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Novi Centralni medicinski blok - Klinički centar Univerziteta u Sarajevu
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Novi Evropski vodič za prevenciju tromboembolizma kod A Fib

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

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

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

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

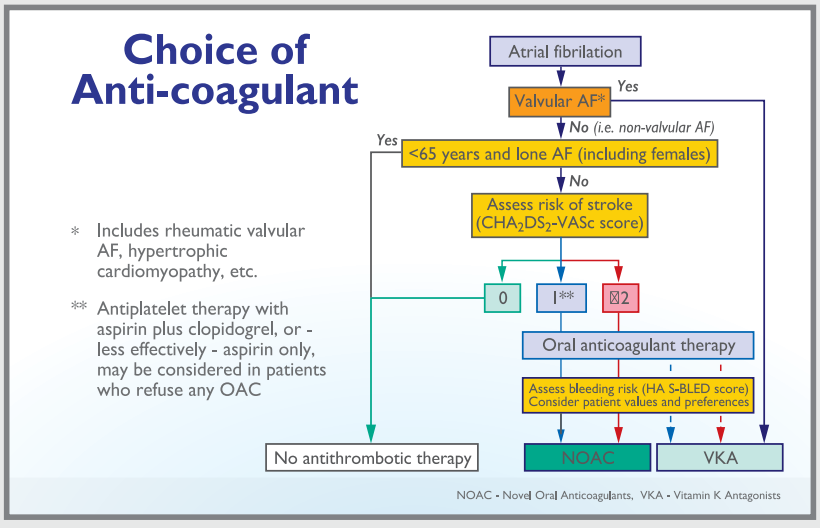
Major i non-major riziko fakori za procjenu tromboembolizma kod A Fib!

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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AIMS AND SCOPE

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Content

The relation between vitamin D and degree of asthma control in children aged 8 to 10

Odnos vitamina D i stepena kontrole astme kod djece starosne dobi 8 do 10 godina života

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ABSTRACT

Introduction: asthma is a chronic inflammatory disease, which in the case of a long-term and inadequate treatment can lead to a remodeling of the lower airways and weakening of lung functions. Asthma pathophysiology is still completely unknown, which to a certain extent can explain the absence of the desired response to the applied therapy. As of recently, the focus has been on the role of Vitamin D. Vitamin D is considered to induce mediation of the Th2 inflammatory response by increasing the effect of IL-4, IL-5 and IL-13 cytokines, which play a significant role in the pathophysiology of asthma. All the above, rightly raises the issue of the influence of Vitamin D in the pathophysiology of asthma. Aim: to determine the correlation between the degree of asthma control and the value of vitamin D in the peripheral blood. Materials and methods: the study included a total of 200 respondents aged 8 to 10, who, due to diagnosed asthma, were monitored through the Pulmonology Department of the Pediatric Clinic of the CCUS. The degree of asthma control was determined using the Asthma Control Test (ACT) designed for use with children, supplemented by auscultatory findings, spirometric measurements, and determination of FeNO. The level of vitamin D was determined in a peripheral blood sample. Conclusion: lower Vitamin D values were closely correlated with poorer asthma control. Higher vitamin D levels reduced the risk of poor asthma control, so that with each higher concentration unit, the risk was reduced by 10%.

Keywords: asthma, Vitamin D, asthma control

SAŽETAK

Uvod: astma je hronična inflamatorna bolest, koja u slučaju dugotrajnosti i neadekvatnog tretmana može dovesti do remodeliranja donjih disajnih puteva i slabljenja vrijednosti plućnih funkcija. Patofiziologija astme, je do danas u potpunosti nepoznata, čime u pojedinim slučajevima možemo objasniti pojavu izostanka željenog odgovora na primjenjenu terapiju. U posljednje vrijeme u fokusu je uloga Vitamin D. Za vitamin D, se smatra da inducira posredovanje Th2 inflamatornog odgovora povećavajući uticaj citokina IL-4, IL-5 i IL-13, koji igraju značajnu ulogu u patofiziologiji astme. Na osnovu svega iznesenog sa pravom se postavlja pitanje uticaja Vitamina D u patofiziologiji astme. Cilj: nam je bio utvrditi korelaciju između stepena kontrole astme i vrijednosti vitamin D u perifernoj krvi. Materijal i metode: u istraživanje je bilo uključeno ukupno 200 ispitanika starosne dobi 8 do 10 godina života, koji se zbog dijagnosticirane astme prate kroz Pulmološko savjetovalište Pedijatrijske Klinike KCUS. Stepen kontrole astme smo utvrđivali primjenom Astma Kontrol Testa namjenjenog djeci (ACTC), upotpunjenog auskultatornim nalazom, spirometrijskim mjerenjima, i određivanjem FeNO. Nivo vitamin D smo određivali u uzorku periferne krvi. Zaključak: niže vrijednosti Vitamin D su bile u uskoj korelaciji sa slabijom kontrolom astme. Više vrijednosti vitamin D smanjivale su rizik od slabe kontrole astme, i to sa svakom jedinicom koncentracije više, rizik je bio manji za 10%.

Ključne riječi: astma, Vitamin D, kontrola astme

INTRODUCTION

Asthma is the most common chronic inflammatory disease of the respiratory system of children. The incidence of the disease varies from region to region and in different countries of the world it ranges from 1-18% (1). In the last two decades, there has been a steady increase in the number of patients. It is believed that 14% of the child population suffers from asthma, with a mortality rate of 0.7/100,000 (2). Inadequate treatment of asthma and the long course of the disease will cause the remodeling of the lower airways, which as a final result will have permanent changes in the sense of impairment - decrease in the value of pulmonary function (3). Asthma pathophysiology is still completely unknown, which to a certain extent can explain the absence of the desired response to the applied therapy. Vahlkvist S, et al. proved that there was a significant correlation - the difference in lung function values in

asthmatic children who used adequate therapy and had good disease control compared to children who were not under adequate treatment (4).

The Th2 immune response is the most common phenotype in allergic asthma which has been demonstrated in the majority of pediatric and adult patients with mild to moderate asthma. These patients show increased levels of Th2 cytokines (IL-4, IL-5, IL-13) produced by CD4+ Th2 cells. IL-5 is the initiator of eosinophil recruitment, while IL-4, IL-13 promote mucosal cell metaplasia, airway hyperreactivity and their remodeling (5). Vitamin D receptors are found in numerous cells of various organ systems such as the brain, heart, pancreatic beta cells, muscles, fat tissue, eyeballs, and in almost all cells of the immune system (6). It is believed that vitamin D induces the mediation of Th2 inflammatory response by increasing the influence of cytokines IL-4, IL-5 and IL-13, which role in the pathophysiology of asthma is unquestionable. The diet, working habits and lifestyle have led to the fact that today we have more and more people with various difficulties, in whom reduced vitamin D values have been detected. In 2016, Kim MJ, et al. published the results of a meta-analysis which included 24 studies. The results showed that children with atopic dermatitis had lower 25(OH) D values compared to healthy children (7). Ozkars MY, et al determined the relationship between vitamin D levels and spirometry values. They proved a significant negative correlation between the level of vitamin D and the FEV1 value, and also a significant positive correlation between the maximal reduction of FEV 1 and the level of vitamin D in children with proven asthma (8). Taking into account above stated, the question arises as to the place and role of vitamin D in the clinical manifestation of the disease, as well as the influence of vitamin D on the degree of asthma control.

AIM

The aim of the study was to determine the correlation between the degree of asthma control and the value of vitamin D in the peripheral blood.

MATERIALS AND METHODS

The study was designed as a clinical, cohort, observational and retrospective-prospective. It included the total of 200 respondents, aged 8 to 10, diagnosed with asthma and monitored through the Pulmonology Consultation Center of the Pediatric Clinic of the CCUS. Respondents who could not adequately cooperate during the examination, respondents with other associated chronic diseases and those with signs of acute infection were excluded from the study. Asthma control was classified based on the Asthma Control Test (ACT), physical examination (auscultation), FEV1 and FeNO measurements. Asthma control was classified based on the GINA guidelines, as well controlled, poorly controlled and uncontrolled. The vitamin D value was determined from a peripheral blood sample obtained after venipuncture.

To examine the simultaneous influence of independent and confounding variables (predictors) on the categorical outcome with more than two categories, multinomial logistic regression was used, after previously checking that its assumptions were met: linearity, absence of outliers, independence of variables and absence of collinearity. The final model was obtained by backward deletion procedure. Quality of the final model was examined with the Likelihood ratio test, and the Pearson Chi-square Test. The extent to which the final multinomial logistic regression model explained outcome variability was assessed by calculating Nagelkerke pseudo R2 and Cox & Snellen. The results of all used statistical tests were considered statistically significant if the probability of the null hypothesis was less than 0.05

RESULTS

Table I **Demographic representation of the distribution of respondents in relation to gender.**

Demographic representation of the distribution of respondents in relation to gender		
	Total number of respondents	Value expressed in percentage (%)
Female gender	98	48.7
Male gender	102	51.3
Total	200	100.0

The study included a total of 200 respondents. Although guided by the method of random sampling, our sample had equal representation of men and women.

Table 2 **Descriptive statistics.**

Descriptive Statistics						
	N	Range	Minimum	Maximum	Mean	Std. Deviation
Vitamin D level	200	51.0	13.0	64.0	35.314	12.1924
Valid N (listwise)	200					

When determining the level of vitamin D, the reference values were in the range of 30-100 ng/ml.

The minimum value of vitamin D in our sample was 13.0 ng/ml, while the maximum value was 64.0 ng/ml. We did not prove vitamin D values closer to the upper limit, i.e. vitamin D values higher than the reference values, in any of the respondents.

Table 3 **Tabular representation of the influence of different variables on the degree of asthma control.**

Tabular representation of the influence of different variables on the degree of asthma control					
	Variables	Well controlled asthma	Poorly controlled asthma	Uncontrolled asthma	Probability zeros hypotheses
		(n=25)	(n=94)	(n=81)	(p) **
Maternity mass (g)		3150.0 (645.0)	2900.0 (770.0)	3330.0 (1385.0)	0.411
FeNO (pbb)		14.0 (9.0)	74.0 (47.0)	88.0 (36.0)	0.046
Level vitamin D (ng/ml)		42.0 (14.5)	29.0 (14.0)	27.0 (7.0)	0.002
GENDER M/F		44/49	45/36	13/12	0.553
		(47.3 % / 52.7 %)	(55.6 % / 44.4 %)	(52.0 % / 48.0 %)	
FEV 1	> 80	87 (93.5 %)	15 (18.5 %)	0 (0.0 %)	0.002
	< 80	6 (6.5 %)	66 (81.5%)	25 (100.0 %)	
** statistically significant predictor*					

If the clinical manifestation of the disease was seen as the degree of asthma control (controlled, poorly controlled and uncontrolled), the influence of the FEV1 value, corrected with the effect of other monitored factors, was examined by using multinomial logistic regression. The dependent variable in the multinomial logistic regression model was the degree of asthma control; factors taken into account were: gender, FEV1 values. Covariates taken into account were FeNO and vitamin D level (Table 3). The obtained model was significant, because the Likelihood ratio test for the final model was Chi-square = 230.985, p = 0.000, while the test of how well the final model corresponded to the saturated model indicates that there was no significant difference, i.e. that the model was well fitted to the observed data (Pearson's Chi-square = 211.032, p = 1.000). Nagelkerke pseudo R2 was as much as 0.804, and Cox & Snellen 0.690, meaning that the model explained as much as 80% and 69% of the variability of the outcome, i.e. asthma control. FEV1 > 80% significantly reduced the risk of poor asthma control (odds ratio = 0.030 [95% confidence interval 0.002 – 0.607], p=0.022) by about 97%. When it comes to uncontrolled asthma, the risk of the occurrence increased with increasing FeNO values (odds ratio = 1.051 [95% confidence interval 1.001 – 1.104], p=0.046), by about 5% with each additional FeNO unit.

In addition to better FEV1 values, a higher plasma vitamin D level also reduced the risk of poor asthma control (odds ratio = 0.900 [95% confidence interval 0.842 - 0.962], p=0.002), and with each additional concentration unit, the risk was smaller by 10%.

DISSCUSION

Asthma is a significant health problem worldwide. It is the most common childhood chronic inflammatory disease. According to World Health Organization (WHO) data, 262 million people suffered from asthma in 2019, and asthma caused 455,000 deaths (1). Inadequately treated asthma results in irreversible changes in the architecture of small airways, which is why adequate treatment is an imperative.

Our study included a total of 200 respondents. The discrepancy between the development of the lung parenchyma and the respiratory tree in relation to the air flow rate was first described by Mead in 1980, who at the same time noticed that boys were more often affected than girls at a younger age. This relationship changes during life, and the changes are explained by differences in growth and development, and the hormonal status between males and females (9). In their review article, Miyasaka T, et al. showed that in older age the rate of relapse and the need for hospital treatment

was higher in female respondents. They believed that female sex hormones in older age enhanced type 2 immune responses, unlike male sex hormones, which in this study were characterized as suppressive (10). Taking into account all the above stated, and the fact that patients in our study were selected based on random sample method, the obtained results were not in favor of male dominance. Namely, our sample had an equal distribution of males and females.

The results of this study support the importance of clarifying the real role of hormonal status in the pathogenesis of asthma, which could contribute to a personal approach to the treatment of asthma patients through various reproductive stages of life.

ACTC has long been used to classify asthma control. In order to hide their problems, sometimes children deliberately ignore their problems and do not talk about them. With the aim of a more complete and adequate classification of asthma control, the ACTC was supplemented with a physical examination (presence of wheezing), FEV1 measurement and FeNO determination.

According to many authors, FeNo is considered as an important asthma biomarker. In their study, which included a total of 306 subjects, Dupont LJ, et al., proved significantly higher FeNo values in younger respondents diagnosed with asthma compared to healthy respondents (11). Jones SR, et al. in their work stated that the use of ICS influenced the decrease of FeNO values, which was why they considered it an important biomarker for asthma control monitoring. After termination of ICS therapy, an increase in FeNo by more than 60% of reference values had a predictive role for poor asthma control and severe obstructive attacks (12). The results of our study showed that the risk of uncontrolled asthma developing increased with the increasing FeNO values (odds ratio = 1.051 [95% confidence interval 1.001 - 1.104], p=0.046). For each additional FeNO unit, the risk of poorer asthma control increased by 5%. The stated results are in favor of the importance of FeNO values, as asthma biomarker, but we still have to keep in mind possible associated moments that can influence higher FeNO values.

Cross-sectional studies conducted on preschool and school children show contradictory opinions regarding the relationship between the value of vitamin D in the circulating blood and the degree of asthma control. In school children, higher levels of vitamin D were closely associated with better asthma control, lower risk of requiring hospital treatment and reduced number of serious broncho-obstruction attacks (13). In a randomized clinical study which included a total of 192 children, Forno E, et al. monitored the influence of vitamin D supplementation on the frequency and severity of the clinical expression of asthma. They concluded that vitamin D supplementation compared to placebo did not significantly affect the frequency of shortness of breath attacks, thus questioning the need for vitamin D supplementation in this group of patients (14). On the other hand, Bugadze L, et al. stated that higher values of vitamin D were closely related to higher values of FEV1 and FVC in school children (15). In their meta-analysis, Stefanidis C, et al. reviewed Medline, PubMed, the Cochrane Register of Controlled Studies (CENTRAL), Web of Science and Clinical Trials data bases using electronic research strategies and concluded that there was evidence that vitamin D reduced the risk of asthma exacerbations in adults, while high levels of vitamin D in preschool and school children significantly reduced the risk of acute respiratory tract infections and repeated wheezing attacks. Finally, they concluded that further research was needed to evaluate the mechanism of the effect of vitamin D supplementation on the pathogenesis of acute wheezing in children (16).

Having in mind the above stated, during the laboratory diagnostic processing of the respondents, we also determined the level of vitamin D in the peripheral blood. The minimum value of vitamin D was 13.0 ng/mL, which was in favor of significantly low values, while the maximum value was 64.0. ng/mL. We did not determine values close to the upper limit, or values that exceeding the set limit, in any of the respondents. The mean value of vitamin D in both groups of respondents was 35.31. The clinical expression of the disease observed as the degree of asthma control (controlled, poorly controlled and uncontrolled) in relation to the vitamin D values in the blood was examined by multinomial logistic regression. The results of the conducted tests show that a higher level of vitamin D in the plasma reduces the risk of poor asthma control (odds ratio = 0.891 [95% confidence interval 0.859 - 0.924], p=0.000), and with each additional concentration unit, the risk is lower by 10.9%. In the case of uncontrolled asthma, a higher level of vitamin D in the plasma also reduces the risk (odds ratio = 0.882 [95% confidence interval 0.839 - 0.929], p=0.000), and with each additional concentration unit, the risk is lower by 11.8%.

As stated by Maes K, et al. low levels of vitamin D in the blood were closely related to more frequent asthma exacerbations, although the exact mechanism of the pathophysiological processes was still not clear. They emphasize the fact that asthma exacerbations are accompanied by vitamin D deficiency, but they believe that this deficiency is not a trigger for exacerbations or poorer disease control (17).

As previously stated in this study, low values of vitamin D were closely related to poorer asthma control, and the question arises as to a true role in the complex asthma pathophysiology. All authors agree that asthma is a heterogeneous disease, occurring as a result of the interaction of numerous factors on which the control of the disease itself depends, some of which can be significantly influenced (18).

CONCLUSION

Our study had an equal number of male and female respondents. The results of the conducted tests indicate that a higher level of vitamin D in the plasma reduces the risk of poor asthma control (odds ratio = 0.891 [95% confidence interval 0.859 - 0.924], p=0.000). With each additional unit of vitamin D concentration, the risk of poorer asthma control was 11.8% lower.

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Impact of stress on the work efficiency of healthcare professionals

Utjecaj stresa na radnu efikasnost zdravstvenih profesionalaca

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ABSTRACT

Introduction: in the second half of the 20th century, there was increased interest in occupational medicine regarding the psychological aspects of work, aiming to assess opportunities for enhancing work efficiency. It was already recognized then that prolonged exposure to stress can undermine health and influence each individual's behavior, quality of life, and work. However, particular attention is given to the healthcare profession, where high stress and its consequences are experienced by doctors and nurses (health professionals) upon whom the health and lives of others depend. Aim: to identify the presence of stress and its impact on the work efficiency of healthcare professionals at the primary, secondary, and tertiary levels of healthcare. Materials and methods: the participants in the study were employed in healthcare institutions: Primary level - Sarajevo Health Centers; 50 doctors, 100 nurses, Secondary level - General Hospital "Prim. Dr. Abdulah Nakaš"; 50 doctors, 100 nurses, Tertiary level - Clinical Center Sarajevo; 50 doctors, 100 nurses (BSc/MSc and BSc). The total number of participants from the mentioned healthcare institutions was 450. The research was conducted in 2017 and 2018 in the mentioned institutions, with the approval of the healthcare institutions. The research method was a cross-sectional, comparative, descriptive-analytical study. A modified combined closed-open type questionnaire was used for the intended research according to the Likert model with a scale from 1-5, where 1- strong disagreement and 5- complete agreement with the statement. Results: the results show a positive correlation between different examined groups and great similarity in attitudes between various levels of healthcare institutions. According to the participants, there is a high level of stress in the workplace. A difference in the presence and negative impact of stress is identified at different levels of healthcare. The highest stress level is present at the tertiary level, followed by the secondary level, to a lesser extent at the primary level. Conclusion: a large amount of stress hurts the work efficiency of healthcare professionals. The healthcare profession is highly stressful, undermining employees' mental and physical health at all levels of healthcare institutions.

Keywords: stress, stressors, healthcare professionals, work efficiency

SAŽETAK

Uvod: u drugoj polovini 20. stoljeća povećano je zanimanje medicine rada za psihološke aspekte rada, sa ciljem sagledavanja mogućnosti za povećanje efikasnosti na radu. Već tada je uočeno da dugotrajna izloženost stresu može narušiti zdravlje i utjecati na ponašanje i kvalitetu života i rada svakog pojedinca. Međutim, posebno mjesto zauzima zdravstvena profesija, u kojoj su visokom stresu i posljedicama stresa, izloženi ljekari i medicinske sestre (zdravstveni profesionalci) o kojima ovise zdravlje i životi drugih ljudi. Cilj: evidentirati prisustvo stresa i njegov utjecaj na radnu efikasnost zdravstvenih profesionalaca na primarnom, sekundarnom i tercijarnom nivou zdravstvene zaštite. Materijali i metode: ispitanici u istraživanju su zaposleni u zdravstvenim ustanovama: Primarni nivo ZZ-JU Domovi zdravlja Sarajevo; ljekara 50, medicinskih sestara 100, Sekundarni nivo ZZ-Opća bolnica "Prim. dr. Abdulah Nakaš"; ljekara 50, medicinskih sestara 100; za tercijarni nivo ZZ-Klinički centar Sarajevo; ljekara 50, medicinskih sestara 100(VSS/VSŠ i SSS). Ukupan broj ispitanika iz navedenih zdravstvenih ustanova je 450. Istraživanje je realizirano 2017 i 2018 godine u navedenim, uz odobrenje zdravstvenih ustanova. Materijali i metode: ovo je presječna (cross-sectional) komparativna, deskriptivno-analitička studija. Za predviđeno istraživanje korišten je modifikovano kombinovani zatvoreno-otvorenog tipa upitnik prema Likertovom modelu sa skalom od 1-5, pri čemu 1- izrazita negacija; 5- potpuno slaganje sa postavljenom tvrdnjom. Rezultati istraživanja: Rezultati pokazuju pozitivnu koleraciju između različitih ispitivanih grupa, kao i velike sličnosti u stavovima između različitih nivoa ZZ. Prema mišljenju ispitanika prisutan je visok stepen stresa na radnom mjestu. Evidentira se razlika u prisustvu i negativnom djelovanju stresa, na različitim nivoima zdravstvene zaštite. Najveći stepen stresa prisutan je na tercijarnom nivou, zatim na sekundarnom nivou ZZ, u nešto manjoj mjeri na primarnom nivou ZZ. Zaključak: veliki količina stresa ima negativan utjecaj na radnu efikasnost zdravstvenih profesionalaca. Profesija zdravstvenih radnika je jako stresna, koja narušava mentalno i fizičko zdravlje zaposlenika na svim nivoima ZZ.

Ključne riječi: stres, stresori, zdravstveni profesionalci,efikasnost na radu

INTRODUCTION

A healthcare organization consists of its employees, who, as individuals, have their characteristics: temperament, character, opinions, interests, needs, motivations, attitudes, and emotions. In addition, they belong to different social ethnic groups, layers of society, and religious organizations. They have different systems of cultural values, other knowledge, and personal abilities. Because of all above stated, conflicts arise among employees during work.

The lower the organizational culture level, the greater number and type of disputes. Conflicts are a constant and inherent characteristic of every healthcare organization. The only uncertain aspect is when they will occur, in what form, and at which level. Conflicts should be anticipated and accepted as the reality of every organization, even the most successful ones.

The responsibility of human resources management is to address areas of identifying potential conflicts and developing programs for their prevention. Conflicts are not the most critical issue, but they do harm the organization: they lead to demoralization, a decrease in employee motivation, and reduction in the quality of work. Not all conflicts are simultaneously harmful, as high-quality radical changes within a group and society begin from conflict situations. Gutić and Rudelj classify conflicts as follows (2).

1. Intrapersonal conflicts are, briefly stated, conflicts of employees "within themselves." An individual consciously or unconsciously transfers their internal disputes to other members and introduces their conflict as tension to other team members.
2. Interpersonal conflicts are conflicts between employees within one organization. An organization often has different viewpoints, interests, and directions within individual departments and sections. For example, the interests of intensive care nurses may differ from those of surgical nurses.
3. Intra-organizational conflicts - within the workgroup, two types of disputes most commonly occur:
   a) Conflicts of interest are most common in the struggle for power and leading positions in the organization, with two conflicting sides.
   b) Conflicts of values are much more profound in content and sources of origin but also last longer than conflicts of interest. They usually arise from different ideological divisions and attitudes (3).

Reactions to stress can be psychological, social, and physiological.

Psychological reactions to stress are most often increased anxiety, concentration problems, negative emotions, loss of attention, depression, fatigue, burnout syndrome, or an increase in suicides.

Social reactions to stress are most often withdrawal and isolation at work or home, increased accidents, increased consumption of cigarettes, alcohol, or coffee, irritability, aggression, sexual dysfunctions, low motivation for work and interpersonal relationships, and an increase in violence at work and home.

Physiological reactions to stress include increased cortisol levels, increased blood pressure, palpitations, chest pain, insomnia, the appearance of certain types of cancer, digestive disorders, headaches, musculoskeletal problems, and a decrease in immune system function (4).

The expert team, consisting of an occupational medicine specialist, psychologist, manager, occupational safety engineer, and lawyer, carries out a series of activities, such as job analysis, task, and work organization analysis, assessment of exposure duration to harmful influences, and study of psychological factors and physical workload at work (5).

Based on the "risk assessment" by the expert team, health protection measures for employees are implemented in work processes, which also includes carrying out health surveillance. Existing methods for hazard assessment in their methodology do not involve measuring the level of work-related stress. It has also been observed that prolonged exposure to stress can undermine health and affect individuals' behavior, quality of life, and work. A high sick leave rate is primarily conditioned by diseases resulting from prolonged stress. With the development of modern society, no one is immune to stress. The contemporary development of healthcare activities regarding work, work environment, and work organization, the introduction of new technologies, new scientific and professional knowledge, and the growing development of diagnostic and therapeutic possibilities, along with increasing psychophysical demands on healthcare workers, can cause new epidemics of diseases caused by work and working conditions (6).

The healthcare profession is classified as a highly stressful profession, considering its high responsibility towards human life and health and exposure to specific stressors such as harmful chemical, biological, and physical influences. Extended working hours, shift and night work, poor interpersonal relationships, decision-making responsibility, contact with patients and their families, and emotional exhaustion (burnout) among healthcare workers contribute to increased morbidity from psychological disorders and psychosomatic illnesses (7).

AIM

The purpose of this study was to identify the presence of stress and its impact on the work efficiency of healthcare professionals at the primary, secondary, and tertiary healthcare levels.

MATRIALS AND METHODS

Participants in the study were employees in healthcare institutions: for the primary level of healthcare, the Public Health Center (PHC) Sarajevo; 50 physicians, 100 nurses (Bachelor's/Master's and Secondary School of Nursing), a total of 150 participants. For the secondary level of healthcare, General Hospital (GB) "Prim. Dr. Abdulah Nakas" Sarajevo; 50 physicians, 100 nurses (Bachelor's/Master's and Secondary School of Nursing), a total 150 participants. For the tertiary level of healthcare, Clinical Center (CC) Sarajevo, 50 physicians, 100 nurses (Bachelor's/Master's and Secondary School of Nursing), a total of 150 participants. The total number of participants from the mentioned healthcare institutions was 450. The study was conducted in the course of 2017 and 2018, with the approval of healthcare institutions.

Inclusion criteria for the study: participants were physicians (specialists and resident physicians) and nurses (Bachelor's/Master's and Secondary School of Nursing) employed in the mentioned healthcare institutions.

Exclusion criteria from the study: failure to meet the predetermined criteria for inclusion.

Research methods

The research was a cross-sectional, comparative, descriptive-analytical study.

Research instruments: for the planned research, a modified combined closed-open type questionnaire according to the Likert model was used. Answers to the posed statements were on a scale from 1 to 5, where 1 was strong denial, 2 denial of the statement, 3 undecided, 4 agreement with the statement, and 5 related to complete agreement with the statement.

The content of the questionnaire provided answers to the posed statements related to factors affecting the work efficiency of employees: job analysis, job position systematization, human resource planning, professional selection, work process design, management and managerial style, work team, material rewards for employees, non-material motivation strategies, employee education planning, personal career development, and stress in healthcare institutions.

Ethical aspect of the research

The study was conducted following the basic principles of the Helsinki Declaration (last revision 2008). The realization of this study was voluntary and conducted anonymously by employees. Participants' data were not entered into the questionnaire.

RESULTS

Participants were doctors (specialists and residents) and nurses (Bachelor's/Master's and Secondary School of Nursing) of various ages and genders, regardless of their length of work experience and job position. Table 1 shows the structure of participants according to professional qualifications.

Table 1 **Demographic characteristics of participants: profession affiliation and professional qualifications.**

	Doctors	Registered Nurses with Bachelor's Degree	Registered Nurses with Highschool Diploma	Total
Primary Health Care	50	21	79	150
Secondary Health Care	50	19	81	150
Tertiary Health Care	50	44	56	150
Total	150	84	216	450

Table 2 **Stressful profession of healthcare workers.**

	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		MEAN	SD
Health Care Level	N	%	N	%	N	%	N	%	N	%		
Primary Health Care	4	2.6	4	2.6	7	4.6	26	17.3	109	72.6	4.54	0.91
Secondary Health Care	3	2.0	2	1.3	16	10.6	37	24.6	92	61.3	4.42	0,88
Tertiary Health Care	3	2.0	10	6.6	11	7.3	35	23.3	91	60.6	4.36	1.01
Total	**10**	**2.2**	**16**	**3.5**	**34**	**7.5**	**99**	**22.0**	**292**	**64.8**	**450= 100%**	

(x^2=14.49, p>0.05)

The chi-square test of independence did not show a statistically significant difference among the three groups in the respondents' attitudes toward the statement "The profession of healthcare workers is very stressful" ($\chi 2$=(8, n=450) = 14.490, p = 0.06878). There was no statistically significant difference in the respondents' attitudes toward the statement ($\chi 2$ = 14.49, p > .05).

Table 3 **Job affects my mental and physical health.**

	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		MEAN	SD
Health Care Level	N	%	N	%	N	%	N	%	N	%		
Primary Health Care	4	2.6	21	14.0	43	28.6	36	24.0	46	30.6	3.66	1.13
Secondary Health Care	20	13.3	26	17.3	40	26.6	47	31.3	17	11.3	3.1	1.21
Tertiary Health Care	11	7.3	33	22.0	33	22.0	42	28.0	31	20.6	3.32	1.23
Total	35	7.7	80	17.7	116	25.7	125	27.7	94	20.8	450= 100%	

(x^2=29.30, p<0.05)

The chi-square test of independence showed a statistically significant difference among the three groups regarding the respondents' attitudes toward the statement "Job affects my mental and physical health" ($\chi2$=(8, n=450) = 29.30, p = 0.000212). There was a statistically significant difference in the respondents' attitudes toward the statement ($\chi2$ = 29.30, p < 0.05).

Table 4 **Everyone around me is nervous and aggressive.**

	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		MEAN	SD
Health Care Level	N	%	N	%	N	%	N	%	N	%		
Primary Health Care	5	3.3	24	16.0	42	28.0	45	30.0	34	22.6	3.52	1.11
Secondary Health Care	13	8.6	44	29.3	35	23.3	45	30.0	13	8.6	3	1.14
Tertiary Health Care	7	4.6	30	20.0	39	26.0	45	30.0	29	19.3	3.26	1.15
Total	**25**	**5.5**	**98**	**21.7**	**116**	**25.7**	**135**	**30.0**	**76**	**16.8**	**450= 100%**	

(x^2=20.75,p<0.05)

The chi-square test of independence showed a statistically significant difference among the three groups in the respondents' attitudes toward the statement "Everyone around me is nervous and aggressive" ($\chi2$=(8, n=450) = 20.75, p = 0.007851). There was a statistically significant difference in the respondents' attitudes toward the statement ($\chi2$ = 20.75, p < 0.05).

Table 5 **Fatigue has a strong impact on my concentration and work quality.**

	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		MEAN	SD
Health Care Level	N	%	N	%	N	%	N	%	N	%		
Primary Health Care	8	5.3	23	15.3	27	18.0	58	38.6	34	22.6	3.58	1.16
Secondary Health Care	13	8.6	31	20.6	41	27.3	36	24.0	29	19.3	3.24	1.23
Tertiary Health Care	4	2.6	42	28.0	18	12.0	45	30.0	41	27.3	3.51	1.24
Total	**25**	**5.5**	**96**	**21.3**	**86**	**19.1**	**139**	**30.8**	**104**	**23.1**	**450= 100%**	

(x^2=27.31, p<0.05)

The chi-square test of independence showed a statistically significant difference among the three groups in the respondents' attitudes toward the statement "Fatigue has a strong impact on my concentration and work quality" ($\chi2$=(8, n=450) = 27.31, p = 0.000623). There was a statistically significant difference in the respondents' attitudes toward the statement ($\chi2$ = 27.31, p < 0.05).

Table 6 **There are challenging circumstances present when performing work tasks.**

	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		MEAN	SD
Health Care Level	N	%	N	%	N	%	N	%	N	%		
Primary Health Care	17	11.3	24	16.0	22	14.6	50	33.3	37	24.6	3.44	1.32
Secondary Health Care	7	4.6	20	13.3	32	21.3	73	48.6	18	12.0	3.15	1.02
Tertiary Health Care	11	7.3	16	10.6	32	21.3	65	43.3	26	17.3	3.52	1.12
Total	**35**	**7.7**	**60**	**13.3**	**86**	**19.1**	**188**	**41.7**	**81**	**18.0**	**450= 100%**	

(x^2=19.36, p<0.05)

The chi-square test of independence showed a statistically significant difference among the three groups in the respondents' attitudes toward the statement "There are challenging circumstances present when performing work tasks" ($\chi2$=(8, n=450) = 19.36, p = 0.0130). There was a statistically significant difference in the respondents' attitudes toward the statement ($\chi2$ = 19.36, p < 0.05).

Table 7 **Organizational communication is at a low level.**

	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		MEAN	SD
Health Care Level	N	%	N	%	N	%	N	%	N	%		
Primary Health Care	24	16.0	25	16.6	45	30.0	24	16.0	32	21.3	3.1	1.35
Secondary Health Care	9	6.0	21	14.0	64	42.6	40	26.6	16	10.6	3.23	1.01
Tertiary Health Care	13	8.6	27	18.0	43	28.6	46	30.6	21	14.0	3.23	1.16
Total	**46**	**10.2**	**73**	**16.2**	**152**	**33.7**	**110**	**24.4**	**69**	**15.3**	**450= 100%**	

(x^2=26.82, p<0.5)

The chi-square test of independence showed a statistically significant difference among all three groups in the respondents' attitudes toward the statement "Organizational communication is at a low level" ($\chi2$=(8, n=450) = 26.82, p = 0.000759). There was a statistically significant difference in the respondents' attitudes toward the statement ($\chi2$ = 26.82, p < 0.05).

Table 8 **Organizational culture is at an admirable level.**

	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		MEAN	SD
Health Care Level	N	%	N	%	N	%	N	%	N	%		
Primary Health Care	37	24.6	43	28.6	35	23.3	21	14.0	14	9.3	2.54	1.26
Secondary Health Care	9	6.0	46	30.6	46	30.6	48	32.0	1	0.6	2.9	0.94
Tertiary Health Care	23	15.3	41	27.3	47	31.3	31	20.6	8	5.3	2.73	1.1
Total	**69**	**15.3**	**130**	**28.8**	**128**	**28.4**	**100**	**22.2**	**23**	**5.1**	**450= 100%**	

(x^2=41.64, p<0.05)

The chi-square test of independence showed a statistically significant difference among the three groups in the respondents' attitudes toward the statement "Organizational culture is at an admirable level" ($\chi2$=(8, n=450) = 41.64, p < 0.00001). There was a statistically significant difference in the respondents' attitudes toward the statement ($\chi2$ = 41.64, p < 0.05).

Table 9 **Presentation of results on the presence of stress experienced by healthcare professionals.**

	Strongly Disagree		Disagree		Undecided		Agree		Strongly Agree		MEAN	SD
Health Care Level	N	%	N	%	N	%	N	%	N	%		
Primary Health Care	102	9.7	174	16.5	210	20.0	279	26.5	285	27.1	3.45	1.31
Secondary Health Care	118	11.2	225	21.4	250	23.8	269	25.6	188	17.9	3.18	1.27
Tertiary Health Care	81	7.7	231	22.0	228	21.7	256	24.3	254	24.1	3.35	1.27
Ukupno	301	9.5	630	20.0	688	21.8	804	25.5	727	23.0	3150=100%	

(x^2=40.96, p<0.05)

The chi-square test of independence showed a statistically significant difference among the three groups in the respondents' attitudes regarding the topic "Stress in healthcare organizations" ($\chi 2$=(8, n=3150) = 40.960, p < 0.00001). There was a statistically significant difference in the respondents' attitudes toward the group of statements related to the presence of stress in healthcare organizations ($\chi 2$ = 40.96, p < 0.05).

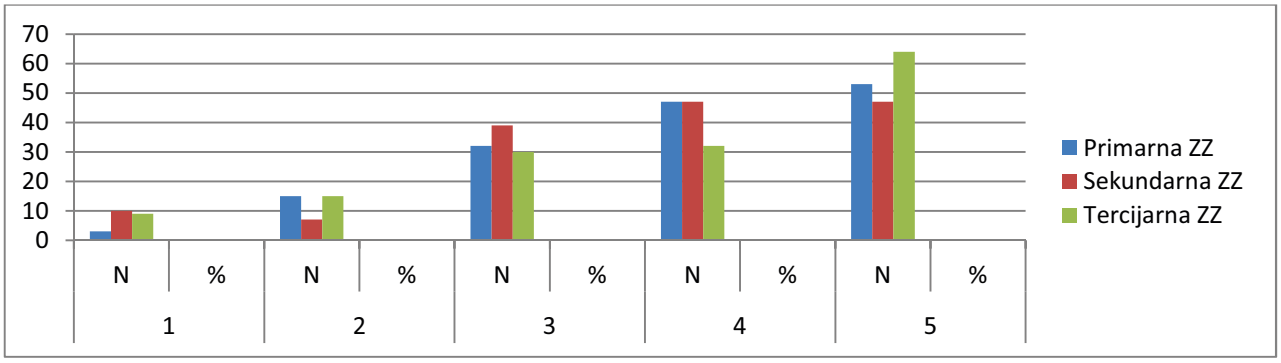

Figure 1 **Self-assessment of the level of stress experienced by healthcare professionals, on a scale from 1 to 5.**

The chi-square test of independence did not show a statistically significant difference among the three groups in the respondents' attitudes toward the statement "Assess the level of stress in the workplace" ($\chi 2$=(8, n=450) = 14.990, p = 0.059414). There was no statistically significant difference in the respondents' attitudes toward the question "Assess your level of stress in the workplace" ($\chi 2$ = 14.99, p > .05).

DISCUSSION

Numerous studies have been conducted on the presence of stress in the workplace, particularly focusing on doctors and nurses. Healthcare professionals consider the profession of healthcare workers to be very stressful (86.8%). The work affects the mental and physical health of 48.5% of respondents. Indecisive responses were given by 25.7% of respondents, while 17.7% of respondents do not work in positions that could compromise mental and physical health.

There is evident general haste and nervousness in the workplace, with 46.8% lacking patience and tolerance. A changeable atmosphere is felt by 25.7% of respondents, while 21.7% of respondents experience a pleasant working environment.

Doctors and nurses feel that fatigue strongly affects their concentration and the quality of their work (53.9%), while a certain number of employees (21.3%) do not feel excessive fatigue. Fatigue, due to the synergies it produces in the body, negatively affects work efficiency.

Employees feel the presence of challenging circumstances in performing work tasks, with 59.7% of respondents, particularly at the hospital level. Organizational culture is perceived to be at a low level, with 61% of respondents often observing poor communication or conflicts. Indecisive responses were given by 23.7% of respondents, while 16.2% of respondents believe that there is good organizational culture in their work environment.

According to respondents, the behavior of employees, their appearance, and their attitude toward colleagues and the organization are not at a satisfactory level (72.6%). Indecisive responses were given by 28.4% of respondents.

A large amount of stress impacts work efficiency, according to 86.8% of healthcare professionals. The healthcare profession is considered highly stressful, compromising the mental and physical health of employees at all levels.

Numerous studies conducted in the population of nurses have shown a connection between certain diseases and work-related stress, such as emotional exhaustion, physical exhaustion, and lower back pain. Low decision-making levels and high demands, characteristic of the nursing profession, may be associated with an increased risk of coronary heart disease and mental disorders. In

transition countries, there has been an increase in the number of nurses leaving their jobs.

These results align with the findings of this research. Ante Buljubašić states, "Healthcare workers are described as a group with high work-related stress, and preserving their work capacity is of particular importance, both for themselves and for the broader society due to the significance and sensitivity of the work they perform" (8).

Disruption of a positive work atmosphere leads to reduced work efficiency, unnecessary errors, and a decrease in service quality. Conversely, a good work atmosphere, effective communication, consideration of others' tasks, well-designed work processes, clearly defined tasks by hierarchy, flexibility in work, dedication, willingness to help and cooperate, contribute to increased work motivation. The work atmosphere depends not only on the manager but on all employees. This aligns with the study conducted by Saltmon and colleagues (9).

CONCLUSION

Work-related stress is identified as a negative factor. There is a presence of high levels of stress among healthcare professionals at all levels of healthcare, which negatively impacts work efficiency. The presence and negative effects of stress differ at different levels of healthcare. The highest stress level is at the tertiary level, followed by the secondary level. Fatigue negatively affects abilities, knowledge, skills, and motivation. As fatigue increases, so does the stress level, decreasing work efficiency. It is essential to develop a "safe workplace" program and demonstrate care for the health and safety of employees, aiming to reduce the number of work disabilities and protect the mental and physical health of staff.

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The effect of quetiapine administration in the treatment of addiction with or without comorbidity on arbitrarily treatment dropout and drug dosage

Efekti primjene kvetiapina u tretmanu bolesti ovisnosti sa ili bez komorbiditeta u odnosu na prijevremeno napuštanje liječenja i način doziranja

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ABSTRACT

Introduction: according to the definition of the World Health Organization, addiction is a chronic, relapsing, long-term disease primarily of the brain and central nervous system, which leads to the need for continuous and further intake of the substance. The most common psychiatric comorbidities among psychoactive substances addicts are mood disorders, anxiety disorders and personality disorders. Quetiapine, atypical antipsychotic, is commonly used in treatment of addiction nowadays. Aim: to evaluate the difference between patients treated with quetiapine who only had a diagnosis of addiction and those who have a dual diagnosis in relation to quetiapine dosage, as well as to evaluate the difference between patients in relation to arbitrarily dropout from treatment. Materials and methods: the research was cross-sectional and included a review of the medical histories of 68 patients aged 21-64 with confirmed addiction hospitalized at the Institute for Addiction Diseases of Canton Sarajevo in the period from January to December 2023, and who were treated with quetiapine during hospital treatment, classified into two groups. Results: the largest number of patients used quetiapine in a single dose and in the evening, without a significant difference between the groups ($p>0.05$). Patients diagnose only with addiction more often voluntarily left treatment in 31.0 cases compared to 15.4% of patients with multiple diagnosis, but without statistically significant difference between the groups. Conclusion: quetiapine was used in same dosage in treatment of subjects with only addiction as well as subjects with dual diagnosis. Patients who were diagnosed only with addiction voluntarily left treatment more often compared to patients with dual diagnoses.

Keywords: quetiapine, addiction, psychiatric comorbidity

SAŽETAK

Uvod: prema definiciji Svjetske zdravstvene organizacije, ovisnost je hronična, recidivirajuća, dugotrajna bolest prvenstveno mozga i centralnog nervnog sistema, koja dovodi do potrebe za kontinuiranim i daljim unosom supstance. Najčešći psihijatrijski komorbiditeti među ovisnicima o psihoaktivnim supstancama su poremećaji raspoloženja, anksiozni poremećaji i poremećaji ličnosti. Kvetiapin, atipični antipsihotik, danas se često koristi u liječenju ovisnosti. Cilj: procijeniti razliku između pacijenata liječenih kvetiapinom koji imaju samo dijagnozu ovisnosti i onih koji imaju dvojnu dijagnozu u odnosu na dozu kvetiapina, kao i procijeniti razliku između pacijenata u odnosu na proizvoljno odustajanje od liječenja. Metode: istraživanje je presječno i obuhvata pregled historija bolesti 68 pacijenata starosne dobi 21-64 godine sa potvrđenom ovisnošću koji su bili hospitalizirani na Zavodu za bolesti ovisnosti Kantona Sarajevo u periodu od januara do decembra 2023. godine i koji su liječeni sa kvetiapinom tokom hospitalizacije, klasifikovani u dvije grupe. Rezultati: najveći broj pacijenata koristi kvetiapin u jednoj dozi i uvečer, bez značajne razlike između grupa ($p>0,05$). Pacijenti sa samo dijagnozom ovisnosti češće su samovoljno napuštali liječenje i to u 31,0 slučajeva u poređenju sa 15,4% pacijenata sa dualnom dijagnozom, ali bez statistički značajne razlike između grupa. Zaključak: kvetiapin je korišten po istom doznom obrascu u liječenju pacijenata sa dijagnozom samo ovisnost i pacijenata sa dualnom dijagnozom. Pacijenti sa samo dijagnozom ovisnosti samovoljno su napuštali liječenje češće u odnosu na pacijente s dualnom dijagnozom.

Ključne riječi: kvetiapin, bolesti ovisnosti, psihijatrijski komorbiditet

INTRODUCTION

According to the definition of the World Health Organization (WHO), addiction is a chronic, relapsing, long-term disease primarily of the brain and central nervous system, which leads to the need for continuous and further intake of the substance. The criteria for developed addiction to psychoactive substances (PAS) and alcohol are: tolerance (the need to take a larger amount of PAS or alcohol to achieve the desired effect), withdrawal syndrome or taking the substance to avoid withdrawal symptoms, taking the substance in larger amounts or for a longer period of time than intended, craving or unsuccessful craving to control or reduce the

intake of the substance, most of the time spent in activities related to the acquisition, use or recovery from the effects of the substance, interruption of important socio-social activities due to consumption of PAS or alcohol, continuation of the intake of the substance despite knowledge of the existence of a permanent psychological and physical problem which is caused by the effect of the substance (1,2).

WHO defines "dual diagnosis" as co-existence of PAS addiction and another psychiatric disorder. In a 2015 report, the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) pointed out the high prevalence of comorbidity among drug addicts, about 50% of whom also have a mental disorder. According to the National Survey on Drug Use and Health (NSDUH) in the US approximately 7.9 million adults had both problems (2,3). The most common psychiatric comorbidities among drug addicts are depressive disorder, anxiety disorder (mainly panic and post-traumatic stress disorder) and personality disorders (mainly dissocial and borderline). Compared to patients with only one disorder, patients with a concurrent mental disorder and drug addiction show more severe psychopathology, more hospitalizations, increased risk of suicide, and a higher rate of HIV and hepatitis C infection, as well as psychosocial damage, including criminal behaviour (4).

Quetiapine is a drug that belongs to the group of atypical antipsychotics or antipsychotics of the second generation. It is used to treat schizophrenia, bipolar affective disorder (BAP) in the phase of depression, acute mania. It is structurally close to clozapine, and according to its chemical structure it belongs to the group of dibenzothiazepines. From the pharmacological aspect, it has an antagonistic effect on serotonin 5HT2A and dopamine D2 receptors. It does not show significant anticholinergic or antihistaminergic effects, but it reportedly blocks α1-adrenergic receptors. However, quetiapine shows the greatest affinity for histamine H1 receptors, which explains the pronounced sedation, but also the increase in appetite. The total pharmacological effect of quetiapine is actually the sum of the effects of the original compound and its active metabolite norquetiapine. Various studies have been conducted and it has been established that quetiapine exhibits high occupancy of dopamine D2 receptors. However, unlike other antipsychotics, quetiapine rapidly dissociates from dopamine D2 receptors (*kiss and run*) (5). In addition to its antipsychotic effect, quetiapine is also registered in the treatment of manic and depressive phases of bipolar disorder, and in the therapy of prevention of manic and depressive episodes of bipolar disorder, with possible simultaneous use of lithium or valproate. Quetiapine is also used in the treatment of addiction due to dopamine antagonism in the mesocorticolimbic neurons of the reward system, which has a great influence in the pathophysiology of addiction. Doses for the antidepressant effect of quetiapine are around 300 mg (it is considered to be the maximum dose for this indication), while for the manic phase of bipolar disorder and the maintenance therapy of bipolar disorder, it is higher and ranges between 400-800 mg/day. Doses for children and adolescents are understandably lower (6).

AIM

The aim of this study was to evaluate the difference between patients treated with quetiapine who were only diagnosed with addiction and those who had dual diagnosis in relation to quetiapine dosage, as well as to evaluate the difference between patients treated with quetiapine who were only diagnosed with addiction and those who had dual diagnosis in relation to arbitrary dropout from treatment.

MATERIALS AND METHODS

The research was cross-sectional and it included a review of the medical histories of 68 patients (56 men and 12 women) aged 21-64 hospitalized at the Institute for Addiction Diseases of the Sarajevo Canton in the period from January to December 2023. The subjects were patients with a confirmed diagnosis of addiction, as well as those with psychiatric comorbidities who were treated with quetiapine during their hospitalization. The respondents were divided into two groups, those only diagnosed with addiction, 29 patients (42.6%) and those who in addition to addiction had other psychiatric or somatic diagnosis, 39 patients (57.4%).

The results are presented tabularly and graphically through the number of cases, percentage, arithmetic mean (X), standard deviation (SD), standard error of the arithmetic mean (SEM) and range of values. Testing of differences was performed using Mann-Whitney test and Chi-square test, with $p<0.05$ or a confidence level of 95% being considered a statistically significant difference. The analysis was performed using the statistical software IBM Statistics SPSS v21.0 (Chicago, Illinois, USA).

RESULTS

The study included 68 patients with confirmed diagnosis of addiction. The most common comorbidity (2nd diagnosis) in our study group was personality disorder (F60.3), registered in 32 patients (83.1%) (Figure 1) followed by somatic diagnosis diagnosed in 4 patients (10.3%).

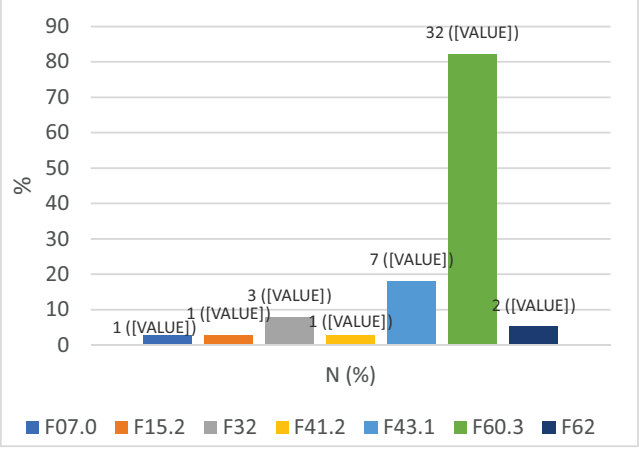

Figure 1 **Most common comorbid diagnose in our study group.**

The largest number of patients use quetiapine in a single dose and in the evening, without a significant difference between the groups ($p<0.05$) (Figure 2).

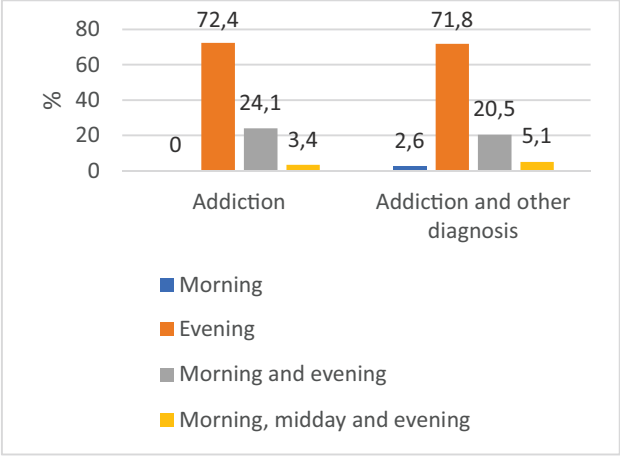

Figure 2 **Comparison of respondents in relation to the dosage of quetiapine.**

Patients with diagnosed only with addiction more often voluntarily left treatment in 31.0% of cases compared to 15.4% of patients with multiple diagnosis, but without statistically significant difference between the groups (p>0.05) (Figure 3).

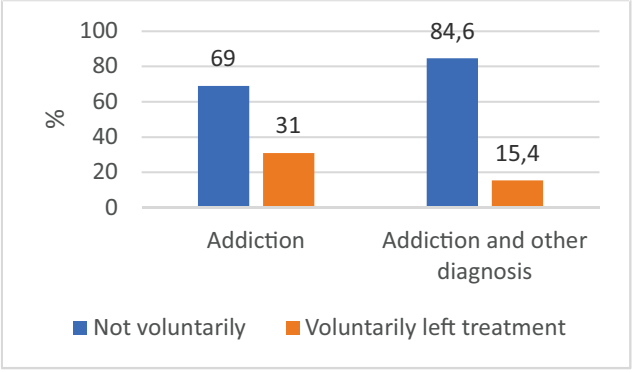

Figure 3 **Comparison of respondents in relation to voluntary abandonment of treatment.**

DISCUSSION

This study included patients who were treated with quetiapine as part of the addiction treatment in Institute for Addiction Diseases of Canton Sarajevo during 2023. The total number of patients included in the study was 68, both sexes, aged 21 to 64, with a diagnosed with addiction disease with or without other psychiatric comorbidities.

In our study, the largest number of patients. 49 of them (72.1%) used quetiapine in one evening dose. Out of that number, 21 patients were only diagnosed with addiction (30.9%), while 28 of them also had comorbid psychiatric diagnosis (41.2%). The second most represented were patients who used quetiapine in two daily doses, in the morning and in the evening, 15 of them (22.1%). Diagnosis of addiction as a unique diagnosis was set in 7 patients (10.3%), while a slightly higher number of patients, 8 of them (11.7%) were also diagnosed with comorbid psychiatric disorder. Three doses (morning, afternoon and evening) were used only by 3 patients (4.4%). Only 1 patient (1.5%), diagnosed with addiction with psychiatric comorbidity, used quetiapine in one morning dose. The largest number of patients uses quetiapine in a single dose and in the evening, without a significant difference between the groups.

In a study published by Sattar SP, et al. (6) it was indicated that initial treatment of patients was an evening dose of 50 mg of quetiapine, which was gradually increased to a maximum dose of 300 mg per day, but it was not indicated whether quetiapine continued to be administered exclusively in the evening or if it was divided into several doses during the day. The range of quetiapine was from 50 to 300 mg, and the average dose was 153 mg per day. In this study, quetiapine was shown to be effective in the treatment of addictive disorders with comorbid anxiety disorder. Review of the available literature did not register more studies which dealt with the distribution of doses of quetiapine in the treatment of addiction diseases with or without psychiatric comorbidity.

Out of the total number of patients, 15 of them (22.1%) left the treatment on their own initiative, while the 53 patients (77.9%) ended hospitalization according to the doctor's advice and as planned. Patients who were only diagnosed with addiction more often voluntarily left treatment in 31.0% of cases, compared to 15.4% of patients with more diagnosis, but without statistically significant difference between the groups.

Discharge from hospital against medical advice is associated with negative health outcomes and readmissions. Patients with substance use disorder are up to three times more likely to be discharged against their doctor's advice than those patients who do not have a developed substance use disorder. Studies suggest that undertreated withdrawal and the perception of stigma may increase the risk, however nowadays there are no published qualitative studies investigating the specific reasons why patients with addiction diseases leave treatment prematurely, but it is believed that four key issues identified as reasons for premature hospital discharge are: insufficiently treated withdrawal and constant craving for drug use, stigma and discrimination, and hospital restrictions (7). In other words, it was identified that quetiapine improved remission rates when taken alongside buprenorphine and methadone (8).

In this regard, the results of our research, which are different from most other studies in which patients voluntarily left treatment in a greater number of cases, show that a greater number of patients remained on treatment until the end. Given that our institution and our medical staff regularly work on improving the quality of service, access to patients, psychological support and breaking stigma, which are one of the criteria for prematurely leaving treatment, we can conclude that this approach to treatment let to positive results and positive treatment outcome and that one of the most important predictors of successful treatment is the support of the patient by the medical staff, given that unfortunately, patients with addiction diseases generally do not have the support of their family and environment.

CONCLUSION

Quetiapine was used in same dosage in treatment of respondents diagnosed only with addiction as well as those with dual diagnosis. Patients diagnosed only with addiction voluntarily left treatment more often in relation to patients with dual diagnoses. Our study is useful to initiate recommendations for further studies about quetiapine and addiction disorders.

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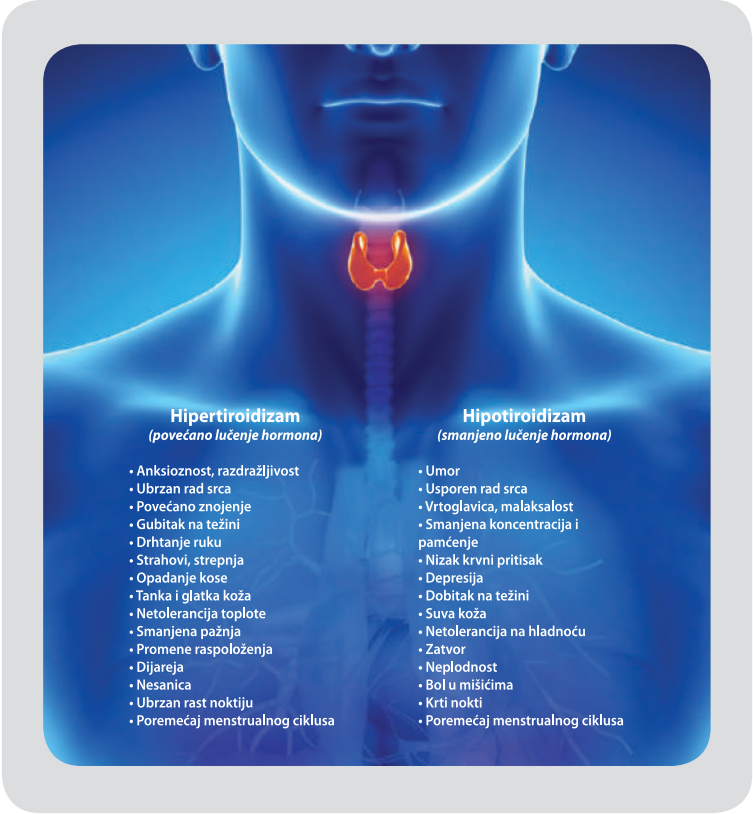

Empiric antimicrobial and corticosteroid therapy and its possible impact to clinical course and outcome in patients with bacterial meningitis in the Clinic of Infectious Disease, Clinical Center University of Sarajevo

Empirijska antimikrobna i kortikosteroidna terapija i njen mogući uticaj na klinički tok i ishod bolesti pacijenata sa bakterijskim meningitisom u Klinici za infektivne bolesti Kliničkog centra Univerziteta u Sarajevu

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ABSTRACT

Introduction: meningitis represents inflammation of the meninges of the brain and spinal cord. Etiology of meningitis includes bacteria, viruses, fungi, and, in some cases, even parasites. Late introduction of adequate therapy can lead to an unfavourable outcome, with long-term consequences or even death. In most cases of confirmed meningitis, patients are initially treated with antibiotics until bacterial etiology is excluded, and that approach can extend the duration of hospital stay. Aim: to investigate possible impact of applied therapy to clinical course and outcome in patients with acute bacterial meningitis hospitalised at the Clinic of Infectious Diseases of the Clinical Center University of Sarajevo. Materials and methods: we conducted a retrospective cohort study at the Clinic of Infectious Diseases of the Clinical Center University of Sarajevo in the period of 10 years: specifically from 1 January 2012 to 31 December 2021. All necessary data were taken from the histories of the patients. Results: the average length of symptom duration before admission to the hospital was 2 days, with a range of 1-10 days. Lumbar puncture was performed in all patients, and 54 (94%) patients had cloudy cerebrospinal fluid. Positive CSF cultures had 24 (43%) patients. Ceftriaxone as empiric therapy proved to be an excellent choice in acute bacterial meningitis. Conclusion: corticosteroids should be added in cases of confirmed bacterial meningitis, even if it will not decrease overall mortality.

Keywords: bacterial meningitis, therapy, ceftriaxone, corticosteroids

SAŽETAK

Uvod: meningitis predstavlja upalu ovojnica mozga i kičmene moždine. Etiologija meningitisa uključuje bakterije, viruse, gljivice, a u nekim slučajevima čak i parazite. Kasno uvođenje adekvatne terapije može dovesti do nepovoljnog ishoda, sa dugotrajnim posljedicama ili čak smrti. U većini slučajeva potvrđenog meningitisa, pacijenti se inicijalno liječe antibioticima dok se ne isključi bakterijska etiologija, a taj pristup može produžiti boravak u bolnici. Cilj: prikazati mogući uticaj inicijalno primjenjene terapije na klinički tok i ishod kod pacijenata sa akutnim bakterijskim meningitisom, hospitaliziranih u Klinici za infektivne bolesti Kliničkog centra Univerziteta u Sarajevu. Materijali i metode: na Klinici za infektivne bolesti Kliničkog centra Univerziteta u Sarajevu radili smo retrospektivnu kohortnu studiju u trajanju od 10 godina, za period 01.01.2012. do 31.12. 2021. Svi potrebni podaci uzeti su iz historija bolesti pacijenata. Rezultati: prosječna dužina trajanja simptoma prije prijema u bolnicu bila je 2 dana, u rasponu od 1-10 dana. Svim pacijentima je urađena lumbalna punkcija, a 54 (94%) je imalo zamućenu cerebrospinalnu tečnost. Pozitivne kulture likvora imala su 24 (43%) pacijenta. Ceftriakson se pokazao kao odlična empirijska terapija kod akutnog bakterijskog meningitisa.
Zaključak: kortikosteroide treba dodati u slučajevima potvrđenog bakterijskog meningitisa, iako to neće uticati na ukupnu smrtnost.

Ključne riječi: bakterijski meningitis, terapija, ceftriakson, kortikosteroidi

INTRODUCTION

Meningitis represents inflammation of the brain meninges and spinal cord. Etiology of meningitis includes bacteria, viruses, fungi, and in some cases, even parasites (1). Acute bacterial meningitis is usually caused by S. pneumoniae, N. meningitidis, and H. influenzae, and they account for almost 80% of all reported cases (2). Mycobacterium tuberculosis can also be a causative agent, and the prognosis in that situation is mostly poor. Some medications, malignancies, and autoimmune diseases can also cause meningitis (3,4). Lumbar puncture is the gold standard as a diagnostic procedure in the meningitis, but etiology itself is still a great challenge in clinical practice. Late introduction of adequate therapy can lead to an unfavourable outcome, with long-term consequences or even death (5). In most situation of confirmed meningitis, patients are initially treated with antibiotics until bacterial etiology is excluded, and that approach can extend the duration of hospital stay (6). Empiric antimicrobial therapy should cover all possible pathogens for the age of the patient, and it should be de-escalated after microbiological confirmation of the etiology. Role of corticosteroids is still doubtful in certain situations (7).

AIM

The aim of this study was to present possible impact of applied antimicrobial and corticosteroid therapy to clinical course and outcome in patients with acute bacterial meningitis hospitalised at the Clinic of Infectious Diseases of the Clinical Center University of Sarajevo.

MATERIALS AND METHODS

We conducted a retrospective cohort study at the Clinic of Infectious Diseases of the Clinical Center University of Sarajevo in the period of 10 years: from 1 January 2012, to 31 December 2021. All necessary data were taken from the history of the patients, including: age, sex, symptoms presented on admission, duration of symptoms, previously applied antimicrobial therapy, corticosteroid therapy, underlying diseases, micribiological findings, therapy, duration of hospital stay, the need for respiratory support, and outcome. Ethical approval for the study was obtained from the Ethics Committee of the Clinical Center University of Sarajevo. Statistical analysis was done using the licensed IBM SPSS Statistics software version 16.0.

RESULTS

In a period from 1 January 2012 to 31 December 2022 a total of 56 patients with a confirmed diagnosis of acute bacterial meningitis were admitted at the Clinic. There was a total of 31 (56%) male and 25 (44%) female patients. The mean age of patients was 31.6 years, ranging from 4 months to 75 years. Out of that number, 38 (68%) had underlying disease, including diabetes, cardiovascular diseases, kidney or liver diseases. The average length of symptom duration before admission to the hospital was 2 days, with a range of 1-10 days. Almost all of them (54 or 96%) had fever as the dominant symptom, while 46 (80%) had vomiting and 32 (57%) had headache. At admission, 40 (71%) patients had positive meningeal signs.

Lumbar puncture was performed in all patients, and 54 (94%) had cloudy cerebrospinal fluid (CSF), mean number of cells in CSF was 3517 (range 532 to 4294), elevated proteins were present in all samples, and 51 (91%) had hypoglicorachia. Positive CSF cultures were detected in 24 (43%) patients. S. pneumoniae was detected in 17 (30%) patients, followed by N. meningitidis in 4 (7%), while E. coli, L. monocytogenes, and Pseudomonas spp. were detected in 3 patients, respectively. Sterile cultures were recorded in 32 (57%) patients. Blood cultures were positive in 18 (32%) patients, with S. pneumoniae as the most often isolated causative agent.

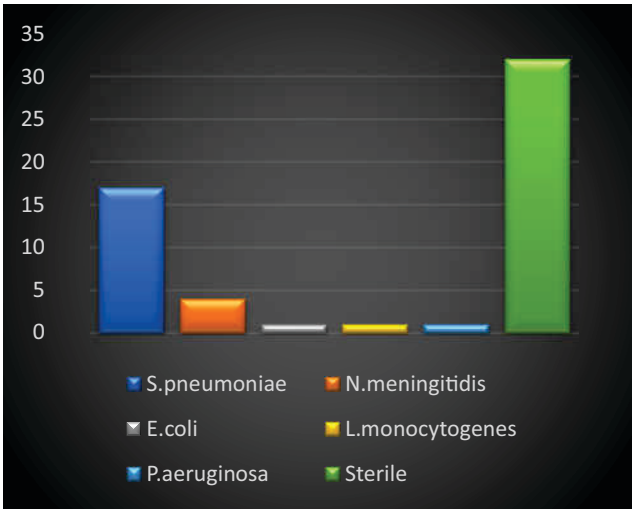

Figure 1 **Isolates from CSF cultures.**

All patients received antimicrobial therapy. The initiated therapy on admission was: ceftriaxone as monotherapy in 32 (57%), ceftriaxone + vankomycin in 9 (16%), ceftriaxone + ampicillin in 9 (16%), ceftriaxone + vankomycin + ampicillin in 3 (5.50%), and meropenem + vankomycin in 3 (5.50%) patients.

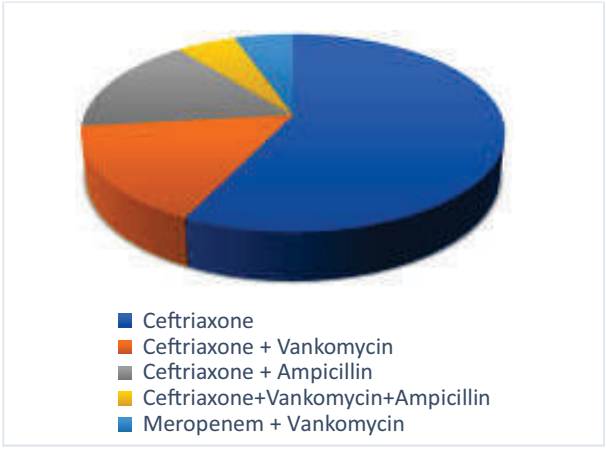

Figure 2 **Applied antimicrobioal therapy.**

After the initiation, the therapy changed during the clinical course in 14 patients. The most preferred combination was meropenem + vankomycin in 13 patients, and one patient also received colistin due to a highly resistant strain isolated from blood culture (A.baumannii).

Table 1 **T-test for duration of hospital stay compared to the used antimicriobial therapy.**

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Diff.	95% Confidence Interval of the Difference	
									Lower	Upper
Hosp. lenght	Equal variances assumed	.865	.357	.494	53	.623	2.062	4.175	-6.311	10.436
	Equal variances not assumed			.488	45.396	.628	2.062	4.225	-6.446	10.571

Table 2 **Chi-Square test for the therapy used and requirement for respiratory support.**

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	1.215[a]	1	.270	
Continuity Correction[b]	.513	1	.474	
Likelihood Ratio	1.280	1	.258	
Fisher's Exact Test				.444
N of Valid Cases[b]	56			

There was no difference in duration of hospital stay, requirement for respiratory support or outcome between patients where ceftriaxone was used as monotherapy and patients with other combination of antibiotics.

Corticosteroids were associated in the therapy in 27 (48%) patients, with dexamethasone as mostly used agent in 26 patients and one patient received hydrocortisone. There were 8 (14%) patients who required respiratory support, either with facial mask or non-invasive ventilation (NIV). None of them received corticosteroids in the therapy.

The average duration of the antimicrobial therapy was 20.5 days, ranging from 8 to 64 days. Treatment in the ICU was required by 38 (67.9%) patients. The length of hospitalization was in the range from 8 to 66 days, with a mean value of 26.5 days. The unfavourable outcome (exitus letalis) was detected in 4 (7%) patients.

Table 3 **Chi-Square test for use of corticosteroids and requirement for respiratory support.**

	Value	df	Asymp. Sig. (2-sided)	Exact Sig.(2-sided)
Pearson Chi-Square	56.000[a]	1	.000	
Continuity Correction[b]	52.027	1	.000	
Likelihood Ratio	76.988	1	.000	
Fisher's Exact Test				.000
N of Valid Cases[b]	56			

Pearson Chi-Square test show statistically significant difference in requirement for respiratory support between patients who received corticosteroids in the therapy and the other who did not ($p<0.0001$).

Table 4 T- test for use of corticosteroids and duration of hospital stay.

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Hosp. lenght	Equal variances assumed	.117	.734	.124	53	.902	.513	4.144	-7.799	8.826
	Equal variances not assumed			.125	52.461	.901	.513	4.112	-7.736	8.763

There was no statistically significant difference between the group which received corticosteroids in the therapy and the other who did not, for the duration of hospitalization (p>0.05). Since there were only four unfavourable outcome (exitus letalis), two in the group who received corticosteroids and two in the group that did not, the sample was too small for any comparison.

DISCUSSION

In the period of 10 years, from 1 January 2012 to 31 December 2021 we had a total of 73 patients hospitalised at the Clinic of Infectious Diseases, Clinical Center University of Sarajevo. Out of the total number of patients, 56 were treated during the complete clinical course, while other 17 were transferred to other clinics, due to further treatment or deterioration of the clinical status. Most of the patients had fever (96.4%) as the dominant symptom at admission, and the other most commonly presented symptoms were vomiting and headache. These data underline the importance of proper anamnesis and a clinical exam, since the decision for the lumbar puncture must rely on these data and findings (8). Lumbar puncture, as the golden standard, was used for clinical confirmation, and all CSF samples were sent for microbiology analysis. We had positive isolates in 24 samples, with predominant S. pneumoniae isolates in 30% of patients.

S. pneumoniae is a common cause of bacterial meningitis in adults, with mortality up to 37% (9). Sterile CSF liquor is not unusual in clinical practice. In most cases it is false negative, but the importance of prompt therapy excludes further CSF culture analysis as necessary. Also, one of the reasons could be previous antimicrobial therapy, but according to other studies, it can have only a small effect on CSF sterilisation (10). After confirmation of the bacterial meningitis, there should not be any delay in the administration of the antibiotics. Empiric therapy must rely on the age of the patient, and a CSF examination. In most cases, preferred antimicrobial therapy included the III generation of cefalosporins to cover expected pathogens, which are S. pneumoniae and N. meningitidis. Elderly people, as well as young children and immunocompromised persons, are also at great risk of having L. monocytogenes as a etiological cause of meningitis, and ampicillin must be added to the initial therapy. Since S. pneumoniae can present resistance to beta-lactams, according to some guidelines, vankomycin should be added to cefalosporins (11,12). Health care - associated or hospital-acquired bacterial meningitis is a complication of surgical procedures, such as the such as the placement of a CSF shunt, following a dural puncture. In these situations, we expect highly resistant bacteria, and empiric therapy should include vankomycin and meropenem (13).

In some situations, when an extended drug-resistant pathogen like A. baumannii is isolated, colistin is an option for treatment, in some cases in combination with tigecyclin, which can also be administered intrathecally (14). Our empiric therapy in the majority of cases was ceftriaxone monotherapy, followed by a co mbination of ceftriaxone and vankomycin and ceftriaxone plus ampicillin. In 14 cases, we had to escalate therapy to meropenem plus vankomycin due to a bad clinical and laboratory response to the initial therapy. Patients treated with ceftriaxone alone had similar clinical course like others treated with combination of two or more antibiotics.

There is insufficient evidence that corticosteroids can reduce overall mortality, except for S. pneumoniae meningitis, but some neurological sequelae and hearing loss can be prevented (15). In our study, 48% of patients received corticosteroids as adjuvant therapy. None of the patients in this group required respiratory support. Overall mortality was very low (7%), but it is mostly because of the limitations of the study, since all patients who required mechanical ventilation have been transferred to another clinic.

CONCLUSION

Ceftriaxone as empiric therapy proved to be an excellent choice in acute bacterial meningitis. Due to the increase in highly resistant strains of A. baumanni, P. aeruginosa, and K. pneumoniae, treatment of these cases will be very difficult, even with newly discovered antibiotics. Corticosteroids should be added in cases of confirmed bacterial meningitis, even though they will not decrease overall mortality.

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The significance of the Ki-67 proliferative index in predicting the size of metastases in axillar lymph nodes in luminal A type breast carcinoma

Značaj Ki-67 proliferativnog indeksa u predikciji veličine metastaza u aksilarnim limfnim čvorovima kod luminal A tipa karcinoma dojke

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ABSTRACT

Introduction: breast cancer is the most common type of cancer in women. The presence and number of metastatic lymph nodes in the armpit are the most important prognostic factors of breast cancer. Ki-67 is expressed in all phases of the cell cycle, but not in the G0 phase, which allows it to be used as a marker for proliferating cells. Aim: to investigate the relationship between the Ki-67 proliferation index in patients with breast cancer and its influence on the size of metastases in sentinel axillary lymph nodes. Materials and methods: this retrospective cohort study included 78 patients with Luminal A breast cancer, who underwent complete axillary lymph node dissection at the Clinic of General and Abdominal Surgery of the Clinical Center of the University of Sarajevo, in the period from September 2016 to February 2019. Ki-67 proliferation index and other traditional prognostic-predictive factors of the size of metastases were recorded from the pathohistological findings of the patients. The patients were grouped into three categories according to the levels of the Ki-67 proliferation index. Results: according to the results of univariate regression, patients with Ki-67 values of 11-14% were significantly more likely to develop macrometastases compared to those with Ki-67 values of 0-10% (p=0.015; OR=4.183). Multivariate regression analysis revealed that tumour stage (p=0.027; OR=3.318) and Ki-67 index in the range of 11-14% (p=0.016; OR=4.728) statistically significantly increased the probability of macrometastases. No statistically significant interaction effect between Ki-67 index and perivascular invasion was demonstrated (p=0.992; OR=1.008). Conclusion: the Ki-67 proliferation index is an important parameter for assessing the probability of the size of metastases in patients with Luminal A breast cancer, so that higher values of this index predict a higher probability of the occurrence of macrometastases.

Keywords: breast cancer, sentinel lymph node biopsy, Ki -67 antigen

SAŽETAK

Uvod: karcinom dojke je najčešći tip raka kod žena. Prisustvo i broj metastatskih limfnih čvorova u pazuhu su najznačajniji prognostički faktori raka dojke. Ki-67 se eksprimira u svim fazama ćelijskog ciklusa, ali ne i u G0 fazi, što mu omogućava da se koristi kao marker za proliferirajuće ćelije. Cilj: istražiti odnos između indeksa proliferacije Ki-67 kod pacijenata sa karcinomom dojke i njegovog uticaja na veličinu metastaza u sentinel aksilarnim limfnim čvorovima. Materijali i metode: ova retrospektivna kohortna studija je uključila 78 pacijentica sa Luminal A karcinoma dojke, koje su bile podvrgnute kompletnoj disekciji aksilarnih limfnih čvorova na Klinici za opštu i abdominalnu hirurgiju Kliničkog centra Univerziteta u Sarajevu u periodu od septembra 2016. do februara 2019. godine. Indeks proliferacije Ki-67 i drugi tradicionalni prognostičko-prediktorni faktori veličine metastaza su bilježeni iz patohistoloških nalaza pacijenata. Pacijentice su bile grupisani u tri kategorije shodno razinama indeksa proliferacije Ki-67. Rezultati: prema rezultatima univarijantne regresije, pacijentice s Ki-67 vrijednostima od 11-14% imale su značajno veću vjerovatnoću za nastanak makrometastaza u odnosu na one s vrijednostima Ki-67 od 0-10% (p=0.015; OR=4.183). Multivarijantnom regresionom analizom utvrđeno je da su stadij tumora (p=0.027; OR=3.318) i Ki-67 indeks u rasponu od 11-14% (p=0.016; OR=4.728) statistički značajno povećavali vjerovatnoću nastanka makrometastaza. Nije dokazan statistički značajan efekat interakcije između Ki-67 indeksa i perivaskularne invazije (p=0.992; OR=1.008). Zaključak: Ki-67 indeks proliferacije predstavlja važan parametar procjene vjerovatnoće veličine metastaza kod pacijentica sa Luminal A karcinomom dojke, na način da veće vrijednosti ovog inteksa predviđaju veću vjerovatnoću za nastanak makrometastaza.

Ključne riječi: karcinom dojke, biopsija sentinel limfnih čvorova, Ki-67 antigen

INTRODUCTION

Breast cancer is the most common cancer in women in the world and the fifth cause of death from cancer in the developed world (1,2).

Kiel antigen 67 (Ki-67) is an index of cell proliferation, which positive protein expression is associated with an increased risk of more aggressive tumor growth, relapse of the underlying disease and a weaker response to systemic therapy (3).

However, due to the inherent methodology of laboratory analysis and non-standardized cut-off values, the Ki-67 proliferation index is still not universally accepted as a prognostic biomarker for the decision to introduce systemic therapy in breast cancer (4).

The status of the axillary lymph nodes represents one of the most important standard prognostic-predictive markers for breast cancer, and the occurrence of metastases in them significantly reduces the survival rate, which has been confirmed by a series of clinical studies (5).

In today's clinical practice, sentinel or "sentinel" biopsy of the axillary (or several) lymph nodes (SLNB) plays a dominant role, since it significantly increases the postoperative benefit for operated patients with breast cancer, without negative impact on the prognostic-predictive value of the status of the axillary lymph nodes after their complete dissection (CALND) (6).

AIM

The aim of our study was to investigate the influence of the level of the Ki-67 proliferative index on the size of metastases in the axillary lymph nodes in patients with Luminal A molecular type of breast cancer.

MATERIALS AND METHODS

Patients and study design

The research was prospective-retrospective and it included 78 patients surgically treated at the Clinic of General and Abdominal Surgery of the Clinical Center University of Sarajevo (CCUS), in the period from September 2016 to February 2019, in which breast cancer was patho-histologically (PH) verified preoperatively by needle biopsy under ultrasound control.

The patients were divided into two groups: 1) the first group consisted of patients with intraoperative axillary micrometastases, which were postoperatively verified by definitive PH analysis; 2) the second group consisted of patients with intraoperative axillary macrometastases, postoperatively verified by definitive PH analysis.

Criteria for inclusion in the study

- Luminal A molecular type of breast cancer (Er+, Pr+, Her2-, ≤14%; IUCC: pT1-2, pN0-2, M0 / stage: 0 - IIIA)
- Patients diagnosed with breast cancer with clinically and radiologically negative axillary lymph nodes.
- Patients diagnosed with micro and macrometastases in the axillary lymph nodes intra and postoperatively.
- Negative history of previous immuno-, chemo-, radio- and hormonal therapies.
- Patients without previous breast surgery (mammoplasty, implant installation, etc.) and axillary lymph nodes.
- Patients who provided complete information for filling out the data collection form and voluntarily signed the informed consent.
- Female patients over 18 years of age.

Criteria for exclusion from the study

- Patients with sentinel-negative axillary lymph nodes or sentinel-positive axillary lymph nodes with isolated tumor cells (ITS).
- Patients with tumor size over 5 cm.
- Patients with an advanced form of breast cancer (infiltration and inflammation of the skin of the mammary region) or multiple breast cancer.
- Patients with systemic diseases of the liver, kidneys and cardio-vascular diseases.
- Patients who did not want to participate in the study.

The research was conducted on the basis of the usual approach to the patient by the method of anamnesis, objective medical examination, mammography and sonography of the breasts, biochemical analyses, needle biopsy, operative procedure and intra and postoperative PH analysis of surgical resectate samples.

Surgical treatment of all patients was carried out at the Clinic of General and Abdominal Surgery of the CCUS in the form of radical modified mastectomy (RMM) or breast conserving surgery (BCS), with SLNB of one or more axillary lymph nodes and subsequent complete dissection of the first and second floors ipsilateral axillary lymph nodes (CALND) (7).

Preoperative injection of the radio-active isotope Tc99 m albumin-nanocolloid was performed at the Clinic of Endocrinology and Nuclear Medicine of the CCUS, repeatedly, subcutaneously, peritumorously in a dose of 0.2 ml.

Intra- and postoperative patho-histological analysis of surgical resected breasts with tumor and sentinel and complete axillary lymph nodes of the patient was performed at the Clinic of Clinical Pathology, Cytology and Human Genetics of the CCUS.

Data on: 1. tumor size - pT (pT1 = tumor ≤ 2 cm; pT2 = 2 cm < tumor ≤ 5 cm); 2. histological tumor grade - G (G 1-3); 3. the presence/absence of lymphovascular (LVI) and perineural (PNI) invasion inside the tumor; 4. status of axillary lymph nodes (pN) (pN0 = there are no metastases in the axillary lymph nodes; pNmic = present micrometastases - less than 0.2 mm in size; pN1 = present macrometastases - sizes from 0.2 to 2 mm (8-12).

The cut-off value for distinguishing between "high" and "low" Ki-67 proliferation index was 14% (13,14). All tumors with proliferative Ki-67 index values ≤14% were divided into three groups: a)

Ki-67 from 1 to 5% of positive cells; b) Ki-67 from 6 to 10 % positive cells; c) Ki-67 from 11 to 14 % positive cells.

Tumor staging was performed based on the "TNM" classification, and according to the pathological (p) "TNM" classification of the American Cancer Society (15).

The postoperative course of the patients was controlled by regular outpatient check-ups at the Clinic of General and Abdominal Surgery of the CCUS (16).

Statistical analysis

IBM SPSS Statistics version 22.0 for Windows was used for statistical analysis. Univariate and multivariate regression analysis were applied to assess the independent and adjusted effects of the examined the size of metastases predictors. Categorical variables with >2 variants were recoded based on the "one vs. all'' type. In order to investigate the interaction effect, by successively inserting and removing one predictor from the multivariate regression

analysis model, it was investigated which of them have the greatest effect on the association of Ki-67 and the size of metastases. The threshold for a significant association was a difference in the odds ratio for Ki-67 with and without predictors greater than 10%. The threshold of statistical significance in the study was $p<0.05$. Key results are presented in tables.

RESULTS

Table I **Frequency of predictors of metastasis size with univariate and multivariate regression analysis.**

T_pg_`jc		N(%)	K cr_qr_qgq qgxc					
			KgK 42(53.8)	K_K 36(46.2)	N(	MP(	N((	MP((
			L (%)	L (%)				
?ec	: 23	/ 1 (16.7)	/ . (76.9)	1 (23.1)	. ,. 57	1,215	. ,042	0,4/ /
	23 mp above	43 (83.3)	10 (49.2)	11 (50.8)				
Rsk mp qgxc (mm)	. ,/ -19.9	00 (28.2)	/ / (50.0)	/ / (50.0)	. ,45.	. ,6. 4	. ,. 53	. ,077
	0. -50	34 (71.8)	1/ (55.4)	03 (44.6)				
Rsk mp grade	Ep_bc /	/ 5 (21.8)	/ 2 (82.4)	1 (17.6)	0.003	1,34.	. ,. 05	1,1/ 6
	Ep_bc 0	24 (59.0)	02 (52.2)	00 (47.8)				
	Ep_bc 1	/ 3 (19.2)	2 (26.7)	/ / (73.3)				
Jwk nf nodes status	L ce_rgtc	7 (11.5)	6 (88.9)	/ (11.1)	. ,. 4.	. ,2/ 1	. ,. 41	. ,1. 2
	/ -3 positive	26 (61.5)	03 (52.1)	01 (47.9)	. ,471	/ ,0. 1	. ,542	/ ,/ 7.
	2-7 positive	3 (6.4)	/ (20)	2 (80)	. ,. 36	/ ,034	. ,. 65	/ ,. 24
	6 _l b more positive	16 (20.5)	3 (31.3)	/ / (68.8)	. ,. 1/	0,572	. ,/ . 1	/ ,107
Ncpgj_qasj_p invasion	L ce_rgtc	/ 5 (21.8)	/ / (64.7)	4 (35.3)	. ,1/ 1	/ ,552	. ,174	/ ,674
	Nmqgrgjc	4/ (78.2)	1/ (50.8)	1. (49.2)				
Ncpgjcsp_j invasion	L ce_rgtc	14 (46.2)	/ 6 (50.0)	/ 6 (50.0)	. ,307	. ,53.	. ,4. 4	/ ,113
	Nmqgrgjc	20 (53.8)	02 (57.1)	/ 6 (42.9)				
I g-67	. -5%	06 (35.9)	0. (71.4)	6 (28.6)	. ,. 53	. ,201	. ,041	. ,32.
	4-10%	14 (46.2	/ 7 (52.8)	/ 5 (47.2)	. ,53/	. ,643	. ,13/	. ,37/
	/ / -14%	/ 2 (17.9)	1 (21.4)	/ / (78.6)	. ,. / 3	2,/ 61	. ,. / 4	2,506

*Univariate regression analysis for predictors of metastasis size
**Multivariate regression analysis for predictors of metastasis size
MiM, micrometastasis; MaM, macrometastasis, OR, odds ratio; Ki-67, antigen Kiel 67.

Univariate regression analysis determined that the increase in the stage of the disease increases the probability of the occurrence of macrometastases by 3.56 times ($p = 0.003$; OR = 3.560). Also, the results of univariate regression showed that patients with eight

or more positive lymph nodes had a 2.794 times higher probability of macrometastases than patients with 1-7 positive lymph nodes (p=0.031; OR=2.794).

According to univariate regression results, patients with Ki-67 values of 11-14% were 4.183 times more likely to develop macrometastases compared to Ki-67 values in the range of 0-10% (p=0.015; OR=4.183). Other predictors, such as age, tumor size, presence of PVI and PNI, according to univariate regression results, did not show a statistically significant influence on the probability of macrometastases (p > 0.05).

Multivariate regression analysis revealed that tumor stage (p=0.027; OR=3.318) and Ki-67 index level in the range of 11-14% (p=0.016; OR=4.728) statistically significantly increase the probability of macrometastases. The status of lymph nodes, age, tumor size, PVI and PNI did not prove to be statistically significant predictors of the probability of occurrence of macrometastases (p>0.05).

Table 2 **Interaction effect between Ki-67 index and perivascular invasion on metastasis size.**

Variable				P**	OR**	P***	OR**
PVI	Negative	Ki-67	0-5%	0.558	0.833	0.992	1.008
			6-10%	0.499	0.642		
			11-14%	0.086	1.750		
	Positive	Ki-67	0-5%	0.077	0.370		
			6-10%	0.300	0.538		
			11-14%	0.029	3.910		

*Univariate regression analysis of the impact of Ki-67 on metastasis size probability based on PVI
** Univariate regression analysis of the impact of Ki-67 levels on metastasis size probability based on PVI
*** The interaction effect of Ki-67 and PVI on the probability of metastasis size
PVI, perivascular invasion; Ki-67, Kiel 67 antigen; OR, odds ratio;

In the group of patients without PVI, no statistically significant influence of the Ki-67 index on the probability of macrometastases was demonstrated: 0-5% (p=0.558; OR=0.833); 6-10% (p=0.499; OR=0.642); 11-14% (p=0.086; OR=1.750).

In the group of patients with PVI, patients with a Ki-67 level of 11-14% were statistically significantly more likely to develop macrometastases (p=0.029; OR=3.910) compared to patients with lower levels of the Ki-67 index.

No statistically significant effect of interaction between Ki-67 index and PVI was demonstrated (p=0.992; OR=1.008).

DISCUSSION

The results of our study show a significant positive correlation between the stage of the disease and the appearance of macrometastases in sentinel lymph nodes of the axilla in patients with Luminal A molecular type of breast cancer. This finding suggests that as the stage of the disease progresses, the probability of the presence of macrometastases in the axillary sentinel lymph nodes increases. This is in accordance with the results of previous studies which indicated the importance of the influence of disease stage on the prognosis of breast carcinoma (17,18).

The correlation between tumor stage and Ki-67 index in the range of 11 to 14% and macrometastases, proven by multivariate regression, supports previous knowledge about the prognostic significance of tumor size and proliferative index Ki-67 in different molecular subtypes and is in favour of improving the understanding of the heterogeneity of breast cancer and its potential influence on the outcome and dynamics of the disease itself (19-21).

Although the traditional prognostic factors considered in our study did not show a statistically significant association with the occurrence of macrometastases in the axillary lymph nodes, considering the results of multivariate regression, they should be taken into account when assessing the influence of tumor stage and Ki-67 index on the size of metastases.

Our results confirm that there is a significant relationship between the level of the Ki-67 index and the probability of macrometastases in patients with PVI (22). However, the influence of Ki-67 on the size of metastases does not depend on PVI status (23).

The analysis of axillary lymph nodes is crucial for the accurate determination of the stage of the disease and the adjustment of therapy, especially in patients with more positive lymph nodes. A worse prognosis in breast cancer is associated with the appearance of metastatic cells in the lymph nodes. The presence of metastatic cells in the lymphatic tissue represents an interaction between the action of the tumor and the body's immune system and can result in the appearance of cancer at distant sites (24-26).

Regardless of the large number of studies in the domain of determining the clinically relevant "cut-off" value for Ki-67, a consensus has not yet been reached regarding the optimal cut-off value for the Ki-67 index, so according to the recommendation of the International Working Group for Ki- 67 breast cancer values from 5% to 30% can be useful in assessing the prognosis of earlier stages of luminal breast cancer (27).

In our study, we determined three subgroups within the values of the Ki-67 proliferative index characteristic of Luminal A breast cancer type (< 14%) and we found a positive correlation of higher values of individual subgroups, tumor size and size of metastases in positive SLN axilla, which may have a certain role when making a decision on axilla dissection or not, in combination with other clinical-pathological variables (28-32).

The above indicates that the Ki-67 proliferation index can be used to segregate breast cancer into prognostically significant subgroups with the potential for micro or macrometastases in sentinel-positive patients of the Luminal A molecular subtype of breast cancer.

Limitations of our study relate to the lack of genetic analysis or molecular features that could influence the prognostic and predictive significance of these biomarkers (33-35). The lack of long-term follow-up, since the "follow-up" included only 1-month postoperative period, can be considered a limitation of the study (36).

The scientific novelty of this research lies in the effort to integrate the Ki-67 proliferation index in the prediction of the size of positive axillary sentinel lymph node metastases in patients with clinically negative axillary Luminal A molecular subtype of breast cancer. This integration provides additional information that can personalize the treatment approach, potentially reducing the need for invasive procedures such as axillary dissection in selected patients.

CONCLUSION

The Ki-67 proliferation index, either independently or taking into account traditional prognostic-predictive parameters, represents a significant parameter for assessing the probability of the size of metastases in patients with Luminal A breast cancer. As the value of this index increases, the probability of developing macrometastases increases. Further prospective studies with larger samples, longer follow-up and a wider spectrum of prognostic-predictive factors are needed in order to more reliably highlight the most important ones and additionally investigate their influence on the association of Ki-67 level with the size of metastases.

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Value of NICE classification in predicting the pathohistological structure of small and intermediate colorectal polyps

Vrijednost NICE klasifikacije u predviđanju patohistološke građe malih i srednjih kolorektalnih polipa

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ABSTRACT

Introduction: colorectal cancer is the third most common cancer worldwide. Most colorectal cancers arise from adenomatous polyps. Targeted biopsies of polyps and referral for histopathological processing require a significantly longer period to obtain a final diagnosis, and the procedure itself entails significant material costs. On the other hand, "in vivo" histology employs established classification schemes to reduce or eliminate the need for "ex vivo" pathological analysis. Aim: to assess the reliability of the NICE classification using NBI technology in characterizing and predicting the histopathological structure of small and intermediate colorectal polyps. Materials and Methods: the study was conducted as a clinical, prospective, longitudinal study at the Clinic of Gastroenterohepatology of the Clinical Center University of Sarajevo. The target population in this study included patients of both sexes who underwent colonoscopy. The final sample included 68 patients and 100 polyps. Results: in the case of small polyps, Cramer's V coefficient indicates a strong, the contingency coefficient a moderately strong, and the polychoric correlation coefficient a very strong relationship between NICE type and histopathological categorization of colorectal polyps. For intermediate polyps, Cramer's V and the contingency coefficient indicate a strong, and the polychoric correlation coefficient a very strong relationship between NICE type and histopathological categorization of colorectal polyps. The area under the ROC curve is 0.834 and statistically significant, implying that the NICE classification has very good to excellent predictive power in identifying the malignant nature of small and intermediate colorectal polyps. Conclusion: this study suggests the possibility of reliable endoscopic "in vivo" assessment of the biological potential of colorectal polyps.

Keywords: colorectal polyps, NICE classification, NBI, colonoscopy, histopathology

SAŽETAK

Uvod: kolorektalni karcinom je treći najčešći karcinom u svijetu. Većina kolorektalnih karcinoma proizilazi iz adenomatoznih polipa. Kod ciljanih biopsija polipa, te upućivanja na patohistološku obradu, potreban je značajno duži period do dobivanja konačne dijagnoze, a sama procedura zahtijeva i značajnije materijalne troškove. Sa druge strane se kod „in vivo" histologije koriste već usvojene sheme klasifikacije za smanjenje ili uklanjanje potrebe za „ex vivo" patološke analize. Cilj: procijeniti koliko je pouzdana NICE klasifikacija koristeći NBI tehnologiju u karakterizaciji i predviđanju patohistološke građe malih i intermedijarnih kolorektalnih polipa. Materijali i metode: istraživanje je provedeno kao klinička, prospektivna, longitudinalna studija na Klinici za gastroenterohepatologiju Kliničkog centra Univerziteta u Sarajevu. Ciljana populacija u ovom istraživanju uključivala je pacijente oba spola koji su podvrgnuti kolonoskopiji. Konačni uzorak obuhvatao je 68 pacijenata i 100 polipa. Rezultati: u slučaju malih polipa, Cramerov V koeficijent ukazuje na jaku, koeficijent kontingencije na umjereno jaku, a koeficijent polihoričke korelacije na vrlo jaku vezu između NICE tipa i PH kategorizacije kolorektalnih polipa. Za intermedijarne polipe, Cramerov V i koeficijent kontingencije ukazuju na jaku, a koeficijent polihoričke korelacije na vrlo jaku vezu između NICE tipa i PH kategorizacije kolorektalnih polipa. Površina ispod ROC krivulje iznosi 0,834 i statistički je značajna, što implicira da NICE klasifikacija ima vrlo dobru do odličnu prediktivnu moć u identifikaciji maligne prirode malih i intermedijarnih kolorektalnih polipa. Zaključak: ovo istraživanje ukazuje na mogućnost pouzdane endoskopske „in vivo" procjene biološkog potencijala kolorektalnih polipa.

Ključne riječi: kolorektalni polipi, NICE klasifikacija, NBI, kolonoskopija, histopatologija

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth leading cause of cancer death (1), with nearly 1.8 million new cases and 881,000 deaths in 2018 (2). Due to its continuous increase in incidence, it represents a significant diagnostic and therapeutic challenge. Despite on-going improvements in treatment, about 40% of patients die from this disease, indicating a considerable room for improvement in preventive strategies, early detection and treatment (3). Most colorectal cancers, regardless of etiology, arise from the proliferation of glandular tissue in the colon, known as adenomatous polyps or adenomas. The estimated time interval for an adenoma to progress to cancer is five to ten years (4).

Colorectal polyps are often asymptomatic and clinically unnoticed for a long time. In exceptional cases, if they are large, polyps can cause symptoms such as bleeding, diarrhea, and obstruction (4,5). Clinically, the likelihood that an adenomatous polyp is a malignant lesion depends on the number, size, macroscopic appearance of the lesion, and its histopathological characteristics. Since its introduction into clinical practice in the 1970s, colonoscopypolypectomy has become the standard procedure for treating adenomas and neoplasms, aiming to reduce the incidence of invasive carcinoma. In the era of CRC screening, detecting and resecting all polypoid lesions represent the standard of care and the main goals of quality colonoscopy (6). Most newly discovered polyps are small (0-5mm) and intermediate (6-10mm), and it is known that these polyps initially have a low malignant potential (7).

Removal of these polyps exposes patients to the risk of polypectomy (bleeding, perforation of the colon), and sending them for histopathological analysis prolongs the time to obtain a final diagnosis, increasing the material costs of tissue processing and microscopic examination of biopsies. Polyps are classified according to the Paris classification based on their endoscopic appearance, and in vivo characterization is often done according to the Kudo classification and the Narrow-band imaging International Colorectal Endoscopic Classification (NICE). The NICE classification is a validation system used in endoscopic diagnosis of colorectal polyps using NBI technology. It assesses the colour of the lesion, appearance of blood vessels, and surface appearance of mucosal crypts, the so-called "pit pattern." After assessing polyp characteristics according to this classification, all colorectal polyps are classified into three types: type 1 - hyperplastic polyp, type 2 - adenoma, and type 3 - invasive submucosal carcinoma (8). Narrow Band Imaging (NBI), developed by Olympus (Tokyo, Japan), is an optical chromoendoscopy technique used during colonoscopy to visualize the surface structure of the lesion mucosa in detail. This technique enables visualization of mucosal patterns and blood vessels in high resolution, facilitating the characterization of polyps in vivo, i.e., during the colonoscopy procedure itself. This is often referred to as "virtual biopsy" because it allows assessment of polyp characteristics that would otherwise require a real biopsy and histological analysis (9).

Given the importance of angiogenesis in the process of premalignant lesion progression to malignant ones, a diagnostic method based on morphological changes in blood vessels would be ideal for early detection and diagnosis of neoplastic lesions. NBI enables just that, providing a detailed view of the vascular pattern of the mucosa, which can aid in the early diagnosis and characterization of tumor lesions (9-11). The ability to make an in vivo distinction between non-neoplastic and neoplastic polyps would enable selective polypectomy and selective referral of polyps for further examination.

AIM

The aim of this research was to assess the reliability of the NICE classification using NBI technology in the characterization and prediction of the histopathological structure of small and intermediate colorectal polyps during routine colonoscopy examinations.

MATERIALS AND METHODS

The study was conducted as a clinical, prospective, longitudinal study at the Clinic of Gastroenterohepatology of the Clinical Center of the University of Sarajevo. The target population in this study included patients of both sexes who underwent colonoscopy due to suspected colorectal polyps. The final sample comprised 68 patients and 100 polyps. The inclusion criteria were: patients of both sexes aged between 40-80 years with an indication for endoscopic screening, i.e., diagnostic colonoscopy; patients with verified polyps up to 10 mm in diameter; patients who met adequate pre-procedural preparation (endoscopic assessment of bowel preparation for endoscopic examination according to the Boston Bowel Preparation Scale – BBPS 2 and 3). Excluded from the study were patients with a previous history of colorectal cancer, patients with verified inflammatory bowel disease (IBD), patients with familial adenomatous polyposis (FAP), patients using anticoagulant therapy, and inadequately prepared patients – BBPS 1. The research protocol was approved by the Ethics Committee and organizational units of the Clinical Center of the University of Sarajevo. An Olympus CF – H180AI video colonoscope was used in the study. Each verified polyp was classified using the NICE classification with NBI technology. After polypectomy, the resected polyps underwent histopathological analysis at the Pathology Clinic of the Clinical Center University of Sarajevo. After standard histopathological processing of tissue samples, during microscopic analysis of polyps, they were classified according to generally accepted histopathological criteria for colorectal polyp classification. The findings of histopathological analysis of removed polyps were recorded and compared with specific types of lesions according to the NICE classification. Considering the qualitative nature of the variables of interest, an appropriate chi-square statistical test was used to determine the relationship between NICE type and histopathological categorization of small and intermediate colorectal polyps. The contingency coefficient, Cramer's V coefficient, and the polyserial correlation coefficient were used to measure the strength of association between NICE type and histopathological categorization of polyps. The diagnostic power of NBI technology, i.e., its specificity and sensitivity in detecting non-neoplastic and neoplastic polyps, was analysed using ROC analysis. Stata v. 14.0 and SPSS v.25.0 were used for statistical data processing.

RESULTS

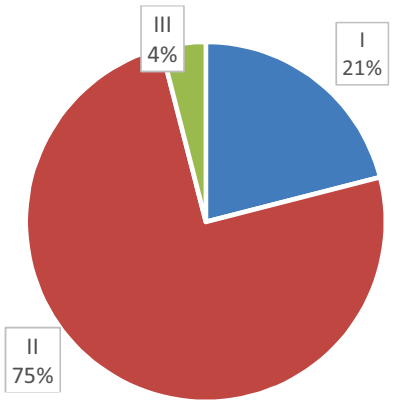

Figure 1 **Sample structure according to the NICE classification.**

Table 1 **Chi-square test for the analysis of the association between NICE type and PH category (small and intermediate polyps).**

NICE * PH findings, Crosstabulation category					
Count					
		PH finding, category			
		Hyperplastic polyp	Adenoma	Carcinom	Total
NICE	I	14	7	0	21
	II	2	70	3	75
	III	0	0	4	4
Total		16	77	7	100

Chi-Square Tests				
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	105.403[a]	4	.000	.000
Likelihood Ratio	65.919	4	.000	.000
Fisher's Exact Test	60.563			.000
N of Valid Cases	100			

a. 5 cells (55.6%) have expected count less than 5. The minimum expected count is .28.

Considering that more than 20% of cells have expected frequencies less than 5, the result of the Fisher's Exact test is interpreted (Fisher's Exact statistic = 60.563, p=0.000) (Table 1), NICE type of small and intermediate colorectal polyps and their histopathological categorization are mutually associated.

Table 2 **Chi-square test for the analysis of the association between NICE type and PH category of small polyps (0-5 mm).**

NICE * PH finding, Crosstabulationcategory					
Count					
		PH finding, category			
		Hyperplastic polyp	Adenoma	Carcinoma	Total
NICE	I	11	4	0	15
	II	1	20	1	22
Total		12	24	1	37

Chi-Square Tests[a]				
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	19.369[b]	2	.000	.000
Likelihood Ratio	21.450	2	.000	.000
Fisher's Exact Test	19.526			.000
N of Valid Cases	37			

a. Velicina = 0-5 mm

b. 3 cells (50.0%) have expected count less than 5. The minimum expected count is .41.

As in the previous test, more than 20% of cells have expected frequencies less than 5, so the result of the Fisher's Exact test is interpreted (Fisher's Exact statistic = 19.526, p = 0.000) (Table 2), NICE type of small colorectal polyps and their histopathological categorization are mutually associated.

Table 3 **Chi-square test for the analysis of the association between NICE type and PH category of intermediate polyps (6-10 mm).**

NICE * PH finding, Crosstabulationcategory					
Count					
		PH finding, category			
		Hyperplasticpolyp	Adenoma	Carcinoma	Total
NICE	I	3	3	0	6
	II	1	50	2	53
	III	0	0	4	4
Total		4	53	6	63

Chi-Square Tests[a]				
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	61.567[b]	4	.000	.000
Likelihood Ratio	33.399	4	.000	.000
Fisher's Exact Test	30.730			.000
N of Valid Cases	63			

a. Velicina = 6-10 mm

b. 6 cells (66.7%) have expected count less than 5. The minimum expected count is .25.

Based on the result of the Fisher's Exact test (Fisher's Exact statistic = 30.730, p = 0.000) (Table 3), NICE type of intermediate colorectal polyps and their histopathological categorization are mutually associated.

Table 4 **Measures of the strength of association between NICE Type and PH categorization of small and intermediate colorectal polyps.**

Strength of associationmeasure	Value
Cramer's V	0,726
Contingency Coefficient	0,716
Polychoric Correlation Coefficient	0,946

The first two measures of association strength between NICE type and PH categorization of small and intermediate colorectal polyps indicate a strong association, while the polyserial correlation coefficient indicates a very strong association.

Table 5 **Measures of the strength of association between NICE Type and PH categorization of small colorectal polyps.**

Strength of association measure	Value
Cramer's V	0,724
Contingency Coefficient	0,586
Polychoric Correlation Coefficient	0,924

Table 6 **Measures of the strength of association between NICE type and PH categorization of intermediate colorectal polyps.**

Strength of association measure	Value
Cramer's V	0,699
Contingency Coefficient	0,703
Polychoric Correlation Coefficient	0,939

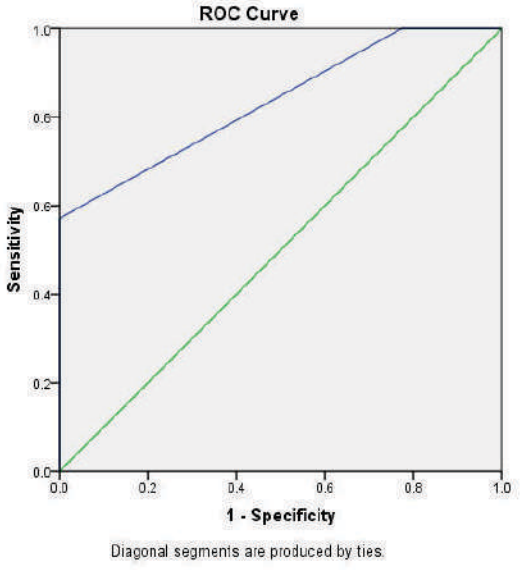

Figure 2 **Prediction of malignancy based on NICE classification of small and intermediate polyps.**

Area Under the Curve

Test Result Variable(s): NICE

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval		Sensitivity	Specificity
			Lower Bound	Upper Bound		
.834	.093	.003	.652	1.000	57.1%	100%

The area under the ROC curve is 0.834 and statistically significant, indicating that the NICE classification has very good to excellent predictive power in identifying the malignant nature of small and intermediate colorectal polyps.

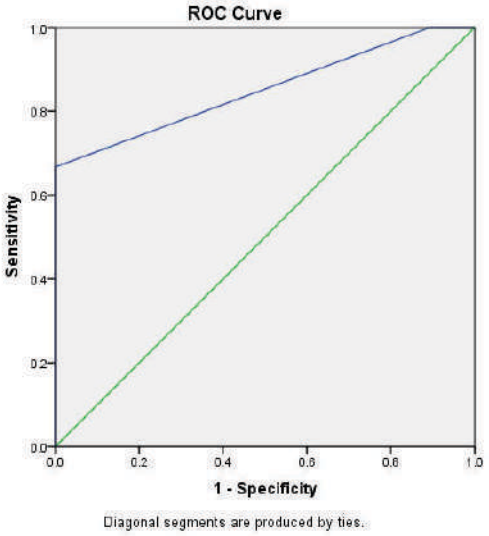

Figure 3 **Prediction of malignancy based on NICE classification of intermediate polyps.**

Area Under the Curve

Test Result Variable(s): NICE

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval		Sensitivity	Specificity
			Lower Bound	Upper Bound		
.851	.107	.005	.641	1.000	66.7%	100%

The area under the ROC curve is greater than in the case of all (small and intermediate) polyps and statistically significant, indicating very good to excellent predictive power of the NICE classification in predicting the malignancy of colorectal intermediate polyps.

DISCUSSION

The detection of polyps by endoscopic methods has its difficulties due to various shapes, textures, sizes, colours, and the presence of different lesions that mimic polyps during colonoscopy (4). According to the research by Leufkens , et al., cited by Shin Y, et al. (4), colonoscopy is a procedure dependent on the experience, meticulousness, and knowledge of the endoscopist, with a polyp detection miss rate of around 25%. Chromoendoscopy in combination with standard endoscopy is the preferred method for

detecting various mucosal patterns within the GI tract (12). Narrow Band Imaging (NBI) is an innovative high-resolution endoscopic technique that utilizes the optical characteristics of light to enable detailed imaging of mucosal and vascular details. The advantages of NBI technique include more precise detection of irregularities in blood vessels, which is of great importance in the diagnosis of colorectal polyps (12).

Optical diagnosis remains an attractive idea due to its potential to reduce costs and streamline healthcare (13). Using the NICE classification, many endoscopists have adopted the DISCARD strategy (Resect and Discard), which involves the removal and discarding of polyps. The DISCARD strategy was proposed by Ignjatović et al., as mentioned by Tsuji S, et al. (14). Polyps and adenomas <5mm are removed and discarded without histopathological analysis if they are assessed to have no malignant potential (15). Ignjatović et al. demonstrated the DISCARD strategy in a prospective cohort study, which involves omitting formal histopathological diagnosis and discarding small colorectal polyps, based solely on optical diagnosis. The "resect and discard" strategy, based on high-confidence endoscopic diagnosis, omits the formal pathological diagnosis of certain lesions. Since the standard practice of colonoscopy requires the removal and histopathological classification of almost all small (<10mm) and very small (≤5mm) polyps (16), this study has generated considerable interest and paved the way for further research into this strategy. Earlier studies evaluating the accuracy of optical diagnosis using NBI, compared to histopathological assessment and recommendations from national bodies, suggest that optical diagnosis could replace pathological analysis of small polyps (13).

According to the guidelines of the American Society for Gastrointestinal Endoscopy, for small colorectal polyps (≤ 5 mm) to be left in situ using solely endoscopic technology for predicting histology, this technology must show a negative predictive value of 90% or higher for adenomatous histology (17). A meta-analysis from 2019 with data from 4491 patients from randomized controlled trials showed that NBI significantly improved the adenoma detection rate compared to white-light endoscopy, with a greater effect with optimal bowel preparation (18). Our results showed a strong to very strong association between NICE type of small and intermediate colorectal polyps and their histopathological categorization, and ROC analysis indicates a very good to excellent predictive power of NICE classification in predicting malignancy of colorectal polyps, with slightly better results for intermediate polyps.

Previous studies on this topic (13,17,19) have suggested the potential of the NICE classification to replace the traditional histopathological diagnostic process, although the diagnostic accuracy of NICE classification has not yet reached a satisfactory target level. The prospective methodology is an advantage of this study. All polyps detected during colonoscopy were subjected to histological assessment using the NICE classification. After that, the polyps were removed and sent for histopathological analysis to confirm the histological diagnosis. The study was conducted at a tertiary healthcare institution, providing important insights into the real-world application of the NICE classification in daily clinical practice. A limitation of this study is its single-center nature; therefore, further research with a larger sample of polyps is needed.

CONCLUSION

This study indicates the possibility of reliable endoscopic "in vivo" assessment of the biological potential of colorectal polyps. The results of comparing endoscopic assessment and histopathological analysis further confirm the significance of advanced endoscopic techniques such as NBI, as well as the justification for using the DISCARD strategy. The value of this research lies in being the first in Bosnia and Herzegovina to address the application of the NICE classification system in endoscopic diagnostics, laying the groundwork for further related research and eventual implementation into routine clinical practice. Implementation of this method can lead to faster identification and early intervention in the treatment of colorectal polyps, ultimately improving treatment outcomes and reducing healthcare costs.

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Immunological aspects of asthma and chronic obstructive pulmonary disease

Imunološki aspekti astme i hronične opstruktivne bolesti pluća

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ABSTRACT

Introduction: asthma and chronic obstructive pulmonary disease (COPD) are both obstructive airway diseases that involve chronic inflammation of the respiratory tract. Aim: to determine different patterns of inflammatory cells and mediators being involved in both diseases. Materials and methods: a number of studies have been reviewed in the literature in order to get results. Results: the differences in inflammation between asthma and COPD are linked to differences in the immunological mechanisms that underlie these two diseases. Bronchial biopsies from asthmatic subjects reveal an infiltration of eosinophils, activated mucosal mast cells at the airway surface and activated T cells. In the biopsies of the bronchial airways, small airways and lung parenchyma from patients with COPD, there is no evidence for mast-cell activation, but there is an infiltration of T cells and increased numbers of neutrophils, particularly in the airway lumen. In asthmatic patients, there is an increase in the number of CD4+ T cells in the airways and these are predominantly T helper 2 (Th2 cells). The CD4+ T cells that accumulate in the airways and lungs of patients with COPD are mainly Th1 cells. While in mild asthma Th2 cells predominate, in more severe asthmatic disease there is a mixture of Th1 and Th2 cells present in bronchial biopsies, as well as more CD8+ T cells and this more closely resembles the immune cell infiltration seen in COPD. Conclusion: the different inflammatory cells are involved in both diseases. There are distinct consequences of inflammation and differing responses to therapy too. In patients with severe asthma and in asthmatic individuals who smoke, there is a neutrophilic pattern of inflammation as is the case in COPD.

Keywords: asthma, chronic obstructive pulmonary disease, immunology

SAŽETAK

Uvod: astma i hronična opstruktivna bolest pluća (HOPB) su opstruktivne bolesti disajnih puteva koje podrazumijevaju hroničnu inflamaciju respiratornog trakta. Cilj: odrediti različite obrasce upalnih stanica i medijatora uključenih u obje bolesti. Materijali i metode: brojne studije su pregledane u literaturi kako bi se dobili rezultati. Rezultati: razlike u upali između astme i HOBP povezane su s razlikama u imunološkim mehanizmima koji su u osnovi ove dvije bolesti. Bronhijalne biopsije kod astmatičara otkrivaju infiltraciju eozinofila, aktivirane mukozne mastocite na površini disajnih puteva i aktivirane T ćelije. U biopsijama bronhijalnih disajnih puteva, malih disajnih puteva i plućnog parenhima pacijenata sa HOPB-om, nema dokaza za aktivaciju mastocita, ali postoji infiltracija T ćelija i povećan broj neutrofila, posebno u lumenu disajnih puteva. Kod astmatičara dolazi do povećanja broja CD4+ T ćelija u disajnim putevima, a to su pretežno T helper 2 (Th2 ćelije). CD4+ T ćelije koje se akumuliraju u disajnim putevima i plućima pacijenata sa HOBP su uglavnom Th1 ćelije. Dok kod blage astme prevladavaju Th2 ćelije, kod teže astme prisutne su i Th1 i Th2 ćelije u bronhijalnim biopsijama, kao i više CD8+ T ćelija, što više liči na infiltraciju imunih ćelija koja se vidi kod HOBP. Zaključak: različite upalne ćelije su uključene u obje bolesti. Takođe su različite posljedice upale i različiti odgovori na terapiju. Kod pacijenata sa teškom astmom i kod astmatičara koji puše, postoji neutrofilni obrazac upale kao što je slučaj kod HOPB-a.

Ključne riječi: astma, hronična opstruktivna bolest pluća, imunologija

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are critical public health issues that cause significant morbidity and mortality around the world. COPD is characterised by persistent respiratory symptoms and chronic inflammation of the airways, whereas asthma is defined by chronic airway inflammation. Asthma alone accounted for 6.2% of the global prevalence, while COPD alone accounted for 4.9 %. According to a recent meta-analysis, the global prevalence of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) standard is 10.3% (1). This discrepancy could be attributable to different diagnostic criteria or the inclusion of a high-risk population (2).

Asthma and chronic obstructive pulmonary disease (COPD) are both obstructive airway diseases that involve chronic inflammation of the respiratory tract. Despite the similarity of some clinical features of asthma and COPD, there are marked differences in the pattern of inflammation that occurs in the respiratory tract, with different inflammatory cells recruited, different mediators produced, distinct consequences of inflammation and differing responses to therapy.

In both diseases there are acute episodes or exacerbations, when the intensity of this inflammation increases (3).

Asthma

Bronchial biopsies from asthmatic subjects reveal an infiltration of eosinophils, activated mucosal mast cells at the airway surface and activated T cells.

In the last years, the classification of asthma phenotypes has evolved into *asthma endotypes* such as the *type 2-high or –ultra-high* (essentially eosinophilic) and the *type 2-low* (non-eosinophilic, sometimes neutrophilic, and metabolic) (4).

Endotypes are defined by underlying pathophysiological mechanisms which might lead to direct differences in responsiveness to common therapies such as inhaled corticosteroids or specific biologicals (5,6,7). The *type 2-low endotype* is more complex and no biomarkers have been identified so far (8). Obese patients with a type 2-low signature are often female gender with late-onset asthma. In these patients, studies have identified increases in the IL-6 pathway in epithelial brushings and sputum cells (9).

Inflammatory cells and mediators

There are many differences between mild asthma and COPD in the type of inflammation that occurs in the lungs (3). Many of the cytokines and chemokines that are secreted in both asthma and COPD are regulated by the *transcription factor nuclear factor-kB (NF-kB),* which is activated in airway epithelial cells and macrophages in both diseases, and may have an important role in amplifying airway inflammation (10,11). The role of *epithelial cells* in asthma has advanced greatly in the last years. They are recognized as immunologically active cells that can orchestrate inflammatory responses to external triggers. Epithelial cell damage is present in all phenotyes of asthma and correlates with disease severity (12).

T cells

In asthmatic patients, there is an increase in the number of CD4+ T cells in in the airways and these are predominantly *T helper 2* (Th2 cells), whereas in normal airways Th1 cells predominate (14). *Th 2 cells and their cytokines control type 2-high asthma* (14,15,16). Th2 cells have a central role in allergic inflammation by secreting the cytokines IL-4 and IL-13, which drive IgE production by B cells, then IL-5 which is solely responsible for eosinophil differentiation in the bone marrow, as well as IL-9 which attracts and drives the differentiation of mast cells (Figure 1). The *transcription factor GATA 3* (GATA -binding protein 3) is crucial for the differentiation of uncommitted naive T cells into Th2 cells and it also regulate the secretion of Th2-type cytokines. Accordingly, there is an increase in the number of GATA3 T cells in the airways of asthmatic subjects compared with normal subjects (3,17) (Figure 2).

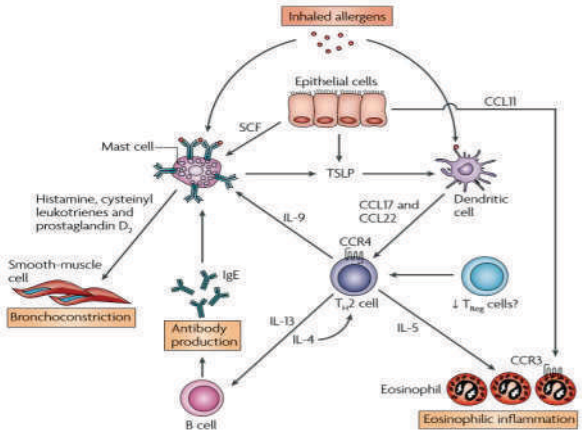

Figure 1 **Inflammatory cells involved in asthma** (Source: Barnes JP. Peter. Immunology of asthma and chronic obstructive pulmonary disease. Nat Rev Immunol 2008 Mar; 8(3):183-92)

Peter J. Barnes. Pathophysiology of asthma

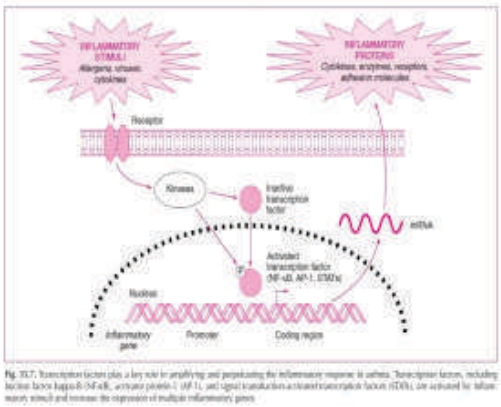

Figure 2 **Transcription factors play a key role in amplifying the inflammatory response in asthma.** (Source: Barnes PJ. Pathophysiology of asthma. In: Barnes P, Drazen J, Thomson N et al. Asthma and COPD: Basic mechanisms and Clinical Management. Second edition 2009 Elsevier)

Resident memory T cells: The new players in asthma

Mainly CD4+ resident memory T (Trm) cells reside in the lung very long after cessation of allergen exposure and can be found in the lungs of mice subjected to experimental asthma and in patients with type 2-high asthma (18,19). Trm cells produce more Th2 cytokines that circulating Th2 cells and get reactivated rapidly *in situ* after re-exposure to allergens, although the mechanism of allergen-specific Trm cell reactivation in tissues is still not very clear (19,20). These cells were mainly found near the airways and induced mucus production, eosinophil activation and bronchial hyperresponsiveness (21).

Dendritic cells

Dendritic cells (DC_s) have an important role in asthma as regulators of Th2 cells and in the presentation of processed peptides from inhaled allergens to Th2 cells (22,23). They are not only involved in the initial sensitization to allergens, but also in driving the chronic inflammatory response in the lungs, and therefore provide a link between allergen exposure and allergic inflammation in asthma (24). Cigarette smoking is associated with an expansion of the DC_s population and with a marked increase in the number of mature DC_s in the airways and alveolar walls of people who smoke (25).

Recent studies proved that *neutrophils* can be real effector cells in *severe non-type 2 asthma* and that environment in the lung of these patients drive neutrophil pathogenic functions (26).

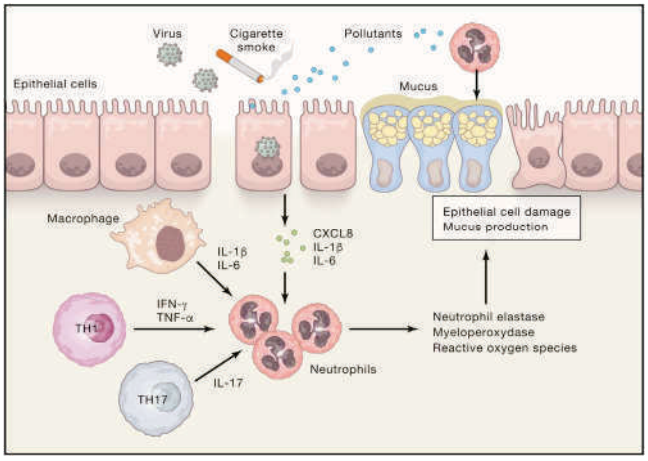

Figure 3 **Proposed role of neutrophils in non-type 2 asthma.** (Source: Hammad H, Lambrecht BN. The Basic Immunology of Asthma. Cell 2021 Mar 18;184(6):1469-148.)

The airway epithelium and alveolar macrophages can get activated by environmental triggers such as microbes or pollutants. In response to these stimuli, they produce pro-inflammatory cytokines (IL-1b, IL-6) and the epithelium also produces CXCL8 (also known as IL-8), a potent neutrophil attractant. Under the influence of the cytokine environment, Th1 and Th17 cells are induced and further contribute to neutrophil recruitment and activation. Activated neutrophils release factors such as neutrophil elastase, myeloperoxidase, or ROS that will induce epithelial damage and contribute to increased mucus production (Figure 3) (8).

Chronic obstructive pulmonary disease (COPD)

In the biopsies of the bronchial airways, small airways and lung parenchyma from patients with COPD, there is no evidence for mast-cell activation, but there is an infiltration of T cells and increased numbers of neutrophils, particularly in the airway lumen. In contrast to asthma, the CD4+ T cells that accumulate in the airways and lungs of patients with *COPD* are mainly *Th1 cells* (27).

However, there is some evidence that Th2 cells are also increased in lavage fluid of patients with COPD (28), likewise, in patients with more severe asthma. Th1 cells are activated, as well as Th2 cells (10), making the distinction between the Th-cell patterns in these two diseases less clear.

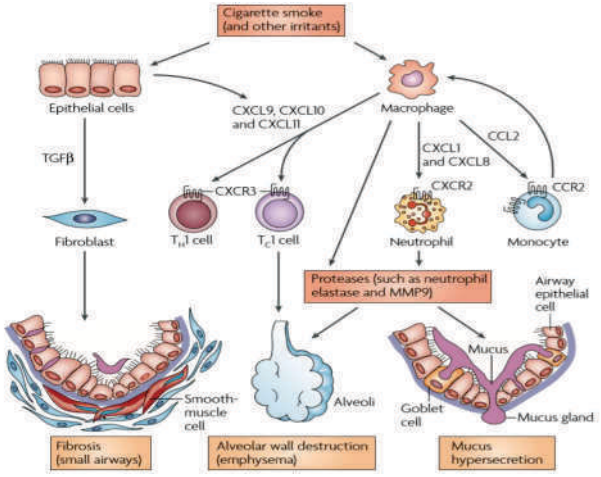

Figure 4 **Inflammatory and immune cells involved in chronic obstructive pulmonary disease (COPD).** (Source: Barnes JP. Peter. Immunology of asthma and chronic obstructive pulmonary disease. Nat Rev Immunol 2008 Mar; 8(3):183-92)

Inflammatory and immune cells involved in chronic obstructive pulmonary disease (COPD)

Inhaled cigarette smoke and other irritants activate epithelial cells and macrophages to release several chemotactic factors that attract inflammatory cells to the lungs, including CC−chemokine ligand 2 (CCL2), which acts on CC−chemokine receptor 2 (CCR2) to attract monocytes, CXC-chemokine ligand 1 (CXCL1) and CXCL8, which act on CCR2 to attract neutrophils and monocytes (which differentiate into macrophages in the lungs) and CXCL9, CXCL10 and CXCL11, which act on CXCR3 to attract T helper 1 (TH1) cells and type 1 cytotoxic T (TC1) cells. These inflammatory cells together with macrophages and epithelial cells release proteases, such as matrix metalloproteinase 9 (MMP9), which cause elastin degradation and emphysema. Neutrophil elastase also causes mucus hypersecretion. Epithelial cells and macrophages also release transforming growth factor−β (TGFβ), which stimulates fibroblast proliferation, resulting in fibrosis in the small airways (3) (Figure 4).

Other subtypes of CD4+ T cells that may have an important role in airway diseases are *regulatory T cells*, which have a suppressive effect on other CD4+ T cells and may have a role in regulationg Th2 cell function in asthma (13). Analysis of sputum from COPD patients suggests that the numbers of regulatory T cells are reduced, but similar changes are also seen in people who smoke, but do not have airflow obstruction (29,30).

Th17 cells and airway inflammation

Another subset of CD4+ T cells, known as *Th17 cells,* has recently been described and shown to have an important role in inflammatory and autoimmune diseases. Increased concentrations of IL-17 (the predominant product of Th17 cells) have been reported in the sputum of asthma patients (31).

IL-17 and IL-17F have been linked to neutrophilic inflammation by inducing the release of CXCL1 and CXCL8 from airway epithelial cells (32,33) (Figure 5).

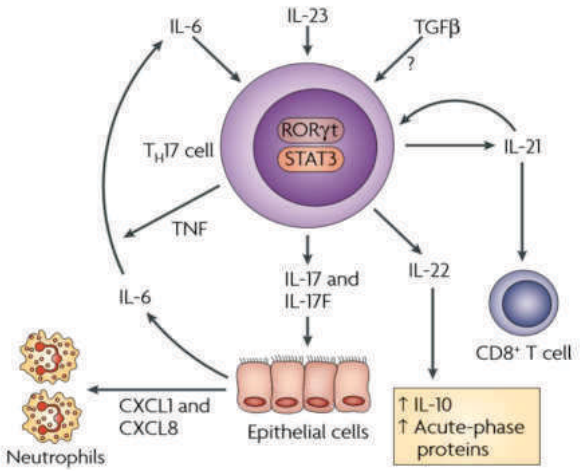

Figure 5 **Th 17 cells and airway inflammation.** (Source: Barnes JP. Peter. Immunology of asthma and chronic obstructive pulmonary disease. Nat Rev Immunol 2008 Mar; 8(3):183-92)

CD8 T cells in chronic obstructive pulmonary disease

CD8+ T cells predominate over CD4+ T cells in the airways and lung parenchyma of patients with COPD. Type 1 cytotoxic T (T_c 1) cells, which secrete IFN gamma, predominate and express CXCR3, suggesting that they are attracted to the lungs by CXCR3-binding chemokines (34,35,36,37) (Figure 6). In asthma, CD8+ T cells are present in patients with more severe disease and irreversible airflow obstruction (38) and these cells may be of either the T_c 1 or T_c 2 type (39,40,41).

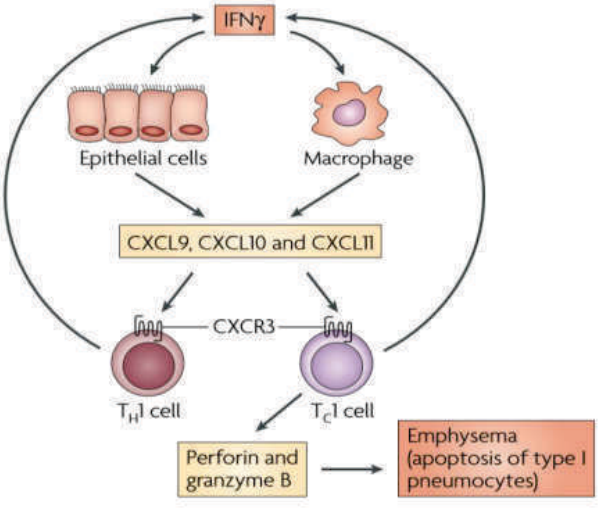

Figure 6 **CD8 T cells in chronic obstructive pulmonary disease** (Source: Barnes JP. Peter. Immunology of asthma and chronic obstructive pulmonary disease. Nat Rev Immunol 2008 Mar; 8(3):183-92)

Interestingly, IgE secretions is not observed in patients with COPD, but in the peripheral airways of patients with more severe disease there is a marked increase in the number of B cells, which are organised into lymphoid follicles that are surrounded by T cells (42,43). The class of immunoglobulin they secrete and how they are regulated is currently unknown, but they might be activated by bacterial or viral antigens as a consequence of the chronic bacterial colonizations or latent viral infection in the airways of those patients. Alternatively, it has been suggested that COPD might have an autoimmune component characterized by the development of new antigenic epitopes as a result of the tissue damage induced by cigarette smoking, oxidative stress or chronic bacterial infection (44,45,46). CD4 T cells isolated from the lungs of patients with severe emphysema are oligoclonal, which is consistent with antigenic stimulation by infective organisms or autoimmunity (47). Indeed, in a mouse model of emphysema induced by tobacco smoke, an autoimmune mechanism has been proposed with a role for antibodies specific for neutrophil elastase (48

Similarities between asthma and COPD

Although the inflammatory and immune mechanisms of asthma and COPD described above are markedly different, there are several situations where they become more similar and the distinction between asthma and COPD becomes blurred. However, it is now becoming clear that the distinction between these diseases becomes blurred in patients with severe asthma, in asthmatic subjects who smoke and during acute exacerbations. This has important implications for the development of new therapies (3,49).

Severe asthma

In patients with severe asthma and in asthmatic individuals who smoke, there is a neutrophilic pattern of inflammation.

Although Th2 cells predominate in mild asthma, in more severe asthmatic disease there is a mixture of Th1 and Th2 cells present in bronchial biopsies, as well as more CD8+ T cells and this more closely resembles the immune cell infiltration seen in COPD. The inflammatory pattern refers to an increased number of neutrophils in the sputum and increased amounts of CXCL8 and tumour-necrosis factor increased oxidative stress (50) and a poor response to corticosteroids as is observed in patients with COPD.

In mild asthma Th2 cells predominate, but in more severe asthmatic disease there is a mixture of Th1 and Th2 cells present in bronchial biopsies, as well as more CD8+ T cells and this more closely resembles the immune cell infiltration seen in COPD (3,31,32,36,51,52,53).

The neutrophilic inflammation seen in cases of severe asthma may be induced by IL-17 production by Th17 cells, which induces the release of the neutrophilic chemokine CXCL8 from airway epithelial cells (54). A neutrophilic pattern of inflammation, with high levels of CXCL8, is also found in the sputum of asthmatic individuals who smoke (31,32,55). Similar to patterns with severe disease or COPD, these individuals also have a poor response to corticosteroids, even if given orally at high doses (56,57).

Acute exacerbations

In both diseases, exacerbations are associated with a further increase in airway inflammation. In exacerbations of asthma triggered by viruses, there can be increases in the number of neutrophils, as well as of eosinophils (58), whereas in COPD exacerbations, particularly those due to viruses, there may be an increase in eosinophil numbers (59,60,61). During episodes of disease exacerbation, the pattern of inflammation becomes similar in COPD and asthma (3).

Implications for therapy

Corticosteroid responsiveness

Asthma is usually highly responsive to corticosteroid therapy and inhaled corticosteroids have become the mainstay of disease management (62). Corticosteroids suppress inflammation by inducing the recruitment of the nuclear enzyme histone deacetylase 2 (HDAC2) to multiple activated inflammatory genes, which leads to deacetylation of hyperacetylated genes, thereby suppressing inflammation (63). By contrast, patients with COPD respond poorly to corticosteroid treatment, and even high doses of inhaled or oral corticosteroids fail to suppress inflammation. This appears to be related to decreased activity and expression of HDAC2 in the inflammatory cells and peripheral lungs of COPD patients (64,65,66).

The poor response to corticosteroid therapy seen in patients with severe asthma, in asthmatics who smoke and during acute exacerbations may also reflect a reduction in HDAC2 protein levels and function, as oxidative and nitrative stress are also increased in these situations (67).

CONCLUSION

Although both COPD and asthma involve chronic inflammation of the airways, the pattern of inflammation differs significantly between the two diseases. Type 2-high (eosinophilic) and type 2-low (non-eosinophilic, sometimes neutrophilic) are endotypes of asthma. COPD is characterized by neutrophilic inflammation that can be driven by a significant increase in the number of macrophages found in the lungs, which also attract CD4+ and CD8+ T cells to the lungs. This lymphocytic infiltration can also be induced by chronic stimulation with viral and bacterial antigens or autoantigens released after lung injury. Mast cells and DCs, which play such a key role in asthma, have little or no known involvement in COPD. However, these differences between asthma and COPD may not be as clear as previously believed, since there is a neutrophilic pattern of inflammation in patients with severe asthma and in asthmatics who smoke. Acute exacerbations of asthma and COPD have similar inflammatory characteristics.Th17 cells in severe asthma and COPD are the driving mechanism of neutrophilic inflammation.

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The habenular complex and schizophrenia

Habenularni kompleks i shizofrenija

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ABSTRACT

Introduction: the habenular nuclear complex presents bilateral part of epithalamus, and it is a "crossroads" of pathways of the limbic system and basal ganglia, consisting of medial (nc. habenularis medialis - MHb) and lateral (nc. habenularis lateralis - LHb) habenular nucleus. The human habenular complex is involved in control of brain reward system and it is considered to play a very important role in emotional processes. It participates in determination of behavior and motor responses, acting through motivational processes and it is involved in the regulation of the activity of dopaminergic, serotonergic, noradrenergic and cholinergic neurons. These structures are involved in cognitive processes. It participates in determination of behaviour and motor responses, acting through motivational processes. The dysfunction of the complex may be important for the development of a variety of mental disorders. Lesions of habenular complex lead to cognitive and motor dysfunction, behavioural changes, changes in response to pain, stress, sleep disorders, mood and attention disorders and inadequate value-based decision-making. There is a growing interest of scientists in this brain structure, as it represents the target area of new therapeutic methods of treatment of psychiatric disorders.

Keywords: epithalamus, habenula, mental disorders

SAŽETAK

Uvod: habenularni kompleks je parna struktura epitalamusa i predstavlja "raskrsnicu" puteva limbičkog sistema i bazalnih ganglija, koji se sastoji od medijalnog (nc. habenularis medialis - MHb) i lateralnog (nc. habenularis lateralis - LHb) habenularnog jezgra. Uključen je u kontrolu učestvuje u kontroli moždanog sistema zadovoljstva i ima veoma važnu ulogu u emocionalnim procesima. Oblikujući motorne odgovore kroz motivacione procese reguliše aktivnosti dopaminergičkih, serotonergičkih, noradrenergičkih i holinergičkih neurona moždanog stable, kao i njihovu transmisiju u strukturama uključenim u kognitivne procese. Disfunkcija kompleksa može biti važna za razvoj raznih mentalnih poremećaja. Lezije habenularnog kompleksa dovode do kognitivne i motoričke disfunkcije, promjena u ponašanju, u odgovoru na bol, stresa, poremećaja spavanja, raspoloženja, pažnje i neadekvatnog donošenja odluka na temelju nagrada. Za ovu moždanu strukturu se povećava naučni interes, jer predstavlja ciljno područje novih terapijskih metoda liječenja psihijatrijskih poremećaja.

Ključne riječi: epitalamus, habenula, mentalni poemećaji

INTRODUCTION

The human brain consists of billions of neurons that communicate with each other and transmit information using neurotransmitters, enabling all brain functions. During the process of neurogenesis, new neurons develop at the highest speed during the first years of life, as well as during the entire lifespan of an individual. Neuroplasticity is, metaphorically speaking, the "flexibility" of the brain, i.e. its incredible ability to change, adapt during various life changes and is one of the main mechanisms through which our species has evolved and adapted over time. Anatomically speaking, the brain will not change for centuries. Habenula (diminutive of the Latin word habena originally meaning spur) - in neuroanatomy - originally referred to the stalk of the pineal gland (epiphyseal habenula; shaft or stalk of the epiphyseal body), but the term gradually came to refer to a neighboring group of nerve cells that were believed to be connected to epiphysis, as the habenular nucleus (1,2)

The habenular complex is a phylogenetically old brain structure that, in most vertebrates, has a clearly visible asymmetry in the size of the right and left complex (3,4).

AIM

The paper presents new knowledge about the role of the habenular complex in physiological processes, as well as the pathogenesis of schizophrenia.

THE HABENULAR COMPLEX

The habenular complex represents the main connection between the basal ganglia and the limbic parts of the telencephalon, on the one hand, and the mesencephalon, on the other. The epithalamus is the smallest part of the midbrain, which is located on the dorsocaudal part of the thalamus, and by its anatomical position, but also by its neuronal connections, it represents a "crossroads" where the paths of the limbic system, basal ganglia, and many other neural circuits cross. Morphologically, it consists of the pineal gland (gl.pinealis), habenular nuclei (nuclei habenulae), interhabenular joint (commisura habenularum) and striae medullaris. It represents a paired structure of the epithalamus composed of two nuclei - medial (nc. habenularis medialis - MHb) and lateral (nc. habenularis lateralis - LHb). The medial core of the habenula is made up of

dense nerve cells which, based on their cytoarchitectonic characteristics, are classified into five subnuclei, 10 subnuclei are described within the lateral habenular nucleus (5).

The sails of the habenula, due to their anatomical location and mutual connections, participate in the regulation of many physiological mechanisms, but also in the pathology of psychiatric disorders.

FUNCTION OF THE HABENULAR COMPLEX

The lateral nucleus of the habenula is of particular importance, because it has a direct influence on serotonergic, dopaminergic and noradrenergic transmission. This core is considered a hub through which limbic and striatal structures modulate the work of brainstem monoaminergic neurons to which they send and from which they receive projections (6,7,8).

The medial part of the LHb receives fibers mainly from parts of the limbic system that are directly or indirectly innervated by the cerebral cortex (9), while the lateral part of the LHb receives fibers mainly from the basal ganglia, especially the globus pallidus internus, which receives cortical information via the striatum. Efferent fibers from the LHb mainly go to monoaminergic neurons of the brainstem: dopaminergic neurons of the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), serotonergic neurons of the raphe nuclei and cholinergic neurons of the laterodorsal tegmentum. Some of the dopaminergic neurons are reciprocally connected to the LHb. According to the projections of the substantia nigra, the neural circuit is closed by which the limbic system, through the habenula, is involved in motor functions (substantia nigra - striatum - pallidum - habenula - substantia nigra). The medial habenular nucleus has an indirect influence on the regulation of monoaminergic transmission (5,10). The lateral core of the habenula represents the point of convergence of neural information from the basal ganglia and the limbic part of the telencephalon, while the afferent connections it receives from the limbic system allow emotions and motivation to modulate the motor response. (11). It performs its role by tonic inhibition of monoaminergic activity of dopaminergic neurons of the ventral tegmental area and serotonergic neurons of the raphe nuclei (12,13).

To the mentioned monoaminergic neurons of the mesencephalon, it sends glutamatergic projections that make synapses predominantly with GABAergic neurons of the ventral tegmental area, substantia nigrae and rostromedial tegmental nucleus (6,14), which have an inhibitory effect on dopaminergic and serotonergic neurons whose activity they reduce. Both habenular fibers receive afferent fibers through the striae medullaris, while they send their fibers through the fasciculis retroflexus creating a dorsal diencephalic conducting system (15). Lesions of the habenula nuclei cause an increase in serotonin and dopamine metabolism in the central nervous system, while electrical stimulation causes a decrease in the activity of serotonergic and dopaminergic neurons (16). The habenular complex has the role of a complex and coordinated brain network involved in processing information that participates in emotional and motivational processes (17).

The lateral core of the habenula is also involved in cognitive processes, regulation of sleep and wakefulness, attention, pain processing and stress response (5,17), for which monoaminergic neurotransmission is very important (13). The human habenular complex participates in the control of the brain's pleasure system and plays a very important role in emotional processes (18,19,20). The lateral core of the habenula is a brain region that is inhibited by pleasant stimuli, and activated by stimuli that result in dissatisfaction and chronic stress (17). An increase in the activity of LHb neurons leads to a transient inhibition of serotonergic neurons of the raphe nuclei (14,19) and dopaminergic neurons of the ventral tegmental area, as well as a decrease in dopamine levels, especially in the dorsal and ventral striatum, which leads to suppression of motor and cognitive responses. The results of research using functional magnetic resonance have shown that habenula neurons are activated in response to a negative reaction, that is, criticism after a mistake has been made, as well as if a positive reaction, that is, praise after a correctly chosen answer is absent (11,19). Many patients with disorders of dopaminergic neurotransmission, such as Parkinson's disease and schizophrenia, choose the wrong way of behavior and response when solving problems (10), which may be a consequence of interruption of the habenulo-mesencephalic circuit, as part of the brain center of pleasure.

Conducted research has shown that if there is a morphological change or dysfunction of the lateral core of the habenula, there is a wrong choice of response to the stimulus, that is, a behavioral response occurs even if the supposed consequences of the behavior are unwanted. This can manifest as impulsivity, attention deficit disorder, stereotyped movements (9,21).

THE ROLE IN THE PATHOGENESIS OF SCHIZOPHRENIA

The emergence of cognitive disorders characteristic of schizophrenia may be the result of pathological processes that take place in the nuclei of the habenula (20, 9). Research by Shepard PD, et al. (2006) showed that the dysfunction of the lateral nucleus of the habenula limits a person's ability to learn from mistakes, which is one of the characteristic cognitive disorders in patients with schizophrenia (20).

Attention deficit disorder, which is also characteristic of schizophrenic patients, and which occurs after a lesion of the habenula, has been observed in animal experiments (22).

Dysfunction of the habenular complex has a role in memory disorders, which indicates the role of the habenula in memory processes (9). Cognitive deficits, memory and attention disorders may be the result of a reduced inhibitory effect of LHb on the dopaminergic neurons of the mesencephalon and an increased concentration of dopamine in the nc. accumbens, as well as serotonergic, noradrenergic and cholinergic neurons (22,23).

A higher frequency of habenular and pineal calcifications was also recorded in patients with schizophrenia compared to the healthy population. Functional magnetic resonance imaging in these patients indicates impaired habenula activity, and consequently dysfunction of dopaminergic transmission in the ventral tegmental area and substantia nigrae. Influenza type A virus, if it occurs in the prenatal period, selectively attacks habenulae, as well as monoaminergic brain areas, increasing the risk of developing schizophrenia, which was recorded in experiments on mice (18,24,25).

CONCLUSION

The habenular complex participates in many functions, given that it is located at the junction between the forebrain and midbrain, as well as the neural circuits in which it is also involved. The role in the regulation of emotional behavior is especially highlighted, because it participates in the control of the brain's pleasure system and plays a very important role in emotional processes. It regulates the activities of dopaminergic, serotonergic,

noradrenergic and cholinergic brain stem neurons and their transmission in the structures involved in cognitive processes and participates in shaping motor responses, acting through motivational processes. This brain structure represents a significant area of development and application of new therapeutic methods, i.e. therapeutic action such as deep brain stimulation, especially on the habenulae, in the treatment of mental illnesses in the pathogenesis of which the role of the habenular nuclei has been proven.

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Successful outcome in the treatment of a rare brachial plexus schwannoma: a case report with literature review

Uspješan ishod liječenja rijetkog švanoma brahijalnog pleksusa: prikaz slučaja s pregledom literature

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ABSTRACT

Introduction: plexus brachialis is a network of nerves, which is responsible for the transmission of nerve impulses from the brain to the muscles of the upper extremities Aim: to present a very rare case of schwannoma of brachial plexus. Case report: a 29-year-old female patient was presented with a mass on the posteromedial side of the left upper arm. It was a localized mass with distal paresthesia of the upper arm, firm on palpation. MRI scan showed an expansive mass along with the medial head of the triceps brachial muscle, measuring 25x48x31mm. This mass radiologically showed as Schwannoma which affected the ulnar, radial, and musculocutaneous nerve. During resection, firstly brachial artery and vein were detached from a tumor. Musculo-cutaneal and ulnar nerves were completely separated. The radial nerve was infiltrated with a clear origin and preserved fibers were successfully dissected. Implantation of a sural graft wasn't used, because more than 50% of the radial nerve fibers were preserved. Results: postoperatively, the patient had limited dorsiflexion of the left palm. After physical treatment, the patient made full recovery. Conclusion: schwannoma is a rare tumor that can successfully be removed, and it has a very good prognosis with the possibility of full recovery from neurological deficiency.

Keywords: brachial plexus, neoplasm, nerve, Schwann cells

SAŽETAK

Uvod: plexus brachialis je mreža živaca, koja je odgovorna za prijenos živčanih impulsa od mozga do mišića gornjih ekstremiteta. Cilj: je bio predstaviti vrlo rijedak slučaj švanoma brahijalnog pleksusa. Dvadeset devetogodišnja pacijentica javila se s masom na posteromedijalnoj strani lijeve nadlaktice. Radilo se o lokaliziranoj masi s distalnom parestezijom gornje nadlaktice, koja je bila čvrsta na palpaciju. MRI je pokazao ekspanzivnu masu uz medijalnu glavu tricepsnog mišića, dimenzija 25x48x31mm. Ova masa radiološki se pokazala kao švanom koji je zahvatilo ulnarni, radijalni i muskulokutani živac. Tokom resekcije, najprije su brahijalna arterija i vena odvojene od tumora. Muskulokutani i ulnarni živci su u potpunosto odvojeni od tumorske mase. Radijalni živac bio je infiltriran s jasnim granicama, a vlakana ovog živca su uspješno disecirana. Implantacija suralnog grafta nije korištena, jer je više od 50% vlakana radijalnog živca bilo sačuvano. Rezultati: nakon operacije, pacijentica je imala ograničenu dorzifleksiju lijeve šake. Nakon fizikalnog tretmana, pacijentica se potpuno ozdravila. Zaključak: švanom je rijedak tumor koji se može uspješno ukloniti, a ima i vrlo dobru prognozu s mogućnošću potpunog oporavka od neurološkog deficita.

Ključne riječi: brahijalni pleksus, neoplazma, živac, Schwannove stanice

INTRODUCTION

Plexus brachialis is a network of nerves, which is responsible for the transmission of nerve impulses from the brain to the muscles of the upper extremities. This plexus provides somatic motor and sensory innervation to the mentioned area (1). Brachial plexus is formed by anterior branches of C5 to T1 and this neural network starts as roots and then continues to divide, until it is finally divided into terminal branches. The five terminal branches are the axillary nerve, musculoskeletal nerve, median nerve, ulnar nerve, radial nerve (2). While exceptionally rare, tumors of these nerves can occur, most commonly originating from the supporting cells of the peripheral nerve. Schwannomas are characterized as benign, slow growing and non-infiltrating tumors of peripheral nerves, and they develop from Schwann cells (3). Schwannomas represent less than 5% of all tumors of upper extremities (4). Schwannomas vary significantly in size, and if they are larger than 250 mm, they cause neurological symptoms (Kang et al., 2000.) The differential diagnosis of schwannoma can be made by radiological examinations, and the definitive diagnosis is made by biopsy (4). Recurrence or malignant transformation of schwannomas is very rare (5).

AIM

The aim of this paper was to present a rare case of schwannoma of the brachial plexus, and to gather information about the clinical presentation, diagnosis and treatment modality of this rare tumor through a review of the literature.

CASE REPORT

A 29-year-old female patient was presented with a posteromedial mass located on the left upper arm. The patient reported an initial hazelnut-sized mass that had progressively grown over the past two months. Clinical examination revealed a firm, partially mobile mass that induced paresthesia upon palpation within the innervation area of the ulnar nerve. The patient denied the presence of any other medical conditions. Magnetic resonance imaging (MRI, Siemens Magnetom Avanto 1.5 T, Erlangen, Germany) showed an ovoid, well-defined, expansive mass adjacent to the medial head of the triceps brachii muscle, measuring 25x48x31mm (Figure 1a and b).

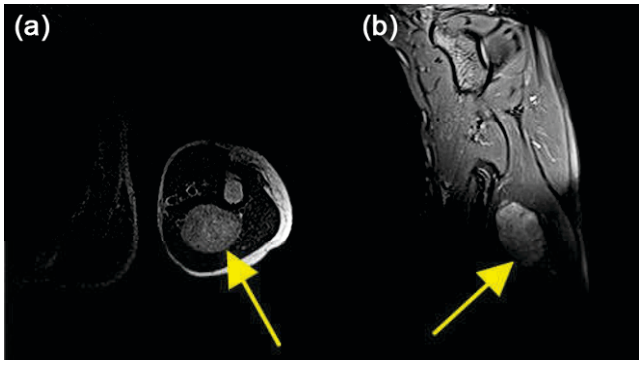

Figure 1 **Preoperative transversal (a) and axial (b) MRI slices showing neoplasm (yellow arrow).**

The lesion was situated in the vicinity of the radial nerve, and imaging indicated minimal contact with the humerus, lacking infiltration, and adjacency to the deep brachial vein without impeding vascular flow. No abnormalities were observed in other anatomical structures, and there was an absence of lymphadenopathy. Considering concerns about potential malignancy, resection of the tumor mass was deemed necessary. The surgical procedure was conducted under general anesthesia, positioning the patient's left upper extremity in extension and abduction, with the left lower leg in flexion and internal rotation, prepared for a potential nerve graft. The initial phase of the resection involved separating the brachial artery and vein from the tumor (Figure 2a). Subsequently, the musculocutaneous and ulnar nerves were meticulously isolated, while the radial nerve, bearing clear origins and intact fibers, was carefully dissected (Figure 2b).

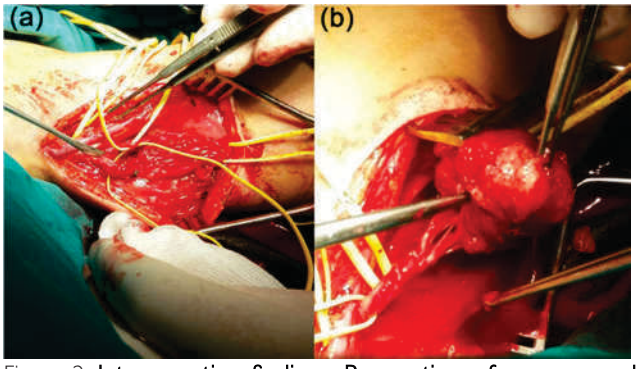

Figure 2 **Intraoperative findings. Preparation of nervous and vascular structures (a) and detachment of neoplastic mass from radial nerve (b).**

Sural graft implantation was not required, as over 50% of radial nerve fibers were preserved. Histopathological analysis confirmed the diagnosis of schwannoma, characterized by dominant Antoni A areas and a lesser presence of myxoid hypocellular components (Antoni B areas). Postoperatively, the patient maintained good general health, albeit with diminished dorsiflexion in the left hand. Upon hospital discharge, the patient was referred to a regimen of physical therapy aimed at achieving full restoration of left-hand function, with regular assessments every 3-4 months. A follow-up MRI conducted nearly two years later revealed no signs of schwannoma recurrence (Figure 3a and b). Concurrently, neurological assessments indicated complete restoration of left-hand function and overall recovery (Figure 4a and b).

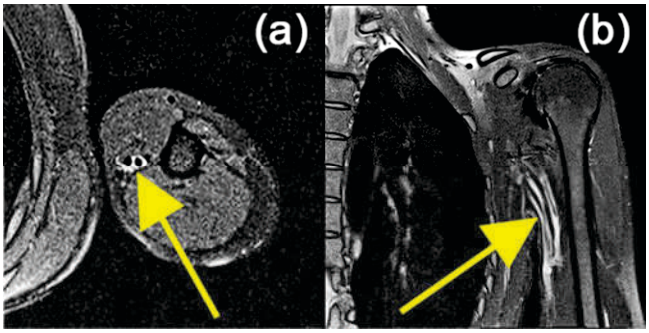

Figure 3 **Postoperative MRI findings on transversal (a) and axial (b) slices. Yellow arrows depict previous tumor site.**

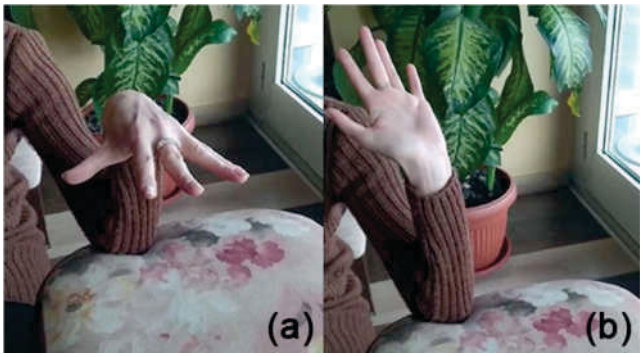

Figure 4 **Full recovery of ventral (a) and dorsal (b) flexion of the wrist.**

DISCUSSION

Schwannomas, by their inherent nature, are classified as benign tumors (1). However, during initial evaluation, healthcare professionals frequently lean towards considering malignant tumors, primarily due to the clinical presentation of these growths (6). Das Gupta TK, et al. (7) conducted a study and 303 schwannomas and found that 19% of tumors were located in upper limbs, 45% of the tumor cases were located in neck and brain. Moreover, it is not uncommon for schwannomas to produce symptoms that can provoke concerns, both in the patient and the medical practitioner, leading to suspicions of a grave, potentially life-threatening condition (8).

For the purpose of this article, we conducted a review of literature, where 11 case reports were found (Table 1). Examination of the gathered data reveals a pronounced predilection for schwannomas among the female population, accounting for 8 out of the 11 documented cases. Retrospective study by Pertea M, et al. (9) also showed a predominance in female gender when it comes to schwannomas of upper limb. The age distribution of affected individuals spans a wide range, with the youngest patient being 10 years old, while the oldest was 72 years.

Schwannoma size exhibits considerable heterogeneity, ranging from the smallest observed in this study at 0.86x0.2x0.17 cm to the largest, which measures 11x7x6 cm. The literature showed that the presentation of schwannomas of the upper extremities is most often related to the ulnar nerve (4). A review of 170 cases of upper limb and thorax schwannomas done by Knight DM, et al. (10) showed that most common distribution was in supraclavicular brachial plexus, and second most common distribution was ulnar nerve. Knight DM, et al. (10) reported that there was no schwannoma of ulnar nerve, and most common distribution were schwannomas of cervical nerves.

A majority of patients in our literature review (6 out of 11) displayed no neurological deficits. Brachial plexus schwannoma presents with diverse symptoms, including motility reduction (11), neck swelling, pain, and tingling in the distal end of the forearm (12), numbness in the fingers (13), painless swelling in the supraclavicular region, numbness and pain in the infraclavicular region (14). For definitive diagnosis of schwannoma, histopathological analysis of tissue is imperative (4). However, challenges may arise in diagnosis, particularly when dealing with non-resectable and inaccessible tumors, making biopsy unfeasible (8). Regarding potential treatment strategies for schwannoma, various options exist. In most instances, surgical mass resection is recommended due to the tumor's nature (4).

Nevertheless, in several other reported cases, nerve grafting was performed, also resulting in preserved neurological function. Remarkably, 10 out of 11 cases concluded with complete recovery and no recurrence of the mass.

Table I **Summary of literature review.**

References	Patient information				Neurological characteristics		Treatment	Outcome
	Age	Sex	Size of tumor (cm)	Symptoms	Deficit	Affected nerves		
Mbaye PA, et al. (11) 2022	10	F	11x7x6	Motility reduction, Left shoulder mass	No	Brachial plexus	Surgical resection with biopsy	Full resection without complications
Ranjan S, et al. (12), 2020.	56	F	5x4	Neck swelling, pain and tingling in the distal end of right forearm	Yes	C6 - C7	Surgical resection with biopsy	Full resection with complications after (numbness, tingling), but it is showing improvement with physiotherapy sessions.
Xiao Y, et al. (15), 2023.	59	F	0.86x0.2x0.17	Axillary mass, numbness in left little finger	Yes	Medial tract of brachial plexus	Microsurgery interfascicular dissection	Full resection without complications
Femia F, et al. (16), 2022.	72	M	5.5x5.4x5.1	History of asthma and hypertension	No	T1	Minimal invasive surgical excision	Full resection without complications
Ryu KH, et al. (17), 2018.	49	F	1.5x1.0x1.0	Neck mass, present for at least a year	No	C5	Follow-ups without resection	Diagnosed with core biopsy
Qu Y, et al. (18), 2023.	17	F	1 cm in diameter	Left palmar mess, painful	No		Surgical excision with biopsy	Full resection without complications
Aleksanyan LV, et al. (14), 2021.	32	M	4.7 x 3.3	Painless swelling in the left supraclavicular region	No	C6 - C7	Surgical resection with biopsy	Full resection without complications
Han C, et al. (13), 2021.	66	F	5 x 3.3	Numbness and pain in the left infraclavicular region	Yes	Median nerve	Surgical resection with biopsy and sural nerve cable graft	Full resection without complications and full recovery
Han C, et al. (13), 2021.	61	M	2.4x3.8	Mass in the left sternocleidomastoid muscle and numbness in the left arm	Yes	C7 - C8	Surgical resection with biopsy and nerve graft	Full resection, however, decreased sensation and muscle power occurred in the fourth and fifth fingers
Wang L, et al. (19), 2023.	21	F	3.3	No symptoms, mass was incidentally discovered	No	Left brachial plexus	Surgical resection with biopsy	Full resection, the patient had diminished sensations in the left upper limb, but it returned to normal in a month.
Sefo H, et al. (this case)	29	F	2.5x4.8x3.1	Posteromedial mass on the left upper arm	Yes	Radial nerve	Surgical resection with biopsy	Full resection, the patient had weakened dorsiflexion, but after physiotherapy the patient had complete recovery.

CONCLUSION

This is a unique case of brachial plexus schwannoma, complemented by a comprehensive literature review of this infrequent tumor. Timely intervention is vital in achieving a complete cure with subsequent full recovery in schwannoma cases. Furthermore, the incorporation of physical therapy plays a crucial role in facilitating the comprehensive recuperation of patients' post-surgery. Our case report has convincingly demonstrated that the segregation of non-infiltrated nerve fibers coupled with a structured rehabilitation regimen constitutes a secure protocol that consistently leads to favorable outcomes.

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Unusual presentation of inflammatory changes mimicking malignancy in a patient with breast carcinoma: a case report

Neuobičajena prezentacija inflamatornih promjena koje imitiraju malignitet kod pacijentice sa rakom dojke: prikaz slučaja

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ABSTRACT

Introduction: breast cancer stands out as the most prevalent form of cancer among women on a global scale, with approximately 2.3 million new cases of invasive cancer diagnosed in 2020. Aim: to present a case of breast cancer patient surgically treated at our institution with a rare axillary mass mimicking malignancy. Case report: a 66-year-old female patient was presented with a palpable mass in the left breast, raising suspicion of malignancy. Core needle biopsy confirmed a diagnosis of G2 NST cancer with positive axillary nodes. Following mastectomy with axillary node dissection (AND), postoperative pathohistology revealed pT2, pN3a Mx, per AJCC TNM staging. The patient underwent adjuvant chemotherapy of Adriamycin and cyclophosphamide, Paclitaxel, irradiation, and hormonal therapy. After 16 weeks of treatment, a control ultrasound revealed pathological lymph nodes in the left axilla. Intraoperative biopsy revealed a challenging mass measuring approximately 9x8x2 cm, situated on the axillary vein. Histopathological examination unexpectedly indicated inflammatory changes with necrosis and proliferation of epithelioid histiocytes, suggesting a reactive nature, without evidence of specific histiocytic neoplasms. Conclusion: awareness of inflammatory mimickers is crucial for accurate diagnosis and optimal patient management.

Keywords: breast carcinoma, inflammatory changes, axillary lymphadenopathy, reactive histiocytes

SAŽETAK

Uvod: rak dojke je najrasprostranjeniji oblik raka među ženama na globalnom nivou, sa približno 2,3 milijona novih slučajeva invazivnog raka dijagnosticiranog u 2020. Cilj: predstaviti slučaj pacijentice sa rijetkom aksilarnom masom koja oponaša malignu bolest koja je hirurški liječena u našoj ustanovi. Prikaz slučaja: 66-godišnja pacijentica dolazi na pregled sa palpabilnom promjenom u lijevoj dojci, suspektnoj na malignitet. Biopsija promjene potvrdi da se radi o G2 NST karcinomu sa pozitivnim pazušnim limfnim čvorovima. Po provedenoj radikalnoj mastektomiji, postoperativna patohistološka analiza ukaže na pT2, pN3a, Mx prema AJCC TNM staging-u. Pacijentica je potom podvrgnuta adjuvantnoj kemoterapiji sa Adriamicinom i cikofosfamidima, Paclitaxel -om, zračenju kao i hormonalnoj terapiji. 16 sedmica po obavljenom operativnom tretmanu, kontrolni ultrazvuk je otkrio tumorsku masu dimenzija 9x8x2 cm, smještenu u blizini aksilarne vene. Patohistološka analiza je neočekivano potvrdila inflamatorne promjene sa nekrozom i proliferacijom epiteloidnih histiocita, ukazujući na reaktivnu prirodu, bez dokazane histiocitne neoplazme. Zaključak: svijest o postojanju oponašanja upale ključna je za tačnu dijagnozu i optimalno liječenje bolesnika.

Ključne riječi: rak dojke, inflamatorne promjene, aksilarna limfadenopatija, reaktivni histiociti

INTRODUCTION

Breast cancer stands out as the most prevalent form of cancer among women on a global scale, with approximately 2.3 million new cases of invasive cancer diagnosed in 2020 (1). Over the past three decades, there has been a nearly 25% increase in the age-standardized rate of invasive breast cancer in the UK (2). The projected incidence and mortality rates of breast cancer among women displayed a twofold fluctuation across EU27 nations, reaching up to 190 new cases and 45 deaths per 100,000 women (3). Over the last five decades, the approach to managing breast cancer has transformed from predominantly surgical interventions to a comprehensive strategy encompassing surgery, radiation therapy, and systemic therapy. This shift is grounded in an enhanced comprehension of invasive breast malignancy as a systemic ailment, emphasizing the improved outcomes associated

with incorporating systemic therapy alongside local and regional treatments. The management of the axilla has been a pivotal aspect of breast cancer patient care for several decades. Evidence from randomized controlled trials, such as the NSABP B-04, has firmly established that axillary dissection does not enhance survival (4). However, the status of the axillary lymph nodes remains a prognostic factor and a crucial component of the American Joint Committee on Cancer (AJCC) staging system. Despite the absence of a survival advantage, the removal of positive lymph nodes can still contribute to local control. With a significant number of patients in the current era presenting with mammographically detected, node-negative disease, there has been a growing interest in reducing the invasiveness of axillary surgery. While axillary clearance, also known as axillary dissection, is clearly efficacious in accurately staging the axilla, it is also associated with significant morbidity, predominantly the lymphoedema.

AIM

The aim of the study was to present a case of breast cancer patient surgically treated at our institution with a rare axillary mass mimicking malignancy.

CASE REPORT

A 66-year-old female patient was admitted at our clinic with a palpable mass in her left breast. Patient history included grade 2 Hypertension and glucose intolerance. 24 years prior to this disease she underwent hysterectomy on the grounds of the cervix cancer. Her family history was negative for malignancy. Clinical palpatory examination revealed two firm masses beneath the nipple of the left breast. Additionally, a larger lymph node was palpable in the left armpit. Ultrasound and mammography were highly suspicious of malignancy, with BI-RADS 5 grade. A core needle biopsy confirmed the presence of cancer cells, characterized as G2 NST carcinoma (NHS 7/9), ER: 100%, PR: 50%, Her2/neu: neg, Ki67: 25%, with positive axillary nodes. Upon multidisciplinary team consultation, surgical intervention was recommended, leading to mastectomy with axillary node dissection (AND). Postoperative pathohistological analysis revealed pT2, pN3a Mx, according to AJCC TNM staging. Subsequently, a treatment regimen comprising 4 cycles of Adriamycin and Cyclophosphamide, 12 weekly cycles of Paclitaxel, irradiation, and hormonal therapy was initiated.

During the treatment, at week 6, the patient experienced angina pectoris, necessitating hospitalization at the Cardiology Clinic, where coronary angiography revealed triple vessel disease, with coronary artery bypass grafting (CABG) scheduled after completion of post-oncological treatment. After 16 weeks of therapy, a follow-up ultrasound detected pathological lymph nodes in the left axilla, with the largest measuring 40x25 mm and 15x5mm. Due to the localization, an operative biopsy was performed, revealing a challenging mass approximately 9x8x2 cm in total size, situated directly on the axillary vein. While awaiting histopathological results, the patient continued hormonal therapy. Surprisingly, the histopathological findings indicated inflammatory changes with necrosis and proliferation of epithelioid histiocytes, primarily reactive in nature, without evidence of specific histiocytic neoplasms or signs of breast cancer metastasis.

Figure 1 **Postoperative axial CT scan (slice) - note the lobulated formation in the left axilla (right side of the picture).**

DISCUSSION

The unexpected histopathological findings in our patient underscore the importance of considering inflammatory processes in the differential diagnosis of breast cancer metastasis. Non-neoplastic proliferations of histiocytes and dendritic cells, both benign and malignant, are a common encounter in lymph nodes. Reactive infiltrates of histiocytes and dendritic cells manifest in response to various stimuli, leading to lymphadenopathy, and can unexpectedly appear in lymph nodes excised for unrelated indications (5). These entities encompass a wide range of etiologies and histopathological features, often presenting diagnostic challenges to pathologists. Understanding the underlying mechanisms and histological characteristics of these proliferations is essential for accurate diagnosis and appropriate clinical management.

One notable entity is sinus histiocytosis with massive lymphadenopathy (SHML), also known as Rosai-Dorfman disease. Rosai J, et al. first described this condition in 1969, characterizing it by painless cervical lymphadenopathy and sinus histiocytosis on histopathological examination (6). SHML typically presents with massive lymphadenopathy due to histiocytic proliferation within the sinuses, accompanied by emperipolesis, the engulfment of lymphocytes and plasma cells by histiocytes (7).

In our case, no emperipolesis was detected. Another reactive process involving dendritic cells is follicular dendritic cell (FDC) hyperplasia. FDCs are stromal cells within lymphoid follicles that play a crucial role in antigen presentation and germinal center formation. FDC hyperplasia can occur in various inflammatory and infectious conditions, leading to expansion of the follicular network and hyperplasia of FDCs (8). Although typically benign, FDC hyperplasia can occasionally mimic lymphoma clinically and radiologically, emphasizing the importance of histopathological evaluation (9). Granulomatous inflammation is a form of chronic inflammation that occurs in response to infectious, autoimmune, neoplastic and unknown causes, and more specifically in response to an antigen that is insoluble or otherwise difficult to eliminate (10). One commonly described cause of benign lymphadenopathy in literature is the silicone lymphadenopathy which usually occurs in regional lymph nodes draining sites of silicone-containing medical

implants, typically silicone gel-filled breast implants (11) or silicone elastomer joint prostheses.

Clinical correlation and ancillary studies, including immunohistochemistry and molecular analysis, are crucial for accurate diagnosis. Immunohistochemical markers such as CD68, CD163, and S-100 can help identify histiocytic lineage, while markers like CD21 and CD23 are useful for highlighting FDCs in the follicular network (8). Molecular studies, including flow cytometry and gene rearrangement analysis, can provide additional diagnostic information, particularly in challenging cases.

CONCLUSION

This case highlights the necessity of careful histopathological examination in breast cancer patients, particularly when atypical features are present. Awareness of inflammatory mimickers is crucial for accurate diagnosis and optimal patient management. Further studies are warranted to elucidate the underlying mechanisms and clinical implications of such inflammatory changes in breast cancer patients.

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Lesion of azygos vein after a blunt chest trauma

Lezija vene azygos nakon tupe povrede grudnog koša

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ABSTRACT

Introduction: blunt chest injuries are usually caused by traffic accidents, in about 70% of patients. Aim: we present the case of a patient with a lesion of the azygos vein and thoracic duct injury sustained after a blunt chest trauma, which was successfully treated. Case report: a female patient was admitted to the Emergency Department after being injured in a traffic accident. She sustained a traumatic hemopneumothorax, therefore a right-sided tube thoracostomy was performed with the evacuation of almost three liters of blood. Due to hemorrhagic shock, an emergency thoracotomy had to be performed and we noticed lesions of the thoracic duct and azygos vein. On the tenth postoperative day, the patient was discharged from our Clinic. Conclusion: in a properly selected group of patients, emergency thoracotomy may be a life-saving intervention. Postoperative care and careful follow-up are of equal importance to establish a full recovery.

Keywords: blunt chest trauma, azygos vein, urgent thoracotomy

SAŽETAK

Uvod: tupe povrede grudnog koša najčešće su uzrokovane prometnim nesrećama, u oko 70% slučajeva. Cilj: prikazujemo slučaj bolesnika sa lezijom vene azygos i ozljedom torakalnog duktusa zadobivenom nakon tupe ozljede prsnog koša, koja je uspješno hirurški sanirana. Prikaz slučaja: pacijentica je primljena u Urgentni centar nakon saobraćajne nesreće. Zadobila je traumatski hemopneumotoraks, pa je učinjena desna torakalna drenaža uz evakuaciju gotovo tri litre krvi. Zbog hemoragičnog šoka hitno je učinjena torakotomija, evidentirane su lezije torakalnog duktusa i vene azygos. Pacijentica je otpuštena sa naše Klinike desetog postoperativnog dana. Zaključak: u pravilno odabranoj skupini pacijenata, hitna torakotomija može biti spasonosna intervencija. Postoperativna njega i pažljivo praćenje jednako su važni za uspostavljanje potpunog oporavka.

Ključne riječi: tupa trauma grudnog koša, vena azygos, urgentna torakotomija

INTRODUCTION

The standard of chest trauma treatment is effective cardiopulmonary resuscitation followed by early detection and treatment of life-threatening injuries. In 70% of patients, blunt chest trauma occurs in traffic road accidents worldwide (1,2). Less than 15% of patients with chest trauma require aggressive surgical treatment (3,4,5). As a rule, urgent thoracotomy in the Emergency Centre (EC) is performed in severely injured patients. The decision for emergency thoracotomy is made individually for each injured person (6). Indications for surgical treatment of patients with sustained blunt chest trauma include: hypotension that does not improve with therapy (blood pressure (BB) less than 70 mmHg), rapid blood loss via chest tube (initially more than 1500 ml of blood), as well as some relative indications, such as traumatic arrest with previously diagnosed heart disease (pre-hospital or intra-hospital). Surgery is contraindicated in patients with: blunt chest trauma without previously diagnosed heart disease, multiple blunt trauma foci, as well as in patients with sustained severe head injury. Emergency thoracotomy performed in the Operating Room (OR) offers a survival rate of up to 75% (7,8).

AIM

The aim of this article was to present the case of a female patient with an azygos vein and thoracic duct injuries, caused by a blunt chest trauma in a traffic road accident.

CASE REPORT

A middle-aged female patient was admitted to the EC after being injured in a traffic accident as a passenger under unknown circumstances. The patient was conscious and agitated, with signs of hemorrhagic shock (BP 80/50 mmHg, heart rate (HR) 150/min, with barely palpable pulse, and extremely pale skin). Laboratory findings showed increased WBC (28.4), with RBC count of 4.44, Hgb count of 126, Htc count of 37, and platelet count of 370. Numerous minor contusions on the skin, a hematoma in the area of the left temple, a larger excoriation of the skin in the area of the rib cage on the right were observed. Diminished lung sounds were detected by auscultation and chest percussion on the right side. Emergency diagnostic work-up in the ED was immediately performed, which included chest-, head-, spine-, pelvis- and hip X-ray, and ultrasound of the abdomen (Figure 1).

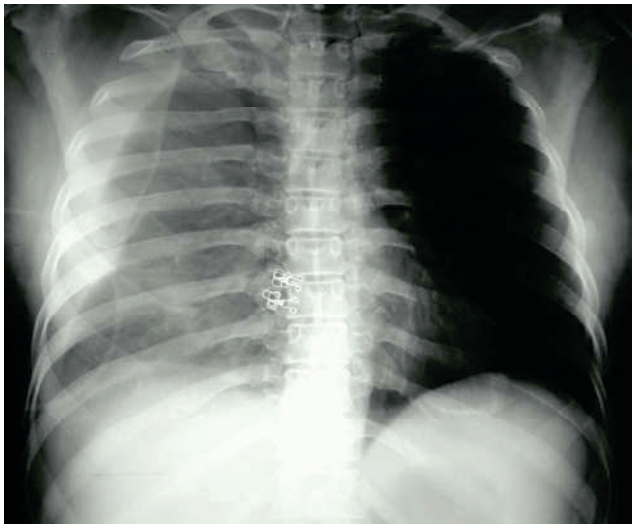

Figure 1 **CXR at the admission to the ED: right-sided hemopneumothorax.**

The chest X-ray (CXR) revealed a homogenous right-sided shadow, highly suspicious of traumatic hemopneumothorax. A thoracic surgeon was called for the examination. A right-sided tube thoracostomy was performed and 1900 ml of fresh blood was evacuated. The follow-up CXR demonstrated a remaining homogeneous shadow of the right hemithorax (Figure 2).

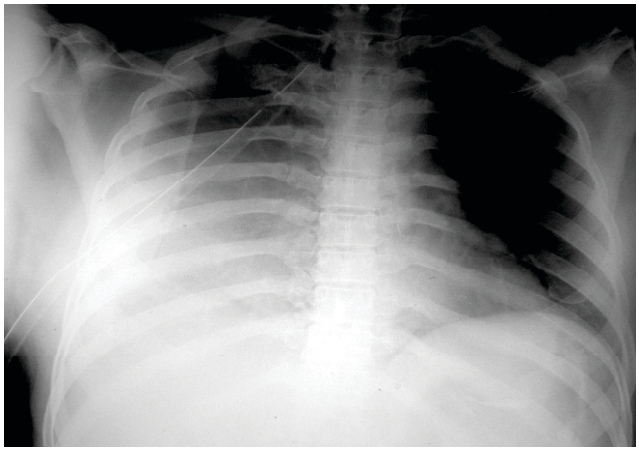

Figure 2 **The follow-up CXR after a right-sided tube thoracostomy: persistent shadowing of the right hemithorax.**

Follow-up laboratory findings after the chest tube placement were as follows: WBC count of 36.2, RBC count of 3.27, Htc count of 27, and platelet count of 271. The patient became somnolent, uncommunicative, with extremely pale and marbled skin, cold, livid lips, tachypneic, tachycardic with a non-palpable pulse, immeasurable pressure on the periphery, vitally endangered. An additional 1000ml of blood were evacuated via tube thoracostomy.

Based on the amount of the evacuated blood and considering the patient's worsening clinical condition, an urgent right-sided thoracotomy was performed. Upon opening of the right pleural cavity, an extensive blood clot extending from the apex to the diaphragm on the back side of the cavity was observed (approximately 1000 ml of blood). Careful evaluation and tissue preparation revealed the lesion of azygos vein, with profuse bleeding. The vein was ligated. After lavage, a further inspection revealed a lesion of the lymphatic duct about 3 cm below the azygos vein. The site of the lesion was treated with clipping. After careful aero- and hemostasis, two chest tubes were placed in the right pleural cavity and the wound was properly sutured. Postoperative CXR revealed a satisfactory regression of the right-sided shadow with properly placed chest tubes in the right hemithorax and pleural cavity (Figure 3).

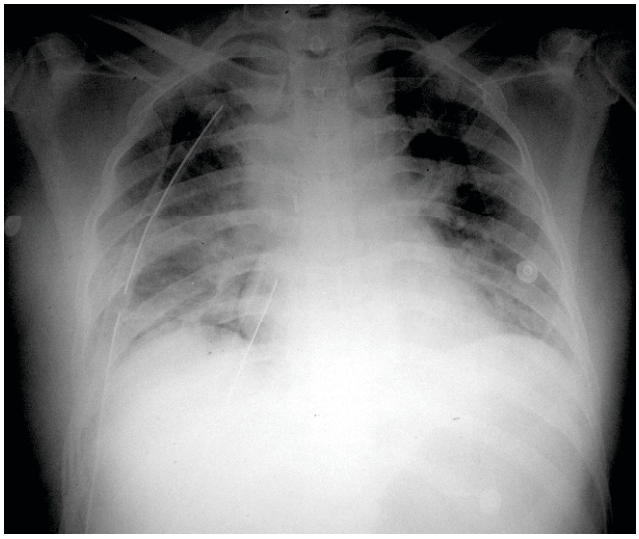

Figure 3 **Postoperative CXR: a noticeable regression of the right-sided hemopneumothorax.**

During the emergency thoracotomy, 15 doses of RBC transfusion, six fresh frozen plasma units, crystalloids, and colloids were administered. After the surgery, the patient was intubated and transferred to the Intensive Care Unit (ICU), where she was connected to a ventilator with non-invasive continuous monitoring.

The following day, the patient was extubated, conscious, respiratory, and cardiocirculatory stable (BP 115/70 mmHg, HR 70/min). Postoperative laboratory findings were unremarkable (RBC count of 4.12, Hgb count of 124, Hct count of 36, WBC count of 4.3, and platelet count of 93.3).

The postoperative course was satisfactory and uneventful, therefore the patient was transferred to the Clinic of Thoracic Surgery on the third postoperative day. Chest tubes were extracted on the sixth and eighth postoperative days.

The patient's CXR before the discharge from our Clinic showed clear lungs, and a clearly outlined chest cavity, without any sign of residual fluid or air inside the pleural cavity (Figure 4). On the tenth postoperative day, the patient was discharged from the Clinic.

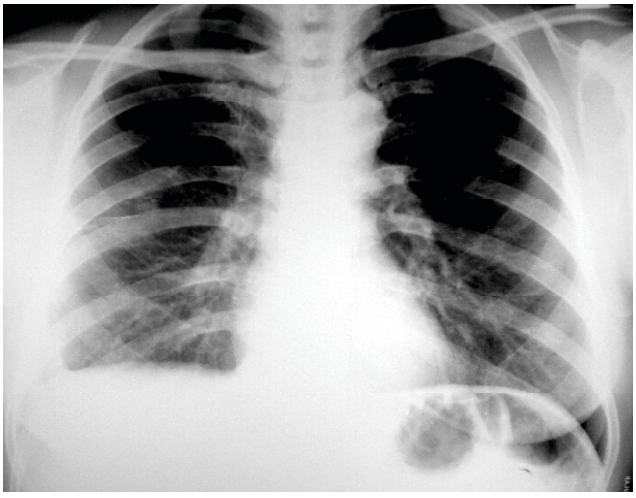

Figure 4 **CXR before the discharge from our Clinic: complete resolution of the aforementioned hemopneumothorax.**

DISCUSSION

In people under 40 and children under 15, traumatic injuries are the leading cause of death. Chest injuries account for 25% of all deaths caused by trauma and are the second leading cause of death (8,9). According to World Health Organization (WHO) data, 15 million people are injured in traffic accidents in the world annually, among which 700.000 die as a result of their injuries (1,8,9). Daily, 50.000 people are injured in traffic accidents, among which more than 820 die, i.e. every second in the world one person is injured, and every 5 seconds one person dies (10,11).

Blunt chest injury is almost exclusively caused by a rapid deceleration during motor vehicle collisions. In isolated chest injuries, hemothorax exists in 35%, pneumothorax in 35%, while 5% of patients may have a traumatic aortic dissection, and 15% have a blunt heart injury.

Surgical intervention in blunt trauma is not common, i.e. it is performed in 8% of cases (12). Most patients are treated with supportive measures and possibly chest tube placement. Careful and continuous observation of patients with a chest injury is as important as the first assessment.

Isolated injuries of the large thoracic veins are extremely rare and are mostly associated with other large vascular elements of the chest (13). Thoracic duct injuries most often occur with thoracic spine injuries. No signs or symptoms are specific to this injury. The diagnosis is confirmed when the chylous content starts to pour via the chest tube (chylothorax).

CONCLUSION

Patients who arrive at the ED in a stable condition can expect a full recovery. The standard of chest trauma treatment is effective cardiopulmonary resuscitation followed by early detection and treatment of life-threatening injuries. Based on a patient's medical history, clinical examination, laboratory findings, and CXR, in more than 80% of cases, the type and severity of an isolated chest injury can be assessed, and the necessary procedures can be performed in the majority of cases. In a properly selected group of patients, emergency thoracotomy is a life-saving intervention.

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Unusual case of acalculous cholecystitis in pediatric age - our experience

Neobičan slučaj akalkuloznog holecistitisa u dječjem dobu - naše iskustvo

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ABSTRACT

Introduction: acute cholecystitis is a common disease in adults but relatively rare in children. It is characterized by inflammation of the gallbladder, most commonly caused by gallstones or bile sludge. Acalculous cholecystitis, which occurs without the presence of stones, is a more common form in children and is often associated with systemic or critical illnesses. Case Report: we present the case of a six-year-old girl who presented with a twenty-five-day history of fever, malaise, abdominal pain, and jaundice. Laboratory findings showed leukocytosis and elevated liver enzymes, while abdominal ultrasound revealed gallbladder distension without the presence of stones. A diagnosis of acute acalculous cholecystitis was made. The patient was admitted to the hospital and started on antibiotic therapy and supportive care. During hospitalization, she developed a rash and episodes of elevated temperature. After a multidisciplinary consultation, the therapy was adjusted, and the patient was discharged home with recommendations for follow-up. At the follow-up appointment, inflammatory markers and bilirubin levels had returned to normal ranges. Conclusion: this case emphasizes the importance of continuous monitoring of patients with systemic symptoms and using imaging methods to assess disease progression. Further investigation is necessary to precisely determine the cause of the systemic inflammatory response in such cases.

Keywords: gallbladder, gallbladder infection, diagnosis of cholecystitis, treatment of acute cholecystitis

SAŽETAK

Uvod: akutni holecistitis je česta bolest kod odraslih, ali relativno rijetka kod djece. Karakterizira je upala žučne kese, najčešće uzrokovana žučnim kamencima ili muljem žuči. Akalkulozni holecistitis, koji se javlja bez prisutnosti kamenaca, češći je oblik kod djece i često je povezan sa sistemskim ili kritičnim bolestima. Prikaz slučaja: predstavljamo slučaj šestogodišnje djevojčice koja se javila sa 25-dnevnom groznicom, malaksalošću, bolovima u stomaku i žuticom. Laboratorijski nalazi pokazali su leukocitozu i povišene enzime jetre, dok je ultrazvuk abdomena otkrio distenziju žučne kese bez prisutnosti kamenaca. Postavljena je dijagnoza akutnog akalkuloznog holecistitisa. Pacijentica je primljena u bolnicu i započeta je antibiotska terapija i uz ostale suportivne mjere. Tokom hospitalizacije, razvila je osip i epizode povišene temperature. Nakon multidisciplinarnog konzilijuma, terapija je prilagođena, i pacijentica je otpuštena kući s preporukama za praćenje. Na kontrolnom pregledu, markeri upale i vrijednosti bilirubina bile su se vratile u normalne vrijednosti. Zaključak: ovaj slučaj naglašava važnost kontinuiranog praćenja pacijenata sa sistemskim simptomima i korištenje slikovnih metoda za procjenu napredovanja bolesti. Daljnje istraživanje je potrebno kako bi se precizno odredio uzrok sistemskog inflamatornog odgovora u ovakvim slučajevima.

Ključne riječi: žučni mjehur, infekcija žučnog mjehura, simptomi kolecistitisa, akutni akalkulozni holecistitis

INTRODUCTION

Acute cholecystitis is a common disease in adults, but it is relatively rare in children. It is characterized by inflammation of the gallbladder, most commonly caused by gallstones or bile sludge. Acalculous cholecystitis is rare in children but it is the most common type of cholecystitis in this age group (1). It is usually associated with an underlying systemic or critical illness that led to its development, such as trauma, burns, sepsis, or prolonged hospitalization. The absence of gallstones in acalculous cholecystitis makes diagnosis more difficult, requiring a high degree of suspicion and the use of multiple diagnostic modalities. The pathophysiology of acalculous cholecystitis in pediatric patients is multifactorial and not fully understood. It is thought to be due to a combination of impaired gallbladder motility, ischemia, biliary obstruction, and altered immune response. Underlying systemic disease or critical

illness can trigger these mechanisms, leading to inflammation and subsequent complications (2). Pathogens include streptococci (groups A and B), gram-negative bacteria, especially salmonella and leptospira interrogans and several viral infections (hepatitis A virus, Epstein-Barr virus [EB], and cytomegalovirus). Parasitic infections with roundworms or giardia may occur. Acalculous cholecystitis may be associated with abdominal trauma or burns or serious systemic diseases such as leukemia, end-stage liver disease, and systemic vasculitis (3). Due to its varied clinical presentation, pediatric acalculous cholecystitis can be mistaken for other intra-abdominal pathologies. Abdominal pain, fever, vomiting, anorexia, and right upper quadrant tenderness are typical symptoms. Since these symptoms are non-specific, an accurate diagnosis requires a thorough clinical assessment and the right diagnostic investigations. Abdominal ultrasonography (US), which is a necessary component of AAC diagnosis, can disclose the following usual findings and diagnostic standards: Gallbladder distension, pericholecystic fluid, mucosal membrane sludge, increased gallbladder wall thickness (>3.5 mm), one or more of these. The diagnosis of AAC in children is typically supported by the presence of at least two of these US criteria as well as the absence of gallstones (4). Acute cholecystitis in children presents particular challenges in diagnosis and management due to its atypical presentation and the limited experience of healthcare providers in managing this disease in children. AAC during primary EBV infection appears to be a more common pathology than previously suspected. Its relatively mild nature and the lack of laboratory abnormalities mean that ultrasonographic examination is required for diagnosis. This might explain why the prevalence in children is underestimated (5).

AIM

This case report aims to describe a rare instance of pediatric acute acalculous cholecystitis (AAC) in a 6-year-old patient, detailing the clinical presentation, diagnostic process, management, and outcomes. The objective is to highlight the challenges in diagnosing and treating AAC in children and to emphasize the importance of a multidisciplinary approach in managing this condition.

CASE REPORT

A 6-year-old female patient was presented to the emergency department with a twenty-five-day history of fever, malaise, abdominal pain, and icterus. In the beginning, she had symptoms of a common cold: fever, coryza, and cough. A symptomatic treatment regimen was suggested by her physician. On the day of the exam in the emergency department, her mother noted that her skin appeared yellow and her sclera. The stool appeared to be white and her urine was dark. From the left ear, yellow secretion was noted. The patient had no past medical history and was not taking any medications. On physical examination, the patient appeared uncomfortable and had no palpatory tenderness but the exam revealed hepatosplenomegaly verified on ultrasound. Laboratory investigations revealed leukocytosis (white blood cell count: 20.0), elevated liver enzymes AST 383 U/L, ALT 227 U/L, GGT 658 U/L, LDH 1531 U/L, total bilirubin 79.9 umol/L, with a high conjugated fraction of bilirubin 38 umol/L, unconjugated 12.7 umol/L elevated C-reactive protein levels (CRP 33.1 mg/L) amylase in serum was normal. An abdominal ultrasound was performed, which showed gallbladder distension, wall thickening, pericholecystic fluid, and no presence of gallstones. An enlarged spleen was noted, and there was no dilatation of intra- or extra-hepatic ducts. These findings were consistent with a diagnosis of pediatric acute acalculous cholecystitis.

Figure 1 **Rash that developed on the trunk.**

The patient was admitted to the Pediatric Gastroenterology Department of the CCUS for further management. Nothing by mouth (NPO) status was initiated, and intravenous fluids were administered to maintain hydration. Empiric broad-spectrum agents, such as ceftriaxone and metronidazole were started to cover potential bacterial causes. The patient's pain was managed with intravenous analgesics, and ursodeoxycholic acid was started. The Pediatric Surgery Department was consulted and a conclusion was made to continue conservative management. An ENT specialist was consulted, and a diagnosis of acute otitis media was made. On the second day of hospitalization, a diffuse macular rash was noted which appeared to be most prominent on the face, trunk, palms, and soles. Iching was present, and slight swelling on the cheeks. 5% albumin was started in an I.V. solution for four hours, with furosemide, antihistamine, and methylprednisolone. The rash subsided but reappeared again on the third day of hospitalization. On the fourth day of hospitalization, changes in the skin spread.

Figure 2 Rash spreads to extremities.

In the morning, an abdominal ultrasound was performed on an empty stomach, as well as the chest X-ray. The chest X-ray findings were normal. Follow-up ultrasound revealed thet the gallbladder was appropriately located, moderately distended with bile content, with wall thickness of up to 3mm, and visible pronounced pericholecystic reaction and edema measuring up to 9mm, along with a linear fluid zone in the gallbladder bed. Intrahepatic bile ducts and common bile ducts were not dilated. The pancreas was in an appropriate position, with the head slightly larger than normal, measuring 22.5mm in the anteroposterior (AP) diameter (the reference range for maximum size in this age is up to 20mm), and the body and tail were of regular size. The parenchyma appeared normal with mild echogenicity, without isolated focal lesions. A significant amount of free fluid was visible in the pelvic area. The abdominal CT findings indicated hepatosplenomegaly, pronounced edema of the gallbladder wall, and free intraabdominal fluid. On MR sequences, hepatosplenomegaly was observed. The craniocaudal diameter of the right liver lobe measured 178.9mm, and it had homogeneous parenchyma without areas of altered signal intensity. The spleen measures 126.7mm longitudinally, with homogeneous parenchyma. The gallbladder was moderately distended, showing pronounced pericholecystic edema throughout its circumference, with a diameter of approximately 8.4mm, as well as periportal edema. The intrahepatic bile ducts and common bile duct were not dilated, and the common bile duct was traced to the intrapancreatic segment. The pancreas was in an appropriate position, shape, and size, with a homogeneous appearance. The pancreatic duct was not dilated. There was a minimal amount of free fluid in the Morrison's pouch and peri splenic region. Haemocultures were taken in febrile spikes and came back negative. Immunoglobulin values were normal, EBV ELISA IgG and IgM were also negative as well as serology for mycoplasma pneumoniae and leptospira IgM was negative but IgG positive. Herpes simplex mono test IgM was in the retesting zone, and IgG was positive. Stool cultures were also negative as well as hepatitis markers. Direct coombs test was positive and Ferritine 4890 ng/ml, IL 6 26 pg/ml, NT-proBNP 121 pg/ml. The infectious disease specialist, pediatric surgeon, and immunologist are consulted. The therapy is modified, and instead of ceftriaxone, amoxicillin-clavulanic acid I.V. is introduced. A 5% albumin with furosemide is continued, and methylprednisolone with antipyretic, hepatoprotective, and antihistamine medications are prescribed. Additional microbiological and immunological tests are performed according to the recommendations of the infectious disease specialist and immunologist, and an echocardiogram is planned and carried out. Fluid balance is continuously monitored, also treatment with 5% albumin and diuretics was continued. An interdisciplinary consultation was held, involving a pediatric gastroenterologist, hematologist, immunologist, pediatric surgeon, infectious disease specialist, and radiologist. Based on the consultation's recommendation, imipenem was added to antibiotic therapy. A follow-up abdominal ultrasound and abdominal CT scan were performed, with monitoring by the pediatric surgeon, adequate parenteral rehydration, and vitamin support.

Regular check-ups and monitoring by the cardiologist and infectious disease specialist continued. The patient was in a relatively stable and satisfactory general condition. She continued to present with sub icteric skin coloration but could perform daily activities without any difficulties. She displayed a cheerful demeanor, except when experiencing episodes of elevated body temperature. The child intermittently developed a rash accompanied by itching, resembling urticaria. Additionally, there were occasional spikes in body temperature. The abdomen appeared painless, tense, and positioned above the level of the chest. Both bowel movements and urine output were normal. The episodes of elevated temperature became less frequent and lower. In the later stages of the disease, there was a decline in transaminase levels, as well as reductions in LDH and CRP values. The ferritin level also decreased from 5000 to the measurement of 900.

Figure 3 CT scan showing hepatomegaly with a homogenous parenchyma and no visible focal lesions. The gallbladder is correctly positioned, moderately contracted, with a markedly edematous wall measuring 3mm in diameter. Prominent intrahepatic bile ducts and periportal edema are also observed. The common bile duct is not dilated

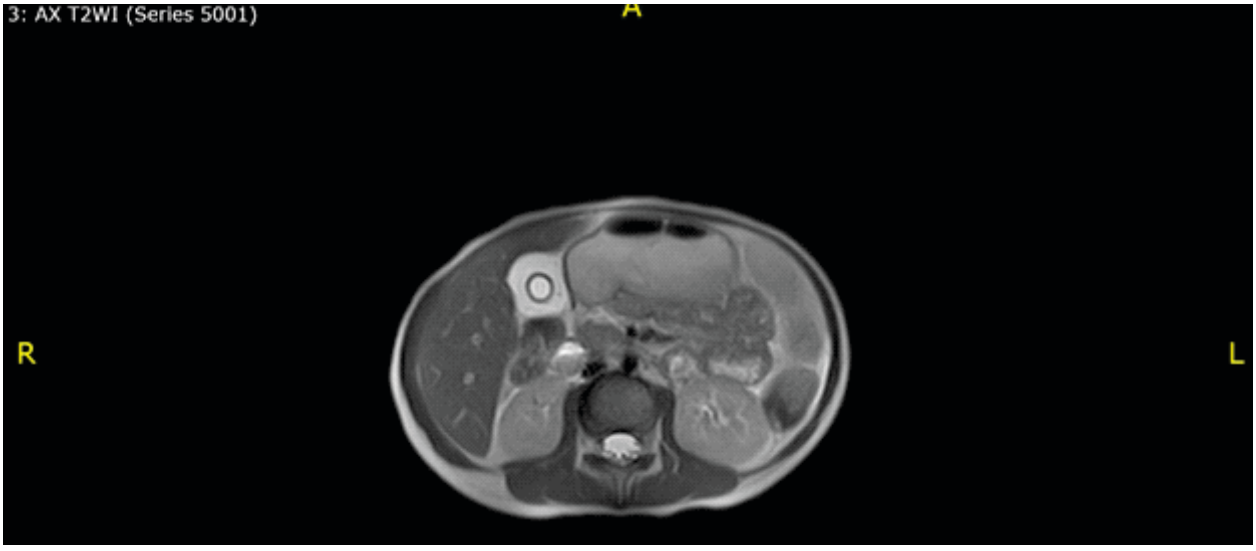

Figure 4 MR sequences showing hepatosplenomegaly. The right liver lobe measures 178.9 mm with homogenous parenchyma. The spleen is 126.7 mm with homogenous parenchyma. The gallbladder is moderately distended with pronounced pericholecystic edema (8.4 mm) and periportal edema. Intrahepatic bile ducts and the common bile duct are not dilated

The presence of intermittent episodes of elevated body temperature, which persisted regardless of antibiotic treatment began to subside, and the rash disappeared. On 29 May, the 17th day of hospitalization, the patient remained afebrile for 36 consecutive hours. Triple antibiotic therapy was received from 19 May, including metronidazole for a total of 15 days, amoxicillin clavulanic acid for 11 days, and imipenem for a total of 10 days. A follow-up ultrasound was made and revealed regression compared to the previous ultrasound examination. Splenomegaly without focal lesions was observed. A lymph node in the hepatic port measuring up to 17.6mm was noted, as well as three lymph nodes in the splenic hilum area with the largest diameter measuring up to 13.5mm. The antibiotic therapy was discontinued based on improvement in clinical, laboratory, and radiological findings. Supportive and diuretic therapy was continued according to the cardiologist's recommendation, with fluid balance monitored throughout the day. The patient was discharged home with recommendations for symptomatic therapy and follow-up. At the two-week follow-up appointment, normal values of inflammatory markers and bilirubin were noted, with slightly elevated transaminase levels above the upper reference range. The ultrasound examination showed normal findings of the liver and gallbladder, with the spleen at the upper limit of the reference range in terms of size and no presence of free fluid in the abdomen. The follow-up electrocardiogram (EKG) and echocardiogram of the heart were normal.

DISCUSSION

Children's acute cholecystitis is a rare but potentially dangerous condition. Acute acalculous cholecystitis (AAC) poses a significant danger, especially in the context of severe illness or post-major surgical procedures. The incidence of AAC is evidently increasing, likely due to heightened vigilance and advancements in diagnostic imaging, leading to improved case detection. The mortality rate, approximately 30%, remains high due to the complexities of diagnosis, the critical condition of affected patients, and the rapid progression of the disease, characterized by a substantial occurrence of gangrene (over 50%) and perforation (over 10%). These combined factors underscore the grave risks associated with AAC (6). This case report describes a rare instance of pediatric acute acalculous cholecystitis and highlights the clinical presentation, diagnostic testing, treatment, and outcomes. This report describes a case characterized by prominent systemic symptoms, including rash and episodic fever, with an insidious onset of the disease. Based on the clinical signs and the outcomes of imaging tests like an ultrasound or CT scan, acute cholecystitis was identified. It is commonly acknowledged that AAC may be linked to serious disease or infection. Ternberg JL, et al. reported that a history of illness that preceded the cholecystitis was elicited in 45 cases (60%), which they used to review 74 children with AAC (67 cases from the literature and 7 of their own) (7).

The two conditions most usually linked to AAC are diarrhea and upper respiratory tract infection (4,7,8). A total of 131 kids with AAC were retrospectively analyzed by Yi DY, et al. In 38% of all children, systemic infectious illnesses such as Epstein-Barr virus infection were shown to be the most frequent cause of AAC (1). Simões AS, et al. describe a case of enteroviral AAC (9). Since delaying treatment can have negative effects like gangrene, perforation, or the emergence of an abscess, early diagnosis is crucial so the patient was admitted to the hospital for further evaluation and treatment. The treatment for pediatric acute cholecystitis typically involves antibiotics to fight infection as first-line treatment and surgery to remove the gallbladder if indicated. However, in some cases, non-surgical treatments such as percutaneous cholecystostomy or endoscopic retrograde cholangiopancreatography (ERCP) may be considered. Laboratory indicators such as ferritin, IL-6, and NT-ProBNP, along with a cardiac ultrasound examination, suggested a systemic inflammatory response to an unidentified infectious agent. Regular ultrasound monitoring was performed to assess the emergence of potential complications and disease progression that might require surgical intervention in our patient. Reviewing the literature showed that the majority of pediatric AAC cases were linked to viral infections, including HAV and EBV, which led to lower complication rates. Supportive care, which included appropriate rehydration, a short cessation of oral feeding, and analgesic therapy, was adequate in these patients. Nevertheless, despite the viral etiology, wide-spectrum antibiotic therapy has been used in almost all instances (10).

The factors associated with AAC mortality were anemia, thrombocytopenia, gallbladder sludge, hepatitis, and sepsis plus hepatitis. These predictors are likely to help clinicians identify patients who are at a high risk of poor prognoses and make appropriate clinical decisions (10). In adolescents and pediatric age groups, a high clinical suspicion of gallbladder perforation is warranted when dealing with acute abdomen, especially when adjunct investigations are not conclusive. Prompt diagnosis and management are crucial in decreasing mortality rates. Radiological investigations may assist in making a presumptive diagnosis, but the definitive diagnosis in most cases is based on intraoperative examination. Adequate follow-up and exploration of the possible causative factors and coexisting etiologies is necessary (12).

The case, exemplifying an unreported manifestation of acute acalculous cholecystitis in a child with systemic juvenile idiopathic arthritis, was presented by AlMutairi AM, et al. (13). This instance serves as a notable illustration within the realm of autoimmune disorders, suggesting a potential link between acute acalculous cholecystitis and systemic juvenile idiopathic arthritis, with implications for therapeutic intervention strategies.

Aguilera-Alonso D, et al. also documented an unusual case illustrating the occurrence of acute acalculous cholecystitis in a pediatric patient with Plasmodium falciparum infection. The patient, a 5-year-old girl from Equatorial Guinea was presented with severe malaria alongside acute kidney injury, thrombocytopenia, and acute acalculous cholecystitis. Treatment encompassed intravenous quinine and clindamycin, complemented by cefotaxime and metronidazole, resulting in complete resolution sans surgical intervention (14).

CONCLUSION

This case report emphasizes the significance of constantly monitoring patients with systemic symptoms and using imaging methods, such as ultrasound, to evaluate illness development and spot possible adverse effects. To pinpoint the particular cause of the systemic inflammatory response in this case, further investigation is necessary. Based on the disease progression, associated symptoms, and review of the available literature, one of the possibilities is that a viral illness could have been the cause of acute acalculous cholecystitis (AAC) and a systemic inflammatory response, ultimately leading to spontaneous recovery with a conservative treatment regimen. However, in almost all cases, wide-spectrum antibiotic therapy has been implemented despite the viral etiology. It is not always possible to immediately achieve a conclusive etiologic diagnosis, and that may be the reason why antibiotics are often or initially used. Therefore, in the management of pediatric AAC, pediatricians should be aware that many cases have a good prognosis and are often due to viral illnesses; however, if or until the viral nature is not completely evident, it is still recommended to start an appropriate antibiotic therapy.

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Prored: 1,5: lijeva margina: 2,5 cm; desna margina: 2,5 cm; gornja i donja margina: 2,5 cm.
Grafikone, tabele, slike i crteže unijeti/staviti u tekst rada, tamo gdje im je mjesto, bez obzira u kojem programu su rađene. Cijeli rad obavezno napisati na engleskom jeziku, a sažetak i naslov još i na našem jeziku.
Rad se dostavlja na CD-u, i/ili e-mailom, uz dva štampana primjerka (ako je moguće). CD se ne vraća.

RAD SADRŽI:

NASLOV RADA NA ENGLESKOM JEZIKU
NASLOV RADA NA NAŠEM JEZIKU

Ime i prezime autora i koautora

Naziv i puna adresa institucije u kojoj je autor-koautor/i zaposlen/i (jednako za sve autore), na engleskom jeziku, te na kraju rada navedena adresa kontakt-autora.

Sažetak na našem jeziku, kao i na engleskom - max. 200–250 riječi, s najznačajnijim činjenicama i podatcima iz kojih se može dobiti uvid u kompletan rad.
Ključne riječi - Key words, na našem jeziku i na engleskom, ukupno do pet riječi, navode se ispod Sažetka, odnosno Abstracta.

SADRŽAJ

Sadržaj rada mora biti sistematično i strukturno pripremljen i podijeljen u poglavlja i to:

- **UVOD**
- **MATERIJAL I METODE**
- **REZULTATI**
- **DISKUSIJA**
- **ZAKLJUČAK**
- **LITERATURA**

UVOD

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

MATERIJAL I METODE

Potrebno je da sadrži opis originalnih ili modifikaciju poznatih metoda. Ukoliko se radi o ranije opisanoj metodi dovoljno je dati reference u literaturi. U kliničko-epidemiološkim studijama opisuju se: uzorak, protokol i tip kliničkog istraživanja, mjesto i vrijeme istraživanja. Potrebno je opisati glavne karakteristike istraživanja (npr. randomizacija, dvostruko slijepi pokus, unakrsno testiranje, testiranje s placebom itd.), standardne vrijednosti za testove, vremenski odnos (prospektivna, retrospektivna studija), izbor i broj ispitanika – kriterije za uključivanje i isključivanje u istraživanje.

REZULTATI

Navode se glavni rezultati istraživanja i nivo njihove statističke značajnosti. Rezultati se prikazuju tabelarno, grafički, slikom i direktno se unose u tekst gdje im je mjesto, s rednim brojem i konciznim naslovom. Tabela treba imati najmanje dva stupca s obrazloženjem što prikazuje; slika čista i kontrastna, a grafikon jasan, s vidljivim tekstom i obrazloženjem.

DISKUSIJA

Piše se koncizno i odnosi se prvenstveno na vlastite rezultate, a potom se nastavlja upoređivanje vlastitih rezultata s rezultatima drugih autora, pri čemu se citiranje literature navodi po važećim Vankuverskim pravilima. Diskusija se završava potvrdom zadatog cilja ili hipoteze, odnosno njihovim negiranjem.

ZAKLJUČAK

Treba da bude kratak, da sadrži najbitnije činjenice do kojih se došlo u radu tokom istraživanja i njihovu eventualnu kliničku primjenu, kao i potrebne dodatne studije za potpuniju aplikaciju. Obavezno navesti i afirmativne i negirajuće zaključke.

LITERATURA - Upute za citiranje - pisanje literature

Literatura se obavezno citira po **Vankuverskim pravilima**.

Svaku tvrdnju, saznanje ili misao treba potvrditi referencom. Reference u tekstu treba označiti po redoslijedu unošenja arapskim brojevima u zagradi na kraju rečenice. Ukoliko se kasnije u tekstu pozivamo na istu referencu, navodimo broj koji je referenca dobila prilikom prvog unošenja/pominjanja u tekstu. Literatura se popisuje na kraju rada, rednim brojevima pod kojim su reference unesene u tekst (ulazni broj reference), a naslov časopisa se skraćuje po pravilima koje određuje Index Medicus. Ukoliko je citirani rad napisalo više autora, navodi se prvih šest i doda "et al.".

Vrlo je važno ispravno oblikovati reference prema uputama koje se mogu preuzeti na adresama National Library of Medicine Citing Medicine http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=citmed.TOC&depth=2 , ili International Committee of Medical Journal Editors Uniform Requirements for Manuscripts Submitted to Biomedical Journals:

Sample References http://www.nlm.nih.gov/bsd/uniform_requirements.html.