctors when the children were concerned, more often administered therapeutic doses of antibiotics, prompted us to investigate this issue in more detail, i.e. whether the children and the lack of adequate prophylactic doses were one of the reasons for prescribing the therapeutic dose of antibiotics. The total share of children in this paper was 29.68% (Table 8). In the group of children, the ratio was equal to patients in whom the antibiotic was administered and those who were not. On the other hand, children made 58.33% of the group of patients administered with an antibiotic, which compared to adults, 41.67%, did not make a significant difference. Children were administered Amoxicillin, for a different duration (2, 10 and 14 days), and Azytromycin for a duration of 5 days.

In general, 31.96% of patients who were not treated with antibiotic and 21.46% of those who recieved prophylaxis, gave us the hope that the practice of administering the therapeutic dose of antibiotics would be abandoned over the time.

In 2007, a small number of doctors were aware of the importance of giving adequate recommendations, and only 11% of patients were advised on this issue, as opposed to 2017, where 65.29% were given the recommendation to follow the tick bite site for the next month and to come for examination in the case of redness (32). In medical jargon, we can often hear that the patient should be "covered" with blanket, not an antibiotic. Regarding the problem of this paper, we could say that the patient should be given an adequate recommendation, and not an antibiotic.

The tick bite itself is not a criterion for the order for serology at the *Borreli burgdorferi*. This practice only unnecessarily increases the cost of the institution in which serology is done. More studies point to this problem and even to the fact that serological tests

have had no effect on the administration of antibiotic therapy (29,30,33). Recommended serology was obviously part of the practice in the management of patients who received a tick bite. Although this percentage in 2017 was significantly lower than in 2007, it was still unsatisfactory (Table 2). In particular, this percentage meant that 39 patients were recommended to implement serology even if there were no criteria for it.

During the analyzed years, practically 50% of doctors did not record whether the tick was attached on the skin for more than 36 hours (Table 5). More studies are available that prove the direct proportionality of the duration of tick attachment on the skin and the risk of borrelia transmission (34,35,36). One such study was carried out in Belgrade, Republic of Serbia, which showed that in all patients in whom a tick was professionally removed within 24 hours, no Lyme disease was reported, and in subjects in whom ticks stayed in the skin for more than 48 hours, the risk of illness was several times higher than in the group of subjects who had a tick in the skin less than 48 hours. The study concludes that there is no dilemma that professional removing in the first 48 hours after tick bite is a key factor in reducing the risk of aquiring *Borrelia burgdorferi* and the development of early stage of Lyme disease (24).

On the other hand, the same study states that the disease most commonly occurred in the group of subjects in which the tick was unskilfully and incompletely removed. In addition to the above, a large number of available studies talk of the importance and ways of proper ticks removing. The fact whether the tick is professionally removed or not is much better recorded in relation to the data on how long the tick was on the skin. And in this case the results do not differ significantly in both years. In only 5% of patients, it was not known whether the tick was professionally removed or not. This result was certainly contributed by the fact that most of the patients were transferred to the clinic just after extirpation of tick. Despite this fact, this information was clearly stated in the finding of an Infectologist who suggests that the status of whether the tick is professionally removed influences the decision on the treatment of the patient in relation to the length of the tick stay on the skin. Considering the fact that most of the patients were admitted shortly after tick was extirpated, most patients fulfilled the requirement to prophylaxis within 72 hours, as indicated in Table 7.

CONCLUSION

Ultimately, if we take into consideration that there were no studies in the territory of Bosnia and Herzegovina that would determine the persentage of tick infestation with *Borrelia burgdorferi* pathogens and that in the chain of health care there were no experts who could recognize that tick species was vector of borreliosis, we could conclude that if the tick was standing on the skin for more than 36 hours and/or was unprotectedly removed, and if possible, within 72 hours of tick removal, to administer prophylaxis, the indication is to adminiter two capsules of Doxycylin per os (200 mg as a single dose) as prophylaxis of Lyme disease. Due to all of the above, we can conclude that there is a great need for the establishment of the Lyme Advice Clinic, where we will study this disease from its very vectors to the most severe chronic forms.

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Reprint requests and correspondence:
Alma Sejtarija-Memišević, MD, MSc
Clinic of Infectious Diseases
Clinical Center University of Sarajevo
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina
Email: almasm8@gmail.com
ORCID ID: 0009-0001-8563-8446

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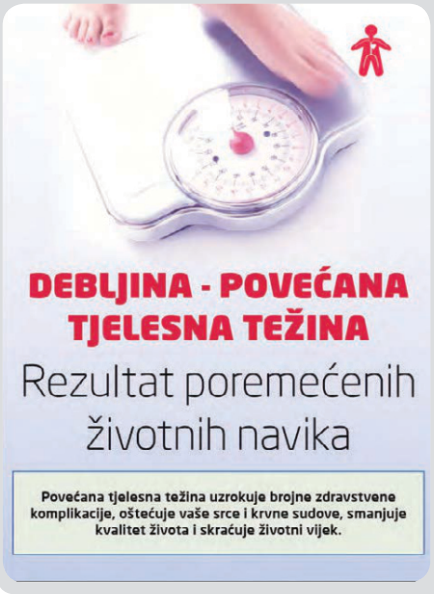

Assessment of the relationship between body mass index and detection of pulmonary embolism

Procjena odnosa indeksa tjelesne mase i detekcije plućne embolije

Spomenka Kristić[1], Amela Begić[2], Sandra Vegar-Zubović[1], Suada Hasanović[1], Belma Paralija[3]

[1]Clinic of Radiology, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
[2]Clinic of Nuclear Medicine and Endocrinology, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
[3]Clinic of Pulmonary Diseases and Tuberculosis ,,Podhrastovi, Clinical Center University of Sarajevo, Bardakčije 90, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: Pulmonary Embolism (PE) represents a life-threatening medical emergency that, given the serious complications, requires urgent application of anticoagulant therapy. In addition to various traditional factors for the development of PE, obesity has recently been considered as an independent risk factor for the development of PE. Aim: to determine whether there is a difference in body mass index (BMI) values in subjects with confirmed and excluded PE. Materials and methods: the study included 100 patients with suspected PE, which was confirmed or excluded by using MSCT and/or V/P SPECT and for all patients BMI was calculated based on body height and weight values. Results: Out of 100 subjects, PE was not diagnosed in 37 subjects, while 63 subjects PE was diagnosed. All subjects were divided into 2 groups: a group of subjects with confirmed PE and a group of subjects with excluded PE. Average BMI values were calculated for both groups. Statistical analysis showed that there was no significant difference in BMI values between subjects with confirmed and excluded PE. Conclusion: the results of our study did not confirm the association between elevated BMI and PE.

Keywords: pulmonary embolism, BMI, MSCT, V/P SPECT

SAŽETAK

Uvod: plućna embolija (PE) predstavlja po život opasno urgentno stanje koje obzirom na ozbiljne komplikacije zahtijeva što hitniju primjenu antikoagulantne terapije. Pored različitih tradicionalnih faktora za nastanak PE u posljednje vrijeme i pretilost se smatra nezavisnim faktorom rizika za nastanak PE. Cilj: utvrditi da li postoji razlika u vrijednostima indeksa tjelesne mase (BMI) kod ispitanika sa potvrđenom i isključenom PE. Materijali i metode: u studiju je uključeno 100 pacijenata kod kojih je postojala sumnja na PE, koja je potvrđena ili isključena korištenjem MSCT i/ili V/P SPECT-a i kojima je izračunat BMI na osnovu vrijednosti tjelesne visine i težine. Rezultati: od ukupnog broja ispitanika kod njih 37 nije dijagnosticirana PE, dok je kod 63 ispitanika dijagnosticirana PE. Svi pacijenti su podijeljeni u 2 skupine: skupina pacijenata kod kojih je potvrđena PE i skupina pacijenata kod kojih je isključena PE. Za obje skupine su izračunate prosječne vrijednosti BMI. Statistička analiza je pokazala da ne postoji značajna razlika u vrijednostima BMI između pacijenata sa potvrđenom i isključenom PE. Zaključak: rezultati naše studije nisu potvrdili povezanost između povišenog BMI i PE.

Ključne riječi: plućna embolija, BMI, CT, V/P SPECT

INTRODUCTION

Pulmonary embolism (PE) is a life-threatening medical emergency where the main pulmonary arteries and/or their branches are obstructed by thrombotic masses, which leads to compromised blood flow (1,2). PE is the third most common cardiovascular disease with an incidence of about 0.5 to 1.0 per 1000 inhabitants (3).

Considering that in the majority of cases PE occurs as a consequence of deep venous thrombosis (DVT), the risk factors for the occurrence of DVT overlap with the risk factors for the occurrence of PE. In addition to traditional risk factors for the occurrence of DVT and therefore PE, such as immobilization, recent surgical procedures, malignant diseases, pregnancy, cigarette smoking, use of oral contraceptives (4-10), recently obesity has also been considered as an independent risk factor (11). Numerous recent studies have shown that the risk of DVT and PE increases with increasing of body mass index (BMI) (12).

According to WHO criteria, obesity is defined as BMI of at least 30 kg/m^2 (12). Obesity is associated with inactivity, raised intra-abdominal pressure, a chronic low-grade inflammatory state, impaired fibrinolysis, high levels of fibrinogen, von Willebrand factor and factor VIII, leading to a prothrombotic condition and elevated risk of DVT and PE. The risk of DVT and PE is higher when obesity interacts with other thrombotic risk factors (13). According to recent studies, there is a linear relationship between BMI and PE, and patients with advanced obesity (BMI ≥ 35) have a six times

higher risk of developing PE than people of normal body weight (14).

If we consider the increased frequency of obesity in the population, i.e. the fact that according to the World Health Organization (WHO) worldwide obesity has nearly tripled since 1975 (15), this risk factor for the occurrence of DVT and PE must be considered with great attention.

AIM

The aim of this study was to determine whether there is a difference in BMI in subjects with confirmed and excluded PE.

MATERIALS AND METHODS

The prospective study conducted at the Clinical Center University of Sarajevo included 100 consecutive adult subjects with preserved renal function in whom the competent clinician suspected the presence of PE and who underwent to MSCT and/or V/P SPECT examination.

The study did not include minors, pregnant women and subjects with impaired renal function (creatinine clearance <60 ml/min).

The subjects with clinically suspected PE were referred for MSCT and/or V/P SPECT examination of the thoracic organs.

All MSCT examinations were performed on a machine with 64 or more rows of detectors. After obtaining the topogram and determining the scanning field that covers the area of the thoracic organs from the tops to the bases of the lungs, a contrast series of scans commenced. Iodine-based contrast agent was applied with an automatic syringe in the amount of 80 to 100 ml, depending on the subject's body weight, at a rate of 4 mL/S. The following parameters were used for scanning: SMART PREP technique, breath-hold scanning in layers of 0.5 mm (120 kV, 250 mA, gantry rotation time 0.75 s). If, during the analysis of the scans, the existence of a partial or complete defect in the contrast filling in the pulmonary arteries and their branches was determined, the examination was classified as positive for PE (16).

V/P SPECT examinations were performed according to a one-day standardized protocol recommended by the European Association of Nuclear Medicine (5). As the first part of the examination, ventilation tomography was performed with previous inhalation of Technegas. Immediately after the completed ventilation tomography, perfusion tomography was performed, after the application of Tc-99m-MAA. Acquisition - Ventilation: 30-50 MBq of Technegas; Acquisition - Perfusion: 100-120MBq 99mTc MAA. A wide-field gamma camera with a low-energy, high-resolution collimator with the following parameters was used for acquisition: matrix size 64 x 64, 128 projections/360°; duration: 10 sec/frame-V; 5sec/frame P. The analysis of V/P SPECT findings was performed according to the interpretation criteria of the European Association of Nuclear Medicine (2). The examination was classified as positive for PE if at least one segmental perfusion defect or two subsegmental perfusion defects were observed, while at the same time ventilation was preserved in the same region/regions - "mismatch".

Subjects with PE confirmed by at least one of the imaging methods (MSCT and V/P SPECT) were classified as positive for the presence of PE.

Data regarding body height and weight were registered for all subjects, and on the basis of this data, the body mass index was calculated according to the formula: BMI = (BMI): weight (kg)/height² (m²). BMI of 25.0 – 29.9 is classified as pre-obesity and BMI ≥ 30.0 is classified as obesity (15).

For statistical analysis of the results the Microsoft Excel 365 (Microsoft Corporation, Redmond, Washington, USA) and IBM SPSS ver. 26.0 (IBM, Armonk, New York, USA) software was used. The significance level $\alpha = 0.05$ was chosen, and p values lower than this were considered statistically significant.

Independent-Samples Mann-Whitney U Test was used to analyze the distribution of body mass index in both groups of patients.

The distribution of body mass index in not normal (Kolmogorov-Smirnov Test, $p = 0.013$) – because of this we used median and interquartile range (IQR) as measures of central tendency and dispersion, respectively.

RESULTS

A total of 100 clinically suspected PE subjects who undergone to MSCT and V/P SPECT imaging studies were included in the study.

Out of the total number of subjects, 45 were male and 55 were female.

The median age of the subjects was 60 years (ΔQ = 26).

Of the total number of subjects included in the study (n = 100), 37 of them were not diagnosed with PE, while 63 subjects were diagnosed with PE and underwent anticoagulant treatment (Figure 1).

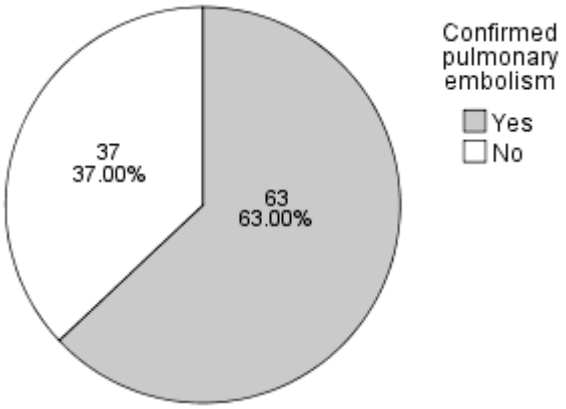

Figure 1 **The percentage of subjects with excluded and confirmed pulmonary embolism.**

All subjects were divided into 2 groups: a group of subjects with confirmed PE and a group of subjects with excluded PE, based on the finding of imaging methods. Average BMI values were calculated for both groups.

Table I **The average BMI of subjects with excluded and confirmed pulmonary embolism.**

	Confirmed pulmonary embolism			
	Yes		No	
	Median	IQR	Median	IQR
Body mass index (kg/m²)	28	3	27	4

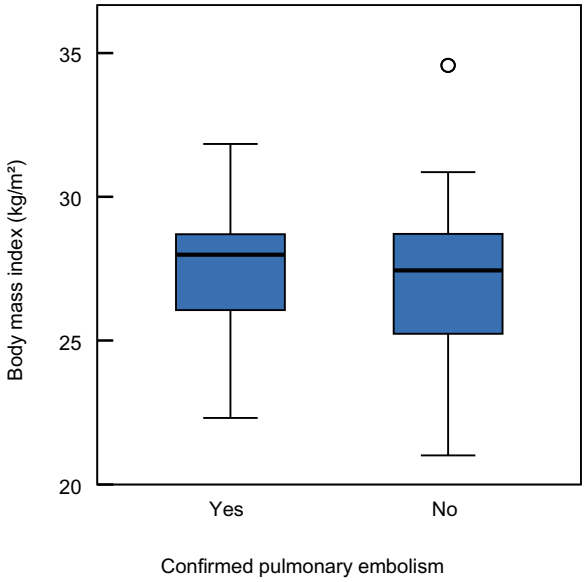

Figure 2 **The distribution of BMI of subjects with excluded and confirmed pulmonary embolism.**

According to the World Health Organization (WHO) criteria, both subjects diagnosed with PE and subjects without PE were classified as pre-obesity according to BMI.

The distribution of BMI was the same in both group of patients (Independent-Samples Mann-Whitney U Test, $p = 0.340$) - we didn't find significant difference in body mass index in group of patients with confirmed and not confirmed pulmonary embolism.

DISCUSSION

The average value of the BMI of subjects in our study corresponds to pre-obesity according to the classification of the World Health Organization, and in our study we did not observe a significant difference between the BMI of subjects with diagnosed and those with undiagnosed PE. Although numerous recent studies have proven that obesity represents a significant, independent risk factor for the development of PE (2,17), which is explained by venous congestion and reduced mobility, factors that are more frequent in this population (18) and that contribute to the development of PE, and on the other hand, due to the fact that other risk factors that are more often present in obese people, such as an increased frequency of risk factors for the occurrence of cardiovascular diseases, heart failure and diabetes also contribute to the occurrence of PE (19), our research did not confirm this results. According to the results of recent studies, it would be expected that the BMI of subjects diagnosed with PE is higher than the BMI of subjects without PE. A possible explanation for the discrepancy between our and results of other studies is most likely related to the relatively limited number of subjects included in our study.

If we consider the epidemic of the obesity in the world, the importance of this risk factor for the occurrence of PE becomes clear (13). Currently in everyday clinical practice is given limited importance to this risk factor and consequently more extensive studies should be conducted in order to assess more precisely the presence of this risk factor in our population.

CONCLUSION

The results of our study did not confirm the existence of an association between elevated BMI and PE. Considering the relatively small number of subjects included in the study, it would be desirable to conduct a more extensive study in order to assess in more detail the association between elevated BMI and PE.

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Reprint requests and correspondence:
Spomenka Kristić, MD
Clinic of Radiology
Clinical Center University of Sarajevo
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina
E-mail: kristic.spomenka@gmail.com
ORCID ID: 000-002-3380-2339

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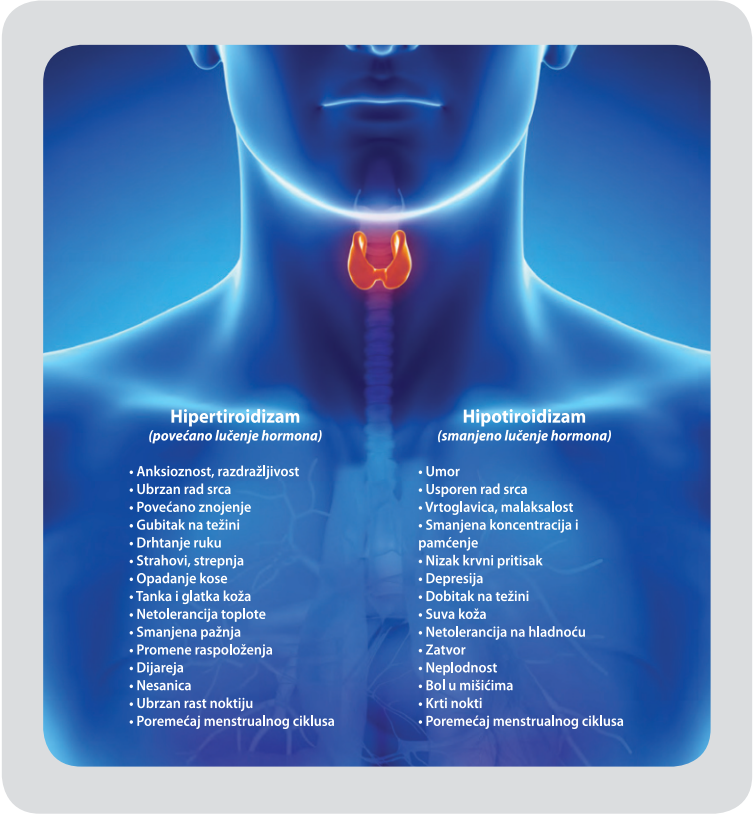

Association between vitamin D deficiency and diabetes mellitus type 1 and 2: a case-control study

Povezanost između nedostatka vitamina D i diabetes mellitusa tipa 1 i 2: case-control studija

Rubina Alimanović-Alagić[1]*, Amira Baždarević-Rašidagić[2], Berina Hasanefendić[2], Amra Macić-Džanković[4], Ismana Šurković[5], Lajla Halilović[3]

[1]Clinic of Nuclear Medicine, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
[2]Public Institution Health Center of Sarajevo Canton, Vrazova 11, 71000 Sarajevo, Bosnia and Herzegovina
[3]Clinical Biochemistry and Laboratory Medicine, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
[4]Internal Medicine Practice, Čemaluša 6, 71000 Sarajevo, Bosnia and Herzegovina
[5]Clinic of Endocrinology, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: vitamin D is a steroid hormone that has important roles in the homeostasis of the human body, and one of them is the stimulation of insulin secretion from the pancreas. Therefore, the aim of this study is to examine the association between vitamin D deficiency and type 1 and type 2 diabetes mellitus. Materials and methods: 60 patients with diabetes mellitus type 1 (DMT1) and 60 patients with diabetes mellitus type 2 (DMT2) were included in the study and two control groups of 60 patients each. Gender, age, HbA1c and vitamin D concentration were compared between these two groups. The association between vitamin D deficiency and type 1 and type 2 diabetes mellitus was examined by comparing vitamin D values in patients with DMT1 and DMT2 and control groups. Results: the group of patients with DMT2 consisted of significantly older people and female patients ($p<0.001$). The concentration of HbA1c is significantly higher in patients with DMT2 ($p<0.001$). Vitamin D concentration was significantly higher in patients with DMT1 ($p<0.001$). An association between DMT1 and DMT2 and vitamin D deficiency was observed ($p<0.001$). Conclusion: the conducted study proved vitamin D deficiency in patients with DMT1 and DMT2 and serves as a valuable indicator in the further treatment of these patients.

Keywords: vitamin D, vitamin D deficiency, diabetes mellitus type 1, diabetes mellitus type 2

SAŽETAK

Uvod: vitamin D je steroidni hormon koji ima važnu ulogu u homeostazi ljudskog organizma, a jedna od njih je stimulacija lučenja inzulina iz gušterače. Stoga je cilj ovog istraživanja ispitati povezanost nedostatka vitamina D i šećerne bolesti tipa 1 i tipa 2. Materijali i metode: u istraživanje je uključeno 60 bolesnika sa šećernom bolešću tip 1 (DMT1) i 60 bolesnika sa šećernom bolešću tip 2 (DMT2) i dvije kontrole grupe od po 60 ispitanika. Uspoređeni su spol, dob, HbA1c i koncentracija vitamina D između ove dvije skupine. Povezanost između nedostatka vitamina D i dijabetes melitusa tipa 1 i tipa 2 ispitana je usporedbom vrijednosti vitamina D kod pacijenata s DMT1 i DMT2 i kontrolnih skupina. Rezultati: skupinu pacijenata s DMT2 činilo je značajno više starijih osoba i pacijentica ($p < 0,001$). Koncentracija HbA1c značajno je viša kod bolesnika s DMT2 ($p<0,001$). Koncentracija vitamina D bila je značajno viša kod bolesnika s DMT1 ($p<0,001$). Uočena je povezanost između DMT1 i DMT2 i nedostatka vitamina D ($p<0,001$). Zaključak: provedeno istraživanje dokazalo je nedostatak vitamina D kod pacijenata s DMT1 i DMT2 te služi kao vrijedan pokazatelj u daljnjem liječenju ovih bolesnika.

Ključne riječi: vitamin D, nedostatak vitamina D, dijabetes melitus tip 1, dijabetes melitus tip 2

INTRODUCTION

Diabetes mellitus (DM) is one of the biggest public health challenges in the world and has significant economic and social effects. Health systems, organizations and the scientific community all over the world invest great efforts in preventing its occurrence and thereby reducing the incidence of diabetes mellitus (1). There are many known risk factors that lead to its occurrence, such as age, eating habits, physical activity, blood pressure, elevated values of lipidogram values and some genetic and/or environmental factors (2). Numerous studies have been conducted to examine the connection between other causes and the onset of diabetes mellitus, and vitamin D is one of them (3).

Vitamin D is a steroid hormone, which has several functions in the human body: normal growth and development of bones, immunostimulatory effects, balance of calcium and phosphorus, important for the bone system, but also plays a role in the stimulation of insulin secretion from the pancreas (4,5). Therefore,

there is a clear connection between vitamin D deficiency and the risk of developing diabetes mellitus or the development of complications in patients with diabetes mellitus. It has also been proven that vitamin D plays a role in reducing insulin resistance. The risk of vitamin D deficiency is very high if people are not exposed to the sun's UV-B light, and previous studies have shown that most people are vitamin D deficient after winter - in spring. Therefore, during this period, it is important to replace the necessary amounts with food and to be exposed to sunlight (6-8). The fact is that vitamin D has multiple beneficial effects on the human body.

AIM

The aim of this study was to examine the association between vitamin D deficiency and type 1 and type 2 diabetes.

MATERIALS AND METHODS

This was a cross-sectional, case-control study carried out with the approval of the Ethics Committee of the Clinical Center University of Sarajevo and in compliance with the Declaration of Helsinki.

The study included patients treated at the Clinic of Nuclear Medicine of the Clinical Center University of Sarajevo, with their prior consent. The study included patients of both sexes diagnosed with diabetes mellitus type 1 (DMT1) and 2 (DMT2), older than 18 years, with complete medical documentation. Patients with gestational diabetes, pregnant women and patients < 18 years of age were excluded from the study. The control group consisted of subjects (n=60) without any health problems, denying the history of any kidney, thyroid, intestinal or any malignant disease.

Data on the patient's sex, age, HbA1c and vitamin D were collected from patient's medical records. A blood sample for the determination of HbA1c and vitamin D was taken in the morning before consumption of food, drink or medication, according to Good Laboratory Practice (GLP) guidelines.

The patients were divided into two groups based on the type of diabetes mellitus - type 1 (60 patients) and type 2 (60 patients). The concentration of vitamin D in the blood was compared between these two groups and the control group based on the reference value of vitamin D in the blood (30-100 ng/ml). Values less than 30 ng/ml were considered vitamin D deficiency and severity was divided according to vitamin D concentration as follows: I severe deficiency (1-10 ng/ml) II deficiency (11-20 ng/ml) and suboptimal levels (21-30 ng/ml).

The SPSS Statistics 26.0 program was used for statistical data processing. Gender of patients was presented in percentages and age, HbA1c and vitamin D values as mean values. Student t-test was used to compare values between two groups of patients. The chi-square test was used to examine the association between vitamin D deficiency and type 1 and type 2 diabetes mellitus. Statistical significance was set at < 0.05.

RESULTS

This study included 120 patients with diabetes mellitus, type 1 - 60 patients and type 2 - 60 patients. The group of patients with DMT2 consisted of significantly more older and female patients ($p < 0.001$). The concentration of HbA1c is significantly higher in patients with DMT2 ($p<0.001$). Vitamin D concentration was significantly higher in patients with DMT1 ($p<0.001$), as shown in Table 1.

Table 1 **Difference among examined parameters between patients with DMT1 and DMT2.**

	DMT1	DMT2	p value
Age	58.98±11.06	61.7±11.66	**<0.001**
Sex (male/female)	23/37	27/33	**<0.001**
HbA1c (%)	7.05±0.96	7.28±1.12	**<0.001**
Vitamin D (ng/ml)	17.92±4.53	17.07±5.29	**<0.001**

47 (73.33%) patients with DMT1 had vitamin D deficiency, as shown in Table 2. An association between vitamin D deficiency and type 1 diabetes mellitus was observed ($p < 0.001$).

Table 2 **Association between vitamin D deficiency and type 1 diabetes mellitus.**

	DMT1	Controls	Chi square test value	p value
Severe deficiency	2	0	104.577	**<0.001**
Deficiency	44	0		
Suboptimal level	14	10		
Upper normal level	0	50		

41 (68.33%) patients with DMT2 had vitamin D deficiency, as shown in Table 3. An association between vitamin D deficiency and type 2 diabetes mellitus was observed ($p < 0.001$).

Table 3 **Association between vitamin D deficiency and type 2 diabetes mellitus.**

	DMT2	Controls	Chi square test value	p value
Severe deficiency	5	0	96.666	<0.001
Deficiency	41	0		
Suboptimal level	14	10		
Upper normal level	0	50		

DISCUSSION

Vitamin D deficiency has already been observed in the general population in Bosnia and Herzegovina and is presented as a public health problem and challenge (9). Therefore, this study presents updated data focused on patients with type 1 and type 2 diabetes mellitus, and aimed to investigate the association between vitamin D deficiency and patients with it.

In our study, we showed that all patients had vitamin D deficiency and that DMT2 patients had lower vitamin D values compared to DMT1 patients. We can explain this inversion with the data on HbA1c, which in both groups of patients were > 7. It has been proven that vitamin D stimulates insulin secretion by binding to VDR (vitamin D receptors) (10). Therefore, we can conclude that lower values of vitamin D caused inversely higher values of HbA1c in DMT2 patients.

Many conducted studies aimed to examine the relationship between vitamin D deficiency and diabetes mellitus type 1 and 2 (11-13), and it was observed that these patients have significantly lower values than healthy control groups. In addition, complications of diabetes mellitus were accompanied by vitamin D deficiency as well (14,15).

Considering that one can undoubtedly talk about the high prevalence of vitamin D deficiency in patients with DMT1 and DMT2, great efforts are invested in the treatment of deficiency and supplementation of these patients with doses of vitamin D. Vitamin D supplementation in such patients has potential in the metabolic regulation of glycemia in DM patients and prevention of complications arising from the primary disease (16,17).

Study limitations

Based on our knowledge, this is the first study in Bosnia and Herzegovina investigating the connection between vitamin D deficiency and type 1 and type 2 diabetes mellitus, which gives it a special significance. On the other hand, the limitations of our study are: 1) a relatively small number of included DMT1 and DMT2 patients, 2) the study was conducted in one institution, and the obtained data cannot be generalized for the whole of Bosnia and Herzegovina, 3) the study did not include the analysis of other clinical and/or laboratory parameters that would give a broader picture of the causal relationship between vitamin D deficiency and diabetes mellitus. The mentioned limitations will be discussed later and some of the following studies will take them into account.

CONCLUSION

Vitamin D deficiency is associated with type 1 and type 2 diabetes mellitus. The HbA1c value was higher in type 2 diabetes mellitus patients with a lower vitamin D level. Given that diabetes mellitus patients have been observed to have vitamin D deficiency, this study serves as basis for further studies on this topic and enabling better treatment of patients with diabetes mellitus.

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Reprint requests and correspondence:
Rubina Alimanović-Alagić, MD, PhD
Clinic of Nuclear Medicine
Clinical Center University of Sarajevo
Bolnička 25, Sarajevo
Bosnia and Herzegovina
Email: rubinaalimanovic@yahoo.com
ORCID ID: 0000-0003-1672-5375

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Our contribution to the reduction of cardiovascular diseases in Bosnia and Herzegovina!
Naš prilog redukciji kardiovaskularnih bolesti u Bosni i Hercegovini!

The Use of CFTR Protein Modifiers (Kaftrio/Kalydeco) at the Pediatric Clinic of the Clinical Center University of Sarajevo

Upotreba CFTR proteina (Kaftrio) na Pedijatrijskoj klinici Kliničkog centra Univerziteta u Sarajevu

Tanja Radoš-Kosić[1], Amina Selimović[2]*

[1]Health Center with Stationary Care Žepče, Prva 37/A, 72230 Žepče, Bosnia and Herzegovina
[2]Pediatric Clinic, Clinical Center University of Sarajevo, Patriotske lige 81, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: Cystic fibrosis (CF) is an inherited disorder that leads to the production of thick, sticky mucus in the lungs and digestive system. CFTR protein modulators, such as Kaftrio and Kalydeco, represent a significant advancement in CF treatment by targeting the underlying molecular defect. Aim: to evaluate the clinical efficacy and safety of CFTR protein modulators in pediatric CF patients at the Clinical Center University of Sarajevo. Materials and methods: eight pediatric patients aged 6 to 18 years with a confirmed CF diagnosis were included. Clinical outcomes such as weight, height, lung function (FEV1), and liver enzyme levels were monitored. Results: all patients showed significant improvements in weight and lung function, with an average FEV1 increase of 13%. Liver enzyme levels normalized in all cases, and no serious adverse events were reported. Conclusion: CFTR protein modulators, particularly Kaftrio and Kalydeco, offer significant clinical benefits for pediatric CF patients, highlighting their potential as a first-line therapy.

Keywords: cystic fibrosis, CFTR modulators, pediatric patients, Kaftrio, Kalydeco

SAŽETAK

Uvod: cistična fibroza (CF) je nasljedna bolest koja uzrokuje stvaranje gustog i ljepljivog sluzi u plućima i probavnom sistemu. Modulatori CFTR proteina, kao što su Kaftrio i Kalydeco, predstavljaju revoluciju u liječenju CF-a ciljajući osnovni defekt na molekularnom nivou. Cilj: procijeniti kliničku efikasnost i sigurnost modulatora CFTR proteina kod pedijatrijskih pacijenata sa CF-om u Kliničkom centru Univerziteta u Sarajevu. Materijali i metode: u studiju je uključeno osam pedijatrijskih pacijenata u dobi od 6 do 18 godina, sa potvrđenom dijagnozom CF-a. Pratili smo kliničke ishode uključujući tjelesnu težinu, visinu, plućnu funkciju (FEV1), te nivoe jetrenih enzima. Rezultati: svi pacijenti su pokazali značajno poboljšanje u težini i plućnoj funkciji, s prosječnim povećanjem FEV1 za 13%. Nivoi jetrenih enzima su se normalizovali kod svih pacijenata, a nisu zabilježeni ozbiljni nuspojave. Zaključak: modulatori CFTR proteina, posebno Kaftrio i Kalydeco, pružaju značajne kliničke koristi kod pedijatrijskih pacijenata sa CF-om, naglašavajući njihov potencijal kao terapiju prvog izbora.

Ključne riječi: cistična fibroza, CFTR modulatori, pedijatrijski pacijenti, Kaftrio, Kalydeco

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive genetic disorder characterized by dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This leads to the production of thick and sticky mucus in the lungs, pancreas, and other organs, causing severe respiratory and digestive complications (1). Without proper treatment, CF can lead to premature death, with most patients experiencing significant morbidity throughout their lives. Traditional therapies primarily focus on managing symptoms and complications of CF, such as infections and malnutrition.

The development of CFTR protein modulators, including Kaftrio (a combination of elexacaftor, tezacaftor, and ivacaftor) and Kalydeco (ivacaftor), marks a substantial breakthrough in the treatment of CF. These therapies directly target the defective CFTR protein, thereby improving its function and addressing the root cause of the disease rather than merely alleviating symptoms (2-5).

This study aims to evaluate the clinical efficacy and safety of these CFTR protein modulators in pediatric patients with CF treated at the University Clinical Center Sarajevo. The focus is on analyzing changes in pulmonary function, growth parameters, and liver function before and after the introduction of CFTR modulators.

AIM

The aim of this study was to evaluate the clinical efficacy and safety of CFTR protein modulators in pediatric CF patients at the Clinical Center University of Sarajevo.

MATERIALS AND METHODS

This study was a retrospective case series analysis involving pediatric patients with CF treated with CFTR protein modulators at the Clinical Center University of Sarajevo. Eight pediatric patients (5 males, 3 females) aged 6 to 18 years were included in the study. All patients had a confirmed diagnosis of CF based on genetic testing and sweat chloride testing and were eligible for CFTR protein modulator therapy based on their specific CFTR mutations.

Five patients were treated with Kaftrio (elexacaftor/tezacaftor/ivacaftor) and three with Kalydeco (ivacaftor). The treatment duration ranged from 3 to 6 months. The dosage and administration of the drugs were tailored according to standard clinical protocols for CF treatment.

Outcome Measures

Clinical outcomes were assessed at baseline and during follow-up visits, focusing on:

- Anthropometric Data: Weight and height of the patients.
- Pulmonary Function: Forced Expiratory Volume in 1 second (FEV1) expressed as a percentage of the predicted value.
- Biochemical Markers: Levels of liver enzymes (ALT, AST) and sweat chloride concentration (6).

Data Analysis

Descriptive statistics were used to summarize the data. Paired t-tests were employed to compare clinical parameters before and after treatment, assessing the significance of changes in the observed outcomes.

RESULTS

Baseline Characteristics

At the begining of the study, the mean age of the patients was 12.5 years (range 6-18 years). The average weight was 35.6 kg (range 20.8-52.3 kg), and the mean FEV1 was 62% of the predicted value.

Clinical Outcomes

- Weight and Height: all patients demonstrated an increase in weight and height. The average weight gain was 2.1 kg over the treatment period ($p < 0.05$).
- Lung Function: significant improvements in lung function were observed, with the average FEV1 increasing from 62% to 75% of the predicted value ($p < 0.01$).
- Biochemical Markers: liver enzyme levels normalized in all patients, indicating an improvement in liver function. Sweat chloride concentrations decreased, reflecting enhanced CFTR function (7).

Adverse Events

No serious adverse events were reported. Mild gastrointestinal symptoms were noted in two patients, which resolved without intervention.

Table 1 **Clinical outcomes before and after treatment with CFTR protein modulators.**

Parameter	Baseline	Post-Treatment	p-value
Weight (kg)	35.6 ± 7.1	37.7 ± 7.0	0.03
FEV1 (%)	62 ± 15	75 ± 13	<0.01
ALT (U/L)	45 ± 10	30 ± 8	0.02
AST (U/L)	35 ± 9	25 ± 7	0.04
Sweat Chloride	90 ± 10	60 ± 12	<0.01

Table 2 **Gender and Age (total: 8).**

Age	Gender
6-18 years	70% males
	30% females

DISCUSSION

Comparison with the existing literature

Our findings are consistent with previous studies that have demonstrated the efficacy of CFTR protein modulators in improving lung function and nutritional status in CF patients (3,4). The significant improvements in FEV1 and weight gain observed in our study align with results from larger clinical trials reported by

Middleton PG, et al., (2020) and Heijerman HGM, et al. (2019) (2,1).

The use of Kaftrio and Kalydeco in pediatric patients has shown promise in not only improving clinical outcomes but also enhancing the overall quality of life by reducing the frequency and severity of exacerbations. The normalization of liver enzyme levels in our cohort suggests that CFTR modulators may also help in mitigating liver-related complications, which are common in CF patients due to the thick mucus obstructing bile ducts. The observed improvements in lung function and nutritional status suggest that CFTR protein modulators should be considered as a first-line treatment for eligible pediatric CF patients. This approach can lead to a significant reduction in disease burden and potentially improve the prognosis of CF patients, who often face a lifetime of complex medical challenges. The data from our study reinforce the importance of early and sustained treatment with CFTR modulators to maximize clinical benefits. However, it is crucial to monitor patients closely for potential adverse effects and to adjust treatment regimens as necessary to ensure the best possible outcomes (8).

Study Limitations

The primary limitation of this study is the small sample size, which may limit the generalizability of the findings. Additionally, the retrospective design and short follow-up period preclude definitive conclusions about long-term outcomes and safety. Further research with larger patient cohorts and extended follow-up is needed to validate these preliminary results and to explore the long-term benefits and risks associated with CFTR modulator therapy.

CONCLUSION

CFTR protein modulators, particularly Kaftrio and Kalydeco, have demonstrated substantial clinical benefits in improving pulmonary and nutritional outcomes in pediatric CF patients treated at the Clinical Center University of Sarajevo. These findings support the use of CFTR modulators as an effective therapeutic strategy in the management of CF. Further studies with larger cohorts and longer follow-up periods are warranted to confirm these results and to provide a deeper understanding of the long-term impact of CFTR modulators on the health and quality of life of CF patients.

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Reprint requests and correspondence:
Amina Selimović, MD, PhD
Pediatric Clinic
Clinical Center University of Sarajevo
Patriotske lige 81, 71000 Sarajevo
Bosnia and Herzegovina
Email: aminaselimovic778@gmail.com
ORCID ID:000-0003-2195-5669

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Transcranial magnetic stimulation (TMS) in the treatment of depression

Transkranijalna magnetska stimulacija (TMS) u terapiji depresije

Neira Bašić-Hamzić[1], Gorana Sulejmanpašić[2]*

[1]Health Center of Canton Sarajevo, Vrazova 11, 71000 Sarajevo, Bosnia and Herzegovina
[2]Clinic of Psychiatry, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Transcranial magnetic stimulation TMS is a non-invasive brain modulation procedure. Magnetic field pulses created in the electromagnetic coil produce electrical activity in the brain. TMS is effective treatment for depression which is the leading cause of disability worldwide and it is a major contributor to the overall global burden of disease. More than 30% of patients treated for depression are resistant to pharmacological treatments. Hereby we present the new insights into transcranial magnetic stimulation (TMS) treatment of depression. Worldwide, the number of centers using TMS to treat depression is increasing.

Keywords: treatment, electromagnetic, non-invasive, depression, effective

SAŽETAK

Transkranijalna magnetska stimulacija (TMS) je neinvazivni postupak modulacije moždane aktivnosti. Magnetsko polje nastalo u elektromagnetskoj zavojnici inducira električnu aktivnost u korteksu mozga. TMS je učinkovit u tretmanu depresivnog poremećaja koji je vodeći svjetski uzrok invaliditeta i glavni poremećaj na ljestvici opterećenja svim bolestima. Više od 30% bolesnika liječenih zbog depresivnog poremećaja su rezistentni na farmakološke tretmane. U radu ćemo predstaviti nove spoznaje u liječenju depresivnog poremećaja transkranijalnom magnetskom stimulacijom (TMS-om). Broj centara koji koriste TMS za liječenje depresivnog poremećaja je u porastu širom svijeta.

Ključne riječi: tretman, elektromagnetni, neinvanzivni, depresija, ekektivno

INTRODUCTION

Depressive disorders are one of the biggest health problems of public importance because they are the most common mental disorder in the general population, in a large number of cases depressions are recurrent or chronic, significantly impair the quality of life and relatively often end in suicide. More than 264 million people worldwide suffer from depression and the World Health Organization predicts that by 2030 it will be the first leading cause of disability. The symptoms of depression very often overlap with the symptoms of other diseases, and that is why the criteria for diagnosing it are defined based on the presence of several symptoms and signs, such as a depressed or sad mood, a decrease in interest in usual activities and a loss of pleasure, a significant loss or increase in body weight , i.e. reduced or increased appetite, sleep disturbances in the sense of disturbed sleep or sleeping too long, fatigue, loss of energy, feeling of own worthlessness or imperceptible guilt, reduced ability to think and concentrate, recurring thoughts of death and suicide. Depression is a disease that occurs in episodes, and when it occurs for the first time, we are talking about a depressive episode, and the symptoms needed to establish a diagnosis should last at least two weeks. An untreated depressive episode lasts from six months to two years. Each new depressive episode leads to neurodegenerative changes in the brain, shortening the time without symptoms, which results in the chronicity of the disease. Chronic depression is one that lasts two years or longer (1).

Treatment of pharmacotherapy-resistant depressive disorder (DRD) has become one of the most important problems in psychiatry. Increasing prevalence of depressive disorder and resistance to psychopharmacotherapy indicate the need for alternative treatments for depression. There are several treatment options for TRD, electrostimulation therapy (EST), transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS). Among these methods, the most preferred method today is TMS because it is a non-invasive method with the least side effects (2).

AIM

The aim of the paper was to present new knowledge about the role of transcranial magnetic stimulation in the treatment of depression.

What is transcranial magnetic stimulation (TMS)?

Transcranial magnetic stimulation (TMS) is a procedure that uses magnetic fields to stimulate nerve cells in the brain. TMS applies a high intensity oscillating magnetic field. In this way, the neural elements in the cerebral cortex are stimulated by a series of pulses. By applying repeated magnetic pulses (several days or weeks in a row), a long-term change in the function of certain brain regions is achieved. The treatment involves the delivery of repetitive magnetic pulses, so it is also called repetitive transcranial magnetic stimulation (rTMS). rTMS represents a unique method of applying pulsed magnetic fields for therapeutic purposes, with an intensity similar to those used in magnetic resonance imaging (MRI), but at the same time it is fundamentally different from the popular use of various "magnets" (in belts, shoes, etc.), which generate static magnetic fields of low intensity.

Such products deliver very weak and non-directional static fields that are unable to activate brain cells.

The electromagnetic device is placed above a certain point on the head from where it stimulates the nerves in the cerebral cortex with a series of short magnetic pulses. The electromagnet painlessly sends a magnetic pulse that stimulates nerve cells in the area of the brain responsible for mood control. This means that it activates parts of the brain that in psychological conditions, such as bipolar disorder and depression, patients have reduced activity. This type of stimulation affects how the brain works, which eases symptoms and improves mood (3).

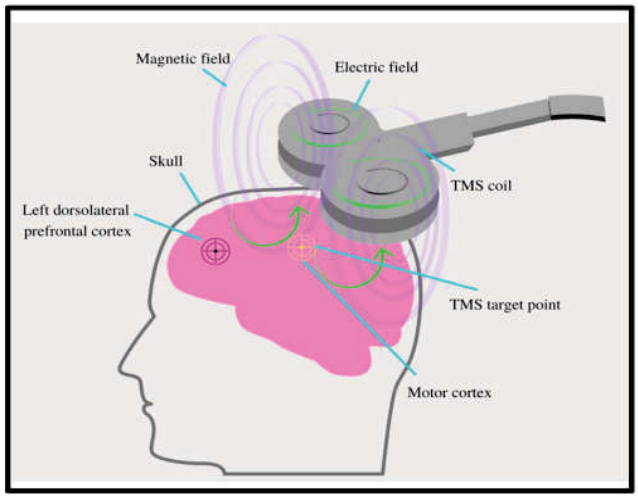
The rationale for applying rTMS over the prefrontal cortex for the treatment of depression stems from the hypothesis of an unbalanced relationship between the prefrontal cortical area and the limbic area underlying mood disorders (2).

RTMS treatment for major depressive disorder usually involves one of three protocols: a high-frequency rTMS protocol (HF rTMS) applied to the left dorsolateral prefrontal cortex (DLPFC), a low-frequency rTMS protocol (LF rTMS) applied to the right DLPFC and bilateral HF/LF rTMS. Before applying rTMS therapy, the DLPFC is located, and the most common method of location without the aid of neuronavigation is the "5 centimeter method". The magnetic coil is first located in the motor area of the brain that stimulates the abductor pollicis brevis muscle of the hand opposite to the stimulated side of the brain, and then the coil is moved 5 cm anteriorly along the surface of the scalp to locate the DLPFC. According to several studies, this procedure locates the DLPFC too posteriorly, and more and more people start with locating the DLPFC 6 to 7 cm anterior to the location of the motor cortex (2).

Deep Transcranial Magnetic Stimulation (dTSM)

Deep transcranial magnetic stimulation (dTMS) is a new technology that enables non-invasive stimulation of relatively deep areas of the brain. dTMS therapy is delivered using an H-coil device designed to stimulate areas of the deep prefrontal cortex that include neural pathways associated with the brain's reward system.

The first double-blind randomized controlled multicenter study evaluating the efficacy and safety of dTMS in depressive disorder was published in 2015. 212 patients with depressive disorder aged 22 to 68 who were resistant to pharmacotherapy (one to four antidepressants) or could not tolerate at least two antidepressants during the current depressive episode participated. They were randomized to an active or control placebo dTMS group. Twenty sessions of dTMS (application of 18 Hz to the left prefrontal cortex) were applied daily for 4 weeks and then twice a week for 12 weeks. HAMD 21 decreased by 6.39 points in the active dTMS group and by 3.28 points in the placebo group. Clinical response in the active group was 38.4% versus 21.4% in the placebo group, and remission was 32.6% versus 14.6% in the same groups. The differences between the active and placebo groups were stable during the 12-week maintenance phase. During the application of dTMS, several minor side effects were recorded, except for one epileptic attack in a patient who violated the protocol. These results indicate that dTMS is a new effective and safe method of treating patients with a severe depressive episode. Given that this is the only double-blind randomized controlled multicenter study evaluating the efficacy and safety of dTMS, it is clear that the current scientific evidence for dTMS therapy in the treatment of depression is insufficient and that ongoing studies will advance the scientific evidence (2).



Indications for the application of transcranial magnetic stimulation:

- Depressive disorder
- Anxiety disorders
- Post-traumatic stress disorder
- Obsessive-compulsive disorder
- Conversion dissociative disorders

• Chronic pain syndromes (psychogenic pain, neuropathic pain, fibromyalgia, migraine)
• Eating disorders
• Diseases of addiction (craving, especially in case of cocaine addiction)
• Mild cognitive impairment
• Dementia
• Schizophrenia
• Prevention of migraine attacks
• Parkinsonism
• Polyneuropathy
• Motor and psychological deficit as a consequence of a stroke
• Vocal and motor tics (touretism)
• Fatigue in multiple sclerosis
• Tinnitus (4).

Duration of the TMS procedure

During the treatment, the person is awake and aware, because TMS does not require any sedation or general anesthesia, so after the treatment, you can continue with your usual activities. TMS therapy consists of a series of treatments. The duration of one cycle is ten to twenty applications. Applications can be carried out daily for 20-30 minutes, the therapy is applied 5 days during the week with a break over the weekend. This average may vary depending on individual response to treatment. During the treatment, 3000 pulses are released at a specific location of the frontal lobe of the left hemisphere. The exact number of treatments cannot be predicted in advance.

The number of applications depends on the patient's mental state, response to treatment and professional assessment of the psychiatrist. rTMS treatments are usually applied five times a week, but the frequency of treatments can vary depending on individual needs. Typically, patients who respond to rTMS feel results in the fourth to sixth week of treatment, but some may show results in less time.

According to world standards, the recommendation is 15-30 treatments, once a day for 37 minutes (depending on the used protocol of the therapeutic device). The first examination and mapping takes 60-90 minutes (5).

The choice of DLPFC (dorsolateral prefrontal cortex) as a site of rTMS application is based on pathophysiological changes. Functional images of the brain in depressed patients showed a decrease in cortical blood flow as well as glucose and oxygen consumption in the left frontal area, which reflects a hypometabolic state, accompanied by hypermetabolism in the right prefrontal area. The DLPFC region is easily accessible to TMS application and is synaptically connected to the limbic system involved in mood regulation (striatum, thalamus and anterior cingulate cortex). It is thought that rTMS through the DLPFC modulates brain networks involved in mood regulation and can affect various neurotransmitters. Lan et al. (2016) described structural brain changes (grey matter volume increased 3.5-11.2%) in patients with depressive disorder during rTMS treatment.

The four regions where these changes were observed were: left anterior cingulate cortex, left insula, left superior temporal gyrus, and right angular gyrus. An increase in the volume of the left anterior cingulate cortex correlates with an improvement in depressive symptoms (2).

The first therapeutic response to bipolar disorder and depression, as well as other psychological and neurological conditions, is medication combined with psychotherapy, physical activity, exercises, depending on the condition in question. If these treatments do not work, TMS is recommended as an alternative treatment. TMS may also be recommended to make the medication work more effectively. People who cannot tolerate medication may also consider this form of therapy.

Side effects

The most common side effects are headache, muscle tension, local discomfort at the application site. Discomfort and headaches disappear over time, and headaches usually go away with the use of common analgesics. If such sensations occur, the patient should inform the sta ff who can then adjust the stimulation settings or make changes to the coil position to make the procedure more comfortable.

Mood changes: acute onset of mania during rTMS over the left prefrontal cortex has been reported in patients with unipolar and bipolar depression.

Epileptic seizure is a rare side effect, but the most concerning side effect. Seizures can be induced by rTMS when pulses with relatively high frequencies and short intervals between stimulation sequences are applied. The risk of epileptic seizure induced by rTMS under usual clinical use with the figure-of-eight coil is estimated to be 1 seizure in 30,000 treatments (0.003%).

Special caution is required in conditions such as a history of serious head injury, substance abuse, conditions following brain surgery, medical/neurological conditions associated with epilepsy (eg, increased intracranial pressure).

Pregnancy: The risks of exposure to TMS during pregnancy are unknown.

There are no known long-term adverse effects associated with the use of repetitive transcranial magnetic stimulation. However, since this is a relatively new treatment, there is the potential for unpredictable risks in the long term that are currently unknown.

Patients who have magnet-sensitive metals inside the head or within 30 cm of the magnetic coil should not use TMS. Failure to observe this restriction could result in serious injury or death.

Items that can have this type of metal are:

• Aneurysm clips or coils
• Stents in the neck or brain
• Implanted stimulators
• Cardiac pacemaker or implanted cardioverter defibrillator (ICD)
• Cardiac stents
• Electrodes that monitor brain activity
• Metal implants in the ears or eyes
• Shrapnel or bullet fragments
• Facial tattoos with metallic or magnetically sensitive ink

DISCUSSION

Based on several large multicenter studies and meta-analyses, it is clear that rTMS therapy is effective in the treatment of depressive disorders. Remission rates are around 30%, and clinical response rates around 40%. Clinicians can safely apply high frequency rTMS at 120% MT and 3000 pulses per session. Antidepressant effects of rTMS are less pronounced in patients with higher levels of depression resistant to psychopharmaceuticals. Accelerated protocols and theta burst stimulation can potentially achieve similar results with a shorter duration. Deep TMS may also be an option in the treatment of TRD (4). Research efforts are focused on improving remission and reducing treatment time and

costs. Future research will help establish rTMS as a safe, effective and affordable treatment for the growing number of patients suffering from depressive disorders. The findings described provide an insight into part of the current research and therapeutic possibilities of treating depression with TMS and are an incentive for the inclusion of patients suffering from a depressive disorder in treatment with TMS (5).

The equipment has progressed over time, so the stimulation is getting deeper and, perhaps most importantly, no longer only one specific region of the brain is stimulated, but entire circuits in the brain, so that the activity of the brain in terms of serotonin, dopamine, noradrenaline, glutamate, GABE and all stable neurotransmitters.

The improvement of the mental state was also recorded by the Beck Depression Questionnaire, which the patient fills out before and after the treatment. TMS therapy was a complement to other methods of treatment for these patients, and only with such an approach can we achieve better treatment success and better psychosocial functioning of the patient.

CONCLUSION

Depression is the leading cause of disability and while there are many effective treatments, first-line approaches such as antidepressants and psychotherapy do not work for everyone. Transcranial magnetic stimulation is often used as an alternative option to assist with improving depression when medications and therapy have not adequately improved depression symptoms. The clinical efficacy of TMS as an antidepressant has been well established, innovative and promising increases neuroplasticity, or the ability to form new pathways in the brain, allowing the patient to get out of a depressive rut.

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Reprint requests and correspondence:
Gorana Sulejmanpašić, MD, PhD
Clinic of Psychiatry
Clinical Center University of Sarajevo
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina
Email: gsulejmanpasic@gmail.com
ORCID ID: 0000-0002-6487-647X

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Liver impairment at hospital admission as possible predictor for required type of oxygen therapy and disease outcome in COVID-19 patients

Parametri jetrenog oštećenja na prijemu u bolnicu kao mogući prediktori potrebe za oksigenoterapijom i ishoda bolesti kod pacijenata oboljelih od COVID-19

Amila Muratspahić*, Enra Lukovac, Ahmed Velić, Rusmir Baljić, Irma Dizdarević, Refet Gojak

Clinic of Infectious Diseases, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzego vina

* Corresponding author

ABSTRACT

Introduction: SARS-CoV-2 primarily affects the respiratory system, but other organs such as liver can also suffer damage during the course of COVID-19. Aim: to examine the influence of liver damage at hospital admission to the severity and outcome of patients with COVID-19. Materials and methods: this retrospective observational study included 690 patients diagnosed with COVID-19 by positive PCR SARS-CoV-2 test who were admitted to the Clinic for Infectious Diseases of the Clinical Center University of Sarajevo from June 2020 to December 2021. Severity of disease was classified by type of required oxygen therapy in two categories: low oxygen therapy group via nasal cannula, facial mask, or high flow ventilation, and high oxygen therapy via non-invasive ventilation, and controlled mechanical ventilation. Liver impairment was assessed by levels of total bilirubin, aspartate aminotransferase, and alanine aminotransferase at admission. Statistical analysis was conducted using SPSS version 17.0. Values of $p<0.05$ were considered statistically significant. Results: total bilirubin values were statistically significantly higher ($p=0.024$) in patients who died in the group of subjects who requested a lower amount of oxygen therapy in comparison to those who needed a higher amount of oxygen support. We did not prove that the values of liver transaminases influence the severity and outcome of the COVID-19 among our subjects. Conclusion: although this study did not prove the impact of elevated liver enzymes on the severity and outcome of the COVID-19, further studies with higher number of subjects should be conducted to assess the impact of liver damage on the severity and outcome of the COVID-19.

Keywords: COVID-19, SARS-CoV-2, liver, outcome

SAŽETAK

Uvod: SARS-CoV-2 prvenstveno utiče na respiratorni sistem, ali i drugi organi poput jetre mogu pretrpjeti oštećenja tokom COVID-19. Cilj: ispitati utjecaj parametara jetrenog oštećenja na prijemu u bolnicu na težinu i ishod bolesnika s COVID-19. Materijali i metode: ovom retrospektivnom kohortnom studijom obuhvaćeno je 690 pacijenata sa pozitivnim SARS-CoV-2 RT-PCR testom koji su bili hospitalizirani na Klinici za infektivne bolesti Kliničkog centra Univerziteta u Sarajevu od juna 2020. do decembra 2021. godine. Težina kliničke slike COVID-19 klasificirana je na osnovu vrste korištene kiseoničke terapije u dvije kategorije: pacijenti zahtjevni za niskim protocima kiseonika preko nazalne kanile, facijalne maske i high-flow ventilacije te pacijenti zahtjevni za visokim protocima kiseonika putem neinvazivne ventilacije i kontrolisane mehaničke ventilacije. Oštećenje jetre procijenjeno je određivanjem vrijednosti ukupnog bilirubina, aspartat aminotransferaze i alanin aminotransferaze na prijemu. Statistička analiza je provedena korištenjem programa SPSS 17.0, a vrijednosti $p<0.05$ su smatrane statistički signifikantnim. Rezultati: vrijednosti ukupnog bilirubina bile su statistički značajno veće ($p=0,024$) kod pacijenata koji su umrli u grupi ispitanika zahtjevnim za manjom oksigenoterapijom u odnosu na one kojima je bila potrebna veća količina iste. Nismo dokazali da vrijednosti jetrenih transaminaza utječu na težinu i ishod COVID-19 među našim ispitanicima. Zaključak: iako ova studija nije dokazala utjecaj povišenih jetrenih transaminaza na težinu i ishod bolesti COVID-19, potrebno je provesti dodatna istraživanja kako bi se procijenio utjecaj oštećenja jetre na težinu i ishod bolesti COVID-19.

Ključne riječi: COVID-19, oštećenje jetre, ishod

INTRODUCTION

During the COVID-19 (coronavirus disease 2019) pandemic, it has been shown that multiple organs can be affected by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). Liver is no exception. Possible mechanism of liver impairment induced by SARS-CoV-2 include direct cytopathic effect by angiotensin-converting enzyme 2 (ACE2) receptor, drug induced liver injury,

aggravation of a previous liver disease and cytokine storm. Key receptor of SARS-CoV-2 is ACE2. Cell-specific expression of the ACE2 receptor in healthy liver tissues been evaluated and it has been found that ACE2 was expressed in 2.6% of hepatocytes and 59.7% of cholangiocytes, suggesting that liver injury may be caused by direct viral invasion (1). Initial clinical guidelines recommended antiviral agents for COVID-19, including lopinavir/ritonavir, and remdesivir, which may have hepatic toxicity in some patients (2). Patients with pre-existing chronic liver disease may be more susceptible to liver damage from SARS-CoV-2. Biological drugs like tocilizumab might also cause HBV reactivation and thus lead to liver function deterioration. On the other hand, it is still unknown whether SARS-CoV-2 infection exacerbates cholestasis in those with underlying cholestatic liver disease (3). Another possible mechanism includes cytokine storm meaning that an immune mediated damage as a result of the severe inflammatory response following COVID-19 infection can also lead to a liver injury (4). It has been documented that hepatitis can occur as a result of anoxia, especially in severe cases (hypoxic hepatitis) (5). So far, COVID-19 associated hepatic impairment was defined as AST (aspartate aminotransferase) or alanine aminotransferase (ALT) exceeds 3 times the upper limit of the normal value, and total biliruin exceeding 2 times the upper limit of the normal value (6).

AIM

The aim of this study was to examine the influence of liver damage at hospital admission to the severity and outcome of patients with COVID-19.

MATERIALS AND METHODS

This study was conducted as retrospective, observational study at the Clinic of Infectious Diseases of the Clinical Center University of Sarajevo. It included the patients treated from June 2020 to December 2021. The presence of SARS-CoV-2 was detected by polymerase chain reaction (PCR) test. Inclusion criteria were: laboratory-confirmed diagnosis of COVID-19 based on PCR, patients older than 18 years, documented changes on chest radiography prior to hospitalization, hospital stay duration equal or more than five days in order to follow the dynamics of laboratory findings, and liver tests performed at least twice during the hospital stay. Exclusion criteria were: diagnosis of COVID-19 based only on rapid antigen test, age under 18 years, hospitalization shorter than five days, lack of liver tests during the hospital stay and previously diagnosed liver disease. Data retrieved from the patients' history records included: sex, age, previous liver disease, antibiotic use prior to hospitalization, duration of hospitalization, requirement for oxygen support via different modalities (nasal cannula, facial mask, high flow ventilation via nasal cannule (HF NC), non-invasive ventilation (NIV) or controlled mechanical ventilation (CMV)), use of tocilizumab, outcome of disease (recovery vs. death), and results of laboratory liver tests: AST, ALT, lactate dehydrogenase (LDH), and total bilirubin. There was no need for informed consent because this was an observational study without any implication to patient's treatment or personal data. Prior to hospital admission, patients signed informed consent for hospitalization and treatment.

All blood samples were analyzed at Department for Clinical Chemistry and Biochemistry of the Clinical Centre University of Sarajevo. The normal values of liver parameters were as follows: AST 0-38 U/L, ALT 0-48 U/L, LDH 123-243 U/L, and total bilirubin 1.7-20.5 μmol/L. Severity of COVID-19 was classified based on type of used oxygen support in two categories: low oxygen support group (via nasal cannula, facial mask or high flow ventilation), and high oxygen support (non-invasive ventilation or controlled mechanical ventilation).

Statistical analysis

Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 17.0 for Windows (Chicago, IL, USA). The normality and variance homogenity of data for quantitative variables were tested using the Kolmogorov-Smirnov or Shapiro-Wilk test. Categorical variables were demonstrated as numbers and percentages. Differences among them were assessed using Chi-square test. Results of descriptive statistics for quantitative variables are presented as arithmetic mean ± standard deviation (SD) for normally distributed variables or as median with interquartile range (25 - 75 percentile) for skewed variables. The significance of the mean differences between two groups was assessed by independent two-sample Student's t-test. The difference in values of parameters which showed a non-normal distribution was assessed by Mann-Whitney U-test or Kruskal-Wallis test. Statistical significance of the obtained results was set at $p<0.05$.

RESULTS

The study included 690 subjects. Low oxygen support (LOS) group consisted of 470 subjects and high oxygen support (HOS) group of 220 subjects. The average age of subjects in low oxygen support group was 66.21 ± 13.14 years and 59.4% were male, whereas average age of patients in high oxygen support group was 66.95 ± 11.06 years and 58.6% of them were male. There was no statistically significant difference between two groups when comparing age ($p=0.642$), but statistically significant difference was noticed when comparing gender in both groups ($p=0.01$). Duration of hospitalization was significantly shorter in the first group with mean of 11.96 ± 5.60 days comparing to 16.60 ± 9.50 days in the second group (p-value<0.0001). 43.6% subjects in LOS group and 33.2% subjects in HOS group used antibiotics before hospital admission ($p=0.12$). During the hospital stay, 11.3% subjects in LOS and 25.9% subjects of HOS were treated with tocilizumab with statistically significant difference ($p<0.0001$) (Table 1).

Table 1 **Baseline characteristics of the respondents.**

		Low oxygen support group (n=470)	High oxygen support group (n=220)	P value
Age (years)		66.21 ± 13.14	66.95 ± 11.06	0.642
Gender	Male	279 (59.4%)	129 (58.6%)	0.11
	Female	191 (40.6%)	91 (41.4%)	
Duration of hospitalization (days)		11.96 ± 5.60	16.60 ± 9.50	0.00*
Antibiotics used before hospital	Yes	205 (43.6%)	73 (33.2%)	0.12
	No	265 (56.4%)	147 (66.8%)	
Use of tocilizumab	Yes	53 (11.3%)	57 (25.9%)	0.00*
	No	417 (88.7%)	163 (74.1%)	

On admission, mean AST value was 58.67 ± 40.23 U/L in LOS and 58.82 ± 41.23 U/L in HOS respectively (Figure 1). No statistically significant difference was found between two groups (p=0.742).

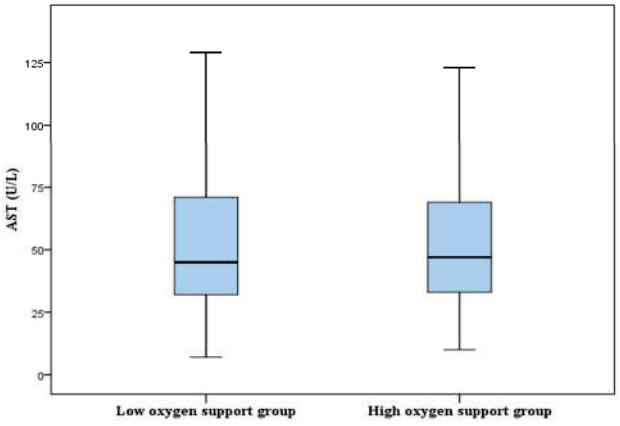

Figure 1 **AST value in low and high oxygen support group.**

Mean ALT value on admission was higher in LOS group with value of 60.08 ± 35.25 U/L compared to value of 49.66 ± 26.87 U/L in HOS group (Figure 2). This difference was statistically significant (p<0.001).

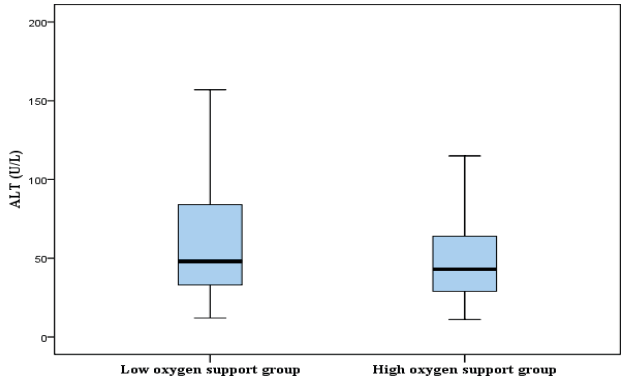

Figure 2 **AST value in low and high oxygen support group.**

Total bilirubin was statistically insignificantly higher in HOS group with mean of 10.35 ± 6.48 comparing to LOS group 9.52 ± 5.31 (p=0.075) (Figure 3).

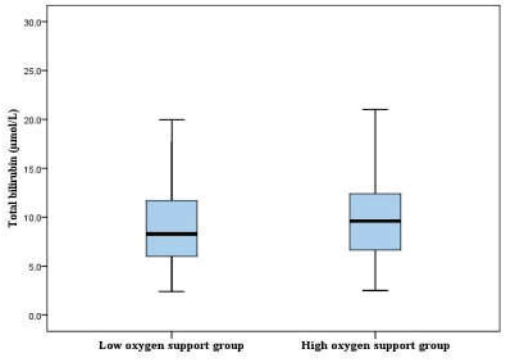

Figure 3 **Total bilirubin value in low and high oxygen support group.**

Value of AST in LOS group didn't differ between subjects who recovered and those who died (mean value 53.55 (± 29.66) U/L vs. 51.75 (± 26.69) U/L; p=0.678), as well as in the HOS group (mean value 50.49 (± 24.64) U/L vs. 53.49 (± 27.95) U/L; p=0.434).

Statistically significant higher values of ALT were documented in recovered subjects in both LOS and HOS group. In LOS group, mean ALT value in recovered subjects was 61.19 (± 35.84) U/L in comparison to 50.96 (±28.65) U/L in subjects who died (p=0.02). In HOS group mean ALT value was 58.08 (± 44.98) U/L in recovered and 44.98 (± 23.01) U/L in deceased subjects (p=0.001).

Total bilirubin was statistically significantly higher in deceased group in comparison to recovered in LOS group (9.21 (± 4.34) U/L vs. 10.72 (± 5.65) U/L; p=0.024). In HOS group values were 9.49 (± 3.79) U/L in recovered subjects and 10.28 (± 4.53) U/L in deceased (p=0.20) (Table 2).

Table 2 **Difference of AST, ALT and total bilirubin value in recovered and deceased patients.**

	Low oxygen support group (n=470)			High oxygen support group (n=220)		
	Recovery	Death	p-value	Recovery	Death	p-value
AST (U/L)	53.55 (± 29.66)	51.75 (± 26.69)	0.678	50.49 (± 24.64)	53.49 (± 27.95)	0.434
ALT (U/L)	61.19 (± 35.84)	50.96 (±28.65)	0.02*	58.08 (± 44.98)	44.98 (± 23.01)	0.001*
Total bilirubin (U/L)	9.21 (± 4.34)	10.72 (± 5.65)	0.024*	9.49 (± 3.79)	10.28 (± 4.53)	0.20

DISCUSSION

Impaired liver function in patients suffering from the COVID-19 disease is not rare. Why liver damage occurs during this disease is not fully known, but in this regard, the emphasis is on inflammatory events during the disease, hypoxemia and hypoxia, predisposing liver diseases, use of hepatotoxic drugs, and activation of the ACE2 receptor. A significant proportion of our subjects, regardless of the examined group, had elevated values of liver transaminases. Any inflammatory event in the body can potentially disrupt liver function. In their research, Mihara M, et al., concluded that elevated levels of IL-6 in COVID-19 disease recruit a large number of neutrophils and amplify the inflammatory response, during which damage to the liver and an increase in liver transaminases can occur (7). Furthermore, according to some studies, the degree of liver function damage may correlate with the severity of the COVID-19. In this regard, Uhm JS, et al., in their study proved that asymptomatic patients and those with a mild clinical features of COVID-19 had normal transaminase values (8), while another study showed that elevated AST values strongly correlated with a poor prognosis in patients with COVID-19. Contrary to the aforementioned study, among our subjects, the values of AST and bilirubin did not differ statistically significantly between the two examined groups (patients with a milder and more severe form of the disease). Moreover, ALT values were statistically significantly higher in surviving patients in both study groups compared to subjects who had a lethal outcome. Total bilirubin values were statistically significantly higher in patients who died in the group of subjects who request lower amount of oxygen support (nasal cannula, face oxygen mask). In this respect, in their study, Chen W, et al., monitored the values of direct bilirubin in patients suffering from COVID-19 and concluded that elevated direct bilirubin is an independent predictor for the development of complications of the COVID-19 disease and the occurrence of death. Furthermore, according to their study, elevated direct bilirubin after the seventh day of hospitalization is a better predictor of disease outcome compared to direct bilirubin values at admission (9). We emphasize that we monitored only total bilirubin values, while bilirubin fractions were only performed in patients with underlying liver disease. Since ALT is a more specific indicator of liver function, the elevation of this marker in our study could correlate with the prehospital use of antibiotics, which in our region was generally highly prevalent during the COVID-19 pandemic. Although the prehospital use of antibiotics was common among both groups of our subjects, there was no statistically significant difference in this regard. However, significantly higher ALT values were recorded among the surviving subjects in both test groups compared to the deceased subjects. As we have seen, some studies have shown that the levels of liver transaminases are predictors of a worse outcome, but anyway it is important to prove and highlight the mechanism of liver damage itself. Among our subjects, hypoxia could be the leading cause of liver damage, given that all subjects needed oxygen support, probably associated with administered drugs that are metabolized in the liver and general inflammatory events during the course of the disease itself. As a shortcoming of our study, we point out that cytokine values, especially IL-6, as well as bilirubin fractions, were not routinely monitored and comparing their values may result in stronger support for the correlation of liver damage and cytokine storm.

CONCLUSION

Given that SARS-CoV-2 affects multiple organ systems, liver function disorders in COVID-19, particularly in severe cases, are unavoidable. In our study, we proved that elevated values of total bilirubin are associated with an increased likelihood of fatal outcomes in patients requiring oxygen support via nasal cannula, facial oxygen mask, and high flow ventilation via nasal cannula compared to surviving patients from the same examined group. We did not prove that elevated values of liver transaminases were associated with a worse prognosis of the disease in the studied groups.

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Reprint request and correspondence:
Amila Muratspahić, MD
Clinic of Infectious Diseases
Clinical Center University of Sarajevo
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina
Email: amila.muhic@hotmail.com
ORCHID ID: 0009-0008-9033-312X

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

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Retrospective study - Spondylodiscitis treated at the Clinic of Infectious Diseases of the Clinical Center University of Sarajevo in the period from 2012 to 2022

Retrospektivna studija- Spondilodiscitisi liječeni na Klinici za infektivne bolesti Kliničkog centra Univerziteta u Sarajevu u periodu od 2012. do 2022. godine

Saliha Topalović-Hamzakadić*, Rusmir Baljić, Ilhama Jusufi-Hurić

Clinic of Infectious Diseases, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: spondylodiscitis is an infection of the intervertebral disc and adjacent vertebral plates. According to data from the available literature, men are affected three times more often than women, and the disease most often occurs between the sixth and eighth decade of life. Etiologically, various microbiological agents can be found in the substrate. Often the etiology is not known. The clinical presentation is often nonspecific, and symptoms and signs include back pain, fever, nausea, and weight loss. Aim: to characterize the clinical picture and identify the etiology, comorbidities and therapeutic modes of spondylodiscitis that were treated at the Clinic of Infectious Disease of the Clinical Center University of Sarajevo in the period from 2012 to 2022. Materials and methods: a retrospective study was conducted in which cases of spondylodiscitis were identified. The data was collected by looking at the patients' medical histories. Results: in the 10 year period, 60 patients met the criteria for inclusion in the study. On average, it took 5 months from the onset of symptoms to the verification of the diagnosis. The average number of hospital days was 32 days and ranged from 15 days to 69 days. Blood cultures were positive in 22 patients (36.6%). Brucellosis was the most common cause of spondylodiscitis in our patients, where as many as 42 patients (70%) had it. A total of 50 patients (83.4%) had an etiological diagnosis. The main source of infection was not identified in 10 patients (16.6%). Simultaneous psoas muscle abscesses were also observed in 10 patients (16.6%), paravertebral abscesses in 4 patients (6.6%) and epidural abscesses in 2 patients (3.3%). Among brucellosis spondylodiscitis, 35 (83.3%) patients were diagnosed with acute brucellosis, 4 (16.8%) with subacute brucellosis and 3 (7.1%) with chronic brucellosis. All patients reported back pain in their anamnestic history. 38 (90.4%) patients reported positive epidemiological data on contact with animals, consumption of dairy products. Conclusion: despite prolonged and microbiologically targeted antibiotic therapy, spondylodiscitis is associated with significantly more severe effects including prolonged hospital stay, persistence of symptoms. Complications with the formation of vertebral abscesses are common. The data from our study show limited possibilities of conservative treatment, therefore we emphasize the need for further research and evaluation of the impact of timely surgical interventions on the course and outcome of the disease.

Key words: spondylodiscitis, brucellosis, antibiotics

SAŽETAK

Uvod: spondilodiscitis predstavlja infekciju intervertebralnog diska i susjednih vertebralnih ploča. Prema podacima iz dostupne literature muškarci su oboljeli oko 3 puta više od žena, a najčešće se obolijeva između šeste i osme decenije života. Etiološki se u podlozi mogu naći različiti mikrobiološki uzročnici. Nerijetko se etiologija ne dokuči. Klinička slika je često nespecifična, a simptomi i znaci uključuju bol u kralježnici, groznicu, mučninu i gubitak težine. Cilj: okarakterizirati kliničku sliku te identificirati etiologiju, komorbiditete i terapijske moduse spondilodiscitisa koji su liječeni na Klinici za infektivne bolesti Kliničkog centra Univerziteta u Sarajevu u periodu od 2012. do 2023. godine. Materijali i metode: provedena je retrospektivna studija u kojoj su identificirani slučajevi spondilodiscitisa. Podaci su prikupljeni uvidom u historije bolesti pacijenata. Rezultati: u periodu od 10 godina, 60 pacijenta su ispunili kriterijume za uključivanje u studiju. Prosječno je od pojave simptoma do verificiranja dijagnoze bilo potrebno 5 mjeseci. Broj hospitalnih dana u prosjeku je bio 32 dana a kretao se u rasponu od 15 dana do 69 dana. Hemokulture su bile pozitivne kod 22 pacijenata (36,6%). U podlozi spondilodiscitisa kod naših pacijenata najčešće se nalazila bruceloza gdje su čak 42 pacijenta (70%). Ukupno 50 pacijenata (83,4%) imalo je etiološku dijagnozu. Osnovni izvor infekcije nije identifikovan kod 10 pacijenata (16,6%) Uočeno je i prisustvo istovremenih apscesa psoas mišića kod 10 pacijenata (16,6%), paravertebralnih apscesa kod 4 pacijenata (6,6%) i epiduralnih apscesa kod 2 pacijenta (3,3%). Među bruceloznim spondilodiscitisima kod 35 (83,3%) bolesnika dijagnostikovana je akutna bruceloza, 4 (16,8%) sa subakutnom brucelozom i 3 (7,1%) sa hroničnom brucelozom. Svi pacijenti su anamnestički naveli podatak o boli u kičmi. Pozitivan epidemiološki podatak o kontaktu sa životinjama, konzumaciji mliječnih proizvoda

navelo je 38 (90,4%) pacijenata. Zaključak: Uprkos produženoj i mikrobiološki ciljanoj antibiotskoj terapiji spondilodiscitis povezan sa značajnim težim učincima uključujući produženi boravak u bolnici, perzistiranje tegoba. Česte su komplikacije sa formiranjem verebebralnih apscesa. Podaci iz naše studije pokazuju ograničene mogućnosti konzervativnog tretmana, stoga naglašavamo potrebu za daljim istraživanjima i procjenom uticaja pravovremenih hirurških intervencija na tok i ishod bolesti.

Ključne riječi: spondilodiscitis, bruceloza, antibiotici

INTRODUCTION

Spondylodiscitis as an infection of the intervertebral disc and osteomyelitis of adjacent vertebral plates occurs more often in developing countries. It is an uncommon disease in developed countries (1). The incidence in developed countries ranges from 0.2 per 100,000 to 2.4 cases per 100,000 inhabitants. In developing countries, this rate is estimated to be significantly higher (1,2). The most common risk factors are diabetes mellitus and older age. Men are affected about 3 times more than women, and patie nts are also more affected between the sixth and eighth decade (3). Etiologically, various microbiological agents can be found in the substrate. Often the etiology is not known. The clinical picture is non-specific, so a diagnosis is often not made in time (4). Sometimes it causes serious complications such as irreversible neurological deficits or even a fatal outcome. For an etiological diagnosis, blood cultures are often the first step in trying to identify the causative agent (5). CT-guided diagnostic puncture is also recommended in patients in whom the microbiological diagnosis has not been established by blood cultures or serological tests (6). Among the available radiological diagnostic methods for diagnosing spondylodiscitis, magnetic resonance imaging (MRI) is the method of choice (7). Early diagnosis is important because spondylodiscitis is often associated with abscess formation in the epidural space and adjacent soft tissues and muscles (8). The effects of local inflammation and abscess formation can lead to spinal cord compression and/or spinal instability, resulting in permanent neurological deficit. Treatment includes a combination of prolonged antimicrobial therapy and surgical intervention (8,9,10).

AIM

The aim od this study was to characterize the clinical picture and identify the etiology, comorbidities and therapeutic modes of spondylodiscitis treated at the Clinic of Infectious Disease of the Clinical Center University of Sarajevo in the period from 2012 to 2022.

MATERIALS AND METODS

Our goal was to describe the clinical characteristics, etiology, comorbidities and treatment modalities of spondylodiscitis and to identify risk factors. Cases of spondylodiscitis treated in our clinic from 2012 to 2022 were identified. The criterion for inclusion in the study was a proven diagnosis of spondylodiscitis, based on a combination of clinical and laboratory findings, confirmed by radiological characteristics. A retrospective study was conducted. The data was collected by reviewing the patients' medical histories. Data of interest were anamnestic data, comorbidities, length of hospitalization, duration of complaints before hospital admission, clinical presentation, laboratory and radiological parameters, principles of therapy.

RESULTS

In a 10 year priod, 60 patients met the criteria for inclusion in the study. The patients in the study had a median age of 60 years (range, 10-83 years). Thirty-seven (61.6%) of these patients were men, twenty-three (38.4%) were women. In addition, 9 (15%) patients had a history of spine surgery in the last three years. On average, it took 3 months from the onset of symptoms to verifying the diagnosis. The complaints lasted from one month to even 2 years. The average number of hospital days was 32 days ranging from 15 to 69 days. The predominant symptoms were fever and back pain. Fever was present in 85% of patients and 100% of patients had pain in the spine. Blood cultures were positive in 22 patients (36.6%). Five patients underwent a puncture under the control of computed tomography, of which 4 patients received a positive microbiological isolate. Brucellosis was the most common cause of spondylodiscitis in our patients, registered in 42 patients (70%). A total of 50 patients (83.4%) had an etiological diagnosis. The underlying source of infection was not identified in 10 patients (16.6%) The diagnostic workup mainly consisted of an initial CT scan followed by a confirmatory MRI. 90% of patients had involvement of the lumbosacral spine.

Description of etiological agents identified in blood cultures:

Microbiological isolate	Study population, n (%)
Staphylococcus aureus MSSA	4 (6.6)
Brucella species	8 (13.3)
Klebsiella pneumoniae ESBL	1 (1.6)
Brucella melitensis	6 (10)
Enterococcus faecalis	2 (3.3)
Streptococcus species	1 (1.6)

Abbreviations: MSSA, methicillin-susceptible S. aureus, ESBL, extended-spectrum beta-lactamase-producing K. Pneumoniae

The presence of simultaneous psoas muscle abscesses in 10 patients (16.6%), paravertebral abscesses in 4 patients (6.6%) and epidural abscesses in 2 patients (3.3%) was also observed. One

patient was radiologically suspected of a specific tuberculous process on the thoracolumbar spine, and she responded positively to the introduced antituberculosis therapy. In patients with brucellosis etiology of spondylodiscitis, the lumbar spine was most often affected.

Regarding patient comorbidities, hypertension was the dominant comorbidity in 10 patients (16.6%), diabetes mellitus was present in 8 patients (13.3%). 4 patients had a urinary infection (6.6%), coinfection with Q fever in 2 patients (3.3%), among other comorbidities were renal insufficiency, liver cysts, various autoimmune diseases, angina and other cardiac problems. Level C-reactive protein (CRP) was elevated in 35 patients (58.3%) and ranged from 15 to 243. Sedimentation was accelerated in 100% of patients. Eighteen patients (30%) had leukocytosis (>10,000). Twenty-two patients (36.6%) had septicemia. Among brucellosis spondylodiscitis, the age of the patients ranged from 45 to 83 years. All patients underwent the Rose Bengal test, and 35 (83.3%) patients had a positive result. The Elisa test showed positivity in all 42 patients. Acute brucellosis was diagnosed in 35 (83.3%) patients, 4 (16.8%) with subacute brucellosis and 3 (7.1%) with chronic brucellosis. All patients had verified spondylodiscitis. Simultaneous psoas muscle abscesses were observed in 10 patients (23.8%), paravertebral abscesses in 2 (4.7%) patients. From the onset of symptoms to hospitalization, an average of 5 months passed (ranging from one month to two years). All patients reported back pain in their anamnestic history. 28 (66.6%) patients had fever. 38 (90.4%) patients reported positive epidemiological data on contact with animals, consumption of dairy products. Leukocytosis was verified in 30 (71.4%) patients, 9 (21.4%) patients had mild thrombocytopenia. Aspartate transaminase and alanine transaminase values were elevated in 25 (59.5%) patients.

Treatment included long courses of antibiotics (>6 weeks in 82% of cases) and surgical treatment, which five patients (8.3%) underwent. In general, patients were treated with systemic antibiotic therapy for at least 6 weeks. Since the etiological basis of our spondylodiscitis was brucellosis, 42 patients were treated with directed anti-brucellosis therapy, which included a regimen of treatment with Gentamicin and Doxycycline during the first two weeks of therapy, and then instead of Gentamicin, Rifampicin was included for at least another four weeks, which of course continued with Rifampicin therapy with Doxycycline.

Other antibiotic courses included dual antibiotic therapy with Ceftriaxone and Vancomycin for 6 weeks for enterococcal, streptococcal, staphylococcal, and spondylodiscitis of unclear etiology. The patient in whom Klebsiella pneumoniae ESBL was etiologically verified was treated with Meropenem. Despite all treatment modalities, 60% of patients left a certain neurological deficit at discharge. In 70% of patients pain in the spine persisted at discharge. The presence of neurological damage on admission, longer duration of symptoms before admission, radiological evidence of spinal cord compression and diabetes mellitus were factors associated with worse recovery. Spondylodiscitis has a significant share in morbidity, and worse recovery can be predicted to a certain extent by factors present at the time of diagnosis.

Data from other studies in developing countries are similar, showing that it takes a long time to establish a diagnosis, a microbiological diagnosis is reached in 80% of cases, treatment consists of long courses of antibiotics and surgical treatment (which in the available literature is performed more often than which is the case at our tertiary level of health care) (11,12,13,14).

DISCUSSION

Our study provides an analysis of the clinical presentation, etiology, diagnosis, and treatment of spondylodiscitis in 60 identified individuals treated over ten years at the Infectious Disease Clinic in Sarajevo. In accordance with previous research, we have shown that spondylodiscitis is more common with increasing age. Regarding gender, our data show that men are affected in a ratio of 1.5:1, which is not the case in the available literature, where men are affected three times more often. This could perhaps be explained by the inadequate recognition of the diagnosis itself at the primary level of health care.

The combination of blood culture and punctate analysis with serological results enabled the establishment of a microbiological diagnosis in most patients. In 70% of patients, the presence of brucellosis as an etiological agent was detected, which confirmed the importance of testing, especially for patients coming from endemic areas and with positive anamnestic findings. One third of the patients had a positive blood culture, which confirms the importance of this simple investigation in patients with suspected spondylodiscitis.

During the follow-up of brucellosis spondylodiscitis already at the end of the first month out of 42 brucellosis patients, 21 of them (50%) had a regression of symptoms in terms of the cessation of fever, they also reported less pain in the spine. Despite the promising data, the rest of the patients did not have the best response to conservative treatment. Therefore, brucellosis remains a significant public health problem. It should be considered in patients who live in areas with a high incidence of brucellosis and have high fever, joint and back pain. The data from our study show limited options for conservative treatment, therefore an assessment of possible surgical treatment is desirable in the clinical course.

Our data show that despite prolonged and microbiologically targeted antibiotic therapy, spondylodiscitis is associated with significantly more severe outcomes including prolonged hospital stay, persistent pain, and less than half of patients fully recover. More surgical interventions would probably be desirable to improve disease outcome.

Regarding the antimicrobial therapy used, the majority of patients received therapy for 6 weeks, including combined antibiotic therapy, with an initial intravenous regimen with an additional oral antibiotic regimen. This approach is consistent with that published elsewhere in the available literature, and international guidelines suggest that at least 6 weeks of antibiotic therapy is required for the treatment of spondylodiscitis (13,14).

CONCLUSION

Spondylodiscitis is a serious disease that leads to significantly long morbidity. Due to the non-specificity of the symptoms of the disease and its indolent nature, it is necessary to establish an adequate diagnosis as soon as possible, since it has been shown that it takes a long time from the onset of symptoms to the verification of the diagnosis. The disease leaves long-term consequences despite adequate treatment of the infection. It seems that risk factors present at the beginning of treatment can predict a worse clinical outcome. We emphasize the need for further research and evaluation of the impact of early surgical interventions on the course and outcome of the disease.

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Reprint requests and correspondence:

Saliha Topalović -Hamzakadić, MD
Clinic of Infectious Diseases
Clinical Center University of Sarajevo
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina
Email: saliha_1993_@hotmail.com
ORCHID ID: 0000-0002-3788-626

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Difference in clinical presentation of people living with HIV and opportunistic infections related to age

Razlike u kliničkoj prezentaciji pacijenata koji žive s HIV-om i oportunističkim infekcijama u odnosu na dob

Ahmed Velić[1]*, Irma Zahirović[2], Mufida Aljičević[2], Enra Lukovac[1], Rusmir Baljić[1], Meliha Hadžović-Čengić[1]

[1]Clinic of Infectious Diseases, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
[2]Medical Faculty, University of Sarajevo, Čekaluša 90, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: the Human Immunodeficiency Virus (HIV) infection has several stages, with the final stage being Acquired Immunodeficiency Syndrome (AIDS), characterized by a low CD4 count and opportunistic infections. These infections are caused by microorganisms that usually don't affect healthy individuals but can cause disease in those with advanced HIV. Aim: to show clinical and laboratory differences in patients with AIDS in relation to the age group to which they belong. Materials and methods: the study included 50 people with HIV and opportunistic infections hospitalized at the Clinic of Infectious Diseases of the Clinical Center University of Sarajevo from 1 January 2018 to 31 December 2022. Clinical and laboratory characteristics were compared based on age groups (younger and older than 45 years). Results: the frequency and number of opportunistic infections did not differ significantly between the two groups. Oropharyngeal candidiasis was the most common infection, and toxoplasmosis was found only in patients over 45 years of age. Younger patients had lower CD4 cell counts, while patients older than 45 experienced more frequent thrombocytopenia. Conclusion: other factors than the age group to which the patient belongs obviously have a significant influence on the emergence of various manifestations in the context of AIDS.

Keywords: HIV, AIDS, opportunistic infections

SAŽETAK

Uvod: infekcija virusom humane imunodeficijencije (HIV) ima nekoliko faza, a završni stadij je sindrom stečene imunodeficijencije (AIDS), karakteriziran niskim brojem CD4 i oportunističkim infekcijama. Ove infekcije su uzrokovane mikroorganizmima koji obično ne pogađaju zdrave osobe, ali mogu uzrokovati bolest kod onih s uznapredovalom HIV infekcijom. Cilj: pokazati kliničke i laboratorijske razlike kod pacijenata sa AIDS-om u odnosu na starosnu grupu kojoj pripadaju. Materijali i metode: istraživanjem je obuhvaćeno 50 osoba sa HIV-om i oportunističkim infekcijama hospitaliziranih na Klinici za infektivne bolesti Kliničkog centra Univerziteta u Sarajevu od 01.01.2018. do 31.12.2022. godine. Kliničke i laboratorijske karakteristike su uspoređene na osnovu starosna grupa (mlađi i stariji od 45 godina). Rezultati: učestalost i broj oportunističkih infekcija nisu se značajno razlikovali između ove dvije grupe. Orofaringealna kandidijaza bila je najčešća infekcija, a toksoplazmoza je pronađena samo kod pacijenata starijih od 45 godina. Mlađi pacijenti su imali manji broj CD4 ćelija, dok su pacijenti stariji od 45 godina imali češću trombocitopeniju. Zaključak: drugi faktori osim starosne grupe kojoj pacijent pripada očigledno imaju značajan uticaj na pojavu različitih manifestacija u kontekstu AIDS-a.

Ključne riječi: HIV, AIDS, oportunističke infekcije

INTRODUCTION

In the 1980s, unusual infections and rare types of cancer appeared in previously healthy young people in California and New York. It was discovered that these individuals were infected with the human immunodeficiency virus (HIV), which leads to acquired immunodeficiency syndrome (AIDS). At that time, patients infected with HIV usually did not have access to the antiretroviral therapy available today, and the infection often led to a fatal outcome (1,2).

There is a common misconception that HIV and AIDS are the same, but they are not. HIV stands for human immunodeficiency virus, which is the virus that causes the infection. AIDS stands for acquired immunodeficiency syndrome and represents the final stage of the HIV infection. The term "syndrome" refers to a collection of symptoms, "acquired" means it is not congenital, and "immunodeficiency" indicates the effect on the immune system (3,4).

In 1984, evidence was established that HIV leads to AIDS. HIV belongs to the Lentiviridae genus. When the virus enters the body, it binds to receptors on the surface of CD4 lymphocytes. Once inside the CD4 lymphocytes, the virus uses the host's resources to replicate and maintain its life cycle, ultimately leading to the premature death of the CD4 lymphocytes. CD4 lymphocytes play a crucial role in mediating immune processes in the body. They are involved in cytokine-mediated activation of macrophages, cytotoxic and B lymphocytes, as well as non-immune cells, and in suppressing

an overactive immune response. The normal range of CD4 lymphocytes in the peripheral blood is between 500 and 1500 cells per cubic millimeter of blood. A reduced number of CD4 lymphocytes prevents an adequate immune response, leaving the body vulnerable to bacterial, viral, fungal, and other infections. When the number of CD4 cells is low, opportunistic microorganisms in the body have an increased chance of causing disease, which is also a determinant of AIDS - a low CD4 lymphocyte count and the presence of opportunistic infections (4-7).

Once the virus enters the body, it initiates acute HIV infection in about 50% of infected individuals. The symptoms can vary, but typically include symptoms similar to infectious mononucleosis such as swollen lymph nodes, sore throat, and fever. After the initial symptoms subside, chronic infection ensues, which is usually asymptomatic until the disease progresses. Throughout all stages, there are significant immune system processes occurring: the virus attacks and destroys CD4 cells, the body produces antibodies against the virus, these antibodies help to clear the virus from the blood but not entirely efficiently, as the virus remains active in the tissues, the number of CD4 cells decreases, and the number of virus copies in the blood increases (8).

As per the information above, opportunistic infections occur in individuals with untreated HIV due to weakened immune defenses. This allows various pathogens to multiply and cause disease throughout the body. Normally harmless pathogens take advantage of the compromised immune system to cause infections, hence they are referred to as opportunistic. It's important to note that opportunistic infections are not unique to HIV and can occur in other conditions that weaken the body's immune defenses. However, they significantly contribute to the illness and mortality of individuals living with HIV, along with malignancies (9).

There is a dearth of scientific research on the subject of HIV and AIDS in Bosnia and Herzegovina. Despite assertions of a low prevalence of HIV infection, there has been a notable rise in newly reported cases in recent years. Regrettably, the surge in new cases, particularly in the period since the onset of the COVID-19 pandemic, has not been accompanied by a proportionate increase in investment in treatment and, specifically, prevention of HIV infection. Our primary objective is to raise awareness about this frequently overlooked domain of infectology, which is often subject to stigmatization and associated with a range of negative connotations when not forgotten altogether. The principal focus of our research is to undertake a comparative analysis of the clinical presentation and laboratory parameters in HIV patients with one or more opportunistic infections across different age groups.

AIM

The aim of the study was to show clinical and laboratory differences in patients with AIDS in relation to the age group to which they belonged.

MATERIALS AND METHODS

A retrospective, comparative, clinical research study was conducted at the Clinic of Infectious Diseases of the Clinical Center University of Sarajevo in the period from 1 January 2018 to 31 December 2022. The study included 50 hospitalized patients with confirmed HIV infection and one or more opportunistic infections. Excluded from the study were patients not hospitalized, those who refused Highly Active Antiretroviral Therapy (HAART), and those not in the stage of AIDS. The patients were categorized into two groups according to age, specifically younger than 45 years and 45 years or older. Variables such as demographic data, patients' admission complaints, and data on the number and types of opportunistic infections were taken into consideration. Furthermore, the study considered basic laboratory parameters and immune status, specifically the count of CD4 and CD8 lymphocytes. All data were obtained through the review of patients' medical histories. Statistical analysis was conducted using the IBM SPSS Statistics program (version 22.0), incorporating tests such as the Student t-test, Mann-Whitney U test, and Chi-square test. A P value of less than 0.05 was deemed statistically significant. The study adhered to the most recent iteration of the Declaration of Helsinki and received approval from the Ethics Committee of the Clinical Center University of Sarajevo.

RESULTS

In the context of the gender structure, a higher representation of male patients was observed in the study (Table 1).

Table 1 **Demographic characteristic of HIV-positive patients. Data are presented as absolute numbers (and percentages).**

	Females	Males
GENDER	8 (16%)	42 (84%)
AGE	< 45 years	>= 45 years
	29 (58%)	21 (42%)

Commencing from 2018, a gradual decrease in the number of hospitalized patients living with HIV and experiencing one or more opportunistic infections was noted until 2021. However, in 2022, an increase in the number of hospitalized patients was recorded (Table 2).

Table 2 **Number of hospitalized patients according to the years. Data are presented as absolute numbers (and percentages).**

Years	2018	2019	2020	2021	2022
Number of patients	16 (32%)	10 (20%)	9 (18%)	4 (8%)	11 (22%)

The predominant opportunistic infection among the subjects was oropharyngeal candidiasis, while toxoplasmosis was exclusively present in subjects older than 45 years (Figure 1).

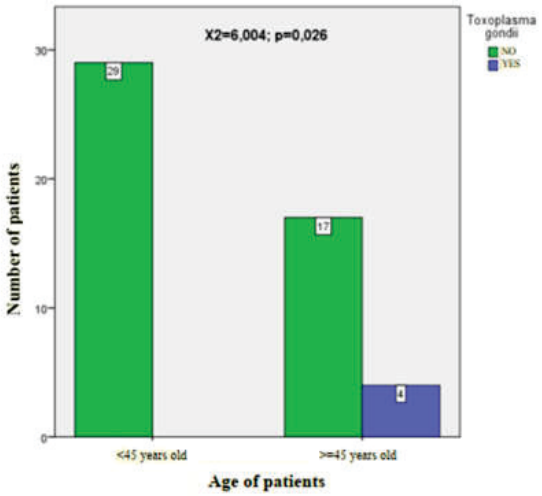

Figure 1 **Prevalence of infection with *Toxoplasma gondii* according to the age of the patients.**

Significantly lower CD4 cell counts were observed in patients younger than 45 years (Figure 2). Thrombocytopenia was notably more prevalent in patients over 45. Furthermore, urea values were found to be statistically significantly higher in the group of patients younger than 45 years, although they did not correlate with elevated creatinine values (Table 3).

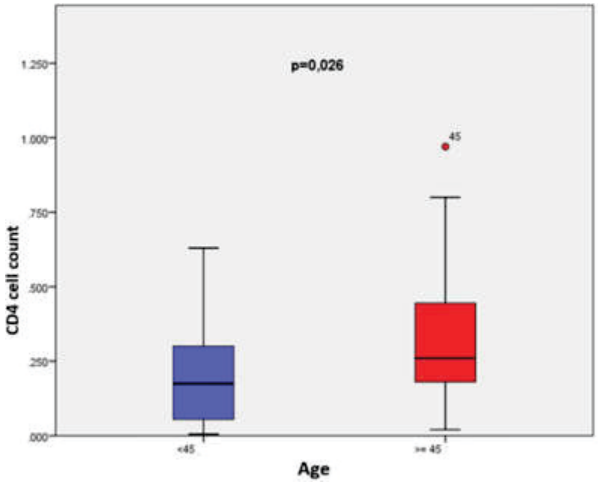

Figure 2 **Difference in the number of CD4+ T lymphocytes according to age groups of patients.**

Table 3 **Values of laboratory parameters.**

	<45 years	>45 years	P value
Platelets ($x10^9$/L)	174.0 (96.2-293.0)	101.75 (101.0-133.5)	0.024
Urea (mmol/L)	4.1 (3.3-4.8)	12.45 (4.45-31.76)	0.044
Creatinine (μmol/L)	70.0 (61.0-90.0)	215.0 (77.0-473.75)	0.376

DISCUSSION

Our research focused on hospitalized individuals with HIV infection and one or more opportunistic infections over a five-year period from 2018 to 2022. Notably, there was a declining trend in the proportion of hospitalized patients living with HIV during this duration, with 32% in 2018, 20% in 2019, 18% in 2020, and a significant decrease to 8% in 2021. Anticipated data for 2022 suggested an increase in 22%. The decline in hospitalizations in 2020 and 2021 may be attributed to factors such as reduced medical consultations, diagnostic procedures, and screenings, likely influenced by the COVID-19 pandemic and associated mobility and gathering restrictions (10).

Based on the results obtained from our survey, it was evident that a majority of our respondents were male, comprising 84% of the total respondents, while 16% were female. The age range of the respondents spanned from 23 to 68 years, with 58% of individuals being under 45 years old and 42% being over 45. The data from the Institute for Public Health of the Federation of Bosnia and Herzegovina indicates that over 88% of individuals living with HIV are male, with the highest prevalence among 20 to 29-year-olds (11). However, consistent and official data regarding the age structure of AIDS patients is not universally available.

Oropharyngeal candidiasis was the most common opportunistic infection in our subjects, affecting 32% of them, followed by progressive multifocal leukoencephalopathy (PML) and HIV encephalopathy at 22%. In third place, pneumonia caused by the fungus Pneumocystis jirovecii affected 16% of the subjects. A study in Nigeria, which included over 17,000 subjects living with HIV, also confirmed the highest frequency of oropharyngeal candidiasis (12). In a study conducted by Meng S, et al, in southwest China, more than 12,000 subjects living with HIV were examined. The most common opportunistic infection among the subjects was pneumonia caused by P. jirovecii, followed by tuberculosis, and candidiasis in third place (13).

The occurrence of specific opportunistic infections is linked to the number of CD4 lymphocytes in the body. It has been observed that the development of tuberculosis bacillus infection in individuals with HIV is not solely determined by the number of CD4 lymphocytes. However, PCP pneumonia and oropharyngeal candidiasis are more common when the number of CD4 cells falls below 200 per mm^3 of blood. HIV encephalopathy is characterized by a CD4 cell count below 100, and for encephalitis caused by Toxoplasma gondii, the CD4 cell count is below 50 per mm^3 of blood (14). When it comes to the CD4 cell count, our study found that subjects from both groups who had PCP pneumonia and oropharyngeal candidiasis had a CD4 cell count below 200 per mm^3 of blood. However, this was not consistently the case for those with HIV encephalopathy and PML. Most of the latter group had CD4 cell counts below 200 but not consistently below 100 CD4 cells per mm^3 of blood. Numerous factors contribute to why certain opportunistic infections occur more frequently than others. Geographical and climatic conditions play a role, in influencing the prevalence of causative agents and diseases like tuberculosis. Social and economic factors also affect the availability of prophylaxis and highly active antiretroviral therapy. Additionally, social circumstances, sexual education, the stigma associated with HIV, and awareness about the need for testing and early detection of HIV infection all influence the prevention of AIDS and the occurrence of opportunistic infections (15). The frequency of HIV encephalopathy and PML among our subjects is 22%, which

represents a significant proportion. This could be explained by the aforementioned: the lack of sexual education in our region, the institutionalized way of testing for sexually transmitted diseases, the absence of practice and regulations regarding self-testing, the presence of stigmatization in society, and even among health workers. All this leads to the fact that patients resist being tested, and are often detected in the late stages of the disease when the number of CD4 cells is extremely low, which is the main prerequisite for the occurrence of opportunistic infections.

The frequency of opportunistic infections in relation to age did not exhibit significant variance between the two analyzed cohorts in our patient sample, with the exception of toxoplasmosis. Toxoplasmosis was absent in the cohort aged under 45 years, while four cases were identified in the cohort aged 45 years and above. Toxoplasma gondii induces a latent infection in immunocompetent individuals, typically causing no significant health complications. Conversely, in the context of immunocompromised states, the causative agent undergoes reactivation, resulting in proliferative behavior and focal inflammation with consequent lesion development in diverse organs, frequently impacting the brain parenchyma. Untreated, this condition can culminate in a fatal outcome if not promptly diagnosed and managed. Findings from two studies conducted in India indicated that seropositivity to T. gondii primarily occurs within the 30 to 40 age range among HIV-positive patients. The studies concluded that the incidence of toxoplasmosis escalates with increasing age, a trend attributed to a higher probability of exposure to the causative agent as individuals age (16,17).

In our study, we found that 74% of the respondents had two or more opportunistic infections, which was related to their CD4 cell count. Additionally, 64% of the patients had a CD4 cell count below 300 cells per mm^3 of blood. We also observed that the number of opportunistic infections was directly linked to longer hospital stays. Furthermore, we noted that patients under 45 years old had a lower CD4 cell count compared to those over 45, which might be due to differences in antiretroviral therapy duration and adherence to regular chronic therapy (18).

Based on the laboratory findings, it was observed that the number of platelets differed significantly between the two groups under investigation. Specifically, individuals under 45 mostly had a normal platelet count, while those over 45 years of age showed a higher frequency of thrombocytopenia. Thrombocytopenia is commonly associated with various infectious diseases, especially viral ones like HIV. It can occur in all stages of HIV infection due to disruptions in the formation and function of blood cells, particularly white blood cells and red blood cells leading to anemia, as well as platelets causing thrombocytopenia. The decrease in platelets during HIV infection can be a result of the virus directly affecting the cells responsible for producing platelets. One mechanism involves platelets being loaded with immune complexes or specific antibodies that bind to platelets and cause their destruction. More frequent occurrences of thrombocytopenia in older individuals may be attributed to age-related decline in bone marrow cellularity, higher prevalence of other health conditions, and greater use of multiple medications. Notably, two studies by Lv X, et al., and Ayanaw MA, et al., demonstrated that thrombocytopenia is more common in older subjects (over 35 and over 40), but age alone does not independently influence the frequency of thrombocytopenia (19,20).

It is important to note that symptoms and signs of acute HIV infection vary, and can even be completely absent in about half of patients. In the late stage of HIV infection, symptoms are mainly consistent with accompanying opportunistic infections (9). In our research, we found that in the under 45 age group, the most common complaint was elevated body temperature, while in the over 45 age group, it was loss of appetite.

In Bosnia and Herzegovina, discussions about HIV and AIDS among health workers are rare, except within a few expert circles. Professional papers on this topic rarely include patients living with HIV treated in our country's HIV centers. Our hope is that future studies will help change this by raising awareness, educating health workers, and reducing the stigma surrounding HIV.

CONCLUSION

It was anticipated that individuals aged 45 and above would demonstrate a heightened degree of immune compromise and an increased frequency of opportunistic infections. However, it is evident that, beyond mere age, variables such as the stage of HIV diagnosis, patient adherence to treatment, presence of comorbid conditions, and the specific antiretroviral drug regimen significantly influence the nature and severity of opportunistic infections and immune system impairment, as evidenced by CD4 cell counts and changes in laboratory parameters. Consequently, it is imperative to undertake further investigations that not only incorporate age but also encompass these aforementioned variables and their collective impact on the trajectory and prognosis of HIV infection.

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Reprint requests and correspondence:
Ahmed Velić, MD
Clinic of Infectious Diseases
Clinical Center University of Sarajevo
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina
Email: avelic113@gmail.com
ORCID ID: 0000-0001-5898-6982

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Clinical and laboratory characteristics in Juvenile - onset systemic lupus erythematosus - overcoming challenges of early diagnosis

Kliničke i laboratorijske karakteristike Juvenilnog sistemskog lupus eritematosusa - prevazilaženje izazova rane dijagnoze

Adisa Čengić[1], Velma Selmanović[1], Sniježana Hasanbegović[1], Danka Pokrajac[1], Izeta Hamza[2]

[1]Paediatric Clinic, Clinical Centre University of Sarajevo, Patriotske lige 81, 71000 Sarajevo, Bosnia and Herzegovina
[2]Health Centre of Canton Sarajevo, Vrazova 11, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: Juvenile-onset systemic lupus erythematosus (jSLE) is a rare chronic autoimmune disease with multisystemic involvement that can cause significant damage, disability and death. jSLE has a more severe disease presentation than lupus in adults, with a higher incidence of major organ involvement. Aim of the study is to determine the presenting clinical and laboratory characteristics of jSLE patients and to compare symptoms at disease onset from our cohort through a review of the literature. Materials and methods: rretrospective review of medical records encompassing all juvenile systemic lupus erythematosus (jSLE) patients treated in department from July 2007 to July 2024. Upon disease presentation, we abstracted array of clinical and laboratory indices: constitutional symptoms, skin and mucosal changes, arthritis, renal and CNS involvement, CRP, ESR, WBC, platelet count, DCT, ANA, anti-DsDNA, anti-Sm, antiphospholipid antibodies, C3, C4, and RF. Results:. Nineteen children (15 girls and 4 boys) were diagnosed with jSLE. The mean age was 11 years. Arthralgia was the most common complaint (78%), followed by fever, (47%). The most common clinical manifestation was arthritis (62%), followed by renal disease (68%), leukopenia (57%), oral ulcers and thrombocytopenia (42%), malar rash (31%), serositis (21%), and CNS symptoms (16%). Four patients (21%) had stage 2 nephritis, one had stage 3 nephritis, and three (16%) had stage 4 nephritis. All exhibited elevated ESR and positive ANA. Majority of patients had elevated anti-DsDNA (83%), anti-Sm (52%), antiphospholipid antibodies(62%), and anti-ribonucleoprotein antibodies in 9 patients (47%). Low C3 levels were observed in 14 patients (73%) and low C4 levels in 17 patients (88%). Conclusion: (jSLE) is a challenging disease in terms of both diagnosis and treatment. Any case of fever of unknown origin, particularly when accompanied by joint pain, should prompt an evaluation for jSLE. In our cohort, the most common presenting symptoms were fever, arthritis, and arthralgia.

Keywords: Juvenile onset SLE, clinical manifestation, laboratory markers

SAŽETAK

Uvod: juvenilni sistemski lupus eritematozus (jSLE) je rijetka i ozbiljna autoimuna bolest koja uzrokuje značajna oštećenja i invaliditet. jSLE se odlikuje težom prezentacijom bolesti u poređenju sa lupusom kod odraslih, sa većom incidencijom zahvaćenosti vitalnih organa. Cilj: ispitati kliničke i laboratorijske karakteristike jSLE pacijenata i uporediti ih s literaturom. Materijali i metode: izvršen je retrospektivni pregled medicinske dokumentacije svih pacijenata sa jSLE koji su primljeni na Kliniku za pedijatriju, Odjel za alergologiju, reumatologiju i kliničku imunologiju, Kliničkog centra Univerziteta u Sarajevu, u periodu od septembra 2007. do jula 2024. godine. Analizirani su: konstitucijski simptomi, promjene kože i sluznice, artritis, bubrežne i CNS manifestacije,CRP, SE, broj leukocita i trombocita, DCT, ANA, anti-DsDNA, anti-Sm, antifosfolipidna antitijela, C3, C4 i RF. Rezultati: kod devetnaestero djece (15 djevojčica i 4 dječaka) dijagnosticiran je jSLE. Prosječna dob bila je 11 godina. Nejčešći prezentirajući simptomi su bili artralgija (78%) i febrilnost (47%). Najčešće kliničke manifestacije lupusa bile su artritis (62%), zatim bubrežna bolest (68%), leukopenija (57%), oralni ulkusi i trombocitopenija (42%), malarni osip (31%), serozitis (21%) i CNS simptomi (16%). Kod četiri pacijenta (21%) dijagnosticiran je nefritis II stadijuma, kod jednog nefritis III stadijuma, dok su tri pacijenta (16%) imala nefritis IV stadijuma. Ubrzana SE i pozitivna ANA detektovane su kod svih pacijenata. Većina pacijenta je imala povišene: Anti-DsDNA(83%), anti-Sm (52%), antifosfolipidna antitijela (62%), antiRNP (47%). Nizak nivo C3 uočen je kod 14 pacijenata (73%), a nizak nivo C4 kod 17 pacijenata (88%). Zaključak: dijagnostika i tretman bolesnika sa jSLE predstavlja veliki izazov u svakodnevnoj praksi pedijatrijskog reumatologa. Najčešći prezentirajući simptomi u našoj kohorti bili su groznica, artritis i artralgija. Svi slučajevi produžene febrilnosti nepoznatog porijekla praćeni bolovima u zglobovima, trebaju biti evaluirani na jSLE.

Ključne riječi: juvenilni SLE, prezentirajući simptomi

INTRODUCTION

Juvenile-onset systemic lupus erythematosus (jSLE), also known as pediatric lupus (pSLE) or childhood SLE (cSLE), is a rare chronic autoimmune disease characterized by multisystemic involvement that can lead to significant damage, disability, and mortality. It is defined by disease onset before the age of 16 and affects approximately 15-20% of all systemic lupus erythematosus (SLE) patients. The incidence of jSLE varies between 0.36 and 2.5 per 100,000 children, with a prevalence ranging from 1.89 to 34.1 per 100,000. Therefore, jSLE meets the criteria for a rare disease classification in Europe (1). Juvenile-onset systemic lupus erythematosus (jSLE) presents a more severe clinical picture compared to adult lupus, characterized by a higher frequency of major organ involvement, a more aggressive disease progression, increased medication requirements, and heightened incidences of renal, cardiovascular, and neuropsychiatric complications (2,3). These factors collectively contribute to elevated morbidity and mortality rates associated with disease-related damage (4,5,6,7). The diagnosis and treatment of jSLE pose significant challenges due to the diverse array of initial symptoms, variability in disease course and severity, as well as differences in treatment responses. The 2017 SHARE (Single Hub and Access point for paediatric rheumatology in Europe) recommendations from emphasize the use of the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for diagnosing SLE in children and adolescents (8). These guidelines aim to standardize diagnostic approaches and optimize treatment strategies for juvenile SLE, thereby improving outcomes for young patients facing this complex autoimmune condition. According to the SLICC criteria, a patient is classified as having systemic lupus erythematosus (SLE) if they meet four or more of the clinical and immunological criteria, with at least one clinical criterion and one immunological criterion. Alternatively, a patient can be classified as having SLE if they have biopsy-confirmed lupus nephritis along with positive antinuclear antibodies (ANA) or anti-dsDNA antibodies. These criteria are essential for ensuring a standardized approach to diagnosing SLE, particularly in children and adolescents (9). jSLE is characterized by extremely variable presentation and clinical courses, from relatively mild disease to severe, life-threatening presentations. Patients may present with fever, oral ulceration, fever, arthralgia, headaches and weight loss. Lupus nephritis (LN) affects up to 80% of patients and up to 19% may develop renal failure (10). Central nervous system involvement is more frequent in jSLE when compared to adult-onset disease. Characteristic of neuropsychiatric disease are highly variable and may include headaches, psychosis, cognitive dysfunction and cerebrovascular disease. Mucocutaneous disease is very frequent and includes malar rash, skin vasculitis, photosensitivity and painless ulcers of oral mucosa (11,12) The most frequently observed hematologic manifestations include anemia, leukopenia, lymphopenia, thrombocytopenia, neutropenia and pancytopenia (13). According to large ethnically diverse population-based registry there is a racial/ethnic differences in the prevalence of jSLE manifestations. Additionally, the presentation and course of SLE appear highly variable between patients of different ethnic origins (14,15).

MATERIALS AND METHODS

The study was conducted at the Department of Allergology, Rheumatology and Clinical Immunology, Pediatric Clinic, Clinical Centre University of Sarajevo. Medical records of 19 juvenile-onset systemic lupus erythematosus (jSLE) patients diagnosed and treated between September 2007 and July 2024 were retrospectively reviewed to collect patients' data. Five patients fulfilled the 1997 American College of Rheumatology (ACR) classification criteria and 14 patients fulfilled 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria. SLICC criteria requires: 1) fulfillment of at least four criteria, with at least one clinical criterion AND one immunologic criterion or 2) Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies (Table 1).

Table 1 **SLIC criteria (ANA- antinuclear antibodies, Anti-DsDNA-anti-double-stranded DNA antibodies, Anti-Sm-Anti Smith antibodies).**

Clinical criteria	Immunologic critera
1. Acute cutaneous lupus	1.ANA
2.Chronic cutaneous lupus	2.Anti-DsDNA antibodies
3.Oral ulcer	3.Anti-Sm antibodies
4.Nonscarring alopecia	4.Antiphospholipid antibody
5.Arhritis	5. Low complement (C3, C4, CH50)
6.Serositis	6-Direct Coombs test
7.Renal	
8.Neurologic	
9.Hemolytic anemia	
10.Leukopenia (< 4000/mm3 at least once)	
11. Thrombocytopenia (<100,000/mm3)	

The study abstracted data on constitutional symptoms including fatigue, fever, arthralgia, myalgia, and weight changes, as well as skin and mucosal changes such as malar rash, photosensitization, skin vasculitis, and painless oral ulcers. Arthritis was defined based on the presence of at least two criteria among inflammatory pain, limited mobility, and/or swelling. The diagnostic indexes for renal disease were persistent proteinuria >0.5 g/day or greater than 3+ by dipstick and/or urine cellular casts. The diagnostic indices for CNS disorders included headaches, psychosis, cognitive dysfunction, and cerebrovascular disease. Laboratory parameters abstracted from the records were C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count (WBC), platelet count (Plt), Direct Coombs test (DCT), antinuclear antibody (ANA), anti-double stranded DNA (anti-DsDNA), anti-Smith (anti-Sm), anti-ribonucleoprotein (anti-RNP), antiphospholipid antibodies, C3, and C4. Trombocytopenia was defined as a platelet count less than 100,000/ mm3, while leukopenia was defined as a WBC count less than 4000/mm3. Statistical analysis was performed presenting the data in tables and charts, including total number of cases, percentages and means.

RESULTS

The study included 19 patients, 15 females (79%) and four males (21%). The mean age at disease presentation was 11 years. The youngest child, diagnosed when he was two years old, was later

found to have monogenic SLE due to a DNASE1L3 mutation (Deoxyribonuclease 1 like) (Table 2).

Table 2 **Patient demographic data**.

Gender and age		
Femal	no./total no. (%)	15/19 (79)
Male	no./total no. (%)	4/19 (21)
Age median (years)		11 (2-17)

Arthralgia was the predominant initial complaint, reported by 15 patients (78%), followed by fever observed in 9 cases (47%). Concurrent fever and arthralgia were noted in 5 patients (26%). The most common clinical manifestations of jSLE included arthritis in 12 patients (62%), renal disease in 13 patients (68%), malar rash in 6 patients (31%), oral ulcers in 8 patients (42%), and serositis in 4 patients (21%). CNS involvement was observed in 3 children (16%). Renal biopsies were performed in 14 cases, revealing stage 2 nephritis in 4 patients (22%), stage 3 nephritis in one patient, and stage IV nephritis in 3 patients (16%). Two patients had normal pathohistological findings on kidney biopsy, while 3 biopsies were inconclusive. One pathohistological result is pending (Table 3).

Table 3 **Clinical characteristics of patients at disease onset.**

Presenting symptoms	no./total no. (%)
Arthralgia	15/19 (78)
Fever	9/19 (47)
Fever and arthralgia	5/19 (26)
Arthritis	12/19 (62)
Malar rash	6/19 (31)
Oral ulcers	8/19 (42)
Serositis	4/19 (21)
Renal disease	13/19 (68)
CNS manifestation	3/19 (16)

ESR was uniformly elevated across all children, with a median of 98 mm/hr. Leukopenia was noted in 11 patients (57%), and thrombocytopenia was present in 8 patients (40%). All patients were tested positive for ANA. Significant elevations in anti-DsDNA antibodies were found in 16 patients (80%), while anti-Smith antibodies were detected in 10 patients (50%), antiphospholipid antibodies in 12 patients (60%), and anti-ribonucleoprotein antibodies in 9 patients (45%). Only one child had a positive result for anti-Ro52 antibodies. Low C3 levels were observed in 14 patients (70%) and low C4 levels in 17 patients (85%) (see Table 4).

Table 4 **Laboratory findings at disease onset.**

Presenting laboratory indicies	No/total no.(%)
Elevated ESR	19/19 (100)
Leukopenia	11/19 (57)
Thrombocytopenia	8/19 (42)
ANA positivity	19/19 (100)
Anti-DsDNA positivity	16/19 (83)
AntiSm	10/19 (52)
Anti-RNP	9/19 (47)
Antiphospholipid antibidies	12/19 (62)
RF	5/19 (26)
Low C3	14/19 (73)
Low C4	17/19 (88)
DCT positivity	17/19 (88)

(ANA - anti-nuclear antibody, anti-dsDNA - anti-double-stranded DNA antibodies, anti-RNP - antibodies to ribonucleoprotein, anti-Sm - antibody against Smith antigen, RF - rheumatoid factor, DCT - direct Coombs test)

DISCUSSION

Juvenile-onset systemic lupus erythematosus (jSLE) is a rare and severe chronic autoimmune disease diagnosed in individuals under the age of 18. It is characterized by multisystemic involvement that can lead to substantial damage, disability, and mortality (1). The pathophysiology of jSLE is significantly influenced by genetic factors, which play a more profound role in disease manifestation compared to adult-onset SLE (2). Additionally, the presentation and clinical course of SLE vary widely among patients of different ethnic backgrounds (14,15). The present study represents the first published analysis of Bosnia and Herzegovina juvenile-onset systemic lupus erythematosus (jSLE) patients, focusing on baseline symptoms and laboratory markers derived from a single medical center dataset. To our knowledge, this study constitutes the first comprehensive national investigation into jSLE. We conducted a study on all jSLE patients treated in our department over the last 18 years, comprising 15 girls and 4 boys. The average age of the children at diagnosis was 11 years. Patients from our cohort were significantly younger at the time of diagnosis compared to the study by Hoffman IE, et al. (16). The onset of lupus at a younger age is associated with a higher risk of developing a more severe clinical disease phenotypes and increased mortality, as highlighted by Massias JS, et al. (17). In that study, the average age of disease onset was 12.1 years, consistent with our findings. It is imperative to enhance awareness among healthcare providers that juvenile SLE (jSLE) can manifest in younger populations. Recognizing and understanding the presenting symptoms is crucial for timely diagnosis and effective management.

In our study, the most prevalent clinical symptoms were arthralgia (78%) and arthritis (62%), with incidences markedly higher than those reported by Rouag H, et al. (18) and Massias JS, et al. (18). This discrepancy may be attributed to the genetic diversity of the participants, originating from various ethnic backgrounds Notably, the incidence of arthritis in our cohort aligns with the prevalence observed in adult SLE patients (16,17,18). Furthermore, we confirmed the higher occurrence of renal disease

in juvenile SLE, as documented in previous research. This contrasts with the lower prevalence of 38.2% reported in the UK jSLE Cohort Study by Massias JS, et al., which included 422 participants (17).Our findings on the incidence of Anti-dsDNA and anti-Smith antibodies are consistent with the results of Massias JS, et al. The significant prevalence of renal disease in our cohort (68%) suggests a more severe disease presentation, necessitating more aggressive treatment strategies for effective management. Additionally, ANA positivity and elevated ESR were observed in all our patients, corroborating the findings of several authors across different genetic backgrounds (16,17,18,19). One notable distinction between jSLE patients in our cohort and those in other published studies is the incidence of thrombocytopenia. This finding could significantly positively influence our clinical approach to patients with chronic low platelet counts. In our cohort, 42% of patients experienced thrombocytopenia, a markedly higher incidence compared to other studies (16,17). In adult studies, 12.1% of immune thrombocytopenia (ITP) cases progressed to SLE during a follow-up period of 7.2 years (20. Hazzan et al. identified several risk factors for the future development of SLE in ITP patients, including female sex, an age group of 12.7 ± 3.6 years, high ANA titers, and chronic ITP, with SLE developing during a follow-up period of 4.2 ± 4.9 years (21). This underscores the necessity for careful monitoring of jSLE patients with thrombocytopenia, as they may be at a heightened risk for developing SLE.

CONCLUSION

Juvenile - onset systemic lupus is a challenging disease, in terms of diagnosis and treatment. All cases of fever of unknown origin, especially if concomitant with joint pain, should undergo evaluation for jSLE, as the most common presenting symptom in our cohort were fever, arthritis and arthralgia. It is necessary to spread awareness of JSLE in the pediatric population where early diagnosis and treatment can bring favorable outcome. Presentation and course of SLE appear highly variable between patients of different ethnic origins. More jSLE epidemiologic study in Bosnia and Herzegovina would lead to better understanding of this rare and potentially fatal pediatric disease as well as the formation of national Juvenile onset systemic lupus erythematosus registry.

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Reprint request and correspondence:
Adisa Čengić, MD
Pediatric Clinic
Clinical Center University of Sarajevo
Patriotske lige 81, 71000 Sarajevo
Bosnia and Herzegovina
Email: adisaus@yahoo.com
ORCID ID: 0009-0003-7763-3463

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Usage of optimal disposable surgical attire aimed at the prevention of intrahospital infections

Korištenje optimalnog jednokratnog hirurškog veša u svrhu prevencije intrahospitalnih infekcija

Nada Malešić[1]*, Muhamed Djedović[1], Bedrudin Banjanović[2], Ivana Malešić[3], Alen Karić[2], Timur Šečić[4], Majda Gazap[1]

[1]Clinic of Vascular Surgery, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
[2]Clinic of Cardiovascular Surgery, Clinical Center University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
[3]Clinic of Pediatrics, Clinical Center University of Sarajevo, Patriotske lige 81, 71000 Sarajevo, Bosnia and Herzegovina
[4]General Hospital "Dr. Abdulah Nakaš", Kranjčevićeva 12, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Disposable surgical attire is an established practice in every developed and standardized healthcare system. Research has indicated its significant advantages in the work process and patient safety. The application of disposable surgical attire is highly justified to prevent hospital infections. The effectiveness of its use depends on understanding the differences in levels of patient and staff protection, as well as its proper utilization. Optimal selection of disposable surgical attire involves maximizing protection with minimal costs, considering numerous risk factors: type of procedure, patient status, type of surgery or intervention, degree of infection risk, and similar. Therefore, we must increase our knowledge of disposable surgical attire's characteristics and potential applications.

Keywords: disposable surgical attire, patient safety, infection prevention, cost reduction

SAŽETAK

Jednokratni hirurški veš ustaljena je praksa u svakom razvijenom i standardiziranom zdravstvenom sistemu. Istraživanja su pokazala njegove značajne prednosti u procesu rada i sigurnosti pacijenata. Upotreba jednokratnog kirurškog veša je opravdana u sprječavanju bolničkih infekcija. Efikasnost njegove upotrebe zavisi od razumijevanju razlika u nivoima zaštite pacijenata i osoblja, te od pravilne upotrebe. Optimalan izbor jednokratnog kirurškog veša podrazumijeva maksimalnu zaštitu uz minimalne troškove, s obzirom na brojne faktore rizika: vrstu zahvata, status pacijenta, vrstu operacije ili intervencije, stepen rizika od infekcije i sl. Stoga moramo unaprijediti znanje o karakteristikama jednokratnog hirurškog veša i njegovim mogućim primjenama.

Keywords: jednokratni hirurški veš, sigurnost pacijenta, prevencija infekcije, smanjenje troškova

INTRODUCTION

According to the World Health Organization data, cardiovascular disease trends continue to rise. The overall prevalence of arterial occlusive disease ranges from 1% to 1.5% (1). In extensive European studies, the overall prevalence varies from 0.9% to 6.9%, particularly in the age group of 50 to 60 years (2). Study results, which have evolved to assess the impact of various factors on cardiovascular mortality, indicate a patient mortality rate of 44% (3). Socio-economic conditions in our country over the last 20 years have led to an increase in the number of cardiovascular disease patients (4-6). The Clinic of Vascular Surgery of the Clinical Center University Sarajevo has seen a significant increase in patients requiring surgical treatment. After the conditions were met, such as educated staff and modern equipment, this clinic provided care for 95% of patients from the Federation of Bosnia and Herzegovina who had required sophisticated surgical procedures over the past ten years. Due to this fact, only 5% of patients seek treatment abroad. The clinic has implemented protocols, procedures, and standardized methods adopted from the major Czech Republic and Sweden educational centers to meet this requirement. These standards mandate healthcare institutions to fully protect patients from potential infections before, during, and after surgery. The Patient Healthcare Protection Act also obligates healthcare institutions to create optimal conditions for surgical interventions during the work process. Due to the above reasons, by adopting work procedures, the Clinic of Vascular Surgery has provided optimal conditions for all types of vascular surgical procedures. Work on open blood vessels and their reconstruction requires high standards regarding professional staff, equipment, and consumables. In 90 to 95% of cases, this type of surgical procedure involves the use of implants, necessitating the highest level of sterility. Therefore, using reusable woven cotton attire during surgical procedures is unacceptable. Drawbacks of those mentioned earlier reusable woven cotton attire include:

- Permeability resulting from wear and tear during washing and sterilization,

- Cross-contamination - prions (CJD) are not destroyed by washing or sterilization,
- Costs of maintenance for washing, sterilization, logistics,
- Non-compliance with EU standards for medical products due to quality limitations.

In contrast, non-woven textiles are flat structures whose compactness is based on fiber cohesion achieved through mechanical, chemical, and thermal processes.

To meet market needs, disposable attire must undergo a series of tests under SIST EN13795-3 standards. The advantages of disposable surgical attire are as follows:

- Non-toxicity,
- Sterilization capability,
- High absorption capacity,
- Compatibility (biocompatibility, bio inertness, bioadhesives, biodegradability),
- Wide selection of materials types and qualities that provide maximum protection for staff and patients,
- Good mechanical properties (new, durable, comfortable, slip-resistant, adaptable)

Table I **The Patient Healthcare Protection Act standards**.

Characteristics of resistance to microbial penetration in dry state	Enota Log_{10} (CFU)	Requirements			
		Standard requirements		Non-standard requirements	
		Critical area	Less critical area	Critical area	Less critical area
		Not req..	≤2	Not req.	≤2
Resistance to microbial penetration in wet state	$/_B$	≥2,8	Not required	6,0	Not required
Microbial cleanliness	Log10 (CFU/dm2)	≤2	≤2	≤2	≤2
Cleanliness for particles/particles	IPM	≤3,5	≤3,5	≤3,5	≤3,5
Air permeability through material	Log10	≤4,0	≤4,0	≤4,0	≤4,0
Resistance to liquid penetration	cmH2O	≥20	≥10	≥100	≥10
Strength in dry state	kPa	≥40	≥40	≥40	≥40
Strength in wet state	kPa	≥40	Not required	≥40	Not required
Stretchiness of material in dry state	N	≥20	≥20	≥20	≥20
Stretchiness of material in wet state	N	≥20	Not required	≥20	Not required

AIM

The study's general objective was to implement standards in the Clinic of Vascular Surgery of the Clinical Center University of Sarajevo operating room. Specific objectives were to develop a model of optimal sets for vascular reconstructive surgical procedures and enhance knowledge and application of preventive measures and procedures for mitigating the risk factors for intra - hospital infections.

MATERIALS AND METHODS

This study included patients who underwent a surgical procedure at the Clinic of Vascular Surgery from 2009 to 2016. It was a retrospective, descriptive-analytical study encompassing all patients who underwent reconstructive surgical blood vessels procedures. Operation protocols and patient operation records were used for data collection. The study observed surgeries on the abdominal aorta, carotid, and limb arteries during the specified period. The study also observed patients who underwent arteriovenous fistula placement for hemodialysis needs, and it also included limb amputation surgeries due to high-risk factors for intra-hospital infections.

RESULTS

During the specified period, a large number (3.017) of reconstructive surgical procedures involving implants were performed at the Clinic of Vascular Surgery (Table 2).

Table 2 **Various variants of disposable surgical attire used for the specified reconstructive operative procedures on blood vessels.**

Type of Surgery	2009	2010	2011	2012	2013	2014	2015	2016	Total
Abdominal Aortic Aneurysm	130	136	125	122	152	119	124	136	1,044
Carotid Artery Reconstruction	36	42	30	44	43	51	71	54	371
Limb Artery Reconstruction	153	120	141	148	109	136	118	144	1,069
Emergency Vascular Surgeries	67	74	65	85	81	62	47	52	533

Various variants of disposable surgical attire were used for the specified reconstructive operative procedures on blood vessels (Table 2). In the early years of the observed period, disposable surgical attire that was not adapted to the different types of mentioned surgical procedures (basic set) or cardiovascular attire that needed to be more modern and affordable was used. An analysis of needs, types, and the number of planned surgical procedures concluded that adequate optimal sets were necessary for vascular operations.

On the market, suppliers did not supply disposable surgical attire with specified sets for vascular surgical procedures. The clinic's management formed a working group to develop specifications for trial sets for different surgical procedures, recognizing the problem of inadequate market offerings. One of the European manufacturers of disposable surgical attire agreed to produce sets according to the clinic's specifications for a trial period of three months.

Set for Abdominal Aortic Aneurysm - Sterile:

- Table cover with reinforced central part 150x200cm, standard EN 20811 - 2 pieces,
- Paper towels (cellulose) 30x40cm - 5 pieces,
- Surgical gown standard 130cm - 1 piece,
- Surgical gown standard 150cm - 4 pieces,
- Cover for instrument table 80x145cm, made of polyethylene film on the bottom side and polypropylene on the top side with reinforcement in the central part, standard EN 20811 - 1 piece,
- Self-adhesive 3-layer cover 175x180cm, adhesive part is on the 180cm side, standard EN 20811 - 1 piece,
- Self-adhesive 3-layer cover 150x240cm, adhesive part is on the 240cm side, standard EN 20811 - 1 piece,
- Self-adhesive 3-layer cover 75x100cm, adhesive part is on the 100cm side, standard EN 20811 - 2 pieces,
- Incisional film 45x50cm - 1 piece,
- Adhesive tape 10x50cm - 2 pieces,
- Cotton abdominal compress 16 layers 40x40cm - 10 pieces,
- Cotton abdominal compress 16 layers 18x8cm - 20 pieces,
- Circular cotton swabs size 8 (the size of a palm) - 6 pieces,
- Self-adhesive polyethylene bag for fluid collection and/or holding instruments 33x30cm - 3 pieces,
- Latex surgical gloves, powdered, size 7 - 1 pair,
- Latex surgical gloves, powdered, size 7 ½ - 4 pairs,
- Latex surgical gloves, powdered, size 8 - 2 pairs.

The Clinic requires that all components of the set must be wrapped in sterile packaging with content labeling.

During the specified period, corrections to the sets and adjustments of their contents were made depending on the type of surgical procedure being performed. The accepted composition of the sets was standardized, and their need for the next period was planned.

During the specified period, arteriovenous fistulas for hemodialysis access and limb amputations were performed at the Clinic of Vascular Surgery.

Table 3 **The arteriovenous fistula surgical procedure**.

Type of Surgery	2009	2010	2011	2012	2013	2014	2015	2016	Total
Arteriovenous Fistula	153	125	137	143	161	104	176	183	1,182
Limb Amputations	74	168	121	182	169	149	178	143	1,184

The arteriovenous fistula surgical procedure (Table 3) carries a high risk of virus transmission, as it often involves patients who are positive for Hepatitis B and C. Due to the exposure of surgical teams, a high degree of prevention is required. Therefore, the surgical procedure for these patients involves using optimal disposable surgical sets. Since the necessary sets were unavailable on the market, the working team specifies the composition of the sets, which is standardized, and their procurement is planned for the next period.

Set for AV Fistulas - Sterile:

- Self-adhesive cover 150x240cm, adhesive part is on the 240cm side, impermeable under pressure of min. 125cm H2O, standard EN 20811 - 1 piece,
- Self-adhesive cover 175x180cm, adhesive part is on the 180cm side, impermeable under pressure of min. 125cm H2O, standard EN 20811 - 1 piece,
- Arm sleeve 75x90cm, made of polyethylene film on the bottom side and polypropylene on the top side, adhesive part on the 90cm side - 1 piece,
- Hand sleeve 18x50cm, made of polyethylene film on the bottom side and polypropylene on the top side, adhesive part on the 50cm side - 1 piece,
- Adhesive tape 10x50cm - 1 piece,
- Surgical gown standard 150cm - 2 pieces,
- Surgical gown standard 130cm - 1 piece,
- Latex surgical gloves, powdered, size 7 - 1 pair,
- Latex surgical gloves, powdered, size 7 ½ - 2 pairs,
- Latex surgical gloves, powdered, size 8 - 1 pair;
- Circular cotton swabs size 2 (size of a pea) - 10 pieces,
- Washing swabs 7.5x7.5cm, thicker (made of 20-thread gauze) - 10 pieces,
- Cotton compresses 12 layers 10x10cm with X-ray threads - 30 pieces,
- Paper towels (cellulose) 30x40cm - 3 pieces;

The Clinic requires all components to be wrapped in sterile packaging with content labeling.

Limb amputation surgeries (Table 3) are indicated due to a high degree of limb infection caused by various pathogens. During the intervention and the handling of surgical instruments, a whole range of different risk factors for both surgical and auxiliary staff and the spread of intra-hospital infections were observed. Therefore, the need for optimal disposable sets for this surgical intervention was recognized in the preoperative, operative, and postoperative processes. Since such sets were unavailable on the market, the working team specifies the composition of the sets, which is standardized, and their procurement is planned for the next period.

All the above-mentioned surgical procedures were performed using disposable surgical sets. Disposable surgical attire was initially inadequate, but they were optimized according to the clinic's needs in the first three years of implementation.

DISCUSSION

The Clinic of Vascular Surgery of the Clinical Center University of Sarajevo has undergone various phases of work and maturation in optimizing surgical attire in operating rooms. During the observed period from 2009 to 2016, we prevented intra-hospital infections despite the increase in the number of surgical procedures with the same number of staff. The following measures were implemented:

- Written clinic operating procedures were introduced,
- The use of disposable surgical attire according to the standards SIST EN13795-3 was introduced,
- The number of complex surgical procedures increased,
- Total preventive measures for intra-hospital infections were implemented,
- Sets for AAA that are also produced for other centers were innovated,
- Sets for carotid artery surgery were innovated,
- Sets for vascular reconstruction were innovated,
- Sets for AVF were innovated,
- Sets for limb amputation were innovated,
- Increased knowledge and application of the use of disposable surgical sets,
- Measures for staff protection in work processes for safe workplaces were implemented,
- Measures to protect patients during surgical procedures were implemented,
- Work quality and safety of staff and patients were increased.

In Europe and worldwide, especially in Scandinavian countries, the USA, and Japan, highly well-organized preventive programs for cardiovascular diseases are being implemented. According to literature data, these programs have reduced the incidence of these diseases by about 25 to 30% and the mortality rate from cardiovascular diseases by up to 50% in the last decade. These programs aim to educate and adequately prepare medical staff (physicians and nurses) for implementing measures to prevent cardiovascular diseases and evaluate achieved preventive programs.

CONCLUSION

The advantage of using optimal disposable surgical sets includes easy and quick start of surgical procedures, easy and fast preparation of patients, equipment, and staff, patient and staff safety, a wide range of packaging options tailored to each type of surgical procedure, high biological stability (non-reactive with blood, non-toxic), comfortable to wear (breathable, resistant to fluid flow), low risk of contamination, supported by European standard (EN 13795). Highly sophisticated surgical procedures on blood vessels performed in tertiary healthcare institutions should adhere to high standards regarding using disposable materials during the process. The experiences of the Clinic of Vascular Surgery of the Clinical Center University of Sarajevo are positive, as disposable surgical sets have effectively prevented infections in operating rooms, reduced treatment costs for patients, and improved the quality of work.

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Reprint requests and correspondence:
Nada Malešić, PhD, DMS
Clinic of Vascular Surgery
Clinical Center University of Sarajevo
Bolnička 25, 71000, Sarajevo
Bosnia and Herzegovina
Email: malesic.nada@gmail.com
ORCID ID: 0009-0006-1761-0325

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Multimodal microsurgical video-assisted occlusion of aneurysms of the anterior brain circulation: importance of the application of indocyanine green contrast and QEVO inspection - preliminary results

Multimodalna mikrohirurška video-potpomognuta okluzija aneurizme prednje moždane cirkulacije: značaj primjene indocijaninskog zelenog kontrasta i QEVO inspekcije - preliminarni rezultati

Almir Džurlić[1,2], Adi Ahmetspahić[1,2], Eldin Burazerović[1], Haso Sefo[1], Bekir Rovčanin[1*], Edin Hajdarpašić[1,2], Eleonora Kujača[2], Hana Rizvanović[2], Ibrahim Omerhodžić[1,3]

[1]Clinic of Neurosurgery, Clinical Centre University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina
[2]Department of Medicine, Sarajevo School of Science and Technology, Hrasnička cesta 3A, 71000 Sarajevo, Bosnia and Herzegovina
[3]Faculty of Medicine, University of Sarajevo, Čekaluša 90, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: Indocyanine green (ICG) video angiography (VA) has been widely used in various medical indications, including neurosurgery. The technique enables real-time assessment of vascular structures during surgery. ICG VA is particularly useful in neurosurgery due to its ability to provide high-quality imaging of vascular structures. The aim of the study was to evaluate the practicality, feasibility, and importance of combining ICG VA with endoscopic inspection tool (QEVO) in improving the outcomes of aneurysm clipping surgery. Materials and methods: the study population comprised individuals admitted to the Clinic of Neurosurgery of the Clinical Center University of Sarajevo (CCUS), who underwent microsurgical clipping of the aneurysm. All patients included in the study were surgically treated with the occlusion of brain aneurysm. After the aneurysm was occluded with the clip video-assisted angiography using ICG contrast and endoscopically-assisted inspection of the occluded aneurysm and surrounding blood vessels, QEVO was used for the best clip positioning. Results: this preliminary study included a total of seven patients who fulfilled the inclusion criteria; five of them (71%) were female. After clipping of the anurysm control microscopic inspection revealed that in five patients (71%) the clip was well placed without the anurysm remains while the remains were detected in two patients. ICG video angiography showed that microscopic remains of the aneurysm were detected in one patient, with no angiographic signs of the aneurysm remains. In one patient where the microscopic clip appeared to be well placed, after ICG video angiography, the remains of the aneurysm were detected and the perforator arteries were occluded. Conclusion: the study aimed to evaluate the practicality, feasibility, and importance of combining ICG VA and QEVO in improving the outcomes of aneurysm clipping surgery. The results suggest that this combination can improve visualization of arteries and enhance the outcomes of aneurysm clipping surgery. The study highlights the importance of using both ICG VA and endoscope during microsurgical clipping of aneurysms to achieve better outcomes.

Keywords: intracranial aneurysm, indocyanine green, contrast media, endoscope

SAŽETAK

Uvod: indocijanin zelena (ICG) video angiografija (VA) je široko korištena u različitim medicinskim indikacijama, uključujući i neurohirurgiju. Tehnika omogućava procjenu vaskularnih struktura tokom operacije u stvarnom vremenu. ICG VA je posebno korisna u neurohirurgiji zbog svoje sposobnosti prikaza visokokvalitetne slika krvnih žila. Istraživanje je imalo cilj evaluirati mogućnost, praktičnost i svrsishodnost kombiniranja ICG VA sa endoskopom (QEVO) u poboljšavanju rezultata operacije okluzije moždanih aneurizmi. Materijali i metode: istraživanje je provedeno na pacijentima primljenim na Kliniku za neurohirurgiju Kliničkog centra Univerziteta u Sarajevu (KCUS), koji su podvrgnuti mikrohirurškoj okluziji aneurizme. Neposredno nakon manevra (stavljanja klipa), korištena je video-assistirana angiografija s ICG kontrastom i endoskop-asistiranim pregledom okludirane aneurizme i pripadajućih vaskularnih struktura uz pomoć QEVO endoskopa kojim se provjeravao položaj klipa. Rezultati: istraživanje je uključilo ukupno sedam pacijenata (pet žena, 71%), koji su ispunjavali kriterije

uključenja. Nakon okluzije aneurizme, mikroskopska inspekcija pokazala je da je kod 5 pacijenata (71%) klip bio dobro postavljen, a u dva pacijenta su pronađeni ostatci aneurizme. ICG video angiografija pokazala je da kod jednog pacijenta, gdje se mikroskopski pronašlo ostatke aneurizme, nije pronađen angiografski znak ostatka aneurizme. Kod jednog pacijenta gdje je mikroskopski klip izgledao dobro postavljeno, nakon ICG video angiografije evidentiran je ostatak aneurizme a adherentni perforatori su bili uhvaćeni u klip. Zaključak: straživanje je imalo za cilj evaluirati praktičnost, mogućnost i važnost kombiniranja ICG VA sa QEVO-om u poboljšanju rezultata operacije okluzije aneurizme. Rezultati sugeriraju da ova kombinacija može poboljšati vizualizaciju arterija i poboljšati ishod liječenja aneurizme. Istraživanje ističe važnost korištenja obje opcije - ICG VA i endoskopa tokom ove mikrohirurške tehnike.

Ključne riječi: intrakranijalna aneurizma, indocijaninsko zeleno, kontrastno sredstvo, endoskop

INTRODUCTION

Indocyanine green (ICG) video angiography has been used for several medical indications in recent decades. This type of angiography enables assessment of vascular structures in real time during surgery (1). ICG was developed for infrared photography by Kodak Research Laboratories in 1955 and was already approved for clinical use in 1956. However, it was used for angiography in the 60s and for retinal angiography in the 70s. The principle of fluorescence imaging used in ICG is simple: illuminate the tissue of interest with light at the excitation wavelength (800 nm) while observing it at longer emission wavelengths (over 800 nm) (2,3). Neurosurgery is ideal for ICG because the operations are already done with a microscope (and camera), and because the blood vessels on the surface of the brain are exposed and thus can be seen more or less directly by visual means. Therefore, ICG applied in vascular neurosurgical procedures has emerged as a valuable option for assessing the intraoperative details of aneurysmal clipping (4,5). The quality of the treatment of brain aneurysms is crucially determined by the complete occlusion of the aneurysm and its neck while maintaining uninterrupted blood flow in the main, branching and perforating arteries. For direct intraoperative assessment of aneurysm and affected vascular structures, the techniques of microscopically integrated near-infrared indocyanine green videoangiography (ICG VA) and microvascular Doppler sonography have been established. Although these techniques provide real-time information on arterial flow, they are still limited to a straight line of sight. Information behind the aneurysm or an angled view of the vessels can only be obtained using a micromirror or endoscope. In particular, currently available high-quality angled endoscopes provide excellent visualization of anatomical structures (6).

In 1994, Fischer and Mustafa were the first to report on the use of an endoscope (fiberscope) to aid in microsurgical clipping of cerebral aneurysms. Since then, the rigid endoscope has become more commonly utilized in aneurysm surgeries, allowing for high-quality imaging of surrounding structures critical to the procedure (7). Endoscopes have the potential to effectively treat anterior circulation aneurysms, as they allow for a minimally invasive approach compared to traditional craniotomies. This method also minimizes the risk of extensive dissections of the Sylvian fissure, reduces brain damage, improves visibility of perforator arteries, particularly on the dorsal side of aneurysm domes, and provides better visualization of the intricate anatomy of the anterior circulation (8). Clinical and cadeveric studies have found that usage of endoscopy in brain aneurysm surgeries improved visualization of the arteries obscured by the aneurysm dorm (8,9). In the literature there is a limited number of studies using both ICG VA and endoscope during the microsurgical clipping of the aneurysms (10).

AIM

The aim of this study was to evaluate the practicality, feasibility and importance of ICG VA and QEVO endoscopic inspection tool (Micro-Inspection Tool, ZEISS, Carl Zeiss Meditec AG, Jena, Germany) to improve the outcomes of aneurysm clipping surgery.

MATERIALS AND METHODS

This is a preliminary report of a prospectively collected case series as a part of ongoing case control study. The research was conducted over a 12-month period from December 2022 to December 2023, forming a component of a project supported by the Ministry of Science and Education of the Federation of Bosnia and Herzegovina. The study population comprised individuals admitted to the Clinic of Neurosurgery of the Clinical Center University of Sarajevo. Eligible participants were adults aged 18 and older diagnosed with brain aneurysms located on the anterior circulation brain vessels amenable to microsurgical clipping, regardless of whether the aneurysm was ruptured or unruptured. Exclusion criteria encompassed individuals lacking signed informed consent by them or by their legal representative, as well as those with a history of previous brain aneurysm surgery. Aneurysms were diagnosed by the computer tomography (CT) angiography, magnet resonance imaging (MRI) angiography or by digital subtraction angiography before the surgery.

All patients included in the study were surgically treated with the occlusion of brain aneurysm. Surgeries were performed by experienced cerebrovascular neurosurgeons, authors of this study. During the surgery KINEVO 900 surgical microscope (ZEISS, Carl Zeiss Meditec AG, Jena, Germany) was used. The KINEVO 900 surgical microscope is a tool used for magnifying and illuminating the surgical area to assist visualization during surgical procedures. It was introduced at the annual meeting of the American Association of Neurological Surgeons and the German Society of Neurosurgery in 2017 and it received full approval and certification for use in the U.S. and Europe. After the aneurysm was occluded with the clip video-assisted angiography using ICG contrast and endoscopically-assisted inspection of the occluded aneurysm and surrounding blood vessels the QEVO ((Robotic Visualization System®, ZEISS) was used. In case that some blood vessels were occluded or the clip was not well placed, the clip was replaced. The QEVO tool, which is part of the KINEVO system, is a visualization device 250 g in weight and 12 cm long, and has a shaft diameter of 3.6 mm with a 45-degree angled view. It is designed to display anatomical details that may not be visible with a microscope and can be inserted into the KINEVO 900 console as an adjunctive endoscope. The high-definition image captured by QEVO is displayed on the system monitor. CE marked, the QEVO complies with the Medical Device Directive 93/42/EEC as a Class III device,

while the QEVO ECU is a Class I device. Both devices are completely sterilizable and designed for optimal visualization during neurosurgical procedures.

After 72 hours post-surgery, a CT scan and CT angiography of the brain were performed to assess the degree of aneurysm occlusion as well as the surrounding blood vessels. Patients underwent neurological examination pre and postoperatively.

Results were collected in Excel tables, appropriately categorized as needed, and statistically analysed using the statistical software MedCalc for Windows, version 10.1.2.0 (MedCalc® Software, Mariakerke, Belgium), p-value <0.05.

RESULTS

This preliminary study included a total of seven patients fulfilling the inclusion criteria. Out of the total number of patients five were females and majority of them fell within the 30-60 age range, encompassing five individuals. Specifically, four patients were presented with subarachnoid haemorrhage resulting from the rupture of a brain aneurysm, while three patients underwent elective surgery for their brain aneurysms. The majority of the aneurysms were located at the anterior cerebral artery or anterior communicating artery (4 out of 7 cases), with two aneurysms located on the middle cerebral artery and one on the distal anterior artery. Most of the aneurysms were small in size, intraoperatively 5 of 7, and 2 were of middle size. The visualization of the relation of aneurysm with surrounding perforator arteries and distal magistral arteries changed when ICG angiography and QEVO endoscopy were used (Table 1, Figure 1, 2 and 3). Statistical analysis of ICG angiography and QEVO endoscopy showed that there was no statistical difference between them in terms of better visualisation, *p=1.00*. With QEVO endoscopy we could visualise more perforating arteries, but with no statistical difference between ICG angiography and QEVO endoscopy in terms of perforator visualisation, *p=0.28*.

Table 1 **Better visualization of perforating and distal arteries after ICG angiography and QEVO endoscopy***

Patients	Visualisation after ICG angiography	Visualisation of lateral and dorsal parts after QEVO endoscopy
Patient 1	1	1
Patient 2	1	1,2
Patient 3	0	0
Patient 4	0	1,2
Patient 5	2	0
Patient 6	1	1
Patient 7	2	1

*ICG- Indocyanine green, 0-Good microscopic visualization, 1-Better perforators visualization, 2-Better distal arteries visualization

After clipping of the anurysm control microscopic inspection revealed that in 5 patients the clip was well placed without the anurysm remains while the aneurysm remains were detected in two patients. ICG video angiography showed that in one patient where microscopic aneurysm remains were detected, there were not angiographic signs of the aneurysm remains. In one patient where microscopic postition was good, after ICG video angiography there was a rest of the aneurysm detected and perforator arteries were occluded (Table 2). QEVO endoscopy found more occluded perforators and rest of the aneurysms but there was no statistically significant difference between QEVO endoscopy and ICG angiography, p=0.28.

Table 2 **Inspection after aneurysm clipping.**

Patients	After clipping microscopic inspection	After clipping ICG video angiography inspection	After clipping QEVO endoscopy inspection
Patient 1	1	2	1,2
Patient 2	0	1,2	1,2
Patient 3	1	0	1
Patient 4	0	0	2
Patient 5	0	0	0
Patient 6	1	1	1
Patient 7	0	0	0

*ICG- Indocyanine green, 0 - good position, 1- rest of the aneurysm, 2-occluded perforator artery

There was no complication reported during the use of ICG and QEVO. After 72 hours all patients had the same neurological finding or got better, with no patients being worse or with death outcome. Postoperative CT and CT angiography did not report a new ischemia.

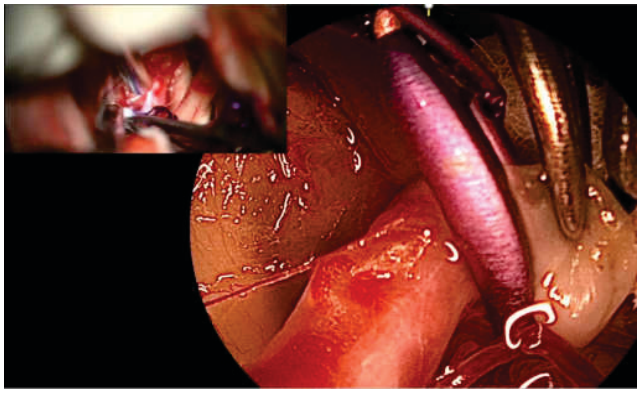

Figure 1 **Microscopic image in the left upper corner and QEVO micro-inspection toll image (large image). Inspection of the dorsal side of the ACoA complex after clipping of the dorsally oriented aneurysm. Small perforator behind the aneurysm was partially occluded by the clip.**

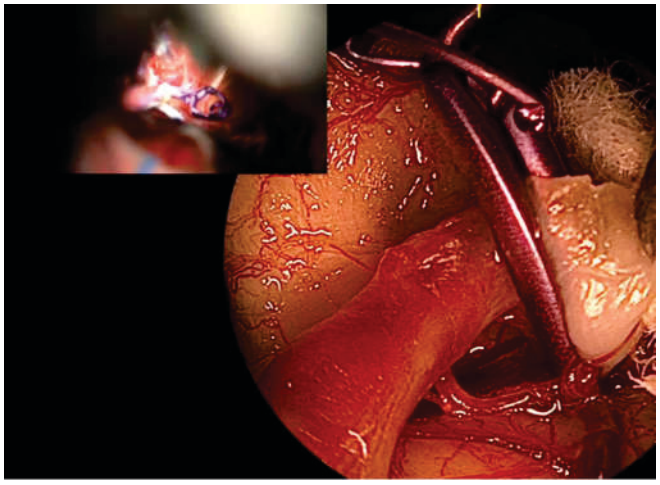

Figure 2 **Microscopic image in the left upper corner and QEVO micro-inspection toll image (large image) after repositioning of the clip. Inspection of the dorsal side of the ACoA complex now demonstrates free wall of the perforator with completely occluded aneurysm**.

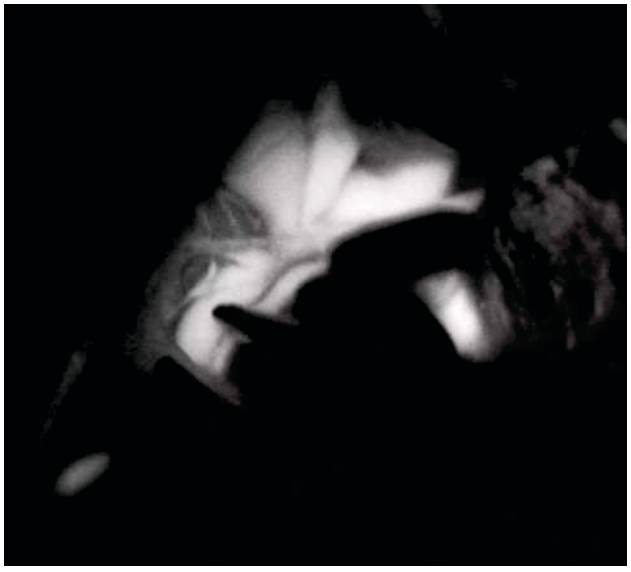

Figure 3 **Use of Indocyanine green contrast video-assisted angiography after the clipping of the saccular aneurysm of the middle cerebral artery. There is a visualisation of the M1 and both M2 segments of the artery, without the rest of the aneurysm.**

DISCUSSION

In this preliminary report, we demonstrated that the combination of ICG video-assisted angiography and the utilization of the QEVO endoscope might potentially correlate with improved outcomes in brain aneurysm clipping surgery, specifically in achieving complete aneurysm occlusion minimizing the risk of occlusion of surrounding arteries.

Despite the utilization of cutting-edge microscopes, achieving a precise visualization of regional anatomical structures, such as the aneurysm neck, wall, parent vessel, branches, and perforators is not always feasible. Apuzzo ML, et al. (7) initially employed the endoscope as a technical support tool during the microsurgical removal of suprasellar pituitary lesions in the late 1970s. Afterward, Fischer G, et al. (8) introduced the integration of endoscopy into microneurosurgery for cerebral aneurysms, aiming to facilitate intraoperative observation of previously inaccessible areas. As outlined by Taniguchi M, et al. (9), endoscope-assisted microsurgery (EAM) is indicated for unruptured aneurysms and contraindicated for ruptured aneurysms (Fisher grade III), or in instances involving brain oedema and blood in the operating field. However, findings by Galzio R, et al. (10) differ, as they report that the presence of blood in the basal cisterns and hydrocephalus did not hinder the usefulness of the endoscope. According to this perspective, endoscopy provides benefits for both ruptured and unruptured aneurysms. Regardless, optimal vision can be achieved after cisternal opening and washing, which occurs during the early stages of microsurgery. The primary advantages of EAM include increased light intensity when approaching an object, precise visualization of features in close proximity, and expanded angles of view. In this context, the micro-inspection endoscopic tool QEVO stands out as a genuine innovation when integrated with the KINEVO microscope. This instrument offers several advantages over traditional endoscopes, featuring a fixed 45-degree viewing angle and displaying images in the microscope's oculars, allowing physicians to maintain focus without the need to divert their gaze upward or the need for a video tower. It is completely sterilizable, so it doesn't require draping, and it has its own internal light source. Its primary purpose is to aid in microsurgery and it does not support the option for full endoscopic surgery. Looking ahead, potential advancements in the technical capabilities of QEVO could lead to improved image resolution, culminating in an ideal integrated visualization device that seamlessly interfaces with a microscope (11). KINEVO and QEVO usage was used also in studies. Authors conclude that the KINEVO 900, equipped with advanced optics and robotics, is a highly accessible and user-friendly microscope that enables surgeons to visualize vascular structures with great accuracy and minimal time spent on adjustments. The FLOW 800 feature is particularly noteworthy, as it enhances the effectiveness of ICG by allowing for the identification of partially clipped aneurysm sacs and preventing accidental clipping of small arterial branches. Meanwhile, the QEVO system further enhances surgical visualization by complementing the microsurgical view and providing a 360-degree view around corners. As a result, the advantages of the KINEVO 900 system led to improved surgical outcomes, characterized by a reduced risk of intraoperative complications (12).

ICG has become a useful choice for examining the specific details of aneurysm clipping during vascular neurosurgical procedures. The principle of fluorescent imaging used in ICG is simple: illuminate the tissue of interest with light at the excitation wavelength (800 nm) while observing it at longer emission wavelengths (over 800 nm). After i.v. injection, it is immediately bound by globulins and remains intravascular until its excretion by the liver. ICG angiography is employed to identify instances such as vessel blockage caused by the clip, any remaining aneurysms post-clipping (referred to as a dog-ear), or ongoing aneurysm filling due to incomplete clipping. ICG and endoscopes produce the best results when used in conjunction, as they are complementary to one another. The patency of the flow in the perforating vessels can be seen with the rigid endoscope, and if we use both together, we can see perforating vessels that are not detected by the ICG-VA

alone, as well as whether any residual neck is present (13). In a recent study, authors concluded that the dual use of these technologies (QEVO and ICG-VA) should be utilized, as it provides a more comprehensive understanding of the clip's status, its internal anatomy, its relationships with surrounding vascular structures, and the complete occlusion of the aneurysm. Using both endoscopy and Vessel Angiography in conjunction with each other is beneficial, as each modality provides unique and valuable information. By utilizing both technologies together, healthcare professionals can gain a more detailed and accurate understanding of the situation, ultimately leading to better treatment outcomes (11).

Also, sodium fluorescein can be used as contrast for video angiography. The main characteristic of sodium fluorescein video angiography (FNa-VA) is its ability to offer a real-time, three-dimensional picture of the surgical area using microscope binoculars. It provides a clear view of deep perforating branches and is preferred in terms of lower cost.

The primary disadvantage of FNa-VA is that FNa's longer half-life prevents it from being used again in reapplications of clips. FNa remains adhered to the artery wall for 20 minutes, or longer, before dissolving (14). To get around this restriction, Kuroda K, et al. used an intraarterial injection of FNa and proposed that several applications per case can be done using this technique because the overall dose of the dye in the arteries is very low (15). ICG is not affected by this problem because ICG leaves the system quickly and allows for many intravenous injections in a matter of minutes. Other advantages of ICG over fluorescein are that the light emission is more intense and easier to detect, and the adverse reactions are also very low (14).

Our study had the some limitations. First of all, this was a preliminary study which included few patients. There is a need for longer follow up of the patients. Also, there is a need for a definitive report of this study.

CONCLUSION

By using video-assisted angiography with the administration of ICG contrast and endoscopically-assisted inspections, we can enhance better occlusion of the aneurysms. They offer the highest level of visibility for perforators and nearby structures, effectively reducing the risk of intraoperative complications and harm to surrounding tissues during surgery.

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Reprint requests and correspondence
Bekir Rovčanin, MD
Clinic of Neurosurgery
Clinical Centre University of Sarajevo
Bolnička 25, 71000 Sarajevo
Bosnia and Herzegovina
Email: bekir_rovcanin@hotmail.com.
ORCID ID: 0000-0002-7298-3240

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Case series: chronic nonbacterial osteomyelitis - importance of early diagnosis

Serija slučajeva: hronični nebakterijski osteomijelitis - važnost rane dijagnoze

Ivana Malešić, Adisa Čengić, Alma Puškar, Velma Selmanović

Pediatric Clinic, Clinical Center University of Sarajevo, Patriotske lige 81, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author

ABSTRACT

Introduction: chronic nonbacterial osteomyelitis (CNO) is an autoinflammatory bone disorder, that most commonly first appears in childhood. Symptoms can be nonspecific at first (fever, night sweats, fatigue), followed by bone pain, bone swelling, nocturnal pain, and impaired function of the affected part of the body. Diagnosis is usually delayed, because there are no widely accepted criteria for CNO, so differentialdiagnoses need to be excluded (malignancy, infection). It can be accompanied by severe complications (vertebral fractures). Case report: this case series presents three female patients who were diagnosed with chronic nonbacterial osteomyelitis. They were referred to a pediatric rheumatologist a minimum of eight months after the first symptoms occurred. The most frequent symptoms were nocturnal bone pain and swelling. None of the patients had a fever. The bones primarily affected were the clavicle, mandible, humerus and vertebra with secondary complications such as compressive vertebral fractures, and scoliosis. One developed paradoxical psoriasis while being treated with TNF inhibitors. Conclusion: this case report highlights the importance of considering chronic nonbacterial osteomyelitis as a potential cause of bone swelling and pain. The key factors for improving the outcome of patients with CNO are early recognition and timely treatment, as well as a multidisciplinary approach due to the complexity of the diagnosis.

Keywords: chronic nonbacterial osteomyelitis, osteomyelitis, bone disorders, autoinflammatory diseases

SAŽETAK

Uvod: hronični nebakterijski osteomijelitis (CNO) je autoinflamatorna bolest kostiju, koja se obično pojavljuje u djetinjstvu. Simptomi u početku mogu biti nespecifični (groznica, noćno znojenje, umor), zatim se javljaju bolovi u kostima, otok kostiju, noćna bol i poremećena funkcija zahvaćenog dijela tijela. Postavljanje dijagnoze je obično odgođeno, jer ne postoje široko prihvaćeni kriteriji za CNO, pa je potrebno isključiti druge dijagnoze (malignitet, infekcije). Može biti praćen teškim komplikacijama (frakture kičmenih kralježaka). Opis slučajeva: ova serija slučajeva prikazuje tri pacijentice kod kojih je dijagnosticiran hronični nebakterijski osteomijelitis. Upućeni su pedijatrijskom reumatologu više od osam mjeseci nakon pojave prvih simptoma. Najčešći simptom je bila bol u kostima i otok, sve tri su se žalile na noćnu bolnost. Nijedna od pacijentica nije imala temperaturu. Primarno zahvaćene kosti su bile klavikula, mandibula i humerus i vertebra, sa sekundarnim komplikacijama kao što su kompresivne frakture kralježaka i skolioza. Jedna od pacijentica je razvila psorijazu u toku tretmana TNF inhibitorima. Zaključak : ova serija slučajeva naglašava važnost razmatranja hroničnog nebakterijskog osteomijelitisa kao potencijalnog uzroka oticanja i boli kostiju. Ključni faktori za poboljšanje ishoda pacijenata sa CNO su rano prepoznavanje i pravovremeno liječenje, kao i multidisciplinarni pristup zbog složenosti dijagnoze i popratnih komplikacija.

Ključne riječi: hronični nebakterijski osteomijelitis, osteomijelitis, bolesti kostiju, autoinflamatorne bolesti

INTRODUCTION

Chronic nonbacterial osteomyelitis (CNO) is an autoinflammatory bone disorder. This condition is sometimes referred to as SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis, and Osteomyelitis), though this acronym is more frequently used in adult rheumatology (1,2).

It most commonly first occurs between the ages of 7 and 9. The reported incidence of CNO is 1:4 000 000 children, and it affects the female gender more frequently (approximately 2:1). Patients are initially referred to different specialties (such as orthopedic surgeons, infectious diseases specialists, oral surgeons, oncologists, radiologists, and others), but once diagnosed, they are primarily treated and followed up by pediatric rheumatologists (1,3). There are no widely accepted diagnostic criteria available for CNO, so diagnosis is usually performed through exclusion of differential diagnosis. There is approximately a 2-year delay between the onset of symptoms and diagnosis. Symptoms include fatigue, fever, night sweats, weight loss, delayed growth, regional swelling, and nocturnal bone pain with local tenderness and warmth during physical examination. It usually affects the following bones: mandible, clavicle, hands and feet, distal fibula, and tibia or pubic bone lesions. Silent bone lesions affect the vertebrae and can cause fractures. Physical and school function is affected and reduced. Very

severe cases are usually referred to as recurrent multifocal osteomyelitis (CRMO). The disease has a high recurrence and high persistence rate. Bone lesions are symmetrical in 22% of patients (1,2,3,4). Laboratory tests for Chronic Nonbacterial Osteomyelitis (CNO) typically show nonspecific results, such as mildly elevated CRP and ESR. In some cases, antibodies like ANA and HLA-B27 may be positive. Additionally, serum levels of TNF-alpha and IL-6 are often mildly elevated and can assist in distinguishing CNO from other potential diagnoses, including infection and malignancy (1,2). X-rays are initially employed to rule out bone fractures, though they may reveal lytic bone lesions, sclerosis, or hyperostosis. Bone scintigraphy is utilized to diagnose Chronic Nonbacterial Osteomyelitis (CNO), identify silent lesions, and monitor disease activity. The gold standard for diagnosing CNO is whole-body MRI (WBMRI, STIR sequence), which not only evaluates bone lesions but also assesses the severity of surrounding tissue inflammation and edema. Bone biopsies remain a common practice to exclude differential diagnoses, including infection, dysplasia, malignancy, and histiocytosis (1,2,4,). The exact pathophysiology of CNO/CRMO remains unknown. Altered cytokine and chemokine expression in innate immune cells is certain. CNO has been observed affecting siblings or several generations within one family, so genetic factors are involved (1,3).

Treatment of CNO is largely empiric and based on personal experience, expert opinion, case reports, and small case series. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line choice in patients without involvement of the vertebral column, but flares are common. For patients who failed to respond to NSAIDs, additional treatments are required, such as corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs - sulfasalazine and methotrexate), biologic treatments (anti-TNF agents), and bisphosphonates. Apremilast, tofacitinib, and secukinumab have been used in cases with overlapping CNO and psoriasis. Pamidronate can induce rapid and long-lasting remission in most CNO patients. The prognosis of CNO is uncertain since there are no studies following patients from childhood diagnosis into adulthood. Early diagnosis and appropriate treatment is associated with favorable outcomes. (1,2,4)

AIM

The purpose of this case series was to raise awareness about chronic nonbacterial osteomyelitis (CNO) in order to secure early diagnosis, well-timed treatment, and to prevent complications. By raising awareness, we hope to shorten the time-lapse from disease onset to diagnosis, prevent unnecessary and incorrect treatment, and improve prognosis for CNO patients.

MATERIALS AND METHODS

This article is a case series presenting three female pediatric patients with a definitive diagnosis of different forms of chronic nonbacterial osteomyelitis. The onset of symptoms occurred at the ages of 5, 7, and 8, and diagnoses were made at the ages of 11, 8, and 9, respectively. Patients were diagnosed and treated at the Pediatric Clinic of the Clinical Center University of Sarajevo from May 2022 to July 2024.

RESULTS

Patient 1 was a 9-year-old girl referred to a rheumatologist six years after the onset of symptoms. At the age of 5, she developed swelling on the left side of her face and was seen by a maxillofacial surgeon who surgically treated her to remove a bone mass on her left mandible. A year later, the symptoms recurred, leading to a second surgery and a biopsy that identified the lesion as a Giant cell granuloma. Six months before the rheumatology consultation, she started experiencing pain from her left temporomandibular joint (TMJ) to the left mandibular angle, with an inability to fully open her mouth. During these painful episodes, her C-reactive protein (CRP) levels were significantly elevated (>100). She was treated with antibiotics and steroids, which were effective. Following this, she was hospitalized at her local hospital for an extensive diagnostic evaluation. A facial CT scan revealed increased bone remodeling on the left mandible and edema of the surrounding soft tissue. Bone scintigraphy confirmed signs of giant cell granuloma on the left mandible and detected lesions on the upper thoracic spine and the second and third ribs, with an indeterminate etiology. A revised bone biopsy suggested possible diagnoses of infective osteomyelitis, noninfective osteomyelitis, or diffuse sclerotic osteomyelitis.

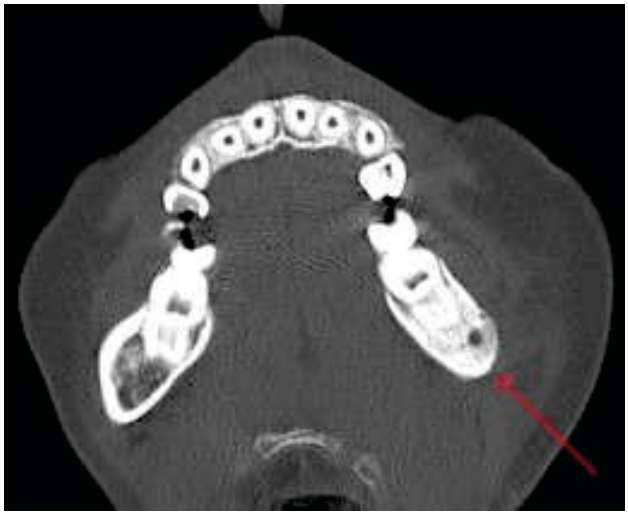

Figure 1 **Patient A - Face CT shows increased bone remodeling on the left mandible and edema of the surrounding soft tissue.**

The patient was subsequently referred to a rheumatologist. During the physical examination, face asymmetry with swelling of the left mandible and a shortened left mandible ramus was observed, along with additional findings including swelling at the medial end of the right clavicle, thoracic scoliosis, and restricted movement in both shoulders. Following this assessment, she was promptly admitted to the hospital. Laboratory tests revealed a slightly elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Abdominal and lymph node ultrasounds, as well as hand X-rays, were unremarkable. The patient was initially treated with NSAIDs, which led to a resolution of pain and swelling. The CT revealed compressive fractures of the thoracal fifth and sixth vertebrae, while the MRI showed acute inflammation and edema in the seventh thoracal vertebra.

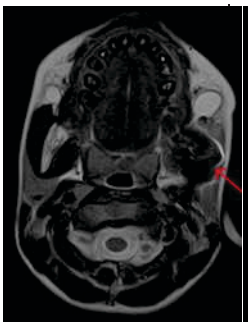

Figure 2 **Patient A: Head MRI T2 WI shows sclerosis in left mandible.**

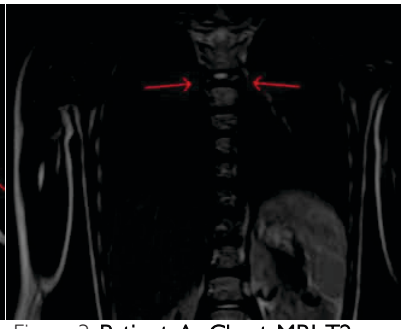

Figure 3 **Patient A: Chest MRI T2 WI shows compressive predominant area of fracture in the Th5 vertebra.**

The mandible lesion was predominantly sclerotic with no active inflammation. A decision was made to start adalimumab, low-dose Methotrexate and Pamidronate after three months of NSAID therapy. Three months later, during a follow-up visit, the patient reported complete symptom regression. Laboratory tests showed normal levels of ESR and CRP. For several months, the patient remained asymptomatic. Nonetheless, a respiratory infection (pneumonia) led to a temporary cessation of immunotherapy, resulting in a flare-up with symptoms including pain in the neck, jaw, shoulders, back, and legs, and elevated ESR and CRP levels. After the reintroduction of immunomodulation, symptoms subside. The patient is now being closely monitored.

Patient 2 was an 8-year-old girl, who was referred to a rheumatologist fourteen months after the onset of symptoms. At the age of 7, her mother noticed swelling in the right clavicle. A month later, a CT scan and MRI were performed, which revealed signs of fibrous dysplasia with fractures.

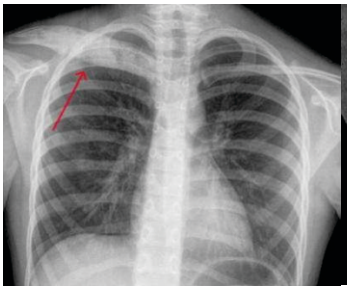

Figure 4 **Patient B - Chest X-ray shows rigth clavicle.**

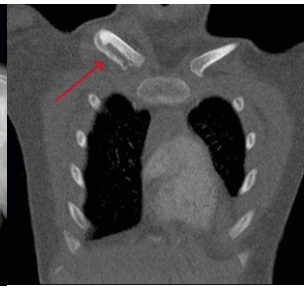

Figure 5 **Patient B - Thoracic CT shows signs of fibrous dysplasia with insufficient fractures.**

An open bone biopsy was advised, but a needle biopsy was instead conducted a month later, effectively excluding Ewing sarcoma from the differential diagnosis. Three months following these procedures, the patient began to experience persistent pain in the right clavicle, occurring both day and night. Administered NSAIDs proved effective. A month later, a follow-up CT scan and MRI demonstrated disease progression, raising the suspicion of Chronic Nonbacterial Osteomyelitis (CNO). A chest x-ray revealed an enlarged right clavicle and dilation of the VIII and IX ribs on the right side. Subsequently, an open bone biopsy confirmed fibrous dysplasia with proliferative tissue. The patient was referred to a rheumatologist, where a thorough physical examination revealed several notable findings: tumorous growth on the right clavicle, erythema on the right shoulder and leg, and onychomycosis affecting the fifth finger on both hands. Laboratory tests indicated a slightly elevated ESR and significantly elevated TNF-alpha levels, while HLA-B27 was negative. Bone scintigraphy demonstrated inflammatory changes in the right clavicle. Four months into treatment, the patient demonstrated significant improvement. However, she developed signs of palmoplantar pustulosis - sign of disease activity and exhibited psoriasis-like changes in the hairline and fingernails, along with areas of hypopigmentation on the legs and arms. Consequently, after eight months, adalimumab was discontinued due to treatment resistance. The treatment was adjusted to include a short course of systemic corticosteroids, Methotrexate, and Pamidronate. Although osteomyelitis symptoms abated, the patient experienced worsening skin and fingernail issues, alongside early signs of lipodystrophy, onychomycosis, and alopecia. In response, anakinra was introduced. A year into this regimen, the patient achieved almost complete resolution of symptoms.

Patient 3 was a 9-year-old girl, who was recently referred to a rheumatologist eight months after the onset of symptoms. At the age of 8, she started having pain in her left arm after trauma. The patient was treated by an orthopedic surgeon by immobilization. For a prolonged period, there was tenderness and swelling on the distal part of the left upper arm. She was referred to an orthopedic surgeon again. Initially, there was limited flexion in the left elbow and edema above the left elbow. The area was not tender to touch. An MRI was performed.

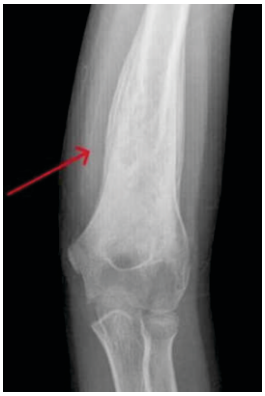

Figure 6 **Patient 3 - Left elbow X-ray shows enlarged distal end of humerus.**

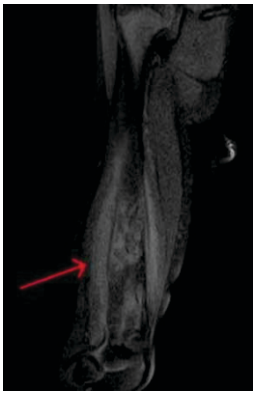

Figure 7 **Patient 3 – Left arm MRI: T2 WI shows periosteal reaction in the humerus with muscle edema.**

She was treated for bacterial osteomyelitis with antibiotics for three months. She experienced some improvement, but intermittent pain continued to occur. A pediatric rheumatologist was consulted and CNO was considered. The bone biopsy showed no signs of infection or malignancy. It was instead described as normal bone tissue with focal zones of hemorrhage and nonspecific proliferative inflammation. Scintigraphy only showed the lesion on the left humerus. During the physical exam, several changes were noted: the skin on hands and feet was covered in papules, and on the distal third of left there was palpable growth, without palpable tenderness. Her laboratory test showed elevated levels of circulating immunocomplex, anti-streptolysin-O, IgE, and slightly

elevated levels of SE and IgM. A lymph node ultrasound was performed, and it showed several chronic lymph nodes in the left armpit and the groin bilaterally. She was prescribed NSAID. The patient experienced partial regression of pain and swelling in response to NSAID therapy. Should the condition remain inadequately controlled with NSAIDs alone, Methotrexate will be considered as a subsequent treatment option.

DISCUSSION

This case series presents three CNO female patients aged 8-9. The most frequent symptoms were bone pain and swelling. None of the patients had a fever. All of them had impaired function. The bones primarily affected were the clavicle, mandible, humerus, vertebra with secondary complications such as compressive vertebral fractures and scoliosis. All of them had nonsignificant laboratory results, apart from elevated ESR and CRP. All three patients were referred to a pediatric rheumatologist a minimum of eight months after symptoms occurred. Two out of three patients had a CT, bone scintigraphy, and open bone biopsy performed. Only one patient had a whole-body MRI performed. All of them were primarily treated with NSAIDs, two are now treated with TNF inhibitors, and the third is a candidate for Methotrexate. One of the patients developed paradoxical psoriasis while being treated with adalimumab, which was successfully treated topically. Other authors have described similar disease presentations in their published work.

Shi X, et al. published a case report in 2023 about a 9-year-old female patient who had a compressive fracture of the thoracic spine and developed scoliosis (5). Ma L, et al. published a case series in 2022, regarding clinical characteristics and outcomes of CNO. The median delay in diagnosis was 10.9 months, and the most frequent presenting symptoms were bone pain and fever (6). Rosenwasser N, et al. published a review in 2021, in which they discussed paradoxical psoriasis after exposure to TNF inhibitors in children with juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD), or chronic nonbacterial osteomyelitis (CNO). They explain that children with JIA, CNO, and IBD have a higher risk of developing psoriasis anyway, but especially when treated with TNF inhibitors, such as infliximab and adalimumab. Topical therapy is effective in treating psoriasis and children can continue TNFi for their primary disease (7).

CONCLUSION

Chronic nonbacterial osteomyelitis (CNO) is a severe autoinflammatory bone disorder. It affects the pediatric population and can cause devastating complications that cannot be cured once present. Awareness of this diagnosis needs to be raised, so that unnecessary procedures may be avoided, patients may be referred to a rheumatologist sooner, and treatment may begin timely to avoid complications. A whole-body MRI should be performed for every patient before treatment, to ensure that the primary evaluation (the number and severity of bone lesions) is accurate.

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Reprint requests and correspondence:
Ivana Malešić, MD
Pediatric Clinic
Clinical Center University of Sarajevo
Patriotske lige 81, 71000 Sarajevo
Bosnia and Herzegovina
Email: ivanamalesic@gmail.com
ORCID ID: 0009-0009-0390-1764

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