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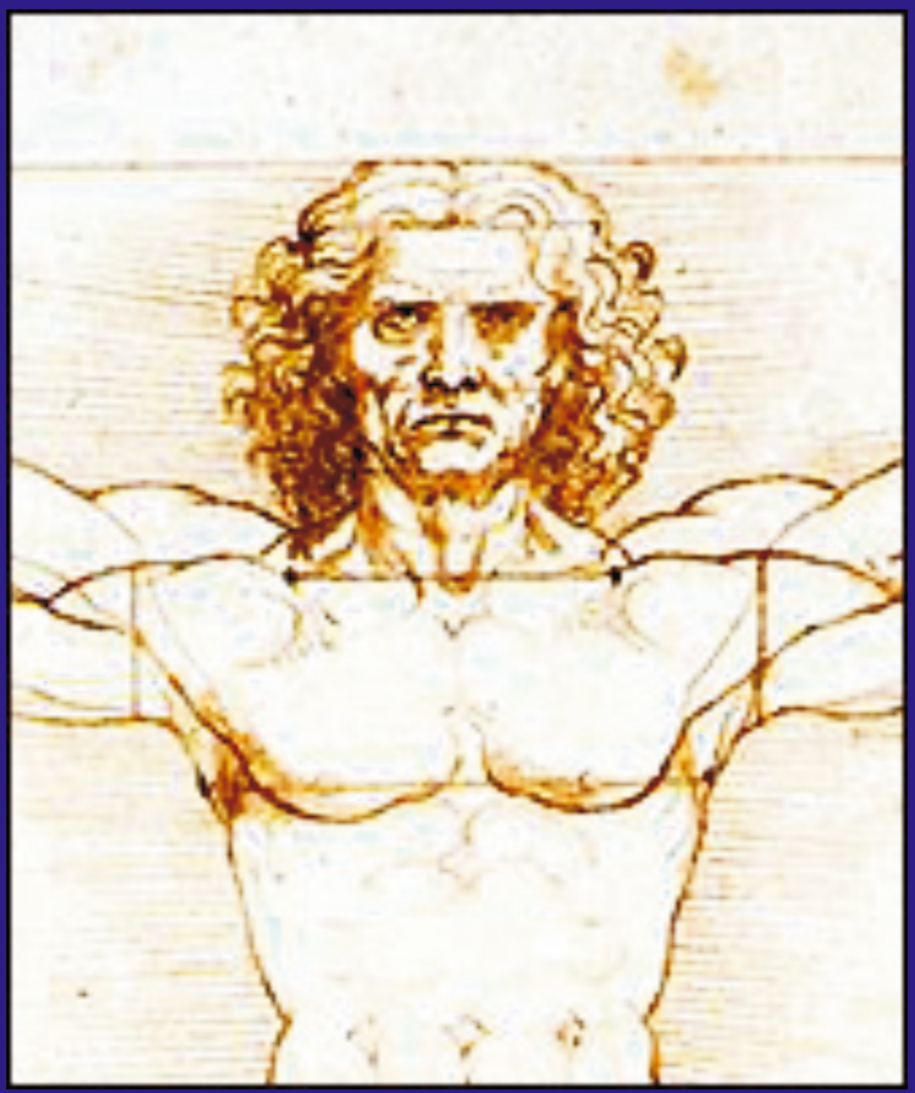

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GRAPHOMOTOR SKILLS IN CHILDREN WITH LANGUAGE DEFICITS IN PRIMARY SCHOOL AGE-FORMATION AND DEVELOPMENT

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Abstract: **Introduction:** The formation and the development of graphomotor skills in children with language deficits in primary school age is a difficult and long process, and its disturbance leads to serious problems not only with the process of literation but also disrupt the purely academical learning.

Purpose: The aim of our study is to show the level of formation of graphomotor skills in children with language deficits in primary school age before and after the implementation of a system of therapeutic techniques, approaches and methods based on both the world's and Bulgarian's experience in the area of therapy of disturbance in graphomotor skills.

Material and Method: The study encompasses a total of 40 children in primary school, aged 7-8, who were subjected to logopedic therapy aimed to overcome difficulties in graphomotor skills. It was conducted for a period of 5 years. The therapy was done either individually or in groups of 2 children.

Results: The data from test 1 and test 2 show development and maturation of structures in the left hemisphere: frontoparietal and basal temporal, responsible for functioning of the spatial orientation and ideomotor apraxia. For this reason the 7-8 years age group can be considered sensible for development of graphomotor skills as a component of formation of the written form of language and is especially suitable for intensive logopedic therapy aimed for its formation.

Conclusion: The implemented therapeutic techniques during the logopedic therapy are aimed not only for establishing the occulo-spacial orientation but also for formation and development of language competence, which are directly linked to formation of the written form of language.

Key words: graphomotor skills, frontopartietal structures, ideomotor apraxia.

INTRODUCTION

The formation and development of graphomotor skills in children with language deficits in primary school age is a hard and a long process and its disturbance leads to serious problems not only with the process of literation but also disrupt the purely academical learning. In this particular age the establishment of literacy, as one of the important processes in human life, starts. This process is dependent on the normal development of senses (vision, hearing and touch), intellect and social environment.

The scientific work in this area show that the formation of the written skills is disrupted by disturbance in the visual- motor coordination in children and school pupils as a result of immaturity or false formation of some of the higher cortical functions which are responsible for development of the graphomotor skills and habits. Their disturbed formation leads to aberration in orientation in space and time, low motivation and insufficient self-control, expressed in difficulty in the process of formation of graphomotor skills and mastering the written form of language (1-4).

From psycho- physiological view and based on neuro-psychological model in the process of masteringwritten language three features take part: visual, kinetic and auditory. Historically speaking the leading role has the discovered by Exner "area of writing" in the posterior part of the second frontal gyrus, the so called premotor field or Brodmann area 8 (1-4).

Purpose of our study is to show the level of formation of graphomotor skills in children with language deficits in primary school age (7-8 years) before and after the implementation of a system of therapeutic techniques, approaches and methods based on both the world's and Bulgarian's experience in the area of therapy of disturbance in graphomotor skills.

MATERIAL AND METHODS

The study encompasses a total of 40 children in primary school- aged 7-8, who were subjected to logopedic therapy aimed to overcome difficulties in graphomotor skills. It was conducted for a period of 5 years (2012-2017). The implemented therapy was done either individually or in groups of 2 children, in speech therapy center in Varna, Bulgaria.Òhå research has Approval of local Ethical committee and adhered to the principles of the Declaration of Helsinki.

The children, part of this study who were subjected to logopedic therapy, after initial evaluation by a medical board were diagnosed with the following disorders according to ICD-10: F80.9 "Developmental disorder of speech and language, unspecified", F81"Specific reading disorder", F81.3 "Mixed disorder of scholastic skills", F81.8 "Other developmental disorders of scholastic skills. Developmental expressive writing disorder", F81.9 "Developmental disorder of scholastic skills, unspecified" (5).

The number of children in this study was 40, divided into males M - 19 (47.5 %) and females F - 21 (52.5 %) (Table 1).

Children from all age groups were evaluated before the initiation of the logopedic therapy with the following tests:

"Head test" (special postural praxis): Aimed for testing ideomotor praxis for new movements. In our study we used a version of the test with 13 movements.

"Test for evaluating written language in children with language deficits in primary school age": The test consists of dictation. The texts used in this experiment were consistent with the age group of the children as well as the National school standards for the particular age group.

Data from the dictation were written in a protocol developed by Yakimova (6) and for a certain number of mistakes an additional evaluation scale was added. The types of mistakes noted in the protocol were grouped in three levels: grapheme, morpheme as well as optically, phonetic-phonematic mistakes and misspellings. The work with the students continued for one year and in the end of the period they are being evaluated again with the described test for the particular age group.

For summarizing the results before initiating logopedic therapy and in the end of the school year the following statistical tools for analysis were used:

Descriptive statistic - measurements of central trend, row width, error rate.

Correlation analysis - relation of data.

T-test - mean value comparison in different conditions of the dependent variable.

RESULTS

Descriptive statistics of the compared methods in the studied group: **Test sample 1 "Head Test"** (Table 2).

Identification of correlation between entry and exit "Head- test" results

The statistical analysis of the compared methods in the 7-8 years age group confirms the described results and shows a significant increase of the total result of both parts of the test after implementation of logopedic therapy.

Significant increase of correctly done tasks from both sides of the test in our study can be explained by the neuropsychological basis of the processes related to increasing the efficacy of selective visual attention according to "response time" index typical for age 7-8 year olds.

Table 1. *Distribution of the number of children during the years /2012-2017/ of the study*

Group	2012/2013	2013/2014	2014/2015	2015/2016	2016/2017	Total
7–8 y.	n = 8	n = 10	n = 7	n = 9	n = 6	n = 40

Table 2. *Correlation between the entry and exit levels using "HEAD TEST" for the children subject to the study*

Methods	Mean	Total	Standard deviation	Standard error of the mean
Head 1entry	7.1375	40	0.86963	0.13750
Head 1exit	7.5250	40	0.68827	0.10883
Head 1.2. entry	5.9375	40	0.64239	0.10157
Head 1.2. exit	6.5125	40	0.59364	0.09386
Headtotal entry	13.075	40	0.68827	0.10883
Headtotal exit	14.0375	40	0.77944	0.12324

The results gathered after implementation of T- test for comparison of the mean value in different conditions of the dependent variable for the indicators in "Head test", represented in Table 3 after comparison, show significant difference in the two parts of the test study.

Those differences can be contributed to the fact that in the second part of the test (upon instruction) the children subjected to our study, 7-8 year olds have better level of formation of graphomotor skills.

Test sample 2 - Dictation

Table 4 represents percentage distribution of the types of mistakes on the different levels according to incidence rate at entry level. The results can be interpreted from the psychophysiological and neuropsychological model of initiation of the act of writing.

Underdevelopment of the complex manifestation of the visual-motor coordination in children with language deficits leads to difficulties in the already mentioned linguistic level.

Column "Others" encompasses a sum of punctuation mistakes and misspellings, poor level of literacy, lack of knowledge on graphemes. The percentage is relatively uniform in all linguistic levels.

Table 5 represents the percentage distribution of the types of mistakes on the different levels according to incidence rate at exit level after one year of logopedic therapy:

The results at exit level of the test study show positive influence of the therapeutic methods that we used. The difference of almost 20% drop of the "rearrangements and merging/splitting on lexeme and syntaxeme level" shows that the age of 8 years in children with language deficits is crucial for the formation of normal language functions. It is important to point out also the drop of nearly 20% of phonetic and graphic replacements on phoneme, morpheme and lexeme levels.

Descriptive statistics of compared methods in Test 2 (Table 6).

Table 3. *Results when using a T-test to compare the mean values under different conditions of the dependent variable on the indicators of the "Head Test"*

Head test	Mean	Standard deviation	95% Confidence interval		t	total	Significance
			Lowest	Highest			
Entry 1- Exit 1	-.38750	.40012	-.51546	-.25954	-6.125	40	.000
Entry 1.2- Exit 1.2	-.57500	.52563	-.74310	-.40690	-6.919	40	.000
EntryTotal- ExitTotal	-6.51250	.59364	-6.70235	-6.32265	-9.384	40	.000

Table 4. *Distribution of the types of errors by individual levels by frequency in "Test sample 2 - auditory dictation", entry level - before starting therapy*

Types of mistakes	Errors	Phonetic replacements	Graphic replacements	Additions	Repetitions	Rearrangements	Merging / Splitting	Others
Phoneme level	3.2%	54.5%	26.8%	6%	-	-	-	9.5%
Morpheme level	3%	29.8%	20.2%	5.8%	3.8%	15.9%	11.5%	10%
Lexeme level	2.5%	3.7%	14.7%	4.2%	2%	22.7%	39.4%	10.8%
Syntaxeme level	1%	3.9%	13.6%	3.5%	5.3%	22%	40.6%	10.1%

Table 5. *Distribution of the types of errors by individual levels by frequency in "Test sample – 2 – auditory dictation", exit level – after one year of logopedic (speech) therapy*

Types of mistakes	Errors	Phonetic replacements	Graphic replacements	Additions	Repetitions	Rearrangements	Merging / Splitting	Others
Phoneme level	3.2%	54.5%	26.8%	6%	-	-	-	9.5%
Morpheme level	3%	29.8%	20.2%	5.8%	3.8%	15.9%	11.5%	10%
Lexeme level	2.5%	3.7%	14.7%	4.2%	2%	22.7%	39.4%	10.8%
Syntaxeme level	1%	3.9%	13.6%	3.5%	5.3%	22%	40.6%	10,1%

Table 6. *Comparison of the results in "Sample test 2 – auditory dictation" – entry and exit levels*

Methods	Mean	Total	Standard deviation	Standard error of the mean
Test 2 entry	14.9750	40	3.60546	0.57007
Test 2 exit	19.5000	40	3.36650	0.53229

Table 7. *Results from "Test sample 2 – auditory dictation" using "T-test" entry and exit levels*

	Total	Correlation	Significance
Test 2 entry&Test 2 exit	40	0.390	0.013

Table 8. *Results from "Test sample 2 – auditory dictation" at entry and exit levels on the three indicators – the compared methods, correlation between entry and exit levels, comparison of the mean values*

Test 2	Mean	Standard deviation	95% Confidence interval		t	total	Significance
			Lowest	Highest			
EntryT2-ExitT2	-4.52500	3.85631	-5.75831	-3.29169	-7.421	40	0.000

Identification of relation between entry and exit levels (Table 7).

T –test for comparison of mean values in different conditions of the dependent variable according to the indicators in Test 2 (Table 8).

Also in the results of Test 2, showed in (Tables 6, 7, 8) significant correlations were marked at entry and exit levels and in the three indicators- compared methods, relations between entry and exit levels, comparison of the mean values indifferent conditions of the dependent variable of the indicators.

DISCUSSION

Results show that the group of 7-8 years old children with language deficits is the sensitive moment which marks the start of formation with higher rate and maturation of structures of the left hemisphere: frontoparietal and basal temporal, responsible for development of spatial orientation and the ideomotor praxis. Hence the implementation of intensive logopedic therapy aimed for strengthening and development of the affected components related to visual- motor organization is crucial for developing graphomotor skills and establishing and development of the written form of language.

Similar data has been published by Machinskaya et al (7). Other authors who study the visual gnosis within children also describe the age of 7-8 years as crucial for maturation of the executive control and increasing of the activity of structures, responsible for the ventral visual system.(8-12). Our results also confirm the increased active attention and maturation of the visual gnosis within children in that particular age group.

The origin and existence of phonetic replacements in certain linguistic level can be attributed to deficits of different origin of auditory perception and articulation disorders. The presence of high percentage of phonetic replacements in dictation as well as splitting in writing, seen within words constituted by a lot of consonants strongly inappropriate and hard to be articulately combined, are described by other authors (13, 14).

Clinical studies of Bulgarian children with language deficits show that they have difficulty with: 1) perceptive tasks for differentiating phonemes in accordance to given feature (voiced/voiceless, sibilant/rustling sonority); 2) tasks for phonetic analysis as segmentation of phonemic numbers in words (quantitative sound analysis); defining the place of a given sound in words (quality sound analysis); separation of the first/last sound of words; discriminating different phonemes in paired words, that differ only by one word (15, 16). Phonological deficit is often associated with deficits in verbal memory and sometimes with difficulty in processing of purely verbal information according to instruction.

According to the data in English literature serious deficit in the area of morphology is observed in children with specific language disorders (17-20). Even though they manage to master the grammatical morphemes in consistency similar to that of normal children, language deficit children show an atypical types of control on those morphemes in time of production (15).

We believe that implementation of intensive logopedic therapy aimed for establishment and development of the deficient components related to visual- motor organization in this particular age is very important for development of graphomotor skills and formation and development of the written form of language.

CONCLUSION

The results of the implemented test samples in the age group of 7-8 years show that in children with language deficits this age period is sensitive for developing structures in left hemisphere and its frontal lobes, which are responsible for development of visual- motor coordination but also for establishment of verbal praxis, speech formation and perception.

The implemented therapeutic techniques in the period of logopedic therapy are aimed not only for establishing visual- special orientation but also for formation and development of language competence which is related to developing the written form of language.

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Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

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Sažetak

GRAFOMOTORNE VEŠTINE DECE SA JEZIČKIM DEFICITOM U OSNOVNOŠKOLSKOM UZRASTU - FORMIRANJE I RAZVOJ

Spassova Kalinka

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Uvod: Formiranje grafomotornih veština kod dece sa jezičkim deficitom, u osnovnoj školi, je težak i dug proces, a njegovo narušavanje dovodi do ozbiljnih problema ne samo sa procesom opismenjavanja, već i do narušavanja akademskog usavršavanja.

Cilj: Cilj naše studije je da pokažemo stepen formiranja grafomotrnih veština kod dece sa jezičkim deficitom, u osnovnoškolskom uzrastu, pre i nakon implementacije sistema terapeutskih tehnika, pristupa i metoda baziranih na svetskom i bugarskom iskustvu na polju lečenja poremećaja grafomotornih veština.

Materijal i Metode: Studijom je obuhvaćeno ukupno 40 dece u osnovnoj školi, uzrasta 7-8 godina, koja su bila podvrgnuta logopedskoj terapiji u cilju prevazilaženja poteškoća sa grafomotornim veštinama. Sprovodila se tokom perioda od 5 godina. Terapija se sprovodila individualno ili u grupi sa dvoje dece.

Rezultati: Podaci sa testa 1 i testa 2 pokazuju razvoj i maturaciju struktura leve hemisfere mozga: frontoparijetalne i bazalno-temporalne, odgovornih za prostornu orjentaciju i idemotornu apraksiju. Iz tog razloga, grupa uzrasta 7-8 godina se može smatrati razumnom za razvoj grafomotornih veština kao komponente razvoja pisanog jezika i posebno je pogodna za intenzivnu logopedsku terapiju čiji je cilj njen razvoj.

Zaključak: Primenjene terapeutske tehnike tokom logopedske terapije nisu usmerene samo na uspostavljanje okulo-prostorne orijentacije, već i na formiranje i razvoj jezičke kompetencije, koje su direktno povezane sa formiranjem pisanog jezika.

Ključne reči: grafomotrne veštine, frontoparijetalne strukture, ideomotrna apraksija.

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Original article

ACUTE EFFECTS OF SYNTHETIC CANNABINOIDS ON VENTRICULAR REPOLARIZATION

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Abstract: **Objective:** The usage of synthetic cannabinoids (SCs) has increased both in Turkey and all worldwide. Here, we evaluate if SCs cause ventricular repolarization abnormalities using initial and after 12th-hour electrocardiograms in patients with acute intoxication of SCs. We examined changes in the QTc and cTp-e parameters to demonstrate ventricular repolarization effects of the usage of SCs.

Material and Methods: We used a prospective study design. Twenty patients were included who visited the emergency department, complaining of clouding of consciousness after using SCs. The QT, QTc and Tp-e intervals and several other electrocardiographic parameters were measured at baseline and 12 hours after the usage of SCs.

Results: The QRS duration was significantly decreased (102.1 ± 15.5 ms vs 95.0 ± 10.7 ms; p = 0.022). We noted a significant decrease in cQT measurements at the end of the 12th hour (426.6 ± 47.2 ms vs 390.4 ± 42.9 ms; p = 0.002). Similarly, the Tp-e and cTp-e values decreased significantly when SCs lost its acute effect (93.4 ± 21.1 ms vs 77.4 ± 21.0 ms; p = 0.014, 105.3 ± 28.5 ms vs 88.1 ± 21.5 ms; p = 0.01).

Conclusions: The usage of SCs affects ventricular repolarization heterogeneity based on QTc and Tp-e intervals.

Keywords: Synthetic cannabinoids, Bonzai, ventricular repolarization heterogeneity, adverse cardiovascular effects.

INTRODUCTION

The usage of synthetic cannabinoids (SCs) has increased both in Turkey and all over the world. Synthetic cannabinoids are psychoactive substances showing similar agonistic effects on SC receptors such as Δ9-tetrahydrocannabinole (Δ9-THC), which is the active metabolite of cannabis (1). It has become more attractive than natural cannabinoid (i.e., marijuana) because they are easily accessible, cheap and cannot be detected in blood using a routine toxicological examination. Synthetic cannabinoids are widely used and sold in many countries around the world. It is not accurate to say that each of these brands is restricted to the region indicated. Synthetic cannabinoids can be sold as 'Spice' in Europe, 'K2' in the United States or 'Bonzai' or 'Jamaica' in Turkey (2). More than 140 products have been defined that include SCs (3). All of these products have different amounts and types of SCs and may include psychoactive materials except SCs or substances expressing adrenergic effects. The potency and the short half-life of SCs results in powerful effects. However, the heterogeneous structure of SCs results indifferent clinical effects (4, 5). Hoyte et al. (6) reported that the well-defined side effects of SCs include nausea (in 10% of cases), vomiting (15.3%), tachycardia (40.0%), bradycardia (1.3%), hypertension (8.1%), chest pain (4.7%), anxiety (23.4%), dizziness/lethargy (7.3 %) in a study of 1353 individuals (6). Some of the cases presented only cardiac symptoms. Acute ischemia, ventricular fibrillation and intracranial events have been responsible for the death of patients using SCs. Recently studies have demonstrated the inhibitor effects of cannabinoids on myocardial voltage-gated sodium channels and L-type calcium channels independent of sympathetic nervous system effects (7, 8).

In this study, we evaluated whether SCs were responsible for ventricular repolarization abnormalities using initial and 12th-hour electrocardiograms (ECGs) in patients with acute intoxication resulting from SCs. We examined changes in the QTc and cTp-e parameters to demonstrate the ventricular repolarization effects of the usage of SCs.

MATERIAL AND METHODS

Patient population

The 20 patients included in this study presented clouding of consciousness after using SCs when they visited the emergency department. Patients with a history of any cardiac disease, liver failure or kidney failure were excluded. Patients using multiple drugs (e.g., ecstasy, cocaine, etc.) were excluded as well. All of the patients were smokers with normal biochemical results in the laboratory which effect the repolarization such as calcium and potassium. Because of the importance of the duration of 'Bonzai' usage, only patients who remembered how long they had used 'Bonzai' were enrolled in this study. All of the patients were carefully evaluated for coronary ischemia. We evaluated ECGs, symptoms and consecutive cardiac markers to rule out acute coronary syndrome. Two patients with coronary ischemia underwent a coronary angiography and were excluded from the study. Written, informed consent was obtained from each subject, and the institutional Ethics Committee approved the study protocol (Ethics Committee of Bursa Yuksek Ihtisas Education and Research Hospital; 2011-KAEK-25 2016/01-07). All procedures performed in study were in accordance with the Helsinki declaration.

Study design

Standard 12-lead ECGs were recorded on a 12-channel electrocardiography recorder (Cardipia 800, Trismed, Republic of Korea) for all of the patients in the emergency department. The study was prospectively designed and second ECGs were obtained at the end of the 12^{th} hour according to the declaration of the usage of 'Bonzai.' All of the ECG recordings were scanned and transferred to a computer and then magnified 300 times using Adobe Photoshop (Location) software. Only one observer who was unaware of the patients' clinical status measured the intervals and durations. The QT intervals were measured from the onset of QRS to the end of the T wave. When the end of the T wave could not be reliably identified, the lead was not included in the analysis. Four consecutive QT intervals in each of the six precordial leads were measured and averaged. The QT interval was corrected for heart rate using the Bazett formula: QT/%R-R(cQT). We measured the Tp-e intervals from the peak of the T wave to the end of the T wave. Similarly, we corrected the Tp-e interval (cTp-e) for heart rate using the RR interval: (Tp-e /%R-R).

Statistical analysis

All of the data are presented as mean values ± standard deviation (SD). Comparisons between two ECGs baseline and after 12^{th} hours were performed using paired and unpaired Student's t-tests. A p value less than 0.05 was considered to be statistically significant. All of the statistical calculations were performed using the Statistical Package for Social Sciences 19.0 for Windows (SPSS Inc., Chicago, IL, USA) statistical software package.

RESULTS

Patients admitted to the emergency department with a history of recent usage of SCs were included to the study. 10 patients (50%) experienced loss of consciousness within one hour and somnolence after a few hours. We noted syncope in 3 patients and somnolence (15%), confusion and disorientation in 5 patients (25%).1 patient was admitted with bradycardia and hypotension and one presented only bradycardia. In addition, nausea, vomiting, dizziness and drowsiness were frequently observed in the patients. All of the patients exhibited signs of agitation, anxiety and hallucination to differing degree. The mean age of the 20 patients was 22 ± 4.5 years. All of the patients were male. The mean elapsed time between SCs usage and hospital admission was 180 ± 24 min. None of the patients exhibited a hypertensive response. At the end of the 12^{th} hour, the patients' mean blood pressure tended to decrease because the effect of SCs had nearly ceased. However, it was not statistically significant. The patients' mean heart rate was 76.2 ± 15.5 beats per minute (bpm). The patients' mean heart rate at the end of the 12^{th} hour was 71.8 ± 13.3 bpm (non-significant). Neurologists and internal medicine specialists consulted with all of the patients. The subjects were followed-up in the hospital unit for 24 hours. All of the patients were referred to the psychiatry department for further evaluation.

The mean PR intervals was 149.071 ± 27.7 msec, and the mean QRS duration was 102.143 ± 15.5 msec. When SC lost its acute effect, the mean PR interval was 140.1 ± 20.4 ms. However, it was not statistically significant.

However, the QRS duration was significantly decreased (102.1 ± 15.5 ms vs 95.0 ± 10.7 ms; p = 0.022). When we evaluated the cQT measurements, we noted a significant decrease at the end of the 12^{th} hour (426.6 ± 47.2 ms vs 390.4 ± 42.9 ms; p = 0.002). Similarly, the Tp-e and cTp-e values decreased significantly when SC lost its acute effect (93.4 ± 21.1 ms vs 77.4 ± 21.0

Table 1. *Hemodynamic and electrocardiographic findings on admission and at the 12th hour*

	Baseline	**12th hour later**	**p value**
	mean SD (n = 20)	mean SD (n = 20)	
Heart rate (bpm)	76.2 ± 15.5	71.8 ± 13.3	NS
Systolic BP (mmHg)	128 ± 6.9	121 ± 6.1	NS
Diastolic BP (mmHg)	78 ± 6.1	72 ± 5.9	NS
PR interval (ms)	149.0 ± 27.7	140.1 ± 20.4	NS
QRS duration (ms)	102.1 ± 15.5	95.0 ± 10.7	0.022
QTinterval (ms)	382.1 ± 42.2	376.0 ± 36.0	NS
QTc interval (ms)	426.6 ± 47.2	390.4 ± 42.9	0.002
Tp-e (ms)	93.4 ± 21.1	77.4 ± 21.0	0.014
cTp-e (ms)	105.3 ± 28.5	88.1 ± 21.5	0.010

BP: Blood pressure, bpm: Beats per minute, ms: millisecond, NS: Non-significant.

ms; p = 0.014, 105.3 ± 28.5 ms vs 88.1 ± 21.5 ms; p = 0.01). All of the data are presented in Table 1.

DISCUSSION

We evaluated the effects of SCs, which are increasingly popular around the world, on ventricular repolarization. Synthetic cannabinoids have become a serious problem because they were legal when they were first released. Additionally, they cannot be detected in screening tests, and there is the perception that they are safer than marijuana. More than 140 products are defined as containing SCs (3, 5), and they vary according to the type and amount of SCs. Synthetic cannabinoids are being sold with a combination of dried herbs after being synthesized in the laboratory as an alternative to marijuana (5). In Turkey, the name 'Bonzai' is used occasionally to refer to SCs (5). Hermanns-Clausen et al. declared that the usage of JWH-018 was abandoned in SC-containing products; JWH-122 and JWH-210 were used instead after 2011 (9). In contrast of this study, we found JWH-018 substance when scanned recent studies from Turkey about 'Bonzai'.JWH-018 in 1174 out of 1179 cases (99.4%) in a report published by Gurdal et al. (4). In addition, 777 cases (65.9%) contained both JWH-081 and JWH-018. Dynamic changes in active ingredients are observed over time throughout the world. However, all of these substances are derived from the SC family and likely result in effects on similar receptors.

Synthetic cannabinoids were developed to achieve the curative effects. These substances bind to the CB1 and CB2 receptors and exhibit similar effects as tetrahydrocannabinol, which is the active substance in marijuana (5). The CB1 receptors are primarily localized in the central and peripheral nervous system. Activation of CB1 receptors changes mood and perception, and continued cannabis consumption elicits addictive behavior (9). The CB2 receptors are largely localized in the immune system. Synthetic cannabinoids have typically agonistic effects on CB1 receptors. Synthetic cannabinoids have a stronger affinity to CB1 receptors, which makes them more powerful than Δ9THC (10, 11). There are different usage presentations of SC, and some effects are associated with the cardiovascular system. A first effect is myocardial ischemia. There is few mechanisms known to be responsible for myocardial infarction due to the usage of addictive substances (11). A 2001 study by Mittleman et al. presented clear evidence for a relationship between marijuana and myocardial infarction (12). This can be explained by norepinephrine release and stimulation of the sympathetic system. Myocardial O_2 demands increase with tachycardia induced by the stimulation of the sympathetic system, which results in ischemia. In addition, norepinephrine release with sympathetic nervous system stimulation results in vasoconstriction and worsening of myocardial ischemia (11). In our series, one patient exhibited vasospastic angina, and another exhibited atherosclerotic plaque rupture in coronary angiograms. However, our goal was to evaluate ventricular repolarization dynamics independent of acute coronary ischemia. Therefore, we excluded these two patients from our study. All of the patients that evaluated showed symptoms including angina and equivalents of angina, ECG and cardiac marker analysis. Only patients without ischemia enrolled in the study; patients with ischemia or suspicions of ischemia were excluded from the study. The second effect of SCs ranges from myocardial depression to conduction abnormalities via cannabinoids receptors. These effects result from the strong binding of cannabinoids to CB1 receptors. This action mechanism of SCs on cannabinoid receptors may cause bradycardia, tachycardia, hypotension, hy-

pertension, seizures and QT prolongation (13, 14). Kucuk et al., in a study conducted in Turkey, reported that 37 out of 112 patients had cardiac side effects. Nineteen of these patients (20%) had chest pain and 18 out of the 112 patients (16%) presented palpitation (15). One patient presented bradycardia and hypotension, and another patient presented bradycardia alone. Initial blood pressure and heart rate were higher in the remaining 18 patients compared with the values at the end of the 12th hour. However, this finding was not statistically significant. The effects of endocannabinoids on contractility and calcium signaling have been shown via both cannabinoid receptors and a direct effect on ion channels (14). Small studies have suggested that endogenous cannabinoids such as anandamide show negative inotropic and antiarrhythmic effects using voltage gate sodium channels and L-type calcium channels independent from sympathomimetic activity (7, 8). Animal studies have demonstrated that SCs cause bradycardia; in particular, HU-210 had a negative chronotropic effect (13). Bui et al. reported a case of marijuana with QT prolongation upon initial admission. In this case report, pathological QT prolongation was determined with the usage of marijuana in 34-year-old female patient (16). Von Der Haar et al. (14) reported a two different cases QT prolongation due to usage of SCs. These cases raise concerns about the adverse effects of SCs and the possibility of QTc prolongation and subsequent complications when using antipsychotic medication in the presence of SC abuse (13). The QT and cQT intervals were significantly prolonged compared with the end of the acute effect of SCs in our cases. QT prolongation may be harmful in patients with underlying disease such as coronary artery disease and rhythm abnormalities such as hereditary or acquired long QT syndromes. In these subjects, QT intervals may attain the critical values and be life-threatening with the usage of SC.

Recent studies have demonstrated that the Tp-e interval, which is the terminal part of QT interval and defined as the duration from the peak to the end of the T wave, is a useful index for evaluating cardiac repolarization (17). Siciouri et al. (17) described the relation between ventricular arrhythmias and the Tp-e interval. The middle myocardial M cells have a longer action potential duration then other cells. The peak of the T wave exhibits the terminal part of epicardial action potential where the end of the T wave shows the end of the mid-myocardial action potential (17). Therefore, the Tp-e interval is a reflection of the dispersion of repolarization and can be helpful for predicting the risk of developing life-threatening arrhythmias (18). This hypothesis was studied and evidenced in patients with hypertrophic cardiomyopathies (19), arrhythmogenic right ventricular dysplasia (20) and other pathophysiological conditions. In our study, we examined the Tp-e and cTp-e intervals immediately after the usage of SC . The data before and after SC were significantly different. The Tp-e and cTp-e intervals were significantly prolonged with the usage of SC. The prolongation of the Tp-e and cTp-e intervals is important for predicting ventricular repolarization abnormalities. In our study, there were no life-threatening arrhythmias detected during the follow-up period, which was only approximately 12 hours. However, overdose or chronically usage may induce lethal arrhythmias and cause prolongation of ventricular repolarization.

Study limitations

The most substantial limiting factor of this study was that the substance was not toxicologically classified. Verbal statements of patients who visited the emergency department were taken as truth; patients who stated that they used multiple drugs were excluded from the study. For active substances, failure to achieve identification in a toxicology laboratory was the most substantial limiting factor of this study. Routine screening tests for SCs are not being utilized yet in hospitals of the Ministry of Health (i.e., our clinic). Another limiting factor was the small number of patients. The primary explanation for our small cohort of patients was that a large fraction the patients declared that they used multiple drugs; these individuals were accordingly excluded from the study. The illegality of SC made it difficult to recruit participants and follow up on cases.

CONCLUSIONS

We have demonstrated that the use of SCs slows down ventricular repolarization and lengthens the QTc, Tp-e and cTp-e intervals clinically. This situation may result in the lengthening of the QT interval in pathological limits and the development of vital arrhythmias in patients with underlying ischemic heart diseases or patients with long QT syndrome. Some of cardiac-related deaths may be correlated with ischemia, and some of them may be dependent on arrhythmia. Additional electrophysiological studies are required to address this issue.

Abbreviations

SCs — synthetic cannabinoids
ECGs — electrocardiograms

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Sažetak

AKUTNI EFEKTI SINTETSKIH KANABINOIDA NA VENTRIKULARNU REPOLARIZACIJU

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Uvod: Upotreba sintetskih kanabinoida je u porastu, kako u Turskoj, tako i širom sveta. U ovoj studiji, evaluirali smo da li sintetski kanabinoidi izazivaju poremećaj ventrikularne repolarizacije analizom inicijalnog elektrokardiograma i elektrokardiograma nakon 12h, kod pacijenata sa akutnom intoksikacijom sintetskim kanabinoidima. Pratili smo promene QTc i cTp-e parametara kako bi demonstrirali uticaj sintetskih kanabinoida na ventrikularnu repolraizaciju.

Materijal i Metode: Sproveli smo prospektivnu studiju. Uključeno je 20 pacijenata koji su posetili hitnu službu, žaleći se na pomućenje svesti nakon konzumiranja sintetskih kanabinoida. QT, QTc i cTp-e intervali i određeni elektrokardiografski parametri inicijalnog elektrokardiograma i elektrokardiograma nakon 12h su mereni.

Rezultati: QRS interval je bio značajno produžen (102.1 ± 15.5 ms vs 95.0 ± 10.7 ms; p = 0.022). Zapaženo je i značajno produženje cQT intervala na kraju 12og sata (426.6 ± 47.2 ms vs 390.4 ± 42.9 ms; p = 0.002). Slično, Tp-e i cTp-e vrednosti značajno su porasle kada su sintetski kanabinoidi izgubili svoj akutni efekat (93.4 ± 21.1 ms vs 77.4 ± 21.0 ms; p = 0.014, 105.3 ± 28.5 ms vs 88.1 ± 21.5 ms; p = 0.01).

Zaključak: Konzumiranje sintetskih kanabinoida utiče na heterogenost ventrikularne repolarizacije sudeći po QTc i Tp-e intervalima.

Ključne reči: sintetski kanabinoidi, Bonzai, heterogenost ventrikularne repolarizacije, negativni kardiovaskularni efekti.

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ANALYSIS OF PERIPHERAL BLOOD LYMPHOCYTES IN BURNS OF VARYING DEGREES IN THE ASSESSMENT OF IMMMUNE SUPPRESSION

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Abstract: **Introduction:** Burn, depending on the degree of severity and depth, induces significant pathophysiological response of the body. Our study is the prospective study for assessment of T lymphocyte immunological changes in patients with burns, with different degrees of %TBSA and depth of burns.

Research objectives: Objectives of this study were to assess %CD3+Ly, %CD4+Ly, %CD8+Ly, %CD3+ HLA-DR+Ly, %CD4+Ly /CD8+Ly), of burned body with different %TBSA degrees, different depth burns and to establish predictive value of of immune suppression these parameters.

Patients and methods: According to %TBSA, patients were classified into three groups: mild burns with TBSA% < 15% (30 patients), group of medium burns with %TBSA from 15%-25% (30 patients) and group with %TBSA > 25% to 40% (30 patients). According to the depth of burns, patients were classified into two groups, partial-thickness burns, (39 patients), and full-thickness burns (51 patients). We followed laboratory parameters: % CD3+Ly, % CD3+ CD4+Ly, % CD3+CD8+Ly, % CD3+HLA-DR+Ly, CD4 / CD8 (%) lymphocytes (on day 7th and on day 14th).

Results: Percentage of CD3+ lymphocytes was significantly lower in severe burns compared to the moderate heavy burns andsignificantly lower compared to the mild burns. Percentage of CD3+CD4+ lymphocytes was significantly lower in severe burns compared to moderate heavy burns and in relation to mild burns (results on day 14th); also are lower in moderate severe burn compared to mild burns. On day 14th, the% CD4 / CD8 ratio was not significantly lower in the severe burns versus the moderate burns. On day 14th, the % CD4 / CD8 ratio wassignificantly lower in severe burns compared to mild burns; significantly lower in moderateburns compared to mild burns. % CD3+HLA -DR + cells was significantly lower in severe burn and moderately severe burns compared to the mild burns on day 7th, and also on day 14th. Full- thickness burns have significantly lower %CD3+lymphocytes, %CD3 +CD4+ lymphocytes, %CD3+HLA-DR+ lymphocytes, ratio of % CD4/CD8 lymphocytes compared to partial-thickness burns.

Conclusions: Peripheral blood T lymphocytes are one of the key indicators of immunosuppression of patients with burns of different % TBSA and different degrees of burn depth. Larger %TBSA and full- thickness burns injected stronger systemic immunosuppresion, compared to smaller %TBSA and partial-thickness burns.

Key words: burn, %TBSA, T lymphocytes, thickness of burns, % CD3+Ly, % CD3+ CD4+Ly, % CD3+ CD8+Ly, % CD3+HLA-DR+Ly, ratio % CD4 / CD8 lymphocytes.

INTRODUCTION

Globally, burns are one of the most common thermal injuries (1). Loss of skin barrier function, tissue ischemia and tissue destruction after burns and plasmorrhea over burnt surfaces are just some of the causes that are cited as possible reasons leading to an acute phase response, hematological and immune response in a burnt person. The immune response of the organism after a burn is very complex and is caused by a number of factors. The immune response is initially pro-inflammatory, but later becomes predominantly

anti-inflammatory in order to maintain the organism's homeostasis and restore normal physiological processes. Both responses are mediated by cytokines and the cellular response. The central role in the regulation of the cellular adaptive immune response belongs to lymphocytes, especially CD4 + lymphocytes (2).

RESEARCH OBJECTIVES

The aim of the study was to examine how different degrees of% TBSA and depth of burn affect the T lymphocyte immune response: % CD3 + Ly,% CD4 + Ly,% CD8 + Ly, % CD3 + HLA-DR + Ly and the ratio of %CD4 + Ly/% CD8 + lymphocytes, monitoring the dynamics of parameters on the day 7th day and on day 14th after the burn; then the correlation of the examined parameters with the different % TBSA and the depth of the burn, and determine the predictive significance of individual laboratory parameters for the assessment of immune deficiency.

PATIENTS AND METHODS

The study is a prospective clinical study of patients with burns conducted at the Clinic for Reconstructive and Plastic Surgery of the University Medical Center in Sarajevo (UCC).

The survey was conducted from 2010 to 2017. The study was approved by the UCC Bioethics Committee No. 1893/2009. The study included 90 patients with varying degrees of severity of thermal trauma, aged 18 to 65 years, both sexes, with% TBSA to 40%. The study excluded: patients younger than 18 years and older than 65 years; patients who could not be followed from the beginning of the burn, because they were already treated in another center, and then transferred to the UCC in Sarajevo, due to complications; patients diagnosed with fresh myocardial infarction; patients with already diagnosed cancer of any organ; patients with > 40% TBSA because we could not monitor the dynamics of target laboratory immune parameters in the planned days; patients diagnosed with liver failure, malnutrition, and hypoproteinemia prior to burn; patients with already diagnosed autoimmune diseases, patients undergoing immunosuppressive therapy and patients with burns caused by electric, chemical and radiation burns.

The examination was performed on the basis of the usual approach to the patient with burns by the method of anamnesis and objective medical examination with special reference to the local status of the burn skin. Patients with burns were classified according to the generally accepted classification of burns by the American Burns Association (3). According to the severity of the burn, patients were classified into three groups: group of mild burns with% TBSA < 15% (30 patients), group of moderate burns, with% TBSA of 15%-25% (30 patients) and group of severe burns with% TBSA > 25% to 40% TBSA (30 patients). According to the depth of the burn, we divided the patients into two groups. In group I, partial-thickness burns (39 patients), and in group II, full-thickness burns, (51 patients). We did not have patients with grade IV in this study.

We examined the values of% CD3 + Ly, % CD4 + Ly, % CD8 + Ly, activated lymphocytes (% CD3 + HLA-DR + Ly) and the ratio of CD4 + Ly / CD8 + lymphocytes on the day 7th and day 14th after burn in patients with severe burns, and compared values of the examined parameters with values in patients with moderate burns and with mild burns. The same immune parameters were examined and statistically analyzed in the group of partial-thickness burns, compared to full-thickness burns. We examined the predictor significance of laboratory parameters for assessment the degree of immune deficiency on the day 7th and the day 14th after the burn trauma. We examined the correlation of% TBSA with the already listed laboratory parameters on the day 7th and on the day 14th after burn trauma.

We determined% CD3 + Ly, % CD3 + CD4 + Ly, % CD3 + CD8 + Ly, % CD3 + HLA-DR + Ly, % CD4 / CD8 lymphocytes by flow cytometry, at the Institute of Immunology, UCC Sarajevo. The device on which the test was performed is CytometerBeckton Dickenson FACS Canto II, year of production 2009. Reference values by this method for CD3 + lymphocytes are 59% -85%, for CD8 + lymphocytes: 11-38%, for CD4 + lymphocytes: 30-59%, the ratio of CD4 / CD8 lymphocytes by this methodis 0.9-3.6%, and for CD3 + HLADR + lymphocytes it is 0-10%.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration.

Statistical data

All data collected by this study were prepared for statistical evaluation and stored in the Exel 2010 program, Microsoft Office software package (Microsoft USA), while statistical processing was done in the statistical data processing program SPSS ver.20.

In the part related to descriptive statistics, for all data, depending on the distribution (normal or asymmetric), the following values are shown: absolute frequency (N), structure index (%), average value (X), standard deviation (SD), median (M) and interquartile-rank (IQR). Student t-testwas done for dependent and independent samples of normal data distribution in order to assess the difference between the two groups.

The Mann Whitney U test was done to compare results between two groups, an asymmetric data distribution. The ANOVA test, for symmetrical distribution of data, was applied to compare the obtained results of several examined groups (mild, moderate and severe burns) by days. The Kruskal Wallis test, for asymmetric data distribution, was applied to compare the obtained results of several examined groups (mild, moderate and severe burns) by days. A linear multivariate regression model was used to assess the predictor effect of individual variables (laboratory tests) on the dependent variable (% TBSA). The chi square test (X2 test) was applied to analyze the relationships between frequencies. Values of $p < 0.05$ were accepted as statistically significant. The results of all performed analyzes are presented in a table.

RESULTS

Out of a total of 90 burnt patients, 60 were male patients (66.6%) and 30were female patients (33.4%). Thirty patients had mild burns, 30 patients had moderate burns, and 30 patients had severe burns. 39 patients had partial-thickness burns and 51 patients had full-thickness burns.

Statistical analysis of the incidence of burns, according to the severity of the burn and the sex of the patients, we did not find a statistically significant difference, $p = 0.638$. Statistical analysis of the average age of disease in men between mild, moderate and severe burns, we did not find a significant difference, $p = 0.542$. Statistical analysis of the average age of disease in women between mild, moderate and severe burns, we did not find a significant difference, $p = 0.628$. Mild burns had an average% TBSA of 7.9 ± 2.4, moderate burns had an average% TBSA of 19.5 ± 2.7, while severe burns had an average% of TBSA of 32.6 ± 4.5. There is a significant difference in% TBSA between mild, moderate and severe burns, $p < 0.0005$. We did not find a significant difference in the frequency of the number of patients with full-thickness burns in relation to partial-thickness burns, $p = 0.342$, Table 1.

Analysis of %CD3 + lymphocytes in burns of varying degrees

Mean values of CD3 + (%) lymphocytes were significantly lower in the group with moderate burns and severe burns compared to mild burns on the day 7th andon the day 14th, $p < 0.0005$. The average values of CD3 + (%) lymphocytes were not significantly lower in severe burns compared to moderate severe burns on the day 7th, $p = 0.769$ and on the day 14th, $p = 0.329$.

Mean values of CD3 + (%) lymphocytes were significantly lower by severe burns on the day 7th and on the day 14th, compared to moderate severe burns and compared to mild burns; $p < 0.0005$. Mean values of CD3 + (%) lymphocytes were significantly lower by moderate severe burns compared to mild burns; $p < 0.0005$. In all groups of burns on day 14th, there was an

Table 1. *Demographic and clinical characteristic of the patients according to the degree of severity and depth of the burn*

	THE SEVERITY OF THE BURN			significance
	mild burns	moderate burns	severe burns	
Number	30	30	30	
Men/women relationship	22/8	19/11	19/11	P = 0.638
Average age of men ± SD	45.8 ±15.1	43.8 ± 15.0	42.7 ± 12.9	P = 0.542
Average age of women ± SD	48.7 ± 10.6	50.8 ± 9.2	45.3 ± 3.2	P = 0.628
The average severity of the burn ± SD	7.9 ± 2.4	19.5 ± 2.7	32.6 ± 4.5	P < 0.0005
Partial thicknes burns/ Full thickness burns	15/15	13/17	11/19	P = 0.342

Legend: SD- standard deviation

Table 2. *Analysis of CD3+(%) lymphocytes between the examined groups on the 7th and 14th after burn trauma*

DAYS	DEGREE OF SEVERITY OF THE BURN			significance
	Mild burn	Moderate burns	Severe burns	
	X ± SD	X ± SD	X ± SD	
7th day	64.8 ± 7.0	54.0 ± 7.4	53.2 ± 7.0	P < 0,0005
14th day	68.6 ± 7.1	59.6 ± 6.5	56.5 ± 9.2	P < 0,0005

Legend: X- average value, SD- standard deviation

Table 3. *Analysis of CD3+CD4+(%) lymphocytes between the examined groups on the 7th and 14th day after burn trauma*

DAYS	DEGREE OF SEVERITY OF THE BURN			significance
	Mild burn	Moderate burns	Severe burns	
	X ± SD	X ± SD	X ± SD	
7th day	57.0 ± 7.0	52.8 ± 8.6	38.6 ± 6.3	P < 0,0005
14th day	55.3 ± 7.1	44.7 ± 8.3	33.1 ± 7.9	P < 0,0005

Legend: X- average value, SD- standard deviation

Table 4. *Analysis of CD3+CD8+(%) lymphocytes between the examined groups on the 7th and 14th day after burn trauma*

DAYS	DEGREE OF SEVERITY OF THE BURN			significance
	Mild burn	Moderate burns	Severe burns	
	M(IQR)	M(IQR)	M(IQR)	
7th day	22.2 (17.5-26.5)	21.9 (16.5-25.2)	19.5 (14.7-24.5)	P = 0.150
14th day	25.3 (18.1-28.5)	22.6 (16.4-27.2)	20.4 (16.9-22.6)	P = 0.060

Legend: M- median, IQR- interquarterly rank

Table 5. *Analysis of %CD4/CD8 lymphocytes between the examined groups on the 7th and 14th day after burn trauma*

DAYS	DEGREE OF SEVERITY OF THE BURN			significance
	Mild burn	Moderate burns	Severe burns	
	M(IQR)	M(IQR)	M(IQR)	
7th day	2.7 (2.5-3.0)	2.4 (2.0-2.7)	2.1 (1.8-2.6)	P < 0,0005
14th day	2.6 (2.0-3.1)	2.1 (1.8-2.6)	1.9 (1.5-2.1)	P < 0,0005

Legend: M- median, IQR- interquarterly rank

increase in the average values of CD3 + (%) lymphocytes compared to day 7th, but this increase was significant only in mild burns, p = 0.041 and in moderate burns, p = 0.004, Table 2.

Analysis of CD3 + CD4 + (%) lymphocytes in burns of varying degrees

On the day 7th after burn trauma, the mean values of CD3+CD4+(%) lymphocytes were significantly lower in severe burns compared to moderate burns and also compared to mild burns, p < 0.0005, but did not significantly differ between moderate burns compared to mild burns p = 0.097. On the day 14th after burn trauma, the average values of CD3+CD4+(%) lymphocytes were significantly lower in severe burns compared to moderate severeburns and compared to mild burns, p < 0.0005. The average values of CD3+CD4+(%) lymphocytes was significantly lower in moderate burns compared to mild burns, p < 0.0005, Table 3.

Analysis of CD3+ CD8 + (%) lymphocytes in burns of varying degrees

By statistical analysis of the mean values of CD3+ CD8+(%) lymphocytes between mild burns, moderate burns and severe burns, we proved that there is no significant difference between the groups of burns on the day 7th, p = 0.150, nor on day 14th, p = 0.060. On the day 14th, there was an increase in CD3+CD8 + (%) lymphocytes compared to day 7th in all three groups of burns. However, statistical analysis did not find a significant increase in CD3 + CD8 + (%) lymphocytes either in the group of mild burns, p = 0.090, or in the group of moderate burns, p = 0.556, as well as in the group of severe burns, p = 0.742, on the 14th day compared to day 7th, Table 4.

Analysis of ratio % CD4 / CD8 lymphocytes in burns of varying degrees

On the seventh day, the ratio of % CD4 / CD8 is lower in severe burns compared to moderate burns, p = 0.040; and compared to mild burns, p = 0.011; it is lower in moderate severe burns compared to mild burns, p = 0.041. On the day 14th, the ratio% CD4 / CD8 was not significantly lower in the severe burns compared to moderatesevere burns, p = 0.106; it is significantly lower in severe burns compared to mild burns, p = 0.039; it is significantly lower in moderate burns compared to mild burns, p = 0.043.

Table 6. *Analysis of CD3+HLADR+(%) lymphocytes between the examined groups on the 7th and 14th day after burn trauma*

DAYS	DEGREE OF SEVERITY OF THE BURN			significance
	Mild burn	Moderate burns	Severe burns	
	X ± SD	X ± SD	X ± SD	
7th day	10.1 ± 1.4	9.3 ± 1.4	9.0 ± 1.6	P = 0.021
14th day	11.9 ± 1.7	11.1 ± 1.8	10.2 ± 1.7	P = 0.003

Legend: X- average value, SD- standard deviation

Table *7. Analysis of laboratory parameters according to the degree of burn depth on the seventh day after burn trauma*

Laboratory parameters	DEGREE OF BURN DEPTH		significance
	Partial thickness burn M(IQR)	Full thickness burn M(IQR)	
%CD3	62.3 (58.1-68.8)	53.8 (48.3-53.8)	P < 0.0005
%CD3+CD4+	55.3 (50.2-61.2)	44.4 (38.5-51.2)	P < 0.0005
%CD3+CD8+	21.6 (17.6-26.2)	20.3 (15.7-24.9)	P = 0.140
%CD4/CD8	2.7 (2.5-2.9)	2.1 (1.8-2.6)	P < 0.0005
%CD3+HLADR+	8.9 (7.9-10.5)	6.9 (6.0-8.4)	P < 0.0005

Legend: M- median, IQR- interquarterly rank

The mean values of the% CD4 / CD8 lymphocyte ratio between mild burns, moderate severe burns, and severe burns on the day 7th and on the day 14th after burn trauma were significantly different, p < 0.0005, Table 5.

Analysis of CD3+HLA-DR + (%) lymphocytes in burns of varying degrees

On the day 7th after burn trauma, % CD3 + HLA-DR + lymphocytes were significantly different between mild, moderate, and severe burns, p = 0.021. The average values of% CD3 HLA-DR + lymphocytes were significantly lower in severe burns compared to mild burns, p = 0.030. There is no significant difference between moderateburns and severe burns, p = 0.762, nor between mild burns compared to moderate burns, p = 0.126.

On the day 14th after burn trauma, % CD3 + HLA-DR + lymphocytes were significantly different between mild, moderate, and severe burns, p = 0.003. % CD3 + HLA-DR + lymphocytes were significantly lower in severe burns compared to mild burns, p = 0.003. There is no significant difference between moderate burns compared to severe burns, p = 0.232. There is no significant difference between mildburns and moderate burns, p = 0.170. The results of the analysis are shown in the table 6.

The mean values of% CD3 + Ly, % CD3+CD4+ Ly, ratio o %f CD4 / CD8 lymphocytes and % CD3 + HLA-DR + lymphocytes were significantly higher in partial thickness burn, compared to patients with full thickness burn on the dya 7th after burn trauma, p < 0.0005.Average values of% CD3 + CD8 + lymphocytes did not differ significantly between patients with full-thickness burn compared to patients with partial-thickness burn, p = 0.140; Table 7.

On the day 7th after burn trauma,% TBSA is negatively correlated with CD3+CD4+(%) lymphocytes, negatively correlated with % CD3 lymphocytes,negatively correlated with the ratio of%CD4 + / CD8 + lymphocytes, negatively correlated with % CD +HLA-DR + lymphocytes. There is no correlation of %TBSA with %CD3+CD8+ lymphocytes.

By linear multivariate regression, on the day 7th after burn trauma, we proved that % CD3 lymphocytes have the greatest predictor importance for the assessment of immune damage, while the importance of other parameters is insignificant. The whole model, with all predictors, was statistically significant (R = 0.919, R2 = 0845, F = 108.9, p < 0.0005). The model classified 84% of the variability of the dependent variable, which can be explained by independent parameters.

By linear multivariate regression, on the day 14th after burn trauma, we proved that % CD4 + lymphocytes, % CD3+lymphocytes and %CD3HLA-DR+ lymphocytes have the greatest predictor importance for the assessment of immune damage (R = 0.852, R2 = 0.726, F = 52.932, p < 0.0005), while the importance of

Table 8. *Predictor importance of lymphocytes for the assessment of immune damage*

Model	Non-standard coeff.		Standard coeficient	t	Sig.	95% CI for	
	B	Std. error	Beta			lower limit	upper limit
1 cont.	45.757	6.87		7.359	P < 0.0005	33.445	58.032
CD4	-0.256	0.068	-0.289	-3.774	P < 0.0005	-0.391	-0.121
CD3	-0.212	0.076	-0.183	-2.782	0.007	-0.33	-0.06
C3+HLADR	-0.841	0.408	-0.138	-2.059	0.043	-1.653	-0.028

Dependent variable % TBSA

other parameters is insignificant. The model classified 72% of the variability of the dependent variable, which can be explained by independent parameters Table 8.

DISCUSSION

The consequences of thermal trauma are local and systemic. Responses to thermal injuries include cellular defense mechanisms, inflammation, immune disorders, and in extensive burns, a prolonged hypermetabolic response with weight loss, prolonged catabolic state, and organ dysfunction. Changes affecting the immune system include changes by the endocrine system, activation of the arachidonic acid cascade, and cytokine synthesis. The anti-inflammatory response includes increased levels of vasopressin, aldosterone, growth hormone, cortisol, glucagon, and catecholamines. Increased glucocorticoid levels inhibit the production of IFN-ã and IL-2, but not IL-4 and IL-10. Changes in cytokine levels damage the adaptive immune system during burns, especially the T lymphocyte population.

In our studies, we found pronouncedlymphopenia on the day 14th compared to day 7th in all groups of burns. The severity of the burn affected decrease in T lymphocytes. The% of CD3 + CD4 + lymphocytes, on the day 7th after the burn, is significantly lower in severe burns compared to mild burns and moderate burns and significantly lower in severe burns compared to moderate burns. On the day 14th after the burn, there was a significant decrease in%CD3+CD4+ Ly compared to the day 7th in moderate and severe burns, while in mild burns the decrease was not significant.Immunological T-cells respons are result of the synergistic action of CD4+ Ly with other T-Ly subclasses. The percentage of CD4+ T-lymphocytes is a key criterion for assessing the degree of damage, ie. immune system deficiencies. Immunodeficiency in burns is results a decrease in the% of CD3 + T lymphocytes, and the decrease depends on the severity of the burn. Our study showed that on the day 7th and the day 14th after burn trauma, severe burns and moderate burns have significantly lowe% CD3 + Ly compared to mild burns. The difference between moderate burns and severe burns, on the day 7th and on the day 14th after burn trauma, was not significant, although patients with severe burns had lower mean values % CD3 + lymphocyte compared to patients with moderate burns.

The severity of the burn trauma no significantly reduces% CD +CD8+ lymphocyte on the day 7th after the burn trauma, in our study. The% CD3+ CD8 + Ly, although lower in severe burns compared to the other two groups of burns, were not significantly reduced in severe burns compared to mild and moderate burns, as well as in moderate burns compared to mild burns. Although in our study, the severity of the burn did not significantly affect the decrease in % CD3 + CD8 lymphocytes, indirectly, through reduced % CD3+ CD4+ lymphocytes, it may be an additional reason for immunosuppression. In our study, on the day 7th after burn trauma, the mean values of % CD3 + Ly, % CD4 + Ly, activated lymphocytes (% CD3 + HLA-DR + Ly) and the ratio of CD4 / CD8 lymphocyte were significantly lower in patients with full-thickness burns, compared to patients with partial-thickness burns. % CD8 + Ly did not differ significantly between patients with full-thickness burns compared to partial-thickness burns. CD4+ lymphocytes have an immune memory and their presence is necessary to maintain the effector function of CD8+ cells in inflammation. Decreased % CD3 + CD4 + lymphocytes impaired effectory function of %CD3 + CD8 lymphocytes. In any case, changes in % CD4 T lymphocytes are an important cause of immunosuppression in patients with burns.

On the day 14th after burn trauma, the% CD3 + CD8 + lymphocytes were higher than on the day 7th in all groups of burns, but this increase was not significant compared to the day 7th. That the T cell immunosuppression is higher in higher %TBSA, is shown by the ratio % CD4 / CD8 lymphocyte. On the day 7th andon the day 14th, the ratio % CD4/CD8 was significantly lower in severe burns compared to moderate burns and compared to mild burns. Mean values of ratio %CD4 / CD8 lymphocytes on the day 14th compared to the day 7th, after burn trauma, did not differ signi-

ficantly in moderate and mild burns, but in the group of severe burns ratio of% CD4 / CD8 was significantly lower on day 14th compared to the day 7th.

The total number of lymphocytes is important for the immune defense of the organism, as well as the percentage of lymphocytes that carry HLA-DR antigen,% CD4 + lymphocytes and% CD3 + lymphocytes. Immunosuppression, in our study, observed through the average values of CD3 + HLA-DR + (%) lymphocytes in relation to the degree of severity of the burn, is most pronounced in severe burns. CD3 + HLA-DR +%lymphocytes were significantly lower in severe burns compared to mild burns the day 7th on the day 14th. Our research has shown that the mechanism of antigen recognition and the speed of reaction on the antigens depend on the severity of the burn. This mechanism is particularly weakened in severe burns, compared to the other two groups, in the first two weeks after the burn. Decreased HLA-DR expression is a sign of immunosuppression after a burn. The expression of HLA-DR antigen is associated with the role of lymphocytes as antigen-presenting cells. HLA-DR expression can be activated by anti-inflammatory cytokines, especially IL-10, TGF-â and PGE-2. Catecholamines released after burn trauma may increase HLA-DR expression on lymphocytes. CD3 + HLA-DR + cells are activated T-lymphocytes, with pronounced MHC class II membrane molecules, a class of major tissue tolerance complex. Activated T-lymphocytes, together with memory T-lymphocytes, are important for the rapid initiation of specific immune responses and that the involvement of inflammatory cells is important during the healing process of burned skin (4).

The suppression of the immune response is strongerby more severe the burn. On the day 7th after the burn,% TBSA was negatively correlated with %CD3+ CD4+ lymphocytes, was negatively correlated with %CD3 + Ly, was negatively correlated with the ratio% CD4 / CD8 Ly andwas negatively correlated with% CD3 + HLA-DR + Ly. %TBSA were without significant correlation with% CD3 + CD8 + Ly. The inflammatory response, on the day 7th in our study, and the T-cell immune response were negatively correlated.

Research by Wood JJ et al. (2), and Guanying YY et al. (5) suggest that T cell immunosuppression is associated with decreased production of IL-2, a cytokine that is primarily produced by peripheral blood mononuclear cells and Th1-Ly. Immunosuppression is also affected by increased production of IL-4 and IL-10, cytokines that reduce Th1-Ly function and redirect T lymphocyte differentiation in favor of Th2 lymphocyte subpopulation, andreducing Th1 lymphocyte phenotype. Boyce DE et al, found that IL-2 values return to normal values in a later stage, in burn healing phase (6). The percentage of CD3 T-Ly and CD4 T-Ly in patients with burns is lower compared to healthy controls (7). HLA-DR expression is a sensitive indicator that reflects the activation and proliferation of lymphocytes after burn, and the rapid initiation of specific immunoreactions (4). CD8 lymphocytes recognize foreign antigens within MHC class I molecules. CD4 lymphocytes recognize antigens in complex with MHC class II molecules on the surface of antigen-presenting cells. During the burns, several changes in the T-lymphocyte population were observed. The poor response to mitogens is particularly pronounced (8). After burns, the values of anti-inflammatory cytokines increased: IL-4 and IL-10 (9). IL-4 and IL-10 may inhibit Th1-Ly activation for antigen presentation. Changes in the balance between T suppressor and T helper lymphocytes and the ratio of Th1-Ly to Th2-Ly are an important etiological factor in the suppression of the adaptive immune response.The reason for immunosuppression of patients with burns is also in CD8 lymphocytes, which are inhibited by PG-E2 released from monocytes (10). Nevertheless, a significant mediating role in immunosuppression is attributed to Th2 lymphocytes. Th2-Ly is produced by anti-inflammatory cytokines, including IL-6, which suppresses the production of CD4 + cells (11).

Immunosuppression in patients with burns is associated not only with a reduced number of T-lymphocytes, but also with a change in the capacity and ability of T-lymphocytes to activate after antigen stimulation, whatever its type (necrotic cells, products of thermally damaged cells, bacterial toxins, burnt tissue endotoxins) during thermal injury (8). Horfan AF. et al. examined the mitogenic response of lymphocytes of patients with burns after antigen stimulation and found that patients with severe burns have a reduced cellular immune response, not only due to decreased lymphocyte count, but also due to impaired function of circulating T-helper lymphocytes. T-lymphocyte damage is manifested by decreased mitogenesis in response to mitogens, reduced response to antigen stimulation and activation. The same authors believe that deregulation of the immune response, following burn trauma, occurs as a consequence of redistribution of T-lymphocytes in peripheral blood and tissues. Burn trauma is a trigger for the apoptotic T-Ly pathway, but the exact mechanism of the apoptosis pathway to date is unclear while preventing apoptosis of activated T lymphocytes through reduced Fas-ligand induction in the cell. It is thought that the products of activated macrophages, PGE-2, and transforming growth factor-â (TGF-â) may contribute to T lymphocyte suppression, primarily the Th-1 subpopulation of lymphocytes. In addition, PGE-2 inhibits CD8 + lymphocyte function (10).

Mabrouk et al. (12), on the fourth day after burn trauma, found a decrease in the absolute number of CD3 lymphocytes, CD4 lymphocytes, CD8 lymphocytes, and a decrease in the ratio CD4 / CD8 lymphocyte, compared with healthy controls. They explain the decrease by the presence of immunosuppressive factors in burn patients. One of these factors, in their opinion, is the polymerized lipid-protein-complex of the cell membrane of the tissue damaged by the burn, the so-called burn toxin. The authors demonstrated that burn toxin inhibits the proliferation of normal lymphocytes after antigen stimulation. Not only does it inhibit the proliferation of normal lymphocytes after antigen stimulation, but the burn toxin has a toxic effect on lymphocyte proliferation and lowers the absolute number of lymphocytes in patients with burns, resulting in immunosuppression. Some authors observe certain parameters in isolation, such as e.g. the ratio CD4 / CD8 as indicators of immunosuppression. Rijola LF et al. (7) considered, in moderate burns, only the reduced CD4 / CD8 ratio gives prognostic significance in the further development of immunosuppression after burn trauma.

In the daily clinical practice of treating burns, it is very important to predict the extent to which immunosuppression is present in the burn patient. Our research showed that already on the day 7th after the burn, CD3 lymphocytes have the greatest predictor significance of immunosuppression. On the day 14th, in addition to CD3 lymphocytes, CD4 lymphocytes and CD3 + HLA-DR + lymphocytes have a predictor of immunosuppression. It is possible that the decreased CD4 Ly number is due to the reduced CD3 Ly number (13). There are other reasons that lead to a decrease in the proliferation and maturation of T lymphocytes. Thus Schluter B, et al. (14) believe that IL-7, which grows during the first week after a burn, may reduce the proliferative and maturation capacities of T-Ly.

CONCLUSION

1. Changes in T lymphocytes are an important cause of immunosuppression in burn patients. T-lymphopenia is present in all burns regardless of the severity of the burn. T-lymphopenia is significantly lower on the day 14th compared to the day 7th after the burn.

2. T-lymphopenia, is stronger in higher% TBSA and deeper burns

3. Decreased values of subclass T lymphocytes should be interpreted as important markers of immune suppression assessment. An increase in % CD3+HLA -DR + lymphocytes on the day 14th compared to the day 7th indicates the onset of a specific T immunoreaction. The severity of the burn affects the activation and proliferation of activated T lymphocytes.

4. On the day 7th after burn trauma, % TBSA is negatively correlated with CD3+CD4+(%) lymphocytes, negatively correlated with % CD3 lymphocytes, negatively correlated with the ratio of %CD4 +/CD8+ lymphocytes, negatively correlated with % CD+HLA -DR+ lymphocytes. There is no correlation of %TBSA with %CD3+CD8+ lymphocytes. % CD3+ lymphocytes have the greatest predictor importance for the assessment of immune deficiency, on the day 7th after burn trauma. % CD4+Ly, %CD3+ Ly and%CD3+ HLA-DR+ lymphocytes have the greatest predictive importance for the assessment of immune deficiency, on the day 14th.

5. Immunosuppression observed through the average values of CD3+HLA-DR+(%) lymphocytes in relation to the severity of the burn, is most pronounced in severe burns. CD3+ HLA-DR + (%) lymphocytes were significantly lower in severe burn compared to mild burns on the day 7th and on the day 14th.

6. Deeper burns, full-thickness burns, result in stronger suppression of the immune response. On the day 7th after burn trauma, the mean values of %CD3 Ly,% CD4 + Ly, activated lymphocytes (% CD3 + HLA-DR + Ly) and the ratio CD4 / CD8 lymphocyte were significantly lower in patients with full-thickness burns, compared to patients with partial-thickness burns burns. The depth of the burn has no significant reflection on% CD8 + lymphocytes on the day 7th after burn trauma.

Abbreviations

TBSA — Total Body Surface Area
ABA — American Burn Association
CD — cluster designation
Th Ly — T helper lymphocytes
CD8 T Ly — cytotoxic T lymphocytes
MHC II AC — major histocompatibility class II antigen complex
TNF — tumor necrosis factor
IL — interleukin
PG — prostaglandin
IFN — interferon
TGF — transforming growth factor

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Sažetak

ANALIZA LIMFOCITA PERIFERNE KRVI KOD OPEKOTINA RAZLIČITOG STEPENA TEŽINE U PROCENI IMUNOLOŠKE SUPRESIJE

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Uvod: Opekotina, ovisno o stepenu težine ima za posledicu značajan patofiziološki odgovor.

Cilj istraživanja: Ciljevi istraživanja su ispitati reperkusije % TBSA i reperkusije dubine opekotine na imunološki odgovor procenjujući: %CD3+Ly, %CD4 +Ly, %CD8+Ly, %CD3+HLA-DR+Ly iodnos %CD4 +Ly/CD8+Ly.

Pacijenti i metode: Prema %TBSA, pacijente smo podelili u 3 grupe: blage opekotine sa TBSA% < 15% (30 pacijenata), grupu srednje teških opekotina sa % TBSA od 15%-25% (30 pacijenata) i grupu sa % TBSA > 25% do 40% (30 pacijenata). Prema dubini opekotine, pacijente smo podelili u dve grupe: partial-thickness burns, (39 pacijenata), i full-thickness burns (51 pacijent). Pratili smo sledeće parametre: % CD3+Ly, % CD3+ CD4+Ly, % CD3+CD8+Ly, % CD3 +HLA-DR+Ly, i odnos CD4 / CD8 (%) limfocita (7. i 14. dana nakon opekotine).

Rezultati: %CD3+ Ly signifikantno je niži kod teških opekotina u poređenju sa srednje teškim opekotinama i u poređenju sa blagim opekotinama. % CD3+CD4+ Ly signifikantno je niži kod teških opekotina u poređenju sa srednje teškim opekotinama kao i u poređenju sa blagim opekotinama 14. dana nakon opekotinske traume; takođe je niži kod umereno teških opekotina u odnosu na lake opekotine. Četrnaestog dana nakon opekotinske traume, odnos % CD4 / CD8 nije signifikantno niži kod teških opekotina u odnosu na umereno teške opekotine; ali je signifikantno niži kod teških opekotina u poređenju sa blagim opekotinama, i signifikantno je niži kod umereno teških opekotina u poređenju sa blagim opekotinama. % CD3+HLA-DR + Ly signifikantno je niži kod teških i umereno teških opekotina u poređenju sa blagim opekotinama i 7. i 14. dana nakon opekotinske traume. Full-thickness burns ima signifikantno niže %CD3+Ly, signifikantno niže %CD3+CD4+ Ly, signifikantno niže %CD3+HLA -DR+ Ly i signifikantno niži odnos % CD4/CD8 limfocita u poređenju sa partial-thickness burns.

Zaključak: T limfociti periferne krvi jedan su od ključnih indikatora imunosupresije kod pacijenata sa opekotinskom traumom. Jačina imunosupresije zavisi od % TBSA i dubine opekotine. Veći %TBSA i full-thickness burns imaju signifikantno veću imunosupresiju, u poređenju sa manjim %TBSA i partial-thickness burns. Sedmog dana nakon opekotinske traume, % TBSA u negativnoj je korelaciji sa %CD3+CD4+ limfocitima, u negativnoj korelaciji sa % CD3 limfocitima, u negativnoj korelaciji sa odnosom %CD4 + / CD8 + limfocita i u negativnoj korelaciji sa % CD +HLA -DR + limfocitima. Nema korelacije %TBSA sa %CD3 +CD8+ limfocitima. % CD3+ limfociti imaju najveći prediktorni značaj za procenu imunodeficijencije sedmog dana nakon opekotinske traume. % CD4+Ly, %CD3+ Ly i %CD3+HLA-DR+ limfociti imaju najveći prediktorni značaj za procenu imunosupresije 14. dana nakon opekotinske traume.

Ključne reči: opekotina, %TBSA, full- thickness burns, partial-thickness burns, T limfociti, % CD3+Ly, % CD3+ CD4+Ly, % CD3+CD8+Ly, % CD3+HLA -DR+Ly,omjer CD4 / CD8 (%) limfocita.

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MULTIDRUG RESISTANT INFECTIONS IN INTENSIVE CARE UNITS

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Abstract: **Background:** Intensive care units (ICU) are often the epicentre of development of infections caused by multidrug resistant (MDR) organisms.

Purpose: The aim of our study was to determine the prevalence and types of ICU-acquired infections, pathogens associated with such infections and to determine the antibiotic resistance pattern of the presented pathogens.

Material and methods: In the study were included 130 patients hospitalized into the surgical ICU of the University Clinic for Anesthesiology and Intensive Care in Skopje in period of 2 months, April -Jun, 2017., who developed infection after at least 72 hours of their hospitalization. In all of them the pathogens and their antibiotic resistance pattern were identified.

Results: Twenty of 130 (15.4%) patients developed ICU-acquired infection. Most common infections were pneumonia (50%) and surgical site (30%) infections. Gram-negative organisms were more common isolated than Gram-positive organisms (83% vs.17%). The most common isolated bacteria were *Acinetobacter species* (30, 41.7%) and *Pseudomonas aeruginosa* (15, 20.8%). All isolated species were MDR organisms resistant to the most used antibiotics like Cephalosporins, Gentamicin, Ciprofloxacin and Clindamycin. *Pseudomonas aeruginosa* and *Acinetobacter species* were sensitive to Colistin, Methicillin-resistant Staphylococcus aureus (*MRSA*) to Vancomycin and Linezolid and Enterococcus only to Linezolid. *Klebsiella pneumoniae* and *Proteus mirabilis* showed low resistance only to Amikacin and Carbapenems.

Conclusions: Our study obtained local data about the prevalence and types of ICU-acquired infections, types of pathogens and their antibiotic resistance pattern. Based on this knowledge, clinicians can choose appropriate antibiotics, avoiding antibacterial drug overuse and MDR bacteria development.

Keywords: intensive care unit acquired infections, multidrug resistant bacteria, antibiotic resistance.

INTRODUCTION

Nosocomial infections or ICU-acquired infections are infections which are developed in intensive care units (ICU). The incidence of ICU-acquired infections varies between 12-49% and most of the ICU hospitalized patients develop an infection within 6 days of their admission (1, 2). Because of exposure to multiple invasive procedures which compromise the anatomical barriers' defences, and because of impairment of protective mechanisms such as cough reflex or acid gastric ambient by sedative drugs critically ill patients are more prone to infections than other patients (3, 4). Their inadequate immune response induced by trauma, surgery and sepsis is another factor that leads to higher frequency of infections in these patients (3, 4). Bloodstream infections, lower respiratory tract infections, urinary tract infections and surgical site infections are most common infections seen in these ICU patients (5). According to some studies (6, 7) about 40% of the total expenditure in the ICU is due to infections which has increased the death rate of the hospitalized patients by two times.

The increased prevalence of infections caused by multidrug resistant (MDR) organisms is another problem, which is more common in ICU than in other departments (8). Inappropriate and irrational use of antimicrobial agents especially overuse of broad-spectrum antibiotics leads to development and spread of drug-resistant microorganisms. According to some studies (9,

10, 11), the rate of inappropriate or incorrect antibiotic prescriptions in ICUs varies from 30% to 60% in hospitalized patients. The prevalence of infections caused by multidrug resistant (MDR) bacteria in ICU is different in the different regions of the world. DEFINE study showed a 14.1% rate of MDR infections in critically ill patients with pneumonia in North America. EUROBACT study showed on average a 47.8% MDR infections in critically ill patients with bloodstream infections conducted in 24 ICUs distributed worldwide including 20.5% and 0.5% of isolated microorganisms with extensively drug-resistant (EDR) and pan-drug-resistant (PDR) patterns (12, 13).

Having in mind the fact that there is a considerable variation in the presented MDR pathogens across the countries and geographical region, locally obtained data can be used to predict the resistance of the locally persistent pathogens and to make the choice of antibiotics according to the antimicrobial susceptibility pattern when infections occur.

The aim of our study was to determine the prevalence of ICU-acquired infections, to determine the types and pathogens that cause such infections and to determine the antibiotic resistance pattern of the presented pathogens.

PATIENTS AND METHODS

130 patients admitted into the surgical intensive care unit of the University Clinic for Anesthesiology, Reanimation and Intensive Care in Skopje, Republic of North Macedonia, and hospitalized in the period of two months (April-Jun, 2017) were included in the study. All clinical data for these patients according to prevalence of ICU-acquired infections,types and pathogens that cause such infections and the antibiotic resistance pattern of the presented pathogens were retrieved from the official report of the Commission for prevention of intrahospital infections. All procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration. Only patients who developed clinically manifested infections after at least 72 hours of hospitalization were considered to have ICU acquired infections and were included in the study. Specimens were collected under strict asepsis and sent to the laboratory of the Institute of Microbiologyin Skopje for further analyses. The specimens include urine, tracheal aspirates, blood, urine, and wound swabs. Standard microbiological methods were used in order to identify the presented pathogens (14). Their antibiotic susceptibility was also tested using the antibiotics disk diffusion and Vitec technique. Testing included several antibiotics: Ceftriaxone, Cefixime, Clindamycin, Amikacin, Ciprofloxacin, Vancomycin, Linezolid, Meropenem, Imipenem, Gentamicin, Cotrimoxazole and Colistin. Risk factors for development of ICU-acquired infections were also analyzed.

For the statistical analysis, SPSS 12.0 software was used. Data were presented using means, range and proportions.Comparison of differences was performed with the sample t-test. Statistical significance was defined as p-value < 0.05.

RESULTS

A total of 130 patients hospitalized in ICU were included in the study. Among them 42 (33.8%) were female and 88 (66.2%) were male patients. The mean age of patients was 51.6 ± 17.1 years (range 14 to 84 years). Most patients (36, 27.7%) were between 60 and

Table 1. *Distribution of patients with ICU-acquired infectionsaccording to age and sex*

Characteristics	Number of patients	Number of patients with ICUacquiredinfection	Prevalence (%)
Sex			
Female	42		
Male	88	20	22.73%
Age (years)			
≤ 19	10	2	20.2%
20–29	10	6	60.0%
30–39	14	4	28.6%
40–49	22	2	9.1%
50–59	28	2	7.1%
60–69	36	2	5.6%
70–79	6	2	33.3%
80 >	4	/	

Table 2. *Types of ICU-acquired infections*

Site of infection	Number of patients with ICU-acquired infections	Prevalence (%)
Lower respiratory tract infection	10	50
Surgical site infection	630	
Urinary tract infection	210	
Other site infection	210	

Table 3. *Antibiotic resistance pattern (%) of isolated organisms*

Antibiotics	Organisms					
	Acinetob. spp	P.aeruginosa	MRSA	Enterococcus	Kl. pneumoniae	Pr. mirabilis
Ceftriaxone	100	100	100	80	90	90
Cefepim	83.4	60	100	60	/	70
Clindamycin	100	/	90	80	90	/
Amikacin	83.4	40	80	70	30	30
Ciprofloxacin	100	40	80	70	60	50
Vancomycin	/	/	0	20	/	/
Linezolid	/	/	0	0	/	/
Meropenem	100	40	/	70	20	30
Imipenem	92	20	/	/	10	20
Gentamicin	92	40	80	70	70	60
Cotrimoxazol	50	/	60	/	/	70
Colistin	0	0	/	60	30	100

Acinetobacter species (Acinetob. spp); *Pseudomonas aeruginosa* (P. aeruginosa); *Methicillin Resistant Staphylococcus aureus* (MRSA); *Enterococcus* (Enterococcus); *Klebsiella pneumoniae V. aerogenes* (Kl. pneumoniae); *Proteus mirabilis* (Pr. mirabilis).

69 years old. Twenty of the 130 hospitalized patients developed ICU-acquired infection after at least 72 hours of hospitalization,giving a prevalence rate of 15.4%.All of them were male patients, hence the prevalence of ICU-acquired infections in male patients hospitalized in ICU was 22.73% (Table 1). The prevalence of ICU-acquired infections was highest in younger patients, between 20 to 29 years of age (Table 1).

According to the distribution of the types of ICU-acquired infections (Table 2) lower respiratory tract infection (pneumonia) was the most common infection presented in 10 (50%) of the infected patients. Surgical site infections were presented in 6 (30%) of the infected ICU patients and other infections had less prevalence (Table 2).

Seventy two of 132 taken specimens were positive. In patients with ICU-acquired infections the frequency of isolated Gram-negative organisms was significantly higher than that of the Gram-positive organisms (83% vs. 17%, $p \leq 0.005$). The most common found isolates (Figure 1) were those of *Acinetobacter species* (30, 41.7%) and *Pseudomonas aeruginosa* (15, 20.8%). Fungal growth was also seen in 4 (5.5%) of the isolated cultures.

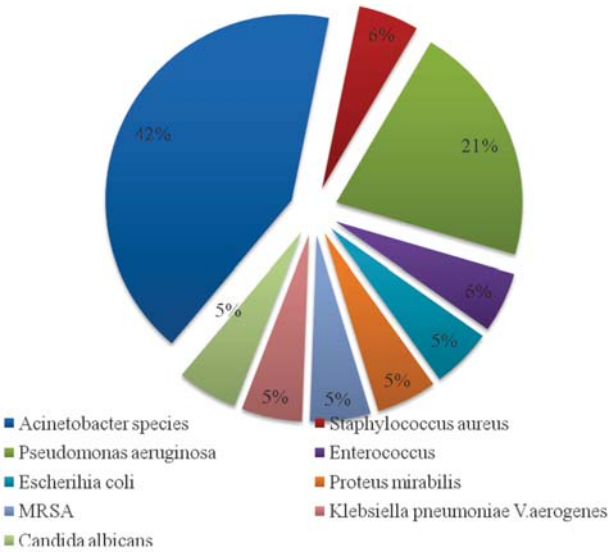

Figure 1. *Distribution of pathogens isolated in ICU infected patients*

The obtained results (Table 3) showed a high level of antibiotic resistance in both groups of organisms. *Acinetobacter species* isolates showed high resistance to most examined antibiotics (83-100%) and medium resistance to Cotrimoxazole (50%). *Pseudomonas*

aeruginosaisolates showed high resistance to Ceftriaxone (100%), medium resistance (40–60%) to Cefepime, Amikacin, Ciprofloxacin, Gentamicin and Meropenem and low resistance to Imipenem (20%). Both bacteria isolates were sensitive to Colistin. *Klebsiella pneumoniae* isolatesshowed high resistance (70–90%) to Ceftriaxone, Clindamycin and Gentamicin, medium resistance (60%) to Ciprofloxacin and low resistance (10–30%) to Amikacin, Colistin and Carbapenems. *Proteus mirabilis* showed high resistance to Colistin (100%) and Ceftriaxone (90%), and low resistance to Amikacin and Carbapenems (20–30%). All *MRSA* isolates showed high resistance over 60% to all examined antibiotics except to Vancomycin and Linezolid. *Enterococcus* isolates showed similar antibiotic resistance pattern as MRSA isolates. The only difference was the resistance to Vancomycin found in 20% of the examined isolates.

In general, the results showed a high level of antibiotic resistance to the most frequently used antibiotics like Cephalosporins, Gentamicin, Ciprofloxacin and Clindamycin.

DISCUSSION

Because of antibacterial drugs overuse, antibacterial drugs have become less effective or even ineffective, resulting in occurrence of multidrug resistant organisms.

According to the U.S. Centers for Disease Control and Prevention (CDC), each year in the United States, multidrug resistant organisms cause approximately 2 million cases of illnesses and 23,000 deaths (15). MDR organisms are organisms with acquired non-susceptibility to at least one agent in three or more antimicrobial categories which were previously proposed by the Clinical Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the United States Food and Drug Administration (FDA) (16).

These problematic pathogens, known as the "ESKAPE" pathogens group, which tend to be resistant to the activity of many antibiotics include: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter species*. *Clostridium difficile* can be also added to the list according to the literature (17). The mechanism of antimicrobial resistance in these pathogens can be explained by: (a)enzymatic degradation of antibiotics by hydrolytic enzymes, (b) alteration of bacterial proteins or target sites, and (c) changes in membrane permeability to antibiotics either by penetration or by expulsion of the actual antibiotic from within the bacteria (18). The Centers for Disease Control and Prevention (CDC) prioritized bacteria into one of three categories: concerning, serious and urgent (19).

In the different regions of the world there is a different prevalence of infections caused by multidrug resistant bacteria in ICUs. EPIC II study showed that about 51% of the ICU patients were considered to be infected with respiratory infection. According to the study, Staphylococcus aureus was isolated in 20.5% of the cases and the Gram-negative organisms (*E. coli*, *Enterobacter spp.*, *Klebsiella spp.*, *Pseudomonas spp.* and *Acinetobacter spp.*) were found in 62.2% of the patients. EUROBACT study showed an average of 47.8% MDR rate. According to this study different countries showed different MDR rate ranging from 8% in Australia to more than 75% in Turkey, Greece, Croatia and Serbia (12, 13).

In our study we found that ICU-acquired infections had a low prevalence rate of 15.4%. Our results corresponded with those presented by Sannusi (20), but were opposite to the results published by Rosenthal, Meric, Erbay, Magnason and Makanjuola (21-25) where higher prevalence rates of 26 - 39% were presented. Similar to the study by Makanjuola *et al.* (25) most of our patients with ICU-acquired infections were males aged from 20 to 29 years.

The most frequently ICU-acquired infections were pneumonia (50%),surgical site infections (30%) and urinary tract infections (10%). Other site infections which included primary bloodstream infections were found in less than 10% of the hospitalized patients.Our study population consisted of patients who were on mechanical ventilation, which is a risk factor for occurrence of ventilator-associated pneumonia (VAP).Similar findings have been reported by Meric *et al.* (22) Erbay *et al.* (23), de Leon-Rosales *et al.* (26), Richards *et al.* (27),Vincent *et al.* (8), Sheth *et al.* (28) and Makanjuola *et al*. (25). This means that considering the results from the previous studies pneumonia is the most common ICU-acquired infections in Nigeria, Turkey, Mexico, United Statesand India, although the study by Sanusi *et al.* (20), contrary to the study by Makanjuola *et al.* (25), showed that urinary tract infection were the most common ICU-acquired infections in Nigeria. Rosenthal et al. (21) found blood stream infections as the most common infections in ICUs in Argentina.

In our study Gram-negative bacteria isolates were more common than Gram-positive bacteria isolates (83% vs. 17%, $p \leq 0.005$). Similar to our results, in Asiancountries including India (29-35) and in some African countries (25), most of the isolates obtained from ICU patients weregram-negative organisms such as *Psudomonas aeruginosa*, *Echerichia coli*, *Klebsiella pneumonia* and *Acinetobacter species*, followed by

gram-positive organismslike *Staphylococcus* and *Enterococcus*. *Acinetobacter species* and *Pseudomonas aeruginosa* were the most common isolated Gram-negative bacteria in our study with prevalence of 41.7% and 20.8%, respectively. According to some studies Acinetobacter species are the most common cause of ICU infection especially in immunocompromised patients (33, 34). *Pseudomonas aeruginosa*, according to some studies (6, 23, 25, 28, 33) appears to predominate globally. The low prevalence of Gram-positive bacteria (*Staphylococus aureus*, *MRSA* and *Enterococcus*) in our study did not correlate with the prevalence presented in the most previously published studies (22, 20, 23, 34, 35). Only the study of Qadeer et al. (33) performed in Pakistan showed similar prevalence rates as ours.

The most important finding was the antibiotic resistance of the most common bacteria isolated in our study. According to our results, there was a very high level of resistance to antibiotics because isolated pathogens in our study showed resistance to multiple antibiotics. We found that *MRSA* was sensitive to Vancomycin and Linezolid and Enterococcus only to Linezolid. *Pseudomonas aeruginosa* and *Acinetobacter species* were both sensitive only to Colistin. This finding corresponds with the reports of the CDC, which presented that 63% of the infections with *Acinetobacter* in the United States were multidrug resistant infections. According to these reports, Acinetobacter causes approximately 12,000 healthcare-associated infections annually in the United States and approximately 1 million cases per year in the world globally. Other species like *Klebsiella pneumonia* and *Proteus mirabilis* showed low resistance only to Amikacin and Carbapenems (Meropenem and Imipenem). Our results did not correlate with those reported by Savanur *et al.* (32), who presented a high resistance of *Klebsiella* isolates, except to Cephalosporins and Gentamicinas well as to Amikacin and Carbapenems because of the persistence of carbapenemase-producing *Klebsiella pneumoniae* bacteria across North America and other word regions. All isolated bacteria species in our study were resistant to the most frequently used antibiotics like Cephalosporins, Gentamicin, Ciprofloxacin and Clindamycin. It means that ICU-acquired infections were caused by MDR organisms.

Our study has some limitations. Firstly, we did not identify some risk factors for occurrence of infections by MDR bacteria among ICU patients: central venous access, pulmonary artery catheterization, stress ulcer prophylaxis, urinary catheterization, mechanical ventilation, trauma, ICU length of stay and, mostly, a previous history of infection or colonization by MDR microorganisms. Secondly, the follow-up time period was only two months, which according to us is not sufficient for obtaining relevant results.

CONCLUSION

Having in mind the fact that there is a considerable variation in the presented MDR pathogens across the countries and geographical regions,the advantages of our study are as follows: it obtained data about the prevalence and types of ICU-acquired infections, determined the pathogens associated with these infections and determined the resistance pattern of the presented pathogens. This knowledge can be used to predict the resistance of the locally persistent pathogens and to make the choice of antibiotics according to the antimicrobial susceptibility pattern when infections occur. Thus, antibacterial drug overuse could be avoided, reducing the risk of MDR bacteria development.

CLINICAL RELEVANCE

Antibiotic resistance is a major upcoming problem in today's clinical practice, especially in patients with ICU-acquired infections. Local data of the prevalence and types of ICU-acquired infections, pathogens types and their resistance pattern are very important in order to obtain good antibiotic response, reducing morbidity and mortality rates and avoiding drug overuse and MDR bacteria development. Studies like ours give an opportunity for early targeted antibiotic therapy reducing the number of antibiotics or using narrower spectrum drugs. This is very important considering that prompt administration with appropriate antibiotics within 1 hour of recognizing infection, sepsis or septic shock has shown to improve survival in these patients with MDR ICU-acquired infections.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

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Sažetak

OTPORNOST INFEKCIJA NA VIŠESTRUKE LEKOVE U JEDINICAMA INTENZIVNE NEGE

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Uvod: Jedinice intenzivne nege (JIN) su često epicentar razvoja infekcija izazvanih mikroorganizmima otpornim na višestruke lekove (MDR).

Cilj: Cilj studije je da se utvrdi prevalenca i tipovi infekcija stečenih u JIN-u, utvrde patogeni povezani sa ovim infekcijama i utvrdi obrazac antibiotske rezistencije kod prisutnih patogena.

Materijal i metode: U studiju je uključeno 130 pacijenata hospitalizovanih u hirurškim JIN univerzitetske Klinike za anesteziologiju i intenzivnu negu u Skoplju tokom perioda od 2 meseca, April-Jun 2017, koji su razvili infekciju najmanje posle 72 sata od hospitalizacije. Kod svih njih identifikovani su patogeni i ispitana multirezistentnost na antibiotike.

Rezultati: Dvadeset od 130 (15,4%) pacijenata razvilo je infekcije stečene u JIN-u. Načešće infekcije bile su pneumonija (50%) i hirurške infekcije (30%). Gram-negativni organizmi bili su češće izolovani od Gram-pozitivnih (83% vs. 17%). Najčešće izolovane bakterije bile su *Acinetobacter species* (30, 41,7%) i *Pseudomonas aeruginosa* (15, 20,8%). Sve izolovane vrste su bili mikroorgaanizmi otporni na višestruke lekove, otporni na najčešće korišćene antibiotike kao što su Cephalosporins, Gentamicin, Ciprofloxacin and Clindamycin. *Pseudomonas aeruginosa* and *Acinetobacter sojevi* su bili osetljivi na Colistin. Methicillin-rezistentan Staphylococcus aureus (*MRSA*) je bio osetljiv na Vankomicin i Linezolid, a Enterococcus samo na Linezolid. *Klebsiella pneumoniae* i *Proteus mirabilis* su pokazali nisku rezistenciju samo na Amikacin i Karbapeneme.

Zaključak: Naša studija prikupila je podatke o prevalenci i tipovima infekcija stečenih u JIN-u, tipovima patogena i obrascu njihove otpornosti na antibiotike. Na osnovu ovih saznanja kliničari mogu da izaberu odgovarajuće antibiotike, izbegavajući prekomernu upotrebu antibiotika i ravoj multirezistentnih sojeva bakterija.

Ključne reči: infekcije stečene u jedinicama intenzivne nege, multirezistentne bakterije, antibiotska rezistencija.

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ILLNESS COGNITIONS IN PATIENTS WITH TEMPOROMANDIBULAR DISORDERS

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Abstract: **Background:** Temporomandibular disorders (TMD) is a term covering heterogeneous musculoskeletal disorders, including the temporomandibular joint and related structures. Pain is a common symptom in TMD. Chronic pain is a condition that affects the physical, psychological, cognitive and social domains of people who frequently have negative effects on quality of life. Illness cognitions is defined that patients who have a chronic illness have their own beliefs about their illness. In another saying, illness cognitions contain patient's perception and understanding of the disease and its treatment.

Material and Methods: This study was performed on 80 patients who applied to clinic with chronic TMD disorder. A written consent was obtained from the appropriate participants and the Illness Cognition Questionnaire (ICQ) forms were filled in by the patients under the guidance of the researchers. The statistical software SPSS (Statistical Package for Social Sciences, Version 20, Chicago IL, USA) was used.

Results: ICQ subscores of individuals with TMD: The mean score was 16.95 (SD = 4.05) for helplessness, 10.36 (SD = 3.14) for acceptance, and 15.55 (SD = 3.70) for perceived benefits. There was a statistically significant intra class correlation of 93.8% (0.915-0.957) among the Acceptance and 92.5% (0.896-0.948) among the Perceived benefits scale scores of the participants.

Conclusion: Psychological interventions that can create a positive perception against TMD and highlight the ability to overcome problem-oriented TMD, can prevent the disease from controlling the daily life of people with TMD in a positive way and can help to affect the health promotion process positively.

Keywords: Illness Cognition Questionnaire, Chronic Disease, Temporomandibular disorders.

INTRODUCTION

Temporomandibular disorders (TMD) is a term covering heterogeneous musculoskeletal disorders, including the temporomandibular joint and/or related structures. It is also accompanied by pain in the hard and soft tissues to which it is associated. Pain is common symptom in subtypes of TMD such as degenerative joint disease, primarily internal derangements and disorders associated with the temporomandibular joints (1).

The incidence of TMD symptoms in the population is between 6-12%. Approximately 80 percent of TMD patients present with signs and symptoms of joint disease, including disc replacement, arthralgia, osteoarthritis, and osteoarthritis (1). Poor understanding of the etiology or pathogenesis of TMD and deficiencies in the treatment approach lead to a process in which patients have to tolerate painful symptoms. This situation adversely affects the quality of life of patients (2).

Illness cognition is defined that patients who have a chronic illness have their own beliefs about their illness. In another saying, illness cognitions contain patient's perception and understanding of the disease and its treatment. A patient's beliefs affect their ability to cope with and adapt to the disease, and illness cognitions can be an important mediator between the situation and the patient's well-being (3,4). If patients perceive their illness as treatable and controllable, they experience less physical, emotional and social problems (5).

Chronic pain and fatigue is a condition that affects the physical, psychological, cognitive and social domains of people lives, and frequently have negative effects on quality of life (4). But it is often limited to fully explain its negative effects. Because there are many variables that can prevent or encourage adjustment, such as self-efficacy, coping strategies, and disease belief

(3, 5). Although there is a wide range of disease beliefs and cognitions related to correction of chronic symptoms. We focus on three general structures of helplessness, acceptance, and experienced benefits of disease. Some studies have found evidence for the beneficial effects of perceived control on symptoms (4, 5). In contrast, the lack of repetition of control over adverse events may lead to helplessness. Similarly, many studies have shown that lack of control is associated with adverse outcomes in chronic pain situations (2-5). There are studies showing that having control over symptoms may be associated with better compliance. Patients, who accepted pain, reported less depression, anxiety, and disability (3, 6).

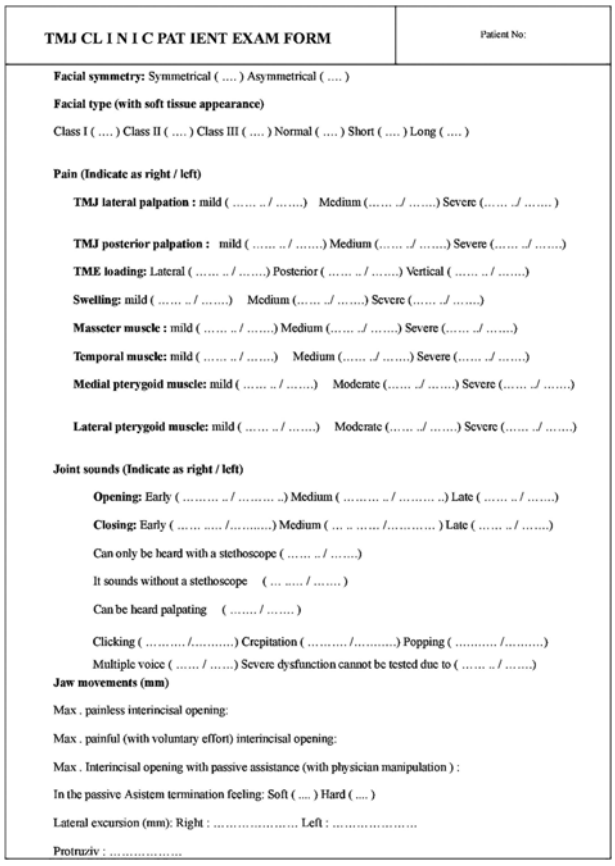
Recently, the Illness Cognition Questionnaire (ICQ) has been developed as a general measure of disease beliefs. ICQ which was developed to determine individuals' cognitive cognition, is very advantageous for research because of its low cost, ease of application, validity and reliability (7). There have been studies using the ICQ questionnaire, but there are no studies on dental-related diseases. Psychological effect of TMD on individuals and cognitive evaluation of patients is quite an issue. In our study, a reliable and valid Turkish version was used (2). The research hypothesis of the study is that ICQ gives significant results in the assessment of the disease cognition of individuals with TMJ disorder and patients focus on the "Helplessness" category.

MATERIAL AND METHODS

Ethics approval was provided by Istanbul Ayd2n University Ethics Committee. This research adhered to the principles of the Declaration of Helsinki. This study was performed on 80 patients whose age range was 18-70 years. The age, gender, marital status, educational status and employment status of the patients were recorded on the form prepared previously.

Intraoral and extraoral jaw joint, gnathology, muscle and occlusion examinations of patients who were directly admitted to Istanbul Aydin University Faculty of Dentistry or were referred by other dentists due to jaw joint, temple, pain in the face area, restriction of movement, and clenching complaints were made.

In extraoral and intraoral gnathological examination included: bilaterally assessment of TMJ sounds, palpation of TMJ, temporal, masseter, lateral pterygoid, sternocleidomastoid and posterior cervical muscles during opening, closing, laterotrusive and protruding movements. For 5 seconds on palpation, when 0.5 or 1.0 kg pressure is applied by calibrating according to the examined area, it was determined whether there was pain (8).The findings were recorded in the prepared "TMJ Clinic Patient Exam Form" (Figure 1).



TMJ CL I N I C PAT IENT EXAM FORM Patient No:

Facial symmetry: Symmetrical (....) Asymmetrical (....)

Facial type (with soft tissue appearance)

Class I (....) Class II (....) Class III (....) Normal (....) Short (....) Long (....)

Pain (Indicate as right / left)

TMJ lateral palpation : mild (..... .. / .....) Medium (..... ../ .....) Severe (..... ../ .....)

TMJ posterior palpation : mild (..... .. / .....) Medium (..... ../ .....) Severe (..... ../ .....)

TME loading: Lateral (..... .. / .....) Posterior (..... .. / .....) Vertical (..... .. / .....)

Swelling: mild (..... .. / .....) Medium (..... ../ .....) Severe (..... ../ .....)

Masseter muscle : mild (..... .. / .....) Medium (..... ../ .....) Severe (..... ../ .....)

Temporal muscle: mild (..... .. / .....) Medium (..... ../ .....) Severe (..... ../ .....)

Medial pterygoid muscle: mild (..... .. / .....) Moderate (..... ../ .....) Severe (..... ../ .....)

Lateral pterygoid muscle: mild (..... .. / .....) Moderate (..... ../ .....) Severe (..... ../ .....)

Joint sounds (Indicate as right / left)

Opening: Early (..... .. / ....) Medium (..... .. / ....) Late (..... .. / .....)

Closing: Early (..... ..... /.....) Medium (... .. .. /.....) Late (..... .. / .....)

Can only be heard with a stethoscope (..... .. / .....)

It sounds without a stethoscope (... ..... / .....)

Can be heard palpating (..... / .....)

Clicking (...../.....) Crepitation (...../.....) Popping (...../.....)

Multiple voice (..... / .....) Severe dysfunction cannot be tested due to (..... .. / .....)

Jaw movements (mm)

Max . painless interincisal opening:

Max . painful (with voluntary effort) interincisal opening:

Max . Interincisal opening with passive assistance (with physician manipulation) :

In the passive Asistem termination feeling: Soft (....) Hard (....)

Lateral excursion (mm): Right : ..... Left : .....

Protruziv : .....

Figure 1. *TMJ clinic patient exam form*

Patients diagnosed with fibromyalgia, trigeminal neuralgia, burning mouth syndrome, atypical facial pain, migraine, atypical odontalgia, cervical and neuropathic pain, were excluded from the study group.

A written consent was obtained from the appropriate participants and the ICQ forms were filled in by the patients under the guidance of the researchers. ICQ is an 18-item scale that assesses individuals' feelings and attitudes towards chronic diseases: it consists of 3 separate sub-categories, each containing 6 questions: 1- "Acceptance reflects the perceived ability of the individual to perceive his / her negative ideas in a positive way. For example, žI have learned to live with TMD'; 2- "Helplessness", focusing on the negative consequences of the disease and generalizing them to everyday life - for example, "My TMJ disorder restricts me to everything that is important to me"; and 3- žPerceived benefits', to investigate the benefits that a person may experience as a result of TMJ disorder; for example, ž'TMJ disturbance has taught me to enjoy the moment. The questions were answered with the Likert scale: "not at all-1" and "completely agree-4". Total increasing scale scores indicate that the helplessness and acceptance of the disease are kept to a greater extent by the participant. In addition to strong internal reliability, ICQ has a good structure and predictive validity under chronic conditions (1, 6).

The statistical software SPSS (Statistical Package for Social Sciences, Version 20, Chicago IL, USA) was used for calculations. All values presented as mean ± standard deviation and mean (Maximum - Minimum) percent and frequencies. The results of normality tests (Shapiro Wilk) were used to decide which statistical methods to apply in the comparison of the study groups. The relationship between the two continuous variables was evaluated by the Pearson Correlation Coefficient and Spearman Correlation Coefficient when the parametric test did not meet the prerequisites. Test-retest reliability coefficients were evaluated by intra class correlation coefficient. P values < 0.05 were considered statistically significant.

RESULTS

The average age of the study group was 39.23 ± 13.74 years.76% of the group was female patients and 24% was male patients. The ratio of female patients to male patients was 3.1 : 1. When evaluated according to the diagnoses, the difference between male and female patients was not statistically significant.

ICQ subscores of individuals with TMD: the mean score was 16.95 ± 4.05 (range min-max = 8-24) for helplessness, 10.36 ± 3.14 (range min-max = 6-18) for acceptance, and 15.55 ± 3.70 (range min-max = 8-24) for perceived benefits.

Intra class correlations were statistically significant among the Helplessness, Acceptance and Perceived benefits scales scores of the participants (Table 1).

There is a statistically significant difference between “Acceptance” and “Helplessness”. There is a 47.1% relationship, as one increases the other decreases (r = -0.471, p = 0.000). There is a statistically significant difference between “Perceived benefits” and “Acceptance”. There is a 48.5% relationship, one increases as the other increases (r = 0.485, p = 0.000).

DISCUSSION

The research hypothesis of the study was accepted because the highest scores were in “Helplessness” subscales. The disease cognition of individuals with TMJ disorder will focus on this category. This study provides evidence about the perceptions of disease cognitions in individuals with TMD and the psychological effect of the disorder. Regardless of sociodemographic, it describes how one perceives TMD and the ability to overcome its negative effects. The results support the view that disease cognitions are an important factor that correlates the disease with psychological well-being in general (7-10). Increased perception of helplessness in chronic disorders is consistent with studies that associate a weaker psychological condition with respect to other individuals (4, 6, 11, 12).

“Acceptance” from disease cognitions suggests that it can be a necessary prerequisite for all areas of TMD. Adaptive emotion change, strategies to eliminate useless thinking, and seeking social support are important protective factors for mental health, and the findings reflect the significant impact of disease cognitions on these domains. Conversely, “helplessness” from the cognitions of her illness is associated with withdrawal from social domains, and she is desperate for fear and anxiety about TMD and does not seek support. Therefore, intervention directed by individuals who do not benefit from cognition or disturbing emotions is essential to make the treatment of psychological state positive or treat people with TMD. Individuals’ perception, attitude and ability to overcome chronic diseases are changeable situations.

CONCLUSION

Factors used and examined in this study, i.e., disease cognition, are dynamic. Future research can produce new results that can be modified and improved us-

Table 1. *Intraclass correlation coefficient of ICQ subscales*

	Intraclass Correlation			F Test with True Value 0	
	ICC	Lower Limit	Upper Limit	Value	p
Helplessness	.838	0.777	0.888	6.188	0.001*
Acceptance	.938	0.915	0.957	16.246	0.001*
Perceived Benefits	.925	0.896	0.948	13.283	0.001*

*p < 0,05
ICC: Intraclass correlation coefficient

ing our findings. In conclusion, psychological interventions that can create a positive perception against TMD and highlight the ability to overcome problem-oriented TMD can prevent the disease from controlling the daily life of people with TMD in a positive way and can help to affect the health promotion.

Abbreviations

ICQ — Illness Cognition Questionnaire
TMD — Temporomandibular disorders
TMJ — Temporomandibular joint

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Sažetak

SPOZNAJA BOLESTI KOD PACIJENATA SA TEMPOROMANDIBULARNIM POREMEĆAJIMA

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Uvod: Temporomandibularni poremećaji (TMD) je termin koji obuhvata heterogene mišićnokoštane poremećaje, uključujući temporomandibularni zglob i odgovarajuće strukture. Bol je čest simptom TMD. Hronični bol je stanje koje utiče na fizički, psihički, kognitivni i socijalni aspekt čovekovog života, što za posledicu ima i negativan uticaj na sam kvalitet života. Spoznaja bolesti je definisana i time da pacijenti koji imaju hronično oboljenje imaju sopstveno ubeđenje o svojoj bolesti. Drugim rečima, spoznaja bolesti sadrži percepciju pacijenta, njegovo razumevanje bolesti i lečenja iste.

Materijal i Metode: Ova studija sprovedena je na 80 pacijenata koji su se javili na Kliniku zbog hroničnog temporomandibularnog poremećaja. Od odgovarajućih ispitanika dobijen je pismeni pristanak, a obrasci Upitnika o spoznaji bolesti (ICQ) su popunjeni od strane pacijenata pod nadzorom istraživača. Statistički program SPSS SPSS (Statistical Package for Social Sciences, Version 20, Chicago IL, USA) je korišćen za statističku obradu podataka.

Rezultati: ICQ rezultati ispitanika sa TMD: prosečna ocena za bespomoćnost bila je 16,95 (SD = 4,05), za prihvatanje 10,36 (SD = 3,14) i 15,55 (SD = 3,70) za opažene koristi. Postoji statistički značajna korelacija unutar grupe ispitanika među ocenama za Prihvatanje od 93,85% (0,915-0,957) i za Opažene koristi od 92.5% (0,896-0,948).

Zaključak: Psihološka potpora koja može razviti pozitivnu percepciju TMD-a i istaći sposbnost prevazilaženja orjentisanosti na TMD kao na problem, može sprečiti negativan uticaj bolesti na svakodnevni život pacijenata sa TMD-om i pozitivno uticati na proces promocije zdravlja.

Ključne reči: Illness Cognition Questionnaire, hronična bolest, temporomandibularni poremećaji.

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TRANSFUSION TRANSMITTED INFECTIONS (TTIs) AMONG BLOOD DONORS IN THE BLOOD BANK OF A TERTIARY CARE HOSPITAL IN INDIA: A RECORD BASED STUDY

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Abstract: **Objectives:** Transfusion Transmitted Infections (TTIs) are infections caused by potential pathogens which are transmitted to the blood recipients through blood transfusion. This study was primarily carried out to detect sero-positivity of the markers of Hepatitis-B virus (HBV), Hepatitis-C virus (HCV), Human immunodeficiency virus (HIV) and Syphilis in the blood donors at a tertiary care hospital in Srinagar, J&K, India over a of 4 years.

Material and Methods: Blood donations over 4 years from Jan.2015 to Dec. 2018 were reviewed retrospectively from the records of blood bank for seropositivity for HBV, HCV, HIV and Syphilis.

Results: A total of 31733 blood units were collected out of which 24494 (77.19%) were replacement and 7239 (22.81%) were voluntary. The seroprevalence of HBV, HCV, HIV and Syphilis was 0.22% (72), 0.16% (52), 0.009% (3) and 0.01% (5) respectively. A decreasing trend of all the major TTIs was observed over these years. Prevalence of all the four TTIs was observed highest in replacement donors as compared to voluntary donors.

Conclusion: Seroprevalence of all the TTIs was low as compared to the studies from rest of the country. Extensive donor selection and screening procedures will help in improving blood safety more. Efforts should be made to maximise voluntary donations and minimise replacement donations.

Keywords: Seroprevalence, Hepatitis B virus, Hepatitis C virus, HIV, Syphlis, Blood donor.

INTRODUCTION

Transfusion Transmitted Infection (TTI) is usually attributed to a pathogen such as a virus or parasite which is transmitted from donated blood to the recipient through a blood transfusion (1). There are also other modes of transmission of these infections, such as use of parenteral rugs, unsafe sexual practices, and from mother to child, but blood transfusion remains the main contributor (2). Literature suggests that TTIs are a serious threat to safe transfusion practices. For monitoring the safety of blood donation and to evaluate the efficacy of currently employed screening tests, correct estimates of risk of TTIs are essential (3). Although advancement in technology has led to the development of accurate methods to detect different markers of TTIs, the problems like false negative results, genetic variability in pathogen strains, window period of the disease, prevalence of asymptomatic carriers and technical errors continue to remain (4). Only continuous improvement and implementation of donor selection by detailed history taking and physical examination of the blood donors, screening of donors for high-risk behaviour, development of screening techniques which are sensitive, and different procedures that can eliminate or reduce the risk of acquiring TTIs (5). Unlike in India which heavily relies on replacement of blood donations, the developed countries have made tremendous advances for screening of TTIs (6).

Concealing of medical history poses a heightened threat to blood safety which can be minimised by proper recruitment strategy, voluntary donations, donor education and motivation (3). It has been seen that most of the voluntary donors in India belong to a higher socioeconomic class who are in a better position to understand the implications of questions being asked to the donors. On the other hand, replacement donors are compelled to donate in a short period of time (7).

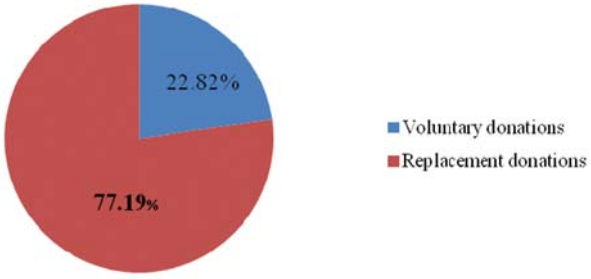
Mandatory screening tests for TTIs such as Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and Syphilis are done in most of the transfusion centres (3). As per a preliminary report by NACO (National AIDS Control Organization) in the year 2016, the prevalence of HBV, HCV, HIV and Syphilis among blood donors in India for the year 2015 was reported to be 0.94%, 0.32%, 0.13% and 0.18% respectively and the prevalence in Jammu and Kashmir was reported to be 0.32%, 0.26%, 0.04% and 0.22% respectively (8). Detection of TTIs in blood donors not only reduce risk of transmission through infected blood, but also gives an idea about the prevalence of these infections in the general population. This study was primarily carried out to detect seropositivity of the markers of HBV, HCV, HIV and Syphilis in the blood donors at GMC & SMHS tertiary care hospital, Srinagar, J&K, India over the period of 4 years. This study was aimed to access the prevalence of TTIs among blood donors at GMC &SMHS hospital and to estimate the proportions of Voluntary and Replacement donations.

MATERIAL AND METHODS

This record based cross-sectional study was conducted after getting permission from Institutional Ethical Committee. The study period was from January 2015 to December 2018. Data of blood donors who donated blood from January 2015 to December 2018 was collected from the blood bank of GMC & SMHS tertiary care hospital, Srinagar J&K, India. Blood donations over 4 years (Jan 2015 to Dec 2018) were revived retrospectively from the records of blood bank. The data consisted of total blood units collected, number of voluntary and replacement donations and the number of seropositive cases for HBV, HCV, HIV and Syphilis. Enzyme linked immunosorbent assay (ELISA, Trivitron's healthcare, India) test kits such as HBsAg ELISA kit, HCV ELISA kit and HIV-Ag-AbElisa kit were used respectively for the detection of HBsAg, HCV and HIV. Rapid test Kits (Immuno Quick Syphilis Ab, Immunoscience Pvt. Limited, Pune, India) were used for detection of Syphilis. Data was analyzed with the help of IBM SPSS version 20, USA (Statistical Package for the Service Solutions).

RESULTS

A total of 31733 blood units were collected over a period of 4 years (January 2015 to December 2018). Of total donations, 24494 (77.19%) were replacement and 7239 (22.81%) were voluntary (Figure 1). Yearly trend in replacement and voluntary blood donations is shown in Table 1. The total number of blood donations in the blood bank showed progressive increase from 6800 in 2015 to 9419 in 2018 but there was a progressive decrease in number of voluntary donations over a period of 4 years. Out of 31733 donations, 30974 (97.60%) were males and 759 (2.40%) were females as



Total blood donations and their distribution.

Figure 1. *Shows that around 3/4th of total blood donations were Replacement donations*

Table 1. *Shows that the total number of blood donations showed progressive increase from 2015 to 2018*

Year	Replacement donation (%)	Voluntary donation (%)	Total donation (%)
2015	4751 (69.87)	2049 (30.13)	6800 (21.43)
2016	5467 (75.93)	1733 (24.07)	7200 (22.69)
2017	6430 (77.34)	1884 (22.66)	8314 (26.19)
2018	7846 (83.30)	1573 (16.70)	9419 (29.69)
Total	24,494 (77.19)	7239 (22.81)	31,733(100)

Yearly distribution of voluntary and replacement blood donation.

Table 2. *Shows percentage of male and female donors*

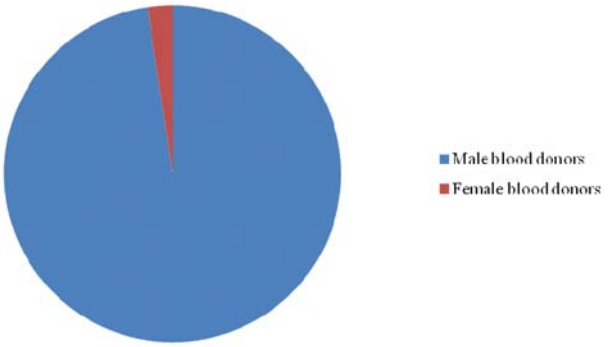
GENDER	Total no of donations	Percentage
Male	30974	97.60%
Female	759	2.40%
Total	31733	100%

Table 3. *Prevalence of HBsAg, HCV, HIV and Syphilis in blood donors*

Year	Total donors	HBsAg positive	HCV positive	HIV positive	VDRL positive
2015	6800	27 (0.39%)	16 (0.23%)	2 (0.02%)	1 (0.01%)
2016	7200	16 (0.22%)	18 (0.25%)	0 (0.00%)	1 (0.01%)
2017	8314	12 (0.14%)	10 (0.12%)	0 (0.00%)	0 (0.00%)
2018	9419	17 (0.18%)	8 (0.08%)	1 (0.01%)	3 (0.03%)
Total	31,733	72 (0.22%)	52 (0.16%)	3 (0.009%)	5 (0.01%)

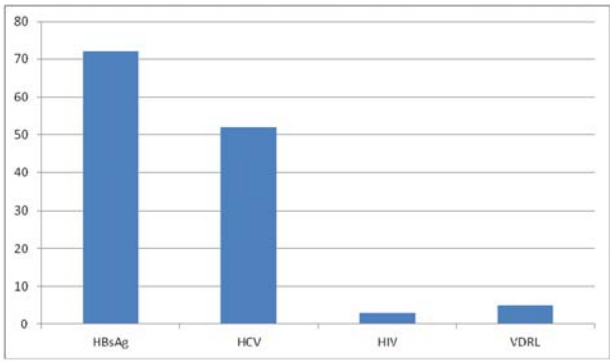
HbsAg; Hepatitis B surface antigen, HCV; Hepatitis C virus, HIV; Human immunodeficiency virus, VDRL; Veneral Disease Research Laboratory.

shown in Table 2 and Figure 2. On screening of 31733 blood donors, 72 donors (0.22%) were seropositive for HBsAg, 52 donors (0.16%) were seropositive for HCV, 3 donors (0.009%) were seropositive for HIV and 5 donors were seropositive for VDRL. The prevalence of HBsAg was observed to range from 0.39% in 2015 to 0.18% in 2019. HCV prevalence 0.23% in 2015 to 0.08% in 2018. HIV prevalence was observed to range from 0.02% in 2015 to 0.01% in 2018. Thus, for all three major TTIs, there was decreasing trend in the prevalence over these 4 years of study as shown in Table 3. This study also evaluated seroprevalence among replacement and voluntary donors and it was observed that prevalence of all the four TTIs was highest in replacement donors as shown in Figure 3. In this study the comparison of seroprevalence of TTIs was made between voluntary and replacement donors as shown in Figure 4. It was observed that replacement donors had a significantly higher prevalence of TTIs.



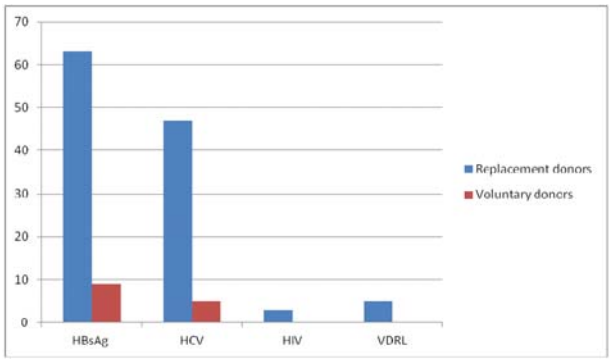
Maximum blood donations (97.60%) were males.

Figure 2. *Shows distribution of blood donors*



HBsAg; Hepatitis B surface antigen, HCV; Hepatitis C virus, HIV; Human immunodeficiency virus, VDRL; Veneral Disease Research Laboratory.

Figure 3. *Shows HBV as most prevalent infection followed by HCV infection*



HBsAg; Hepatitis B surface antigen, HCV; Hepatitis C virus, HIV; Human immunodeficiency virus, VDRL; Veneral Disease Research Laboratory.

Figure 4. *Comparison of seroprevalence of TTIs between Replacement and Voluntary donors*

DISCUSSION

Blood donations save many lives and has a vital role to play in the supportive care of medical as well as surgical patients but the unsafe transfusion of blood from infected donors to recipients puts millions of lives at risk (9). Unsafe practise of blood transfusion carries a significant risk of transmission of blood borne infections (10). Thus screening of every blood donation is important. Ideally, the standard sample for any seroprevalence study should be taken from general population but this is not always feasible. Therefore, detection of seroprevalence among healthy blood donors serves as a proxy for general population. It is a known fact that young adults are the main blood donors which means that seroprevalence of TTIs among children and elderly cannot be detected by this method (6).

In this study, an attempt was made to detect seroprevalence of HBV, HCV, HIV and Syphilis among blood donors and to detect the proportion of blood donations in terms of replacement and voluntary donation over the period of 4 years. It was observed that total number of blood donations in the blood bank showed a progressive increase during these 4 years. It was also observed that the seroprevalence of HBV and HCV infection decreased over these years. This study also highlighted the importance of voluntary donations in the field of transfusion medicine as there is a huge difference in infection rates between replacement and voluntary donors.

In this study low seroprevalence of all the TTIs was observed compared to the rest of the country which is also depicted in NACO 2015 report (8). Low seroprevalence of viral markers (HBV and HCV) as compared to other parts of the country was also observed by Qureshi MZ et al (11) who conducted a 10 year study at a tertiary care hospital. In this study, the seroprevalence of HBV among blood donors was 0.22% over a period of 4 years. This study is in accordance with the WHO classification (12), which reported Srinagar, J&K, India as a low prevalence zone (< 2%) for HBV. In this study among all TTIs, the seroprevalence of HBV was highest in comparison to other infections. Highest seroprevalence of HBV in comparison to other TTIs was also observed by Handoo S et al (13). In this study HCV seroprevalence among blood donors was found to be 0.16%. Mitrovic et al (14) observed HCV seroprevalence of 0.19% in their study.

In this 4 study, only 3 cases (0.009%) of HIV were detected. This may be due to awareness and medical advancement that HIV positive patients are able to come forward and seek medical intervention or it may be because people of high risk behaviour are aware to a certain extent about how to prevent HIV infection and mandatory availability of triple serology tests to be done by patients before any surgical procedure .Moreover, establishment of multiple numbers of Integrated Counselling and Testing Centres (ICTC) for HIV awareness and Opium Substitution Centres (OST) for preventing spread of infection among drug abusers have also limited the cases of HIV in Srinagar, J&K, India. A study conducted by Mahmood et al (15) observed 0% seroprevalence of HIV at their blood transfusion centre.In this study, seroprevalence of VDRL was 0.01%; similar results were observed by Chandra T et al (16). The detection of VDRL is mainly based on sensitivity kits available.

Promotion of voluntary donations would help in reducing the risk of TTIs as recommended by WHO Regional Office for South-East Asia, New Delhi (17). In this study, 22.81% of the total donations were voluntary and it was observed that seroprevalence of all the four TTIs was highest among replacement donors. Nanu A et al (18) also observed that all the three TTIs viz. HBV, HIV and Syphilis were significantly less frequent in voluntary donors. Similarly, Chandra T et al (16) observed in their 5 year study that prevalence of TTIs was more in replacement in comparison to voluntary donors. Therefore, we recommend that a heavy emphasis should be given to maximize voluntary blood donations so as to minimize the risk of TTIs. In our study decreasing trend in voluntary donations over the period of 4 years is of concern. This calls for awareness programs to be held for general public to promote voluntary blood donations, frequent organization of blood donation camps, better donor recruitment and retention strategies and reducing the replacement donations to minimum.

CONCLUSION

TTIs have a profound impact on the development of a nation. Methods to ensure a safe blood supply should be encouraged and emphasised. All the blood donors should be selected and screening after taking a thorough history. Thus it is important to give feedback to the blood banks regarding the prevalence of TTIs. Extensive efforts should be made to maximise the practise of voluntary donations and minimise replacement donations.

Abbreviations

TTIs — Transfusion Transmitted Infections
HBV — Hepatitis-B virus
HCV — Hepatitis-C virus
HIV — Human immunodeficiency virus

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Licensing

Sažetak

TRANSFUZIJOM PRENOSIVE INFEKCIJE (TTIs) MEĐU DONORIMA KRVI BANKE KRVI TERCIJARNE ZDRAVSTVENE USTANOVE U INDIJI: STUDIJA ZASNOVANA NA PODACIMA

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Uvod: Transfuzijom prenosive infekcije (TTIs) su infekcije uzrokovane potencijalnim patogenima koji su preneti primaocima preko transfuzije krvi. Ova studija je prvenstveno sprovedena radi detektovanja seropozitivnosti markera za Hepatitis-B virus (HBV), Hepatitis-C virus (HCV),Virus humane imunodeficijencije (HIV) i Sifilis u krvi donora, u tercijarnoj zdravstvenoj ustanovi u Srinagaru, J&K, Indija, tokom 4 godine.

Materijeal i Metode: Donacija krvi tokom 4 godine, od januara 2015. do decembra 2018., je retrospektivno pregledana iz podataka banke krvi koji su se odnosili na seropozitivnost za HBV, HCV, HIV and Sifilis.

Rezultati: Ukupno 31733 jedinica krvi je prikupljeno, od kojih je 24494 (77,19%) bilo zamena, a 7239 (22,81%) od dobrovoljnih davaoca. Seroprevalenca HBV, HCV, HIV i sifilisa bila je .22% (72), 0.16% (52), 0.009% (3) and 0.01% (5). Trend opadanja svih glavnih TTIs je primećen tokom poslednjih godina. Prevalenca sve četiri TTIs je najveća u jedinicama krvi iz zamene u poređenju sa dobrovoljnim donorima.

Zaključak: Seroprevalenca svih TTIs je bila niža u odnosu na studije iz ostalih delova sveta. Ekstenzivna selekcija donora i skrining procedure će pomoći u poboljšanju bezbednosti transfuzije. Treba uložiti do-

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EVALUATION OF A GROUP OF EPILEPSY PATIENTS IN TERMS OF SLEEP QUALITY, FATIGUE AND DEPRESSION

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Abstract: **Introduction:** The aim of this study is to investigate the relationship between clinical features, sleep quality, fatigue and mental symptoms in epileptic patients.

Material and Methods: This cross-sectional study was conducted at epilepsy outpatient clinic of Bozyaka Training and Research Hospital. 81 patients who were followed up for the diagnosis of epilepsy were included in the study. The patients were administered a sociodemographic data form, Pittsburgh Sleep Quality Index, Beck Depression Inventory, Fatigue Severity Scale.

Results: The median age of the patients included in the study was 37.42 (51.9%) were women and 39 (48.1%) were men with an education period of 8 years. There was no previous family history of psychiatric illness. Seizure control was achieved in 34 (42%) patients. 53 (65.4%) patients were observed for focal type, 28 (34.6%) patients were for generalized type seizures. The median duration of epilepsy was 13 years. The median Beck Depression Inventory score of the patients was 13, and the number of patients with a Beck Depression Inventory score higher than 19 was 25 (30.9%). There was mild tiredness in 47 (58%) and chronic fatigue in 16 (19.8%) patients. The median of Pittsburgh Sleep Quality Index total score was 4 and 18.5% (15) had poor sleep quality. Chronic fatigue was higher in epilepsy patients without seizure control compared to those with seizure control ($p = 0.001$).

Conclusion: The rate of patients with moderate and severe depression is high in our study. This indicates the significance of evaluating the diagnosis of depression in epilepsy patients. In the follow-up of these patients, it is crucial to investigate the causes of fatigue and depression carefully. Especially psychiatric expert opinion and multidisciplinary follow-up should be carried out without ignoring the presence of depression.

Keywords: Epilepsy, sleep quality, fatigue, depression.

INTRODUCTION

Epilepsy is a disease characterized by epileptic seizures causing neurological, cognitive, social and psychological results (1). According to World Health Organization data, epilepsy constitutes a significant part of the burden of disease in the world and affects approximately 50 million people (2). It is also known that it brings about many general medical diseases, psychiatric disorders and psychosocial problems (3). Today, the main goal of the treatment is to provide seizure control, as well as to add approaches to treatment modality to improve quality of life (4, 5).

Depression is more common in epileptic patients than in the general population (6). There is a mutual interaction between the disease and depression (7). Apart from ensuring seizure control in epilepsy management, it has been reported that reviewing and treating additional psychiatric diagnoses will improve the quality of life (3). On the other hand, factors such as presence of life time epilepsy, families with insufficient knowledge of the disease, and persistent social stigma lead to high levels of anxiety, depression symptoms, and a decrease in self-esteem (8-11). Fatigue and sleep problems are among the common symptoms of depression. It has been suggested that epileptic patients may experience significant deterioration in their quality of life and in cases where depression is accompanied by fatigue and sleep problems, when the intervention is not properly managed, the epileptic manifestation may worsen and drug compliance may deteriorate (12).

Fatigue is a symptom that reduces the individual's quality of life, affects mood, and can be seen in some psychiatric and medical illnesses including epilepsy, cancer, inflammatory, endocrinological and rheumatological diseases (13, 14). It can be described as the feeling of tiredness and exhaustion of physical energy, independent of unhappiness or weakness (15). Studies investigating the relationship between epilepsy and fatigue have been reported to be closely associated with depression and sleep problems (16, 17). It was emphasized that high fatigue rates detected in epileptic patients may be related to the presence of depression, socioeconomic and cultural factors rather than seizure related factors and its frequency (16, 18).

In the study of Ettinger et al., the fatigue rate in the presence of depression in epileptic patients was 44%, while Soyuer et al. reported this rate to be as 42.4% in epileptic patients without depression. In another study conducted in our country, fatigue rate in patients with epilepsy is 52.82%. In this study, the relationship between depression, fatigue and poor quality of life was emphasized (17, 19, 20).

Epilepsy and sleep have important effects on each other (21). In fact, the complex relationship between epilepsy and sleep has been initially noted by Aristotle and Hippocrates. In the late 1800s, it has been reported that approximately 1/5 of epileptic seizures occurred during sleep (22). In the study of Ilhan Alp et al., 24.8% of the patients undergoing video EEG monitoring had seizures during sleep only and 55.7% of them had both in sleep and wakefulness (23). While sleep deprivation affects the frequency of epileptic seizures and the development of interictal epileptiform discharges, epileptic seizures also change the microstructural structure of the sleep (24). It has been reported that sleep disorders are more common in epileptic patients than the healthy controls (25). The relationship between epilepsy and sleep disorders is complicated. While sleep deprivation may worsen seizures, some seizures may occur during the sleep (26). Inadequate sleep and poor sleep quality can impair seizure control, and seizures themselves can cause sleep problems. In this way, a mutual vicious circle can occur. In addition, some drugs used in the treatment of epilepsy have adverse effects on sleep (27). In the light of all information, clinicians have been suggested to be sensitive to sleep problems in epileptic patients (26).

Sudden occurrence of seizures in epileptic patients and the inability to control one's own body can decrease self-confidence and leads to embarrassment. This dilemma, defined as "learned helplessness" by Abramson and Hermann, results in problems in one's professional and social relations, and depression occurs as an inevitable conclusion (28, 29). Thus, the role of fatigue, sleep problems and depression that can be seen in epileptic patients are crucial in the treatment.

The aim of this study is to investigate the relationship between clinical features, sleep quality, fatigue and mental symptoms in epileptic patients. The study also aims to investigate the effects of seizure control and some seizure related factors including seizure type and frequency, disease duration on depression, sleep and fatigue.

MATERIAL AND METHODS

This cross-sectional study was conducted in an epilepsy outpatient clinic of a training and research hospital. Approval was obtained from the ethics committee of the hospital for the research in accordance with the Helsinki Declaration. The study included 81 patients who were followed up with the diagnosis of epilepsy (focal or generalized) based on the criteria of 'International League Against Epilepsy'. The patients were administered a sociodemographic data form, Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory (BDI), Fatigue Severity Scale (FSS). Informed written consent of the cases was obtained for their participation in the study. The presence of other chronic neurological diseases except epilepsy, mental retardation, psychotic disorder, substance use disorder, known sleep disorder/sleep disease, hypnotic or antidepressant drug use were determined as exclusion criteria.

Sociodemographic data form: This form prepared by the researchers, included the records of the patients' sociodemographic and disease information.

Pittsburgh Sleep Quality Index (PSQI): It is a sequential likert type self-report scale consisting of 24 questions in total (30). It provides information about the last one month of sleep quality and the type and severity of sleep disturbance. The total PSQI score ranges from 0-21. The sleep quality of those with a total score of 5 or less is considered to be "good". The Turkish validity and reliability study of the scale was conducted (31).

Beck Depression Inventory (BDI): It is a self-report scale developed by Beck in 1961 (32). The scale consists of 21 items, and each question is scored as 0, 1, 2, 3, and scores ranging from 0-63 in total are obtained. Results are evaluated as 0-9 none/minimal depression, 10-18 mild depression, 19-29 moderate depression, 30-63 severe depression. Validity and reliability study has been conducted for Turkish society (33).

Fatigue Severity Scale (FSS): It is a self-report scale consisting of 9 items in total (34). The total score is calculated according to the average of these 9 items. Pathological fatigue cut-off value is accepted as 4 po-

ints or above. Turkish validity and reliability study was carried out by Armutlu et al. (35).

Statistical Analysis

In this study, Statistical Package for Social Sciences (SPSS) for Windows v. 21.0 package program was used. Percentage distributions, median and extreme values of the research data are given. Chi-square test was used to investigate the difference between groups with and without seizure control, and Mann-Whitney U test was used to compare continuous variables. The relationship between the various clinical features of epilepsy and dependent variables in the study was examined with the spearman correlation test. Variables were examined in the 95% confidence interval and $p < 0.05$ was considered significant.

RESULTS

A total of 81 patients, 42 (51.9%) women, 39 (48.1%) men, were included in the study. The median age of the patients was 37 (17-67), their education period was 8 (0-17) years. In terms of marital status, 32 (39.5%) people were single. In the sample, 25 (30.9%) people were housewives and 28 (34.6%) people were working (n = 28, 34.6%). The sociodemographic data of the patients are presented in Table 1. 53 patients (65.4%) were observed with focal type and 28 (34.6%) with generalized type seizure. Median epilepsy disease duration was 13 (1-54) years. Seizure control was achieved in 34 (42%) patients for at least 1 year. The median BDI score of all patients was 13 (0-47) and the number of patients with a BDI score higher than 19 was 25 (30.8%). 47 (58%) patients had mild and 16 (19.8%) had chronic fatigue. The median of PSQI score of the sample was 4 (0-15) and the sleep quality of 28 (34.6%) was worse. There was no significant difference between the genders in terms of scale scores used in the study. Comparison of the scores of scales used in the study by gender is presented in Table 2.

Table 1. *Demographic and clinical features of patients with epilepsy*

Sex n (%)		
Female	42	(51.9%)
Male	39	(48.1%)
Age (years) median (min-max)	37	[17-67]
Education (years) median (min-max)	8	[0-17]
Marital status n (%)		
Single	32	(39.5%)
Married	46	(56.8%)
Widow/Divorced	3	(3.7%)
Job n (%)		
Unemployed	11	(13.6%)
Housewife	25	(30.9%)
Student	5	(6.2%)
Active worker	28	(34.6%)
Retired	12	(14.8%)
Seizure type n (%)		
Focal	53	(65.4%)
Generalized	28	(34.6%)
Duration of epilepsy (years) median [min-max]	13	[1-54]

Table 2. *Evaluation of the distribution of the BDI, FSS, PSQI scores of the sample and comparison of the scores by gender in patients with epilepsy*

	Female (n = 42)	**Male** (n = 39)	**Total** (n = 81)	**p**
Total score of BDI median [min-max]	14.5 [0-47]	11 [1-34]	13 [0-47]	0.246
Score ranges of BDI				0.331
0-9 score	12 (28.6%)	16 (41.0%)	28 (34.6%)	
10-18 score	16 (38.1%)	12 (30.8%)	28 (34.6%)	
19 ve more	14 (33.3%)	11 (28.2%)	25 (30.9%)	
FSS n (%)				0.086
No tiredness	8 (19.0%)	10 (25.6%)	18 (22.2%)	
Mild	22 (52.4%)	25 (64.1%)	47 (58%)	
Chronic	12 (28.6%)	4 (10.3%)	16 (19.8%)	
Total score of PSQI median [min-max]	4 [0-13]	4 [1-15]	4 [0-15]	0.277
Sleep Quality n (%)				0.081
Good	24 (57.1%)	29 (74.4%)	53(65.4%)	
Poor	18 (42.9%)	10 (26.6%)	28(34.6%)	

Table 3. *The relationship of clinical features of epilepsy and BDI, FSS, PSQI scores*

	BDI score median [min-max]	**p**	**PSQI score** median [min-max]	**p**	**FSS score** median [min-max]	**p**
Seizure frequency Controlled (n = 34) Once a month or less (n = 24) More than once a month (n = 23)	 10 [1-36] 14 [0-37] 16 [1-47]	0.224	 4 [1-15] 4 [0-11] 4 [1-13]	0.556	 4,1 [1.3-7] 5 [1.1-6.7] 4.3 [1.3-6.4]	0.208
Seizure Type Focal seizure (n = 53) Generalized seizure (n = 28)	 11 [1-47] 15 [0-37]	0.195	 4 [0-13] 4 [1-15]	0,319	 4 [1.1-1.7] 4,8 [1.7-6.8]	0.106
Duration of epilepsy	r = 0.047	0.68*	r = -0.112	0.318*	r = -0.092	0.412

Spearman correlation analysis, r = correlation coefficent.

Table 4. *Comparison of patients with epilepsy according to seizure control status in terms of BDI, FSS, PSQI scores*

	Seizure control status		**Z/df**	**p**
	Controlled (n = 34, 42%)	**Uncontrolled (n = 47, 58%)**		
BDI (mean ± SD)	12.79 ± 9.01	16.45 ± 10.67	-1.628	0.103
Presense of depression n (%) No Yes	 25 (73.5%) 9 (26.5%)	 31 (66%) 16 (34%)	1	0.467
Total score of PQSI (mean ± SD)	4.79 ± 2.90	4.38 ± 2.86	-0.941	0.346
Sleep quality n (%) Good Poor	 22 (64.7%) 12 (35.3%)	 31 (66%) 16 (34%)	1	0.907
FSS score (mean ± SD)	4.07 ± 1.82	4.50 ± 1.46	-1.034	0.301
Presense of fatigue n (%) No Yes	 14 (41.2%) 20 (58.8%)	 4 (8.5%) 43 (91.5%)	1	**0.001**

When the relationship between epilepsy clinical variables (seizure frequency, seizure type, duration of disease), BDI, PSQI and FSS scores were investigated, no statistically significant relationship was found between the variables (Table 3). There was no significant difference in terms of BDI score, presence of depression, total score of PSQI, sleep quality, fatigue score among epilepsy patients with and without seizure control. Chronic fatigue rate was higher in the group without seizure control (p = 0.001). Comparison of epileptic patients in terms of depression, sleep quality and fatigue scale scores according to the presence of seizure control is reflected in Table 4.

DISCUSSION

As a result of our research, no relation was found between epileptic seizure type, frequency of seizure and disease duration, and depression, sleep and fatigue. It was figured out that patients without seizure control had a higher rate of chronic fatigue.

Depressive disorders are among the most common psychiatric diseases in the general population, and rates ranging from 13-35% have been reported due to the differing evaluation methods used in research (36-39). In our study, moderate and severe depression were detected in 31% (n = 25) of epilepsy patients. The rate was consistent with the research results reported in the literature (3, 36, 39). This high rate of incidence compared to the general population has been associated with bilateral interaction between epilepsy and psychiatric diseases. It has been thought that hyperactive hypothalomo-pituitary axes, limbic structures and dysfunctions, epileptic focus itself, antiepileptic drugs and social problems brought by the disease may contribute to comorbidity (19, 40). However, depression is often not recognized and treated as a comorbid disease. It has been

suggested that depression should be considered in the follow-up of the epileptic patients (6).

Studies have highlighted the relationship between seizure-related factors such as disease duration, frequency of seizures, and seizure types in epileptic individuals with depression. In our study, although 16 of 25 patients with moderate and severe depression in the sample were in the group of patients without seizure control, no significant difference was found between the groups with and without seizure control in terms of BDI scores. A study reporting the frequency of seizures was ineffective on depression symptom levels supported this result (41). In the compiled study made by Scott AJ et al., the frequency of depression was higher than the general population regardless of the rate of seizure control and drug-resistant patients (39). Research suggests that the rate of psychiatric comorbidity is higher in patients without seizure control or drug-resistant cases, but our results do not support these findings (42, 43). This result may be due to the characteristics of the selected sample and the evaluation of depression based on the self-report scale. We believe that follow-up studies in epileptic patients, in which depression comorbidity or development is evaluated in larger samples by structured interview, will be beneficial.

Fatigue is a complaint far from epilepsy symptomatology; although it has not been questioned in clinical practice, it has been reported to be 4 times higher than the general population in this patient group (44). In our sample, not only the fatigue rates but also the chronic fatigue rate of the patients without seizure control were high. It has been reported that chronic fatigue has a negative effect on quality of life of the epileptic patients, where seizure control cannot be achieved (20). For this reason, clinicians are advised to be careful and to question fatigue, especially in cases without seizure control.

When the electrophysiological effects of sleep in epilepsy were investigated, it was shown that ictal and interictal epileptic discharges mostly appeared in NREM sleep, while they were suppressed in REM sleep (22). In other words, while REM sleep shows low activation in the occurrence of seizures, NREM sleep plays a trigger role by showing high activation (45). Impaired sleep quality has been reported to be 16-24.5% in studies with PSQI used to evaluate subjective sleep quality in epileptic patients (46,47). In a similar study by Çillerler et al, they found poor sleep quality in 42.7% of epileptic patients using PSQI (48). Likewise, in our study, 34.6% of patients had poor sleep quality. Although poor sleep quality rate was higher in patients without seizure control, we could not find a statistically significant difference in PSQI scores between the two groups compared to patients without seizures. In the literature, there are studies reporting an increase in the frequency of seizures and a deterioration in sleep quality, there are also studies similar to ours that draw attention to the poor quality of sleep in epilepsy patients and do not find a relationship between seizure frequency and sleep quality (17, 46, 48, 49).

In addition to the limitations inherent in cross-sectional research, our study is among the limitations of the absence of polysomnographic examination on the cases, and no psychiatric interview structured for the diagnosis and types of depression. Despite these limitations, we think that our results will contribute to the literature in order to attract the attention of clinicians to psychiatric comorbidities in epilepsy.

CONCLUSION

Raising awareness of psychiatric symptoms in epileptic patients is essential in treatment management. It should be borne in mind that the study of fatigue, sleep disturbance and depression may affect each other and can be common in patients with epilepsy. In the presence of psychiatric comorbidities, especially depression, multidisciplinary approach and joint monitoring are essential.

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Abbreviations

BDI — Beck Depression Inventory
FSS — Fatigue Severity Scale
NREM — Non-Rapid Eye Movement
PSQI — Pittsburgh Sleep Quality Index
REM — Rapid Eye Movement

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Sažetak

EVALUACIJA GRUPE PACIJENATA OBOLELIH OD EPILEPSIJE U POGLEDU KVALITETA SNA, UMORA I DEPRESIJE

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Uvod: Cilj ove studije je da ispita vezu između kliničkih karakteristika, kvaliteta sna, umora i mentalnih simptoma kod pacijenata obolelih od epilepsije.

Materijal i Metode: Ova studija preseka je sprovedena u ambulanti za epilepsiju Bozyaka Training and Research Hospital. U studiju je uključen 81 pacijent. Pacijenti su popunjavali obrasce sa odgovarajućim sociodemografskim podacima, Pittsburgh Sleep Quality Index, Beck Depression Inventory, Fatigue Severity Scale.

Rezultati: Prosečna starost pacijenata uključenih u studiju bila je 37 godina. Od ukupnog broja ispitanika, 42 (51,9%) bile su žene, a 39 (48,1%) muškarci. Nije bilo pozitivne porodične anamneze u smislu psihijatrijskih bolesti. Kontrola napada postignuta je kod 34 (42%) pacijenta. 53 (65,4%) pacijenta su praćena zbog fokalnog tipa, a 28 (34,6%) zbog generalizovanog tipa napada. Prosečna dužina trajanja bolesti bila je 13 godina. Prosečan Beck Depression Inventory skor pacijenata bio je 13, a broj pacijenata sa Beck Depression Inventory skorom većim od 19 bio je 25 (30,9%). Blagi umor bio je kod 47 (58%) pacijenata, a hronični umor kod 16 (19,8%). Medijana ukupnog skora Pittsburgh Sleep Quality Index bila je 4 and 18.5% (15) je imalo loš kvalitet sna. Hronični umor je bio veći kod pacijenata sa epilepsijom bez kontrolisanih napada nego kod onih sa kontrolom napada ($p = 0,001$).

Zaključak: Stopa pacijenata sa umerenom i teškom depresijom je visoka u našoj studiji. Ovo ukazuje na značaj procene dijagnoze depresije kod pacijenata sa epilepsijom. U toku praćenja ovih pacijenata od krucijalnog značaja je pažljivo ispitati uzroke umora i depresije. Naročito bi trebalo tražiti stručno mišljenje psihijatra i sprovesti multidisciplinarno praćenje bez ignorisanja prisustva depresije.

Ključne reči: epilepsija, kvalitet sna, umor, depresija.

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THE RELATIONSHIP BETWEEN BONE MINERAL DENSITY AND HIGH-DOSE SHORT-TERM CORTICOSTEROID THERAPY IN PATIENTS WITH MULTIPLE SCLEROSIS

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Abstract: **Introduction:** Previous studies were reported that osteoporosis and bone fracture occurs more frequently among Multiple sclerosis patients than the general population. The aim of this study to investigate the affects of total doses of short-term, high dose corticosteroids on bone mineral density and other affecting factors for bone mineral density in Relapsing-remitting type Multiple Sclerosis patients.

Material and methods: Fifty-four patients (37 females, 17 males) with relapsing-remitting type Multiple Sclerosis who filled the diagnostic criteria according to McDonald criteria were included in the study. Femoral and lumbar bone mineral density were measured using dual energy X-ray absorptiometry. Expanded Disability Status Scale, disease duration, number of attacks, cumulative corticosteroid dose were recorded. Serum calcium, potassium, phosphorus, vitamin D, parathormone and osteocalcin levels were measured. Patients were divided into two groups: patients who have received at least 20 g intravenous metilprednisolone (Group I) and patients who have received less than 20 g intravenous metilprednisolone (Group II). We analysed association between cumulative corticosteroid dose and each parameters.

Results: Osteopenia was present in 46.2% and osteoporosis in 5.5% of the study population according to femoral neck bone mineral density. Femoral bone mineral density was significantly lower among patients. There was no correlation between cumulative dose of corticosteroid and bone mineral density.

Conclusion: Low bone mineral density and osteoporosis are common in Multiple sclerosis patients. High-dose steroid therapy is not be the primary cause of osteoporosis in patients with multiple sclerosis.

Key words: Multiple sclerosis, bone mineral density, vitamin D.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, progressive demyelinating disease of the central nervous system that causes significant disability in the young population. Previous studies were reported that osteoporosis and bone fracture occurs more frequently among MS patients than the general population, probably as a result of reduced mobility, vitamin D deficiency and exposure to corticosteroid (CS) (1-5). Oral CS treatment leads to a reduction in bone mineral density (BMD) and a rapid (within 3 to 6 months) increase in the risk of fracture during the treatment period (6). In Relapsing-Remitting MS (RRMS) patients, short-term intravenous high-dose methylprednisolone (IVMP 1g/day) are commonly used during acute relapse (7). It is well known effect on BMD of chronic CS exposure, but, the effect of short-term, high-dose therapy on BMD are still unclear.

The aim of this study to investigate the affects of cumulative IVMP dose and other factors on BMD in RRMS patients.

PATIENTS AND METHODS

This study was conducted in multiple sclerosis outpatient clinic of a training and research hospital,

University of Sciences, Tepecik Training and Research Hospital, between June 2009 and December 2009. Fifty-four patients with RRMS (37 female and 17 male) diagnosed according to the McDonald criteria, aged 20 to 56 years were included in this study. All procedures performed in study were in accordance with the ethical standards of the institutional research committee and with the Helsinki declaration. Patients with a disease (hyperthyroidism, rheumatoid arthritis etc.) or medication use (hormone replacement, oral contraceptive pill etc.) that might affect on BMD were excluded from the study. None of female women patients is menopause. All patients were in remission and had not received CSs in the last three months due to relapse. Clinical data and the glucocorticoids (GC) doses were obtained by carefully searching medical records. Expanded Disability Status Scale (EDSS), disease duration, number of attacks, cumulative CS dose were recorded for all patients.

Serum calcium, potassium, phosphorus, vitamin D, parathormone (PTH) and osteocalcin levels were measured both patients. Laboratory tests included serum concentrations of vitamin D, parathyroid hormone and osteocalcin. 25 hydroxyvitamin D3 (25-OH-vitamin D3) isoform was measured. 25-OH-vitamin D3 concentrations and osteocalcin levels were assessed by a chemiluminescence immunoassay. 25-OH-vitamin D3 concentrations was assessed with Diasorin (Diasorin Inc. Northwestern Avestillwater, USA) kit and osteocalcin levels was assessed with Siemens Healthcare Diagnostics (Siemens Diagnostics Inc. Los Angeles, USA) kit. Parathyroid hormone levels were assessed using routine laboratory methods (normal range: 10-69 pg/ml). The 25-OH-vitamin D3 concentrations, parathyroid hormone and osteocalcin levels in patients were compared to normal reference range. Laboratory referential values for 25-OH-vitamin D3 levels in the serum ranged between 30-80 ng/ml and osteocalcin levels in the serum ranged between 2-21 ng/ml.

Dual energy X-ray absorptiometry (DEXA; Hologic QDR- 4500 °C) was used to measure BMD values at the lumbar vertebrae (L2-L4 in the AP projection) and in the proximal femur (femoral neck), in addition to T and Z scores. T-score is used to make a diagnosis of normal bone density, osteoporosis, or osteopenia according to the World Health Organization (WHO) criteria. T-score of > 1.0 was considered normal. A T-score between -1.0 and -2.5 was interpreted as osteopenia and a T-score of < - 2.5 indicated osteoporosis (8).

According to the total dose of IVMP received during the illness, patients included in the study were divided into two groups: patients who have received at least 20 g IVMP (Group I) and patients who have received less than 20 g IVMP (Group II).

We assessed whether there was any difference in BMD and other parameters between groups.

STATISTICAL ANALYSIS

Statistical evaluations were made with the SPSS 15.0 program. Student's t-test, the Mann-Whitney U test and Pearson correlation coefficient were used in the comparison. Values of $p < 0.05$ were considered significant.

RESULTS

Descriptive characteristics and densitometry measurement results of all patients were summarized in Table 1. Mean age of the all RRMS patients was 37.68 ± 9.31 (20-56) years, mean disease duration was 10.32 ± 6.10 (2-27) years and EDSS was 1.49 ± 0.73 (0-3.5). 68.5% of the patients were women. All of the patients were ambulatory (EDSS < 3.5). All patients had normal range of serum calcium. Mean vitamin D level was 14.4±6.96 ng/ml (2-28.9). 77.7% of the patients had vitamin D level below normal level (vitamin D deficient). Mean osteocalcin level was 4.54 ± 3.16. 77.7 % of the patients had normal osteocalcin levels.

When we classify BMD measurements as normal, osteopenia and osteoporosis according to WHO criteria, femoral neck BMD was observed as normal in 26 (48.8%) patients, osteopenia in 25 (46.2%) patients, and osteoporosis in 3 (5,5%) patients. And, lumbar vertebrae BMD was observed as normal in 29 (53.7%) patients, osteopenia in 19 (35.1%) patients and osteoporosis in 6 (11.1%) patients. Mean BMD on femur neck (0.78 ± 0.14) was lower than lumbar vertebrae BMD (0.95 ± 0.14) ($p > 0.05$). Overall rates of osteopenia and osteoporosis according to femoral neck in RRMS patients were 46.2% and 5.5% respectively. In all patients, no statistically significant difference was found between BMD and other parameters including disease duration, EDSS and vitamin D level (Table 1).

There were 32 patients in group I and 22 patients in group II. No statistically significant differences were found in terms of sex, age, EDSS, disease duration, level of parathormon, vitamin D and osteocalcin, lumbar vertebrae T and Z score, femur neck T and Z score, lumbar vertebrae BMD and femur neck BMD between groups. There was a significant difference between the groups in terms of the number of attacks. Patients who received more than 20 gr of pulse IVMP had more attacks (p: 0.000) (Table 1).

There was no statistically significant difference was determined in terms of mean osteocalcin and PTH levels between the groups (p: 0,22 and p: 0,31).When osteocalcin levels of the groups were compared in

Table 1. *Comparison of parameters between groups*

	Total	**Group I**	**Group II**	**P**
Sex (Female/male)	38/16	21/11	17/5	0.54
Age (mean ± SD) (year)	37.68 ± 9.31	38.73 ± 10.02	36.23 ± 8.37	0.20
Disease duration (year)	10.32 ± 6.10	9.91 ± 6.16	11.50 ± 4.51	0.10
Relaps number (mean ± SD)	4.77 ± 2.70	3.88 ± 2.77	6.18 ± 1.99	**0.00**
EDSS (mean ± SD)	1.49 ± 0.73	1.48 ± 0.74	1.52 ± 0.75	0.64
PTH (mean ± SD) pg/mL	56.49 ± 25.37	61.35 ± 26.12	49.74 ± 23.53	0.31
Osteocalcin (mean ± SD) ng/ml	4.54 ± 3.16	4.67 ± 2.81	4.26 ± 3.73	0.22
Vitamin D (25 (OH)) (mean ± SD) ng/ml	14.4 ± 6.96	14.23 ± 6,64	14.45 ± 7.65	0.91
Lomber vertebrae T score (mean ± SD)	-1.02 ± 1.25	-1.07 ± 1.16	-0.89 ± 1.39	0.82
Lomber vertebrae Z score (mean ± SD)	-0.79 ± 1.21	-0.83 ± 1.12	-0.65 ± 1.34	0.29
Femur neck T score (mean ± SD)	-0.99 ± 1.03	-0.94 ± 0.95	-1.05 ± 1.18	0.80
Femur neck Z score (mean ± SD)	-0.71 ± 0.94	-0.66 ± 0.85	-0.76 ± 1.08	0.65
Lomber vertebra BMD (mean ± SD) g/cm^2	0.95 ± 0.14	0.95 ± 0.13	0.95 ± 0.15	1.00
Femur neck BMD (mean ± SD) g/cm^2	0.78 ± 0.14	0.79 ± 0.12	0.77 ± 0.16	0.78

Table 2. *Descriptive characteristics female and male MS patients*

	Total (mean ± SD)	**Male** (mean ± SD)	**Female** (mean ± SD)	**p**
Age (year)	37.68 ± 9.31	37.23 ± 10.11	37.87 ± 9.08	0.81
MS disease duration (year)	10.32 ± 6.10	8.59 ± 6.15	11.08 ± 6.00	0.11
Relaps number	4.77 ± 2.70	4.71 ± 3.48	4.80 ± 2.34	0.63
EDSS	1.49 ± 0.73	1.26 ± 0.71	1.59 ± 0.73	0.11
PTH pg/mL	56.49 ± 25.37	56.47 ± 21.11	56.49 ± 27.27	0.65
Osteocalcin ng/ml	4.54 ± 3.16	5.32 ± 2.63	4.19 ± 3.34	0.06
Vitamin D (25 (OH))ng/ml	14.4 ± 6.96	18.75 ± 5.64	12.53 ± 6.69	**0.002**
Lomber vertebra T score	-1.02 ± 1.25	-1.74 ± 1.31	-0.70 ± 1.09	**0.003**
Lomber vertebra Z score	-0.79 ± 1.21	-1.61 ± 1.24	-0.42 ± 1.02	**0.00**
Femur neck T score	-0.99 ± 1.03	-1.20 ± 2.63	-0.91 ± 3.34	0.34
Femur neck Z score	-0.71 ± 0.94	-0.81 ± 0.67	-0.67 ± 1.04	0.60
Lomber vertebra BMD g/cm^2	0.95 ± 0.14	0.90 ± 0.14	0.97 ± 0.13	0.62
Femur neck BMD g/cm^2	0.78 ± 0.14	0.79 ± 0.13	0.78 ± 0.14	0.83

BMD lumbar vertebrae measurements, osteocalcin levels of osteoporosis patients were statistically higher than in the normal patients (p: 0.01).

When the patients were classified according to gender, the lumbar vertebrae Z score (p: 0.00) and T score (p: 0.003) of male patients was lower than female patients. No statistically significant difference was found between genders in other parameters (Table 2).

DISCUSSION and CONCLUSION

Our results showed a higher rate of osteoporosis and osteopenia (5.5%) and osteopenia (46.2%) in MS patients compared with the patient population with inflammatory bowel diseases (9). Lower BMD at femoral neck and lumbar vertebrae was present in 51.8% and 46.3% of the patients respectively. In previous studies, osteopenia was documented in 36.1% - 80% patients with MS and osteoporosis in 4.7%–37.5% (10-18). It has been reported that osteopenia and osteoporosis are more common in the femoral neck compared to the lumbar spine in MS (5, 19). We did not found difference BMD loss between femoral neck and lumbar vertebrae.

The studies investigating the effect of IVMP therapy on BMD in MS patients reported conflicting re-

sults. Some authors have reported a negative association between cumulative pulse corticosteroid dosage and BMD (17, 20, 21). Huang et al. explained that high-dose, short-term IVMP treatment is effective in accelerating sudden and permanent decreases in bone formation and a rapid and temporary increase in bone resorption (20). However, in our study and some others reported no significant relationship between cumulative pulse CS dose and BMD (5, 16, 18). Similarly, Olson et al. reported reduced BMD compared to a large cohort of MS patients in Denmark and an age-appropriate reference population, but they found no significant association between glucocorticoids (GC) dose (13).

The previous studies have reported negative correlation between BMD and EDSS (11, 15, 16, 18, 22, 23). In our study, no relationship was detected between EDSS and BMD. The inability to detect such a difference may be explained by all our patients being ambulatory and low EDSS values. In some studies were suggested inverse correlation disease duration and BMD (16, 23, 24). In our study, there were no correlation BMD and other parameters.

In our study, osteoporosis and osteopenia were more frequent in men (46.6% female versus 58.8%males according to femur neck BMD and 37.83% female versus 64.7% males according to lumber BMD). And, the lumbar vertebrae T and Z scores of men were lower than women, which was statistically significant (p: 0.003 and p: 0,00) (Table 2). In most studies on MS and osteoporosis, participants are mostly female patients. This may be due to the predominance of female patients in studies.

Vitamin D is a crucial vitamin in bone health. In addition, multiple studies were suggested that vitamin D have immunomodulatory effect and takes an important place in T cell homeostasis in the course of MS (25). In the our study, mean vitamin D levels of the whole study group was below the sufficiency level. In most studies concerning vitamin D in MS patients, vitamin D levels were observed to be lower in the patient group than in the control group (12, 22, 23, 25, 26). In addition, we found no correlation between BMD and vitamin D levels. Similarly, there are studies that failed to find an relationship between vitamin D levels and BMD (21). However, only one study reported a significant relationship between vitamin D concentration and lumbar T and Z scores (22).

Osteocalcin is a hormone specific to osteoblast and plays a role in glucose homeostasis (27). Osteocalcin levels are a marker of bone formation. Osteocalcin levels were lower in MS patients compared to controls (22, 28). In our study, osteocalcin levels were found in normal range in 77,7 % of patients (normal range: 2-21 ng/ml).But, osteocalcin levels of osteoporosis patients were statistically higher than in others (p: 0,01). High osteocalcin levels are seen with increased bone remodeling and increased bone loss (29). Susanto et al. reported a significant inverse correlation between femoral neck BMD and serum osteocalcin (30). Terzi et al reported that, there was no significant relationship between osteocalcin and BMD (22).

High PTH levels were found in 31.5% of patients. Some studies were found that, the concentration of PTH was higher in the patient group (22). In our study, an inverse correlation was observed between PTH concentration and vitamin D concentration.

Certain limitations of the present study have to be acknowledged. We determined the study groups according to the total dose of IVMP received during the illness. Low disability scores of the patients, the low number of participants and lack of age and sex-matched healthy control group, are limitations of the study.

As a result, our study shows that BMD is decreased in MS patients. However, there is no correlation between cumulative CS and BMD dose in ambulatory MS patients. The presence of unknown factors other than CS dose may explain the difference between CS dose concentration and osteoporosis among MS patients.

Abbreviations

BMD — Bone mineral density
CS — Corticosteroid
DEXA — Dual energy X-ray absorptiometry
EDSS — Expanded Disability Status Scale
IVMP — Intravenous high-dose methylprednisolone
MS — Multiple sclerosis
RRMS —Relapsing-remitting MS

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Sažetak

ODNOS IZMEĐU MINERALNE GUSTINE KOSTIJU I KRATKOROČNE TERAPIJE VISOKIM DOZAMA KORTIKOSTEROIDA KOD PACIJENATA SA MULTIPLOM SKLEROZOM

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Uvod: Izveštaji ranijih studija pokazuju da se osteoporoza i prelomi kostiju češće javljaju kod pacijenata sa multiplom sklerozom nego kod ostale populacije. Cilj ove studije je da istraži uticaj kratkoročne terapije visokim dozama kortikosteroida i druge faktore od uticaja na mineralnu gustinu kostiju kod pacijenata sa relapsno remitentnim oblikom multiple skleroze.

Materijal i Metode: Pedeset četiri pacijenta (37 ženskog i 17 muškog pola) sa relapsno remitentnim oblikom multiple skleroze, koji su ispunjavali McDonald-sove dijagnostičke kriterijume su bili uključeni u studiju. Merena je mineralna koštana gustina femoralne kosti i lumbalne kičme upotrebom DEXA metode (dual energy X-ray absorptiometry). Skala status proširene nesposobnosti, trajanje bolesti, broja napada, kumulativna doza kortikosteroida su beleženi. Serumski kalcijum, natrijum, fosfor, vitamin D, parathormon i osteokalcin su mereni. Pacijenti su podeljeni u dve grupe: pacijente koji su primili najmanje 20gr metilprednizolona intravenski (Grupa I) i pacijente koji su primili manje od 20 gr metilprednizolona intravenski (Grupa II). Analizirali smo odnos između kumulativne doze kortikosteroida i svih parametara.

Rezultati: Osteopenia je bila prisutna kod 46,2% i osteoporoza kod 5,5% ispitane populacije shodno mineralnoj gustini vrata butne kosti. Mineralna gustina butne kosti je bila značajno niža među pacijentima. Nije nađena korelacija između kumulativne doue kortikosteroida i mineralne gustine kostiju.

Zaključak: Niska mineralna gustina kostiju i osteoporoza su česte kod pacijenata sa multiplom sklerozom. Terapija visokim dozama kortikosteroida nije primarni uzrok osteoporoze kod pacijenata sa multiplom sklerozom.

Ključne reči: Multipla skleroza, mineralna gustina kostiju, vitamin D.

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DIAGNOSTIC DIFFICULTIES IN PATIENTS WITH JUVENILE MYOCLONIC EPILEPSY

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Abstract: **Objective:** In this study, we aim to share the data of patients who were followed-up and treated with a diagnosis of juvenile myoclonic epilepsy (JME), and to draw attention to the difficulties in diagnosis and the problems that may occur in treatment.

Method: In this study, seizure types, demographic and EEG characteristics of 75 patients with JME were retrospectively analyzed in our tertiary care center.

Results: Of the total 75 cases, 48 patients (64%) were female and 27 patients (36%) were male. The overall female/male ratio was 1.7/1. The age of onset of seizures ranged from 6 to 24 years old. According to seizure types, all patients had myoclonic seizures, 65 patients (86%) had generalized tonic clonic seizures and 17 patients (22.6%) had absence seizures. Of the cases, 13 patients (17.3%) had febrile convulsions, 4 patients (5.3%) had a history of febrile convulsions in their families and 10 patients (13.3%) had a family history of epilepsy. For 63 (84%) patients, seizures were under control with valproic acid alone. When the patients EEGs were examined, 55 patients (73.3%) had generalized epileptiform activity, 11 patients (14.7%) had focal abnormaly and 9 patients (12%) had no abnormality. It was determined that the diagnosis of JME was not established at the onset of the disease and the seizures were not under control for 40% of the patients who were admitted to our outpatient clinic from different centers.

Conclusion: Physicians should be very careful in the diagnosis of JME and the presence of myoclonia and absence seizures should be questioned in all patients presenting with generalized tonic-clonic seizures between 8-20 years of age in polyclinic practice.

Key Words: Juvenile myoclonic epilepsy, diagnosis, Idiopathic generalized epilepsy.

INTRODUCTION

Juvenile myoclonic epilepsy (JME) is one of the widely occurring idiopathic generalized epilepsies. Its characteristic triad consists of myoclonic jerks, generalized tonic-clonic seizures (GTCS) and absence seizures. Seizures usually begin during adolescence or young adulthood (1, 2). The first known JME was defined in 1867 (3). Although most patients with JME benefit from valproate monotherapy, they require life-long treatment since they are likely to relapse if medications are discontinued (4, 5).

Studies have reported a delay in diagnosis in patients with JME and the possibility of missing the diagnosis even for patients evaluated by a neurologist (6, 7). Although it is a generalized epilepsy, focal EEG features and unilateral and asymmetric myoclonic jerks can be interpreted as focal seizures and this condition may lead to misdiagnosis and inappropriate treatment (8, 9).

In this study, the clinical and electrophysiological data of patients followed-up with a diagnosis of JME in a tertiary care center were examined. In this study, we aim to draw attention to the difficulties that may arise in the diagnosis of JME.

MATERIAL AND METHODS

Our study was a retrospective study with a total of 75 patients with a diagnosis of JME who were followed-up and treated in Epilepsy Outpatient Clinic of Uludag University Faculty of Medicine. Approval for the study was obtained from the Ethics Committee of the Bursa Yuksek Ihtisas Training and Research Hospital. All procedures performed in study were in accordance with the ethical standards of the institutional research committee and with the Helsinki declaration.

Patients with mental retardation and children under 6 years old were excluded from the study.

Demographic characteristics, neurological examination findings, seizure onset age, seizure types, cranial imaging and interictal EEG characteristics, antiepileptic treatments, history of febrile convulsions and family history of epilepsy were evaluated retrospectively. EEG features (normal, generalized or focal abnormalities) and recently used antiepileptic drug treatments were recorded. It was noted whether the patients responded to the antiepileptic treatment or not. For the diagnosis of epilepsy, the International League Against Epilepsy (ILAE) classification criteria (10) were used.

At least two interictal EEG activity tests during wakefulness for all patients were performed. EEGs were measured on an 21-channel EEG device (Nihon Kohden, Neurofax 2) for 30 minutes, according to the international 10-20 system, in which standard activation methods were used. Cranial magnetic resonance imaging (MRI) imaging was performed with a 1.5 T device (Magnetom Vision Plus, Siemens, Erlangen, Germany).

Statistical Analysis

The data indicated that the descriptive statistics corresponded to a normal distribution and are given as mean and standard deviation. For non-compliance with normal distribution, data are expressed as median (minimum: maximum) and average.

RESULTS

Of the total 75 cases, 48 patients (64%) were female, 27 (36%) were patients male. The overall female/male ratio was 1,7/1. The mean age of the patients was 14.31 ± 4.93. It was determined that all patients had myoclonic seizures, 65 (86%) of the patients had GTCS and 17 patients (22.6%) had absence seizures. When the patients were assessed in terms of seizure combinations, it was observed that 8 patients (10.6%) of them had only myoclonic seizure, 50 patients (66.6%) had myoclonic and GTCS, 2 patients (2.6%) had myoclonic and absence seizure, and 15 patients (20%) had myoclonic seizure, GTCS and absence seizures (Table 1).

Fifty-five (73.3%) of the patients had 3–6 Hz spike and polyspike-wave discharges on interictal EEG, while 11 (14.7%) had only focal discharges. However, no abnormality was found in the EEG in 9 (12%) of the patients. The neuroimaging method for all patients was cranial MRI. One patient had cavum septum pellucidum, 1 patient had right hippocampal atrophy, 1 patient had asymmetric enlargement in the right lateral ventricle, and 1 patient had venous angioma in the right precentral gyrus. Cranial MRI examinations of the other patients were normal.

Table 1. *Demographic and clinical data*

Demographic and clinical data of a total of 75 patients		
	Value	**Percentage**
Gender		
Male	27	36%
Female	48	64%
Seizure types		
Myoclonic seizure	75	100%
GTCS	65	86%
Absence seizures	17	22.6%
Only myoclonic seizure	8	10.6%
Myoclonic + GTCS	50	66.6%
Myoclonic + GTCS + absence	15	20%
Myoclonic seizure+absence	2	2.6%
EEG Findings		
Generalized	55	73.3%
Focal	11	14.7%
Normal	9	12%
Antiepileptic treatment		
Single drug	63	84%
Double drug use	12	16%

In the analysis of their medical and family histories was presented that 13 patients (17.3%) had febrile convulsions, 4 patients (5.3%) had febrile convulsions in the family and 10 patients (13%) had a family history of epilepsy. It was observed that seizures were provoked with insomnia in 6 (8%) of the patients. In 63 (84%) of the cases, seizures were kept under control with only valproic acid. In twelve (16%) patients, another drug was added to the valproic acid treatment (lamotrigine to 11, clonazepam to 1) (Table 1). Age of onset for valproic acid was 19.2 years old on average.

In 40% of the patients who applied to our outpatient clinic from external centers, JME was not diagnosed at the beginning of the disease and appropriate antiepileptic treatment was not applied to the patients. In 30 patients who were not diagnosed with JME when they applied to our center, the average time until the correct diagnosis was 4 years. Due to the continuation of seizures despite the antiepileptic treatment in these patients, JME was diagnosed after reviewing their histories again.

DISCUSSION

The prevalence of JME among all epilepsies is 5-10%. Usually the first seizures between 12 and 18 years of age are well recognized (11, 12). There are many studies showing female dominance for JME (13, 14, 15). In our study, in accordance with the literature, 48 (64%) of the patients were female, 27 patients (36%) were male and the female-male ratio was 1.7/1.

Although myoclonic seizures are the most common seizure type in patients with JME, absence seizures and generalized tonic clonic seizures are also observed, and in a small number of patients, myoclonic seizures occur alone (16, 17).While all of our patients had myoclonic seizures, only 20% had all three of myoclonic, absence and generalized tonic clonic seizures. In 10.6% of our patients, only myoclonic seizures were observed. Especially in patients with only myoclonic seizures, the diagnosis of JME may be overlooked unless in doubt. Especially unilateral myoclonic seizures may be misleading in the diagnosis of JME.

Although 3-6 Hz spike-slow wave activity is conventionally observed on EEG in patients with JME (16), comparatively high rates of focal EEG findings can also be observed. (18) The rate of observing asymmetric localizations and / or patterns on EEG may approach 50% (17). The rate of focal findings on EEG in our patients was compatible with the literature (19). In our study, generalized epileptiform activity was present in 55 (73.3%) of the patients and focal anomaly was present in 11 (14.7%) patients. EEG of nine patients was found to be normal. Since the frequency of epileptic anomaly may increase especially in sleep-deprived EEG imaging, EEG with sleep deprivation should be performed in cases with normal EEG.

JME is an inherited disorder. It was found that 40% of JME patients had epilepsy in their families, and 75% of them had epilepsy in a first degree relative (20). In the studies , the prevalence of familial epilepsy in patients with JME was 28%-43% (6, 7, 21). In our study, we found this rate to be 13%.

It is controversial whether febrile convulsions are a risk factor in idiopathic generalized epilepsies (IGE), including JME. Some studies, febrile convulsions have been found to be associated with poor prognosis in JME (22). In the studies conducted, the frequency of febrile convulsion history in JME patients is determined as 11-14% (7, 22). In the patients in the current study, we observed that 13 patients (17.3%) had febrile convulsion history, 4 patients (5.3%) had febrile convulsions in the family.

Patients with juvenile myoclonic epilepsy have a good response to valproate monotherapy (4). Due to the side effects of valproic acid, the European Medicines Agency (EMA) warned against the use of valproic acid in girls with epilepsy and it recommended the use of other treatments for women of childbearing age (23). However, 60% of female patients receiving valproic acid therapy were reported not to support stopping valproic acid therapy because of other antiepileptic drugs have failed or did not intend to become pregnant (24). In our study, seizures were controlled by valproic acid therapy in 84% of patients, and a secondary drug was added to valproic acid therapy in 12 (16%) patients.

In a study performed in Turkey, it was stated that misdiagnosis is seen in 52.6% of JME patients (6). In a second study after seventeen years, it was observed that the rate of misdiagnosis had decreased to 24.5%. This situation has been attributed to an increase in awareness and experience with the disease in Turkey (7).

In all general tonic-clonic seizures (GTCS) occurring during adolescence, JME should be considered primarily as a diagnosis (25). In 40% of patients who applied to our outpatient clinic from external centers, JME was not diagnosed at the beginning of the disease. When the anamnesis of these patients was evaluated in detail in our center, the patients were diagnosed with JME.

CONCLUSION

Insufficiency in the diagnosis of JME is a serious medical mistake. Because of the difficulties in the diagnosis of JME, clinicians can stigmatize patients as clumsy and they may increase seizure frequency with inappropriate antiepileptic drugs.

In clinical practice, the possibility of myoclonic seizures should be kept in mind in cases of incompetence in motor behavior that the patients or their relatives call clumsiness. The history of myoclonus should be questioned in all patients presenting with seizures, including GTCS, especially in patients aged between 8-20 years old, and JME should be considered as a preliminary diagnosis.

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DIJAGNOSTIČKE TEŠKOĆE KOD PACIJENATA SA JUVENILNOM MIOKLONIČNOM EPILEPSIJOM

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Uvod: Cilj ove studije je da se prikažu podaci pacijenata koji su praćeni i lečeni od juvenilne mioklonične epilepsije, i da se skrene pažnja na teškoće u dijagnozi i probleme koji se mogu javiti u lečenju.

Metod: Studijom je obuvaćeno 75 pacijenata sa JME. Tipovi napada, demografske karakteristike i EEG karakteristike su retrospektivno analizirani u našoj tercijarnoj zdravstvenoj ustanovi.

Rezultati: Od ukupno 75, 48 pacijenata (64%) je bilo ženskog pola I 27 (36%) muškog. Odnos između polova ženski/muški 1,7/1. Godine starosti u kojima su se napadi počeli javljati kreću se od 6 do 24 godine. Prema tipu napada, svi pacijenti su imali miokloničnе napade, 65 pacijenata (86%) je imalo generalizovane tonično klonične napade i 17 pacijenata (22,6%) absens napade. Od ukupnog broja pacijenata, 13 (17,3%) je imalo febrilne konvulzije, 4 pacijenta (5,3%) je imalo istoriju febrilnih konvulzija u svojim porodicama i 10 (13,3%) pacijenata je imalo pozitivnu porodičnu anamnezu u smislu epilepsije. Kod 63 (84%) pacijenata napadi su bili pod kontrolom samo sa valproičnom kiselinom. Nakon pregleda EEG-a, kod 55 (73,3%) pacijenata je nađena generalizovana epileptiformna aktivnost, 11 (14,7%) pacijenata je imalo fokalne abnormalnosti I 9 (12%) je imalo uredan nalaz. Utvrđeno je da se dijagnoza JME nije postavila nakon pojave bolesti i napadi nisu bili pod kontrolom kod 40% pacijenata koji su primljeni na našu kliniku iz drugih zdravstvenih centara.

Zaključak: Lekari bi trebalo da budu jako oprezni prilikom postavljanja dijagnoze JME i prisustvo mioklonije i absens napada bi trebalo ispitati kod svih pacijenata koji se javljaju lekaru zbog generalizovanih tonično-kloničnih napada starosti 8-20 godina.

Ključne reči: juvenična mioklonična epilepsija, dijagnoza, idiopatska generalizovana epilepsija.

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EARLY COMPLICATIONS AFTER SECONDARY BREAST RECONSTRUCTION USING LATISSIMUS DORSI MYOCUTANEOUS FLAP AND SILICONE BREAST IMPLANTS

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Abstract: **Introduction:** Secondary breast reconstruction is a multifactorial decision. It is based on the need for neoadjuvant/adjuvant treatment, lifestyle and expected cosmetic outcome of the patient. Aim of this study was to show early complications related with secondary breast reconstruction using latissimus dorsi miocutaneous flap and silicone breast implants.

Material and methods: This retrospective study was made with 24 patients who were treated at the Institute for Oncology Vojvodina in the period from 2007 to 2013. At all patients we underwent secondary breast reconstruction using pedicle latissimus dorsi myocutaneous flap (LDMF) and silicone breast implant.

Results: Almost at all patients we identified prolonged seroma formation like complication related to donor site (21/24 (87.5%)). Radiotherapy and chemiotherapy after first operation have statistical significance on complications after LDMF. Smoking and obesity have no influence on complications.

Conclusion: Breast reconstruction using LDMF is related with small number of early postoperative complications and gives acceptable aesthetic results.

Key words: breast reconstruction, latisimus dorsi myocutaneous flap, breast cancer, breast surgery.

INTRODUCTION

Breast cancer is the most common cancer in females and affects essential part of female sexuality and causes a wide range of psychological traumas (1).

First transfer of the Latissimus dorsi miocutaneous flap (LDMF) to cover chest wall defects was made by Iginio Tansini in 1897. Eight decades later Olivari (1976), Mühlbauer and Olbrisch (1977) rediscovered Tansinis method (2).

Secondary breast reconstruction after amputation could be made with the transfer of autologous tissue from adjacent regions to the breast region. The type and the timing (primary or secundary) of reconstruction is a multifactorial decision and it is based on the need for neoadjuvant and adjuvant chemotherapy, lifestyle of the patient, expected cosmetic outcome and experience and preferences of the surgeon (1, 3-9).

Aim of this study was to show early complications after secondary breast reconstruction using pedicle LDMF.

PATIENTS AND METHODS

This retrospective study included 24 patients who were treated at The Institute of Oncology Vojvodina in the period from 2007 to 2013. Average age of patients was 53.21 years (range 39-69). All patients received adjuvant chemotherapy after the first operation and postoperative irradiation received 21 (87.5%) patient. Minimum six months after the irradiation we performed LDMF. Because of complication after nipple spearing mastectomy (NSM) (large skin flap necrosis etc.), we performed secondary reconstruction using LDMF in 7 cases.

At all patients we underwent secondary breast reconstruction using pedicled latissimus dorsi myocutaneous flap, after NSM or mastectomy and complete axillary lymph node dissection (cALND).

Preoperatively we underwent clinical examination at all patients, as well as imaging procedures (Ultrasound (US), mammography and magnetic resonance imaging (MRI) mammography) to exclude local relapses of primary breast cancer. Also we collected data about diabetes mellitus and smoking by patients to exa-

mine are this conditions related with increased number of complications.

All the patients preoperatively were administrated with prophylactic dose of broad-spectrum antibiotics (1,5 g of Cefuroxime), one hour before the operation and the same dose was repeated the following day.

Preoperatively, all important lines (bra strap area and inframammary crease anterior and transverse skin paddle posterior) were marked. Preoperative clinical examination give us data about latissimus dorsi muscle function. It is immportant that thoracodorsal neurovascular bundle is intact after first operation. Patients should make extension, adduction, and internal rotation of the shoulder joint.

The initial incision for reconstruction is ussually made wherever the original mastectomy incision was made. The location may vary in different patients. After an elipsoid incision at latissimus dorsi muscle projection (with a 90° abducted shoulder), the muscle is elevated with fat tissue and skin (this skin will be used to cover the new breast). Thoracodorsal vessels can be found at the upper lateral edge of the LDMF. After preparation of LDMF the whole muscle with fat and skin is passed through axilar tunnel between the two wound areas and brought to the place of the prior mastectomy. Wound at the back was closed in two layers with Vicryl sutures. Two drains was usually left for two weeks postoperatively (one at the back and another under the transposed flap).

Under the LDMF, in all cases we used Mentor Contour Profile®, (Minneapolis, USA), silicone breast implants, to supplement volume of reconstructed breast. Recipient area is sutured with Vicryl suttures. This study was made in correlation with Helsinki declaration.

Values of $p < 0,05$ were considered as statistically significant.

RESULTS

Average number of hospital days was 11.63 (range 8-21 days). Average volume of silicone breast implants was 340cc (range 155-640cc).

The size of the LDMF skin paddle ranges from 6 to 10 cm wide and 20 to 25 cm long.

Almost at all patients we identified prolonged seroma formation like complication related to donor site (21(87.5%)). Minor skin necrosis was indentified at 4 patients like complication related to flap site (Table 1).

Radiotherapy and chemotherapy after first operation have statistical significance on complications after LDMF. Smoking and obesity have no influence on complications (Table 2).

Table 1. *Early complications after LDMF*

Complication	Flap related Number (%)	Donor site related Number (%)
Epidermolysis	2 (20.00)	0 (0.00)
Minor infection	1 (10.0)	2 (8.33)
Major infection	1 (10.0)	0 (0.00)
Major skin necrosis	1 (10.0)	0 (0.00)
Minor skin necrosis	4 (40.0)	0 (0.00)
Prolonged serosa formation	1 (10.0)	21 (87.50)
Hematoma	0 (0.0)	1 (4.17)
Total	10 (100.00)	24(100.00)

DISCUSION

The main aim in oncoplastic procedures after breast amputation is to create a breast, which is similar to the healthy side. The optimal method should be safe and offer a result that makes the patient feel as natural as possible (1-9).

Our opinion is that the patients age don't have influence on the decision to perform or not, secondary breast reconstruction.

LDMF is the first surgical breast reconstruction procedure, while procedure is simple and use pure autologous tissue from other parts of body (10). In some cases this procedure cannot provide a sufficient vo-

Table 2. *Risk factors for complications*

FACTOR		COMPLICATIONS		p value
		YES	NO	
Smoking	Yes	13	2	p = 0.74
	No	1	8	
Obesity	Yes	6	2	p = 0.71
	No	1	15	
Adjuvant polychemotherapy	Yes	16	7	p = 0.29
	No	1	0	
Adjuvant radiotherapy	Yes	5	16	p = 0.01
	No	0	3	

lume of tissue for breast reconstruction. For womens who have a relatively big breast an extended latissimus dorsi myocutaneous flap (ELD-MC) can sometimes avoid the use of any implant (3, 4, 11-14). One technically simple method, in French called "fleur de lis", imitating the pattern of a lily flower can provide additional fat tissue for reconstruction (11).

LDMF has a solid blood supply, but disadvantages of this procedure are sometimes a difficult surgical technique, a prolonged operational time and posibble postoperative complications at the donor site. Most common postoperative complications is prolonged seroma formation at the donor site, which occurs with an incidence of approximately 20% (8). In our case 87.50%. We explain that because we dont use fibrin glue and quilting suttures. Some authors have minimized this complication by using a quilting suture when suturing the donor site or by using fibrin glue (12). We indentified only few wound healing complications related to flap like epidermolysis in 2, minor infection in 1 and minor skin necrosis in 1 case. Major infection of flap site was indentified only in one case. After prolonged antibiotics therapy (7 days) we were able to preserve LDMF and prosthesis beneath it. Radovanovic (15) have show that in 6% of cases after NSM, extensive flap necrosis is a reason for prosthesis explantation. In that cases secondary reconstruction is only possibility to reconstruct breast.

Obesity, smoking, postoperative irradiation, prognostic stage and the location of cancer in the breast are important factors to consider, before performing breast reconstruction using LDMF (16,17,18). Our results shows that adjuvant chemotherapy and postoperative radiation have influence on postoperative complications after secondary breast reconstruction. Smoking and obesity are not risk factors for secondary breast reconstruction. Breast reconstruction with pedicle flaps in smokers are not associated with a significant increase of the rates of vessel thrombosis, flap loss or fat necrosis compared with nonsmokers (17). Expert consensus is that patients should stop smoking at least 4 weeks before operation. The majority of overweight patients who undertake breast reconstruction complete the reconstruction successfully but have a significantly higher rate of flap complications and donor-site complications (16-18, 19, 20). After irradiation complications rate are more often than in patients than are non-irradiated (39% vs. 25%). The aesthetic outcome is also slightly poorer (18).

Few months after the successful LDMF breast reconstruction we can perform secondary interventions at contralateral breast to achieve symmetry and volume. This secondary procedures help women to appreciate their own appearance and become more self-confident without feeling a loss of their femininity (6, 7, 11, 14, 19, 20).

CONCLUSION

Secondary breast reconstruction using LDMF is related with small number of early postoperative complications. It also gives acceptable aesthetic results.

Abbreviations

LDMF — latissimus dorsi myocutaneous flap

NSM — nipple sparing mastectomy or mastectomy

cALND — complete axillary lymph node dissection

US — Ultrasound

MRI — magnetic resonance imaging

ELD-MC — extended latissimus dorsi myocutaneous flap

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Sažetak

RANE KOMPLIKACIJE NAKON SEKUNDARNE REKONSTRUKCIJE DOJKE UPOTREBOM LATISSIMUS DORSI MIOKUTANOG FLAPA I SILIKONSKOG IMPLANTA

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Uvod: Odluka o izvođenju sekundarne rekonstrukcije dojke je multifaktorijalna. Bazira se na potrebi primene neoadjuvantne/adjuvantne hemioterapije, stila života i estetskih očekivanja pacijentkinje. Cilj rada bio je

da se prikažu rane postoperativne komplikacije povezane sa sekundarnom rekonstrukcijom dojke upotrebom latisimus dorzi miokutanog flapa i silikonskog implanta.

Materijal i metod rada: Retrospektivna studija obuhvatila je 24 pacijentkinje koje su lečene na Institutu za onkologiju Vojvodine u periodu od 2007. do 2013. godine. Kod svih pacijentkinja urađena je sekundarna rekonstrukcija dojke koristeći peteljkasti latisimus dorzi miokutani flap (LDMF) i silikonski implant.

Rezultati: Kod skoro svih pacijentkinja identifikovano je produženo stvaranje seroma kao komplikacija povezana sa donorskim mestom (21/24 (87,5%)). Radioterapija i hemioterapija nakon primarne operacije imaju statistički značajan uticaj na pojavu komplikacija nakon izvođenja LDMF. Pušenje i gojaznost nisu imali uticaja na broj komplikacija.

Zaključak: Sekundarna rekonstrukcija dojke upotrebom LDMF povezana je sa malim brojem postoperativnih komplikacija i daje estetski prihvatljive rezultate.

Ključne reči: rekonstrukcija dojke, latisimus dorzi miokutani flap, karcinom dojke, hirurgija dojke.

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UPPER GASTROINTESTINAL BLEEDING: IS ONLY AN INJECTION OF EPINEPHRINE SUFFICIENT? SUCCES RATES BY FORREST CLASSIFICATION

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Abstracts: **Objective:** Endoscopic treatment is an effective and successful treatment for non-variceal upper gastrointestinal system (GIS) bleedings. In recent years, endoscopic combined therapies have been recommended for hemostasis. The aim of this study was to investigate primary hemostasis rates and re-bleeding rates obtained by epinephrine injection alone.

Material and Methods: We analysed patients who had alone endoscopic epinephrine injection treatment for upper gastrointestinal system bleeding between January 2014 and January 2019. Gender, age, etiology of bleeding, Forrest classification, treatment efficacy and re-bleeding rates of the patients were recorded. The files of the patients were analyzed retrospectively. **Results:** The number of patients who met the study criteria was 107. There were 16 patients in Group 1 (Forrest 1a), 64 patients in Group 2 (Forrest 1b) and 27 patients in Group 3 (Forrest 2a). Primary hemostasis was achieved in 14 (87.5%) of 16 patients in Group 1, 62 (97%) of 64 in Group 2, and 27 (100%) of 27 Group 3. Re-bleeding rates were 4 (28%), 10 (16%), 2 (7%) in groups 1,2 and 3, respectively.

Conclusion: It is thought that endoscopic combined treatment should be applied especially in patients with Forrest 1a and 1b bleeding ulcers, whereas in Forrest 2a ulcer patients, because of both the high rate of primary hemostasis and low rate of re-bleeding according to the results of the present study, the treatment of adrenalin injection alone can be used alone like other hemostasis modalities.

Key words: Endoscopic treatment, Forrest classification, upper gastrointestinal bleeding.

INTRODUCTION

Upper gastrointestinal system bleeding has an incidence ranging from 48 to 160 cases per 100.000 people, depending on geographical regions. It is more common in men and in the elderly population. Different incidences between populations can be explained by various reasons such as drug-induced ulcers and the prevalence of Helicobacter Pylori (1, 2).

The peptic gastroduodenal ulcer is the most common cause of non-variceal upper gastrointestinal bleeding. Mallory-Weiss Syndrome, vascular abnormalities, iatrogenic bleedings after endoscopic procedures and bleedings at the surgical site can be given as other causes (3). Mortality due to upper gastrointestinal bleeding is associated with advanced age and accompanying comorbidities. The risk of mortality increases with recurrent bleeding (4). Despite the use of therapeutic endoscopy and gastric acid suppressors for optimal treatment, it is seen that the mortality rate has remained constant between 6% and 14% in recent years (5).

Endoscopic treatment is an effective and successful treatment for non-variceal upper gastrointestinal system (GIS) bleedings (6). Endoscopic treatment can significantly reduce the risk of bleeding or ongoing bleeding, the need for surgery, the number of packed erythrocyte units required for transfusion, and the length of hospital stay (6, 7).

Endoscopic hemostasis can be achieved using injection, and thermal and mechanical methods. Epinephrine, sclerosing agents (ethanol, ethanolamine, polidocanol) and thrombin/fibrin glue can be used in the treatment of injection (8, 9, 10).

AIM

The present study aims to investigate the primary hemostasis success rates and re-bleeding rates of upper gastrointestinal system bleedings, which are stopped by epinephrine injection alone as an endoscopic

treatment, according to the Forrest classification sub-groups.

MATERIAL AND METHOD

Patients who had endoscopic epinephrine injection treatment for upper gastrointestinal system bleeding between January 2014 and January 2019 in the general surgical endoscopy unit of Bakırköy Dr. Sadi Konuk Training and Research Hospital and had an endoscopic bleeding index of Forrest 1a, 1b and 2a were included in this study. The files of the patients were analyzed retrospectively. Gender, age, etiology of bleeding, treatment efficacy and re-bleeding rates of the patients were recorded. The Forrest classification was used as an endoscopic bleeding index (Table 1). Patients were divided into three groups according to the Forrest classification. Patients in Group 1 were classified as those having Forrest 1a, patients in Group 2 as those having Forrest 1b, and patients in Group 3 as those having Forrest 2a endoscopic bleeding index. Primary hemostasis success and re-bleeding rates of endoscopic injection treatment according to Forrest classification were reviewed. Hemodynamic deterioration, active hematochezia and a decrease of 2 g/dl or more in hemoglobin values within 24 hours during the follow-up of the patients who were provided hemostasis with the first endoscopic treatment were evaluated as re-bleeding and it was determined that the endoscopic procedure was repeated. Epinephrine of 1/10000 was used as the injection treatment. Those with 2b, 2c, and 3 endoscopic bleeding indexes according to Forrest classification, those using oral anticoagulants, those who have non-peptic ulcer bleeding causes in the etiology, and those with marginal ulcer and malignancy in gastrojejunostomy anastomosis were excluded from the study.

All procedures performed in this study, involving human participants were in accordance with the 1964 Helsinki declaration and its latest amendments or comparable ethical standards. Informed consent was obtained from all individual participants of the study.

Table 1. *Description of Forrest classification*

Forrest classification	Description
Forrest 1a	Spurting hemorrhage
Forrest 1b	Oozing hemorrhage
Forrest 2a	Non-bleeding visible vessels
Forrest 2b	Adherent clot
Forrest 2c	Flat pigmented spot
Forrest 3	Clean ulcer base

RESULTS

It was seen that 536 patients underwent endoscopy for upper gastrointestinal bleeding in the endoscopy unit between 2014 and 2019. In 414 (77%) of these patients, gastroduodenal ulcer (49% duodenal ulcer, 28% gastric ulcer) bleeding was detected. The number of patients who met the study criteria was 107. There were 16 patients in Group 1 (Forrest 1a), 64 patients in Group 2 (Forrest 1b) and 27 patients in Group 3 (Forrest 2a).

The F/M ratio in the gender distribution of Group 1 was 4/12 (25%, 75%) and the mean age was 59 (20-82). The F/M ratio in the gender distribution of Group 2 was 14/50 (22%, 78%) and the mean age was 61.6 (19-90) years. The F/M ratio in the gender distribution of Group 3 was 8/19 (29%, 71%) and the mean age was 59 (28-84). In the overall series, the F/M ratio was 26/81 (24%, 76%) and the mean age was 59.9 (Table 2).

When the etiology of bleeding was examined, 5 patients had gastric ulcer and 11 patients had duodenal ulcer bleeding in Group 1, 9 patients had gastric ulcer and 55 patients had duodenal ulcer bleeding in Group 2, and 4 patients had gastric ulcer and 23 patients had duodenal ulcer bleeding in Group 3 (Table 3).

Table 2. *Demographic data*

	Patient, n(%)	Female	Male	Mean Age (SD)
Group 1	16 (15 %)	4 (25 %)	12 (75 %)	59 (17.53)
Group 2	64 (59 %)	14 (22 %)	50 (78 %)	61.6 (16.68)
Group 3	27 (26 %)	8 (29 %)	19 (71 %)	59 (16.60)
Total	107 (100 %)	26 (24 %)	81 (76%)	59.9 (17.16)

Table 3. *Etiology*

	Gastric ulcer, n(%)	Duodenal ulcer, n(%)	Total
Group 1	5 (31 %)	11 (69 %)	16
Group 2	9 (14 %)	55 (86 %)	64
Group 3	4 (15 %)	23 (85 %)	27
Total	18 (17 %)	89 (83 %)	107

Table 4. *Primary hemostasis success rates*

	Hemostasis, n(%)	**Non-hemostasis, n(%)**	**Total**
Group 1	14 (87.5 %)	2 (12.5 %)	16
Group 2	62 (97 %)	2 (3 %)	64
Group 3	27 (100 %)	0	27
Total	103 (96.2 %)	4 (3.8 %)	107

Table 5. *Repeat endoscopy and re-bleeding rates*

Groups, (n)	**Re-endoscopy rate, n(%)**	**Re-bleeding rate, n(%)**
Group 1, (14)	4 (28 %)	4 (28 %)
Group 2, (62)	16 (26 %)	10 (16 %)
Group 3, (27)	3 (11 %)	2 (7.4 %)
Total (103)	23 (22.3 %)	16 (15.5 %)

When the treatment success rates were examined, it was seen that primary hemostasis was achieved in 14 (87.5%) of 16 patients but endoscopic hemostasis could not be achieved in 2 (12.5%) patients in Group 1. In the Group 2, however, primary hemostasis was achieved in 62 (97%) patients but endoscopic hemostasis could not be achieved in 2 (3%) patients. Four patients for whom primary hemostasis could not be achieved were operated. In Group 3, primary hemostasis was achieved in all 27 patients and the success rate was 100%. Primary hemostasis was achieved in 103 (96.2%) of 107 patients in all three groups. In Group 3, primary hemostasis was achieved in all 27 patients and the success rate was 100% (Table 4).

Considering the re-bleeding rates, it was seen that 4 (28%) of 14 patients in Group 1 who had primary hemostasis underwent endoscopy again and 3 patients were re-treated with endoscopic injection and 1 patient was taken into operation due to 4 (28%) patients had bleeding. In group 2, it was seen that endoscopy was repeated in 16 (26%) of 62 patients with primary hemostasis, 10 (16%) patients had re-bleeding, and 6 patients had no active bleeding. It was seen that 7 of 10 patients were given injection treatment again, 1 patient was applied clip, and 1 patient was treated with argon coagulation. One patient underwent surgery. In Group 3, however, endoscopy was repeated in 3 of the 27 patients and 2 (7.4%) of these 3 patients had bleeding in the form of leakage from the ulcer and the injection was re-administered. The endoscopic intervention was not performed in 1 patient since there was no bleeding (Table 5).

When examining the general results of the patients included in the study, it was found that a total of 6 (7.5%) of the 80 patients in Forrest 1a and 1b groups with bleeding ulcer were operated after their first and repeated endoscopy applications. In repeat endoscopy procedures, 1 patient underwent clips and 1 patient underwent argon coagulation, while 72 patients were treated endoscopically with epinephrine injection alone. Of these 72 patients, 10 had endoscopic epinephrine injection treatment on endoscopies for a second time, leading to hemostasis, and 62 (77.5%) had no need for a second procedure after primary hemostasis. None of the patients with visible vessels in the Forrest 2a group required surgery, and only 2 (7.5%) patients underwent repeated injections.

DISCUSSION

The most common cause of non-variceal acute upper gastrointestinal system bleeding is peptic ulcer bleeding, which is observed between the rates of 28% and 59%. Duodenal ulcer rate is seen between 17% and 37% and gastric ulcer rate is between 11% and 24% (11). In the present study, the rate of peptic ulcer (49% duodenal ulcer, 28% gastric ulcer) was 77% (414/536) in endoscopies performed due to GIS bleeding and this result was higher when compared with the studies in the literature.

Studies have shown that endoscopic treatments improve clinical outcomes in GIS bleeding. Endoscopic treatment, especially in patients with high-risk bleeding lesions, significantly reduces the frequency of recurrence bleeding, the need for surgical intervention, and mortality (6, 12, 13).

Considering the timing of endoscopy, it has been reported that emergency endoscopy performed within 24 hours reduces the risk of mortality and surgical intervention in patients with high-risk upper gastrointestinal system bleeding. However, in many studies, there was no significant difference between patients who un-

derwent endoscopy within the first 24 hours and within the first 12 hours. Therefore, emergency endoscopy is recommended for patients suspected of upper gastrointestinal bleeding within the first 24 hours (14-17). In the present study, it was found that 96% (102/107) of the patients underwent endoscopy within 24 hours after admission.

Endoscopic hemostasis can be achieved by injection, and by thermal and mechanical methods. Epinephrine injection can be carried out with the applications of sclerosing agents, thrombin/fibrin glue applications, thermal contact (Heater probe thermocoagulation) and non-contact (Argon plasma coagulation) devices and mechanical clip application. Epinephrine injection provides vasoconstriction while sclerosing agents help to achieve hemostasis by providing thrombosis (9, 11, 18).

Forrest classification was developed more than 40 years ago to standardize gastroduodenal ulcer bleedings. This classification has been used in numerous studies aimed at identifying patients at risk of persistent ulcer bleeding, re-bleeding, and death. Most of these studies have shown that the presence of ulcers classified endoscopically as F1a or F1b is an independent risk factor for permanent bleeding or re-bleeding (11, 19, 20). In the literature, the rates of rebleeding was reported vary between 90 % for a Forrest I a lesion and 5 % for a Forrest III lesion (21).

In the literature, it is stated that hemostasis is achieved in the rates of over 90% with endoscopy in non-variceal upper gastrointestinal bleeding cases (22). In a study by Park et al., hemostasis rate achieved only by epinephrine injection was 97.7% in patients with bleeding ulcers, and hemostasis success rate achieved by combined treatment with epinephrine injection + mechanical clip was 97.7%, and no difference was found between these rates (23). In a study by Gugliemi et al, in patients with Forrest 1a, 1b, 2a and 2b ulcers, the primary hemostasis rate by epinephrine and sclerosing agent injection with endoscopy was reported to be 95.6% (20). In the present study, primary hemostasis rates were 87.5% (14/16) in Forrest 1a and 97% (62/64) in Forrest 1b. In Forrest 2a, however, 100% hemostasis was achieved, and the overall primary hemostasis success rate was 96.2% (103/107) in all three groups. Comparing these rates with both non-epinephrine injection monotherapy treatment modalities and combined treatment modalities, results like those in the literature were found in terms of ensuring primary hemostasis.

In non-variceal upper GIS bleedings, the rate of re-bleeding after endoscopic treatment has been reported to be approximately 24% in the literature (24). In randomized studies, initial hemostasis rates were at approximately 90% with endoscopic monotherapy treatments without taking the hemostatic method into account, and re-bleeding rates were reported to be between 2% and 10% in endoscopic monotherapies other than epinephrine injection. There was no significant difference between monotherapies in ensuring initial hemostasis. Although epinephrine injection is effective in ensuring initial hemostasis in patients with active ulcer bleeding, the rate of re-bleeding has been reported to be between 12% and 30% (25-28).

In a study by Park et al., the rate of re-bleeding in patients with Forrest 1a, 1b, and 2a ulcers was found to be 20.4% (9/44) in the group where hemostasis was achieved only by epinephrine injection. In the combined treatment group, however, this rate was found to be 4.5% (2/44) (23). In another study by Pescatore et al., re-bleeding rates were 57% for Forrest 1a, 24% for Forrest 1b, and 21% for Forrest 2a in patients with GIS bleeding for whom hemostasis was achieved epinephrine alone, while the re-bleeding rates were reported as 25% for Forrest 1a, 14% for Forrest 1b and 25% for Forrest 2a for the combined treatment of epinephrine + fibrin glue. In this study, the combined treatment significantly reduced re-bleeding rates in Forrest 1a and 1b ulcers but did not achieve a decrease in re-bleeding rate in Forrest 2a (28).

In a prospective randomized study by Chu-Lo et al., patients receiving epinephrine injection alone were compared with patients receiving combined therapy with epinephrine and hemoclip, and re-bleeding rates were reported as 21% in patients receiving monotherapy and as 3.8% in patients receiving combined therapy. The need for emergency surgery was observed only in the group treated with epinephrine and was found to be 9% (29). In a review, re-bleeding and the need for surgery were observed less in patients who received endoscopic combined therapy than patients who received endoscopic monotherapy (30). Gugliemi et al. reported the re-bleeding rates in patients with upper GIS bleeding who were provided hemostasis with epinephrine and sclerosing agents as 23.6% for Forrest 1a, as 19% for Forrest 1b, and as 19.5% for Forrest 2a (20). In the present study, however, re-bleeding rates were 28% (4/14) for Forrest 1a ulcer, 16% (10/62) for Forrest 1b ulcer, and 7.4% (2/27) for Forrest 2a ulcer and the re-bleeding rate of the overall series (group 1+2+3) was determined as 15.5% (16/103).

When the re-bleeding rates in the study were compared with other hemostatic methods except for epinephrine, these rates were found to be higher in patients with Forrest 1a and 1b ulcers than in the literature, but they were found to be similar to those in the literature when compared with the results of the studies where epinephrine injection treatment was administered alone. Re-bleeding rates were lower in patients

with Forrest 2a ulcers when compared to the results of the studies in the literature where epinephrine injections were administered alone, but these rates were found to be similar with the results obtained when compared with other non-epinephrine hemostasis methods.The re-bleeding rates of the general series of the present study (15.5%) were found to be consistent with the literature.

When the re-bleeding rates in patients with Forrest 1a and Forrest 1b ulcers were compared with the rates of re-bleeding after combined treatment, these rates were found to be higher than those in the literature. In patients with Forrest 2a ulcer, however, when the rates of re-bleeding were compared with the rates of re-bleeding in combined treatment, they were found to be similar to those in the literature. In the present study, the rate of patients who needed urgent surgery was 5.7% and this rate was lower than the rate of surgical need in patients who underwent monotherapy in the literature, while it was similar to the rate of surgery need in studies where the combined therapy was administered.

The American Society for Gastrointestinal Endoscopy and European Society for Gastrointestinal Endoscopy guidelines recommend the administration of endoscopic treatment for classes Forrest 1a and 1b with bleeding ulcers and ulcers with bleeding but not visible vessels in class Forrest 2a (11, 22). In the guidelines, the administration of a second hemostasis modality with ESGE epinephrine injection is recommended, whereas epinephrine injection alone is not recommended in the classes Forrest 1a and 1b. In Forrest 2a, however, while mechanical, thermal or sclerosing agents were recommended to be administered as monotherapy or in combination with epinephrine injection, epinephrine injection alone was not recommended (11).

CONCLUSION

In conclusion, although adrenaline injection as an endoscopic treatment in GIS bleeding has a high success rate in achieving primary hemostasis, as discussed above, re-bleeding rates are higher than those in combined therapies. Therefore, it is thought that endoscopic combined treatment should be applied especially in patients with Forrest 1a and 1b bleeding ulcers, whereas in Forrest 2a ulcer patients, because of both the high rate of primary hemostasis and low rate of re-bleeding according to the results of the present study, the treatment of adrenalin injection alone can be used alone like other hemostasis modalities.

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Sažetak

KRVARENJE IZ GORNJIH PARTIJA GASTROINTESTINALNOG TRAKTA: DA LI JE SAMO INJEKCIJA EPINEFRINA DOVOLJNA? STOPE USPEHA PO FORREST-OVOJ KLASIFIKACIJI

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Uvod: Endoskopski tretman je efektivan i uspešan vid lečenja nevarikoznih krvarenja iz gornjih partija gastrointestinalnog trakta (GIT). Poslednjih godina, endoskopska kombinovana terapija je preporuka za hemostazu. Cilj ove studije bio je da ispita stope primarne hemostaze i ponovljenog krvarenja koji su tretirani samo injekcijom epinefrina.

Materijal i Metode: Analizirali smo pacjente koji su endoskopski dobili injekciju epinefrina kao jedini tretman zbog krvarenja iz gornjeg GIT-a između januara 2014. i januara 2019. Pol, godine starosti, etiologija krvarenja, Forrest-ova klasifikacija, efikasnost tretmana i stopa ponovljenog krvarenja su evidentirani. Istorije pacijenata su analizirane retrospektivno.

Rezultati: Broj pacijenata uključenih u studiju bio je 107. U Grupi 1 (Forrest 1a) bilo je 16, u Grupi 2 (Forrest 1b) 64 pacijenta, i u Grupi 3 (Forrest 2a) 27. Primarna hemostaza je postignuta kod 14 (87,5%) od

16 pacijenata u Grupi 1, 62 (97%) od 64 u Grupi 2, i 27 (100%) of 27 u Grupi 3. Ponovnih krvarenja je bio 4 (28%), 10 (16%), 2 (7) u grupama 1, 2 i 3.

Zaključak: Prema rezultatima studije smatra se da bi kombinovani endoskopski tretman trebalo primeniti posebno kod pacijenata sa Forrest 1a i 1b krvarećih ulkusa, dok kod Forrest 2a pacijenata, zbog visoke stope primarnih hemostaza i niske stope ponovljenih krvarenja, tretman samo injekcijom adrenalina je dovoljan.

Ključne reči: endoskopski tretman, Forrest-ova klasifikacija, krvarenje iz gorneg gastrointestinalnog trakta.

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Case report

EMERGENCY ABDOMINAL ULTRASOUND AS SUFFICIENT DIAGNOSTIC MODALITY IN THE DIAGNOSIS OF BILIARY ILEUS

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Abstract: **Introduction:** Biliary ileus is a rare emergency condition that mainly affects the elderly population, with a predominance of females and a mortality rate of 12-27%. It is a mechanical intestinal obstruction caused by the impaction of the biliary calculus within the gastrointestinal tract. It occurs due to the formation of bilio-enteric fistula, as a rare complication of cholelithiasis. **Case report:** A 73-year-old male patient with epigastric pain, nausea and vomiting was referred for ultrasound exam. The analysis of the clinical-biochemical status of the patient as well as the ultrasound examination of the abdomen itself raised the suspicion of small intestine obstruction, due to the enclaved biliary calculus. After an urgent exploratory laparotomy, the diagnosis was confirmed, and enterotomy was successfully performed with calculus extraction. Cholecysto-duodenal fistula has been confirmed as a major cause of biliary ileus. The post-operative course was uneventful. Conclusion: This case report highlights the enormous importance of ultrasound diagnostics in diagnosing biliary ileus using the criteria of The Rigler Triad, which includes pneumobilia, intestinal obstruction and ectopic calculus. Initially unrecognisied cause of obstruction and a late diagnosis correlated with bad prognosis. Ultrasonographic examination of these patients, can be a sufficient diagnostic modality in making an accurate diagnosis and further surgical treatment of these patients.

Keywords: cholelithiasis, biliary ileus, ultrasonographic examination of the abdomen.

INTRODUCTION

Biliary (gallstone) ileus is important, though rare, cause of mechanical intestinal obstruction. It is a infrequent complication of cholelithiasis. The frequency of gallstone ileus recurrence is 4%, but increases to 25% in patients older than 65 years. It is mostly a condition in the older female population (1). Ileus is caused by an impaction of a large gallstone (one or more) within the lumen of the small intestine. A gallstone passes through a fistulous tract before becoming impacted and the most common type of fistula is between the gallbladder and the duodenum (2). It can obstruct any part of the gastrointestinal tract, but most frequently affects distal ileum. The mortality rate is high and ranges from 12 to 27%, because these patients are more often elderly people who have associated chronic diseases (2, 3).

CASE REPORT

We present a case of gallstone ileus with cholecystoduodenal fistula in a male patient as first presentation of gall stone disease. This 73-year-old male patient was admitted to the Emergency Center, Clinical Center of Serbia and presented initially with symptoms of abdominal pain, nausea, vomiting and hiccups for the last eight days. He also complained of relative constipation. On examination, painful epigastric sensitivity was found. He was hemodynamically stable without fever or jaundice. Laboratory evaluation revealed a leukocytes level of 23.5 *109/L. Abdominal ultrasound and upright abdominal radiography were performed. Plain radiography of the abdomen showed air-fluid levels in the epigastric area and signs of pneumobilia. Abdominal ultrasound confirmed the presence of air in the biliary tree (Figure 1A). It also showed pronounced dilation of the stomach and jejunal loops, with diameter measured about 30mm (Figure 1B, C). In the projection of the jejunum, a calculus of about 34

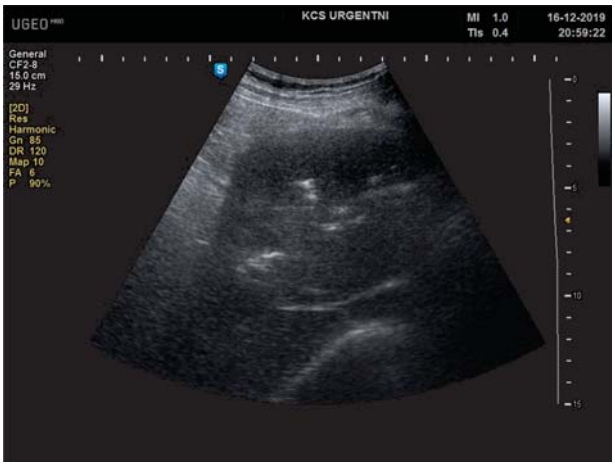

Figure 1A. *Ultrasound image of the liver with focuses of high echogenicity with shadowing that suggest pneumobilia*

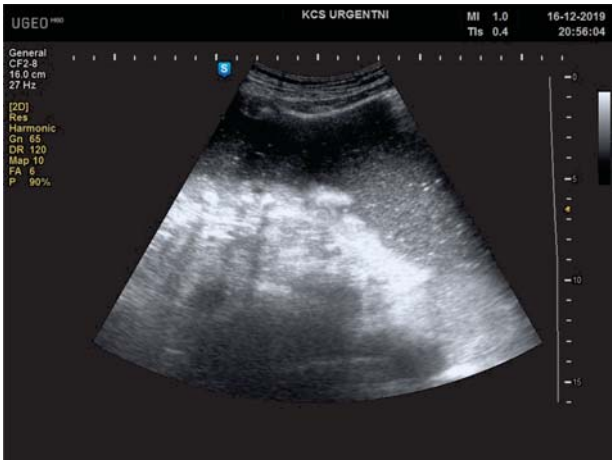

Figure 1B. *Ultrasound image of the stomach with its dilatation*

mm in diameter was detected (Figure 1D). The gallbladder was collapsed. All signs belong to the Rigler's triad (pneumobilia, ectopic gallstone, and intestinal obstruction). Ultrasound in this case was enough to make a definitive diagnosis of gallstone ileus. After urgent exploratory laparotomy, the diagnosis was confirmed. The patient was treated surgically with enterolithotomy. An ectopic gallstone was detected in distal ileum, it measured 4 x 2 cm in diameter and completely occluded the lumen of the small bowel. Cholecystoduodenal fistula was revealed, without any pathological content in the cholecyst. Enterotomy was done with the extraction of calculus (Figure 2). Postoperative recovery was uneventful.

DISCUSSION

Biliary ileus is mechanical intestinal obstruction caused by the impaction of the larger calculus (> 2.5 cm), while smaller calculus is more often asymptomatic because it does not lead to obstruction and passes

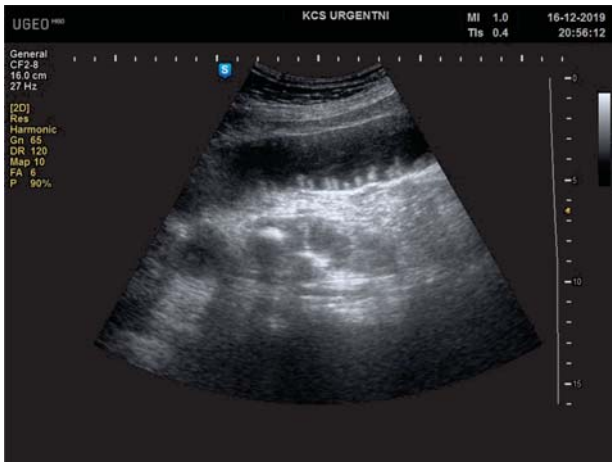

Figure 1C. *Ultrasound image of dilated jejunal loops*

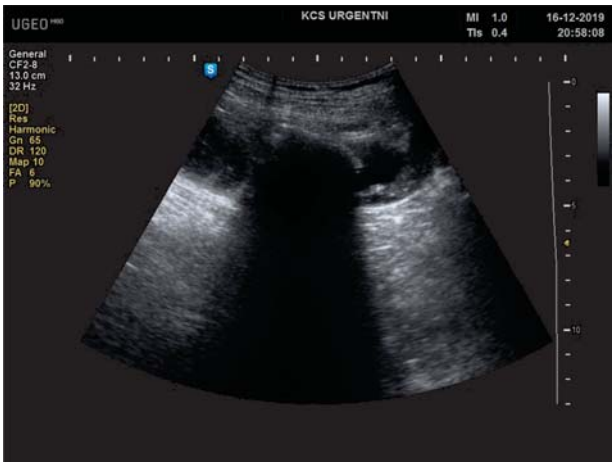

Figure 1D. *Ultrasound image shows a calculus (34 mm) in the projection of the distal ileum*

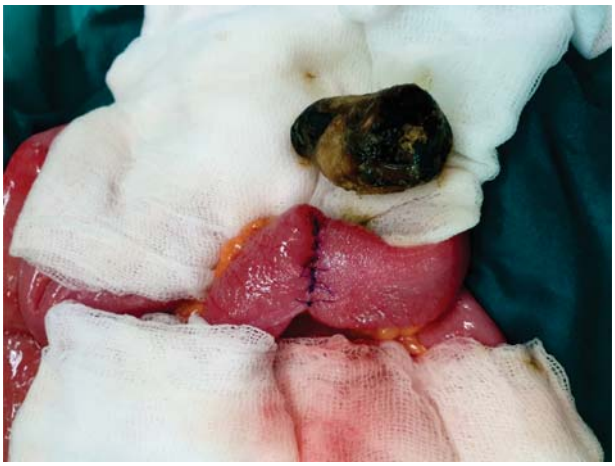

Figure 2. *Intraoperative image - Enterotomy and extracted calculus (4 x 6 cm)*

through intestinal loops like "rolling stones" (4, 5). A gallstone passes through a fistulous tract before becoming impacted and the most common type of fistula is between the gallbladder and the duodenum (68%). Other possible, but less common, fistulization are cholecysto-jejunal, cholecysto-colonic (5–25%), cholecysto-

duodenal-colonic (2.5%), and cholecysto-gastric fistula (5). Fistulisation is the most common but not the only possible mechanism of biliary ileus, so there are also: the passage of calculus through the ampulla of Vater, and iatrogenic causes (during ERCP or a cholecystectomy) (5, 6, 7). It can obstruct any part of the gastrointestinal tract, but frequently at the distal ileum, ileocaecal valve in 60% of cases due to their anatomically narrow lumen. The other sites of stone impaction are jejunum (16%), stomach (14%), colon (4%), and duodenum (3.5%) (5, 7). Gallstone coleus and Bouveret's syndrome are two very rare forms of biliary ileus (7). Gallstone coleus is a gallstone obstruction at the level of the colon, more often sigmoid colon (mostly in combination with diverticulitis) or transverse colon (anatomical proximity to the cholecyst). Gallstone reaches the colon by passing through the ileocecal valve or by direct fistulization with the loops of the colon (8, 9). Bouvert's syndrome is a very rare form of biliary ileus in which the obstruction is at the level of the distal stomach or proximal duodenum, and mostly with calculus larger than 2.5 cm (10).

The symptoms and signs of gallstone ileus are mostly nonspecific. The onset of the presentation can be acute, subacute, or chronic. Gallstone ileus frequently clinically manifests as abdominal pain, nausea, vomiting, fever, distension, and constipation. The character of vomiting depends on the location of the obstruction (6). At the time of intestine obstruction 10-30% of patients have acute cholecystitis. The "tumbling phenomenon", partial obstruction or distal migration of the gallstone may be the cause of why the patient usually present at hospital 4 to 8 day after the beginning of symptoms (6, 7).

Plain abdominal film radiography is usually the first and significant step in diagnosing intestine obstruction regardless of the cause. The advantage is that it is a quick and easy diagnostic test. The sensitivity of plain abdominal film radiography for the diagnosis of gallstone ileus is between 40 and 70% (2). It is very difficult to detect the calculus itself in the case of biliary ileus on plain abdominal film radiography, because it requires that the gallstone contain enough calcium, which occurs in only 10-20% of cases. Another important sign that can be detected on plain abdominal film radiography is pneumobilia, which is specific but not pathognomonic for biliary ileus (5, 6).

The Rigler triad consists of pneumobilia, intestinal obstruction and ectopic gallstone. The presence of two signs of Rigler'striad, has been considered pathognomonic in 20%-50% of cases (6, 7).

When it comes to diagnosing gallstone disease, abdominal ultrasonography has proven to be the most effective method, with an efficiency of more than 95% (7). It is a low-cost, non-invasive and fast diagnostic procedure. Disadvantages are limited visualization at patients with ileus due to discomfort and intestine loops with gas or fluid, as well as dependence on the skill of the sonographer. When it comes to an experienced sonographer, it is possible to detect the signs of the Rigler's triad with the precise location of the gallstone. The combination of abdominal films and ultrasound imaging has a sensitivity of diagnosis of gallstone ileus up to 74% (1, 7, 10-13).

Computed tomography is a diagnostic method that is considered the gold standard in diagnosing biliary ileus. This is supported by the high sensitivity of CT in the detection of the exact location of the obstruction, as well as a more precise measurement of the size of the ectopic calculus. On the other hand, a high dose of radiation is used and a numerous unwanted effects on the application of iodinated contrast media are possible. Therefore, the optimal diagnostic plan could be the primary application of abdominal ultrasound and then, but in case of non-inclusiveness of the findings, in further diagnostic protocol CT exam should be applied (11, 12, 13).

The surgical approach is something that is still being researched. The goal is to resolve the obstruction while reducing the risk of developing complications. Surgical modalities used today are enterolithotomy, enterolithotomy with later cholecystectomy and one-stage surgery that includes enterolithotomy, cholecystectomy and fistula repair (14).

Several factors should be considered when choosing a surgical treatment. Enterotomy at the antimesenteric border with removal of the calculus and transverse closure is first option. Clinically stable patients are main candidates for one-stage surgery. Enterolithotomy alone is the most commonly used surgical option, due to the lowest risk of complications (14, 15). When surgical treatment is contraindicated, endoscopic mechanical lithotripsy handling fragmentation is sometimes possible (15).

Biliary ileus is a rare emergency condition that mainly affects the elderly population, with a predominance of females and a mortality rate of 12-27%. Initially unrecognized cause of obstruction and delayed diagnosis correlate with a worse prognosis. The presentation of this case indicates the enormous importance of a detailed and comprehensive ultrasonographic examination of these patients, which is quite a sufficient diagnostic modality in making an accurate diagnosis and further surgical treatment of these patients.

Abbreviations

ERCP — Endoscopic Retrograde Cholangio-Pancreatography

CT — Computed Tomography

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Patient details have been de-identified such that patien' s identity remains anonymous, and we obteined verbal consent from the patient to publish the case report.

Sažetak

ULTRASONOGRAFSKI PREGLED ABDOMENA KAO DOVOLJAN DIJAGNOSTIČKI MODALITET U POSTAVLJANJU DIJAGNOZE BILIJARNOG ILEUSA – PRIKAZ SLUČAJA

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Uvod: Bilijarni ileus je retko urgentno stanje koje zahvata uglavnom stariju populaciju, sa predominacijom osoba ženskog pola i stopom smrtnosti 12-27%. Predstavlja mehaničku intestinalnu opstrukciju uzrokovanu impakcijom bilijarnog kalkulusa unutar gastrointestinalnog trakta. Nastaje usled formirane bilio-enterične fistule, kao retka komplikacija holelitijaze.

Prikaz slučaja: Pacijent muškog pola, star 73 godine, sa bolnom osetljivošću epigastrijuma, mučninom, povraćanjem i leukocitozom od 23.5 *109/L upućen je na ultrasonografski pregled abdomena. Analizom kliničko-biohemijskog statusa pacijenta kao i samog ultrazvučnog pregleda abdomena postavljena je sumnja na opstrukciju tankog creva sa pretećim ileusom, usled inklaviranog bilijarnog kalkulusa u vijuzi tankog creva promera 40mm. Nakon urgentne eksplorativne laparotomije, dijagnoza je potvrđena, uspešno je učinjena enterotomija sa ekstrakcijom kalkulusa, kao hirurška metoda sa najnižom stopom postoperativnih komplikacija u tretmanu akutnog bilijarnog ileusa. Potvrđena je holecisto-duodenalna fistula kao glavni uzrok bilijarnog ileusa. Postoperativni tok je bio uredan.

Zaključak: Prikazom ovog slucaja ukazuje se na enormni značaj ultrazvučne dijagnostike u postavljanju dijagnoze bilijarnog ileusa uz dijagnostički kriterijum Riglerove trijade koji obuhvata pneumobiliju, intestinalnu opstrukciju i ektopični kalkulus. Inicijalno neprepoznat uzrok opstrukcije i zakasnela dijagnoza koreliraju sa lošijom prognozom. Ovaj dijagnostički modalitet može biti sasvim dovoljan u postavljanju brze i precizne dijagnoze koja vodi pravovremenom hirurškom tretmanu ovih pacijenata.

Ključne reči: holelitijaza, bilijarni ileus, ultrasonografski pregled abdomena.

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Review article

RENAL, PELVIC AND MESENTERIC TUMORS WITH LOW SIGNAL INTENSITY ON T2-WEIGHTED MR IMAGE: A REVIEW

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Abstract: The magnetic resonance (MR) imaging of intra-abdominal tumors is necessary for clinical practice. MR imaging involves the optimal evaluation of masses due to its inherent soft tissue contrast and multiplanar scanning abilities. T2 low-signal tumors are not common, and individuals need to be careful when interpreting them.

The tumors that contain smooth muscle components, a high nucleus-to-cytoplasm ratio, or papillary architecture, among other components, tend to display low signal intensity on T2-weighted images. MR imaging allows for both the detection and characterization of tumors, especially when they have low signal intensity when presented on T2-weighted images. As a result, it becomes essential to identify the various characteristics that define each tumor.

Identification of the tumor spectrum and knowing the cause of low signal intensity on T2 –weighted images helps the radiologist to narrow the differential diagnosis and reach a final diagnosis.

Key words: Magnetic Resonance Imaging, diagnosis, Tumor, Low signal intensity.

INTRODUCTION

Magnetic resonance (MR) imaging of tumors is necessary for clinical practice. On MR imaging of the abdomen, T1 and T2-weighted sequences have always been a key aspect in characterizing tumors. The detection of tumors using T1 and T2-weighted sequences can be affected by various pathological factors. The histological structures tend to impact the T1 and T2 duration of relaxation. MR imaging possesses a unique ability in that it explores intracellular content in a way that allows it to recognize substances that can affect signal generation (1).

In most cases, intra-abdominal tumors have a high cellular water mass, which causes them to appear as a high signal intensity (SI) when viewed using T2-weighted imaging. In such a context, radiologists should be well-informed of the various factors that cause low SI as well as the mechanisms through which it occurs on T2-weighted images. They should possess the ability to identify the organ spectrum of tumors that are presented in various imaging findings (1).

MR Imaging and T2 low signal intensity of renal, Pelvic and Mesenteric tumors

MR imaging involves the optimal evaluation of masses because of its inherent soft tissue contrast and multiplanar abilities. MR imaging aspects of indeterminate masses tend to provide well distinguished morphologic information on tumors such as its location, size, and composition (2). T2-weighted sequences incorporate an integral part of MR imaging that is performed to characterize masses. A greater percentage of intra-abdominal tumors comprise cystic components that display high SI on T2-weighted images. The findings of T2-low signal tumors are not common, which requires care when they are interpreted. These interpretations should be made based on aspects such as pathologic correlates such as smooth muscle, blood products, calcification, high tumor cellularity, and fibrous tissue (2).

Characterizing intra-abdominal tumors requires familiarity with their appearance as well as an analysis of their relationship with the affected or surrounding organs.A wide range of factors cause T2-low signal intra-abdominal tumors. Often, the factors rely on the nature of the tumor as well as the affected organ. Understanding the various causes of intra-abdominal tumors can help in using the correct and most effective method of diagnosis. Some abdominal tumors that are com-

monly affected by T2 low signal tumors are discussed below (2).

Renal tumors

Most renal tumors have been described as benign simple and complex epithelial cysts, oncocytomas, metastases, angiomyolipomas, and renal cell carcinomas (RCCs). Sixty-seven percent of renal tumors have also been described as possessing a high possibility of malignancy. Renal tumors can be significantly differentiated using MR images to distinguish between malignant and nonmalignant tumors (3). Necrosis is among the factors that contribute to the generation of low intensity on T2-weighted MR images. While liquefactive necrosis is high on T2-weighted MR, coagulative necrosis is defined by low signal intensity when presented on T2-weighted MR images. The low signal intensity in coagulative necrosis is usually attributed to their dehydration because they do not contain water (4).

Transitional cell carcinomas (TCCs) also contribute to the development of renal tumors. TCCs occur rarely in the upper tract. Usually, TCCs are divided into papillary and non-papillary tumors. TCCs are mostly multifocal and can occur in any part of the collecting system. Although the hematogenous spread is not as common as in RCCs, lymphatic metastases are observed early (5).

The bright signal caused by urine that is present in the collecting system on T2-weighted images offers an excellent soft tissue contrast to facilitate the detection of TCC tumors that are usually seen as having a low SI filling defect (Figure 1) (6, 7). Infiltrative TCC can be observed on a single shot of a T2-weighted image as a low signal tissue bulk that subverts the renal parenchyma that possesses an intermediate SI (6). On post-contrast images, infiltrative TCC can be identified as a hypo-enhancing mass, although avid enhancement can take place. MR images produced from the post-contrast acquisition offer a display format that is similar to intravenous pyelograms. In some cases, they can render the findings more conspicuous through contrast with the contralateral kidney.

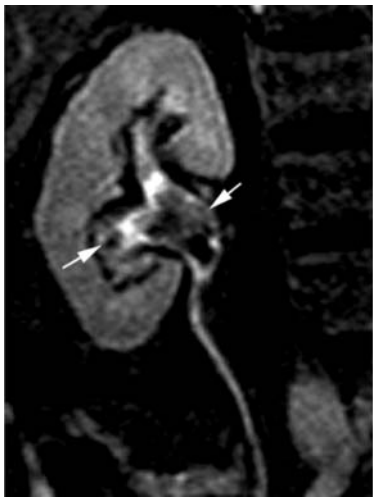

Figure 1. *A transitional cell carcinoma as viewed on a low-intensity T2-weighted image (7)*

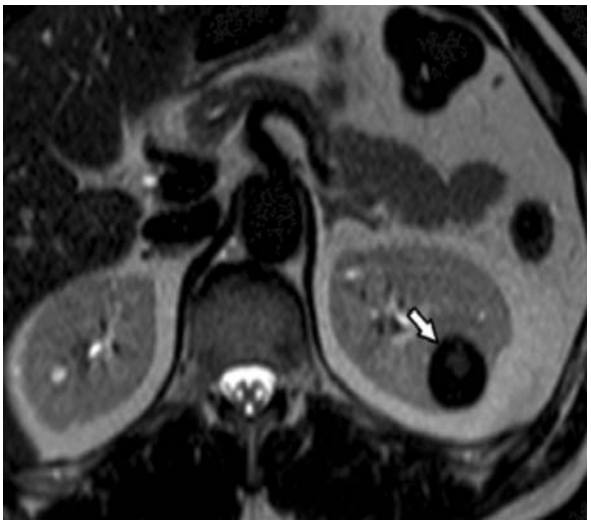

Figure 2. *A T2-weighted MR image of low SI papillary renal cell carcinoma (9)*

Papillary RCC (pRCC) forms part of the most commonly occurring RCC types. The tumors present distinctive imaging features that facilitate their differentiation from other types, especially the clear RCC (cRCC). The tumors account for approximately 14 percent of RCC tumors. In most cases, it affects people in the third to eighth decades of life. pRCCs are usually defined by a papillary, tubular, or tubo-papillary pattern of growth (7, 8). Compared to clear cell carcinomas, pRCCs have a smaller diameter and are usually at a lower stage of development. pRCCs have histologic characteristics that are closely related to those of papillary adenoma, which is a benign type of renal tumor.

MR images are commonly used to characterize renal tumors. MR imaging is known to provide a tissue contrast that is superior to other imaging techniques. Thus, it is used in imaging pRCCs because it can differentiate solid from cystic tumors. In both T1 and T2-weighted images, pRCC demonstrates a pseudo-capsule and usually has a low SI (Figure 2) (7). MR images of pRCC show less enhancement compared to cRCC.

Angiomyolipoma (AML) makes one of the most common non-malignant solid renal tumors. A larger percentage of AMLs have a fat content that is easily visible on MR images and CT scans, which makes the tumors diagnosable without surgery or biopsy (10). An estimated five percent of renal AMLs contain little fat that can hardly be identified in MR images. Preoperatively, AMLs with minimal fat are usually difficult to

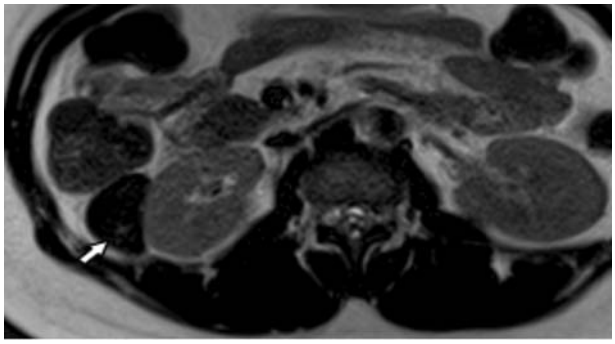

***Figure 3**. A hypo-intense T2-weighted image showing a fat-poor mass in the renal area (9)*

differentiate from RCC when using radiologic examination. Thus, they tend to be diagnosed after surgery (9). On T2-weighted images, AMLs with a high fat content are usually hyper-intense (high signal) contrary to the renal parenchyma. Lipid poor AMLs are T2 hypo-intense (low signal), but they differ in homogeneity depending on the fat distribution (Figure 3).

Pelvic Tumors

The pelvic area is usually prone to tumors that mostly originate from the uterus, fallopian tubes, ovaries, peritoneum, and cervix. MR imaging is used for diagnosis and is usually influenced by the tumor location.

Uterus

Often, a larger percentage of pelvic tumors are linked to endometrial cancer, which is also the most commonly occurring uterine cancer. On examination, tumors can appear as exophytic masses and in other cases as diffuse endometrial thickening (11). The location of endometrial carcinoma is often based on the extension of the primary tumor. When viewed on T2-weighted images, endometrial cancer tumors have an intermediate low SI (Figure 4) (11). On early contrast-enhanced MR imaging, endometrial carcinoma is enhanced less

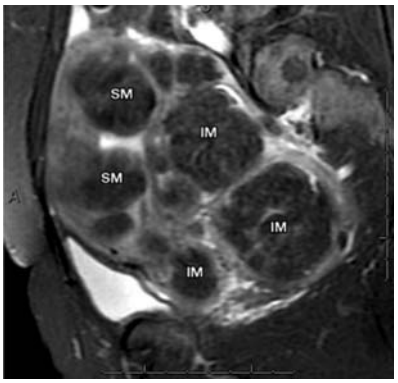

***Figure 5.** Representation of multiple intramural (IM) and submural (SM) fibroid tumors on a T2-weighted image (13)*

than the myometrium on delayed scans, while there is less enhancement differentiation on delayed scans.

Leiomyoma, which is the most common uterine neoplasm, is mostly found in middle-aged women. Leiomyomas contain spindle-shaped cells in a trabecular configuration, creating a whorled appearance. The amount of fibrous tissue, extracellular matrix, and collagen is usually variable (11). The tumors are commonly classified as cervical, intramural, subserosal, and submucosal, depending on where they are located. On T2-weighted images, the tumors appear to be well arranged and have a low SI on T2-weighted images (Figure 5). However, they can have different appearances that depend on the presence of necrosis, cystic degeneration, cellular-type leiomyoma, and hemorrhage.

Ovary

The ovaries can be affected by a wide range of tumors, which can be malignant or benign, cystic, or solid. Among the variety of tumors that can affect the ovaries are cystadenofibroma, Brenner tumors, and granulosa cell tumors. The ovarian cystadenofibroma is a benign tumor that has both stromal and epithelial constituents (6). It can be malignant on rare occasions,

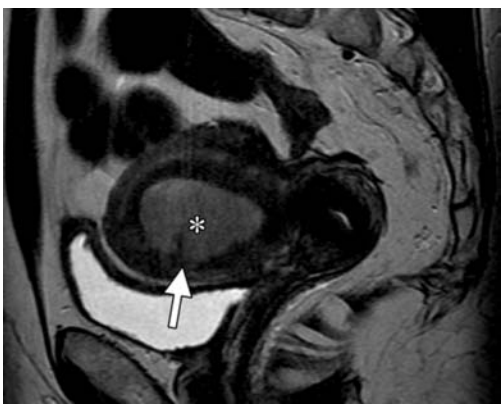

***Figure 4.** A T2-weighted image of a low signal endometrial cancer (12)*

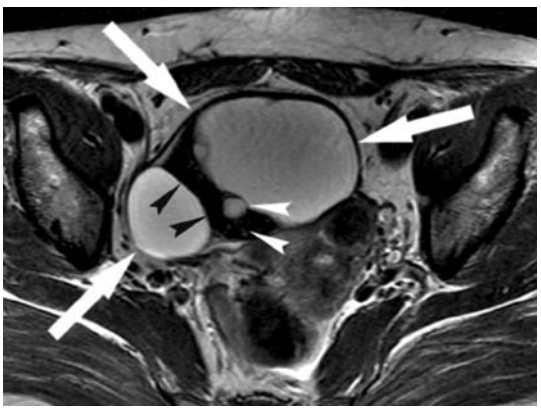

***Figure 6.** A low-intensity T2-weighted image of a mucinous cystadenofibroma (14)*

but it usually mimics malignancy during imaging because of a well-enhanced solid element that is located in the cystic mass. The solid element displays a low SI that is similar to what is observed in skeletal muscle on T2-weighted MR images because of the fibrous tissue that is present. The characteristic findings of ovarian cystadenofibromas include small cysts that are located within the solid component (6). The diagnosis for cystadenofibroma has a T2 low signal intensity within multilocular cystic masses and large cystic gaps in the glandular elements (Figure 6).

Ovarian fibromas and fibrothecomas form an uncommon group of benign tumors that originate from the stroma. These tumors represent approximately four percent of ovarian neoplasms. Fibromas normally originate from mesenchymal spindle cells that produce collagen, and they can in some cases be linked to Meigs syndrome, which includes ovarian tumors, ascites, and pleural effusion (10). Fibrothecomas originate from spindle cells, but they can contain intracellular lipids. The tumors may also show estrogenic activity. Fibromas and fibrothecomas are normally asymptomatic, and they are usually found incidentally. Often, they occur in post-menopausal and perimenopausal patients in their fifth and sixth decades of life (10). On MR images, the tumors appear with a low SI on T2-weighted images (Figures 7 and 8). Although fibromas and fibrothecomas are often defined as solid masses, they rarely contain cystic components.

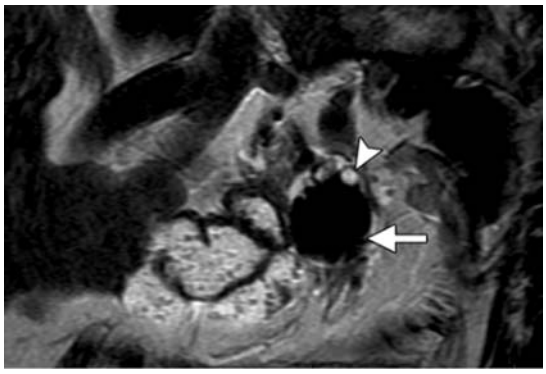

Figure 7. *An axial view of a T2-weighted MR image showing a low-intensity mass in the fibroma (15)*

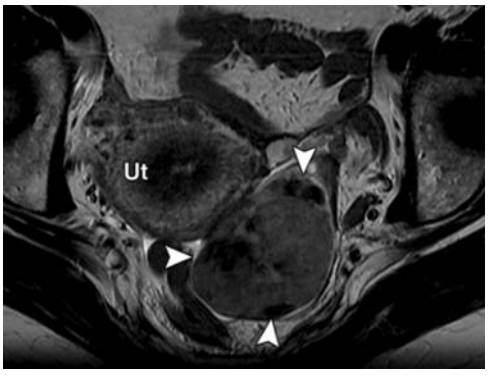

Figure 8. *A T2-weighted image of a fibrothecoma showing an intermediate low SI ovarian mass (15)*

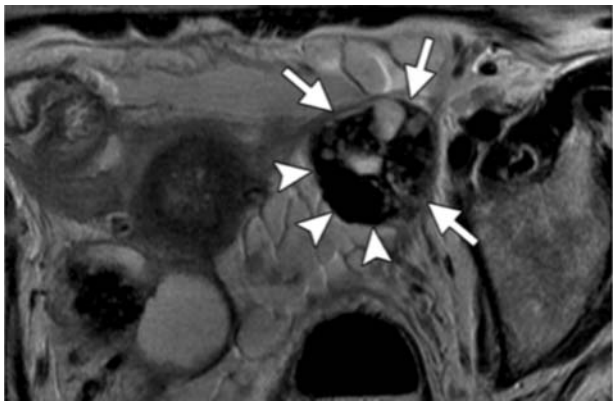

Figure 9. *A low-intensity T2-weighted image of a Brenner tumor (15)*

Brenner tumors are usually uncommon, and they usually affect women in the fifth decade of life. The tumors are predominantly solid on pathologic and imaging examinations. However, an association with mucinous and serous cystadenomas in approximately 30 percent of patients may show a cystic appearance when the tumor is very small or visually inseparable from the coexisting cystic neoplasm (9). On pathologic examination, Brenner tumors can range from 0.3 to 12 cm and contain epithelial nests that are surrounded by proliferating dense stromal tissue. MR imaging shows T2-weighted hypo-intense (low SI) solid elements that have fibrous tissue that is similar to fibromas (Figure 9).

Clear cell adenocarcinomas form between five and ten percent of ovarian tumors. Often, nulliparity is associated with endometriosis as well as endometrioid cysts. The symptoms of the tumor can range from abdominal discomfort, distention, and pain to gastrointestinal symptoms. Gross examination of the tumor shows that it appears to contain solid and cystic constituents (16). A larger percentage of the tumors are usually unilocular cystic masses. The solid components of the cyst are usually hypo-intense (low signal) on T2-weighted MR images. In cystic tumors, gadolinium-based contrast of solid components is displayed as being helpful during the diagnosis process (16). Peritoneal and ascites enhancement is essential for predicting the tumor malignancy.

Prostate

Prostate cancer causes approximately ten percent of cancer-related deaths. An examination of prostate carcinoma shows a recognizable pattern of glands. In other cases, it can display nests, cords, or sheets of cells. T2-weighted images tend to define anatomic aspects of the tumor and present a clear distinction between peripheral and transition locations. The typical

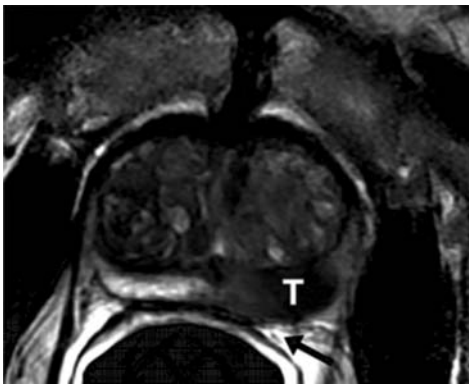

Figure 10. *A low-intensity T2-weighted image of the prostate carcinoma (17)*

prostate carcinoma displays a focal low SI on T2-weighted images (Figure 10). The diagnosis for prostate carcinoma includes two-dimensional electrophoresis and a positive prostate biopsy (1).

Mesenteric and bowel tumors

Mesenteric tumors form part of the most common hypo-intense (low signal) tumors on T2-weighted images. Depending on where they are located, leiomyomas

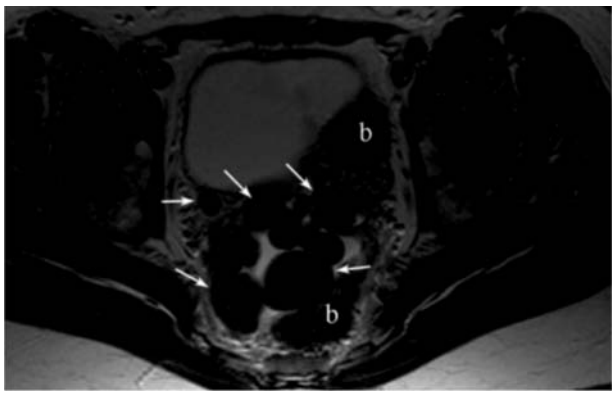

Figure 11. *A low-intensity T2-weighted image of a peritoneal leiomyomas (19)*

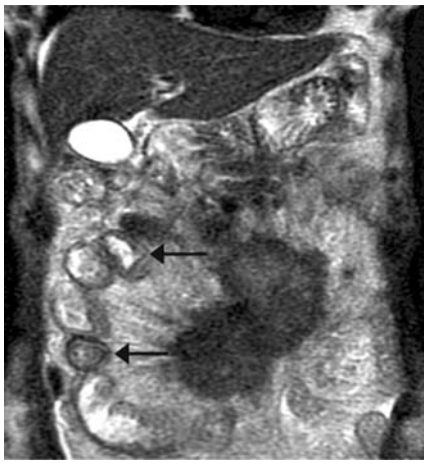

Figure 12. *A T2-weighted image of a carcinoid tumors (14)*

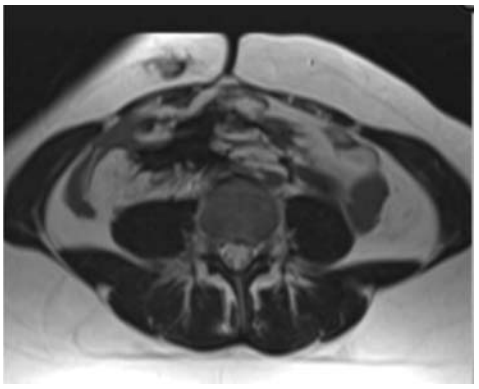

Figure 13. *A low intensity T2-weighted MR image of the desmoid tumor (21)*

can in some cases project into the lumen or cause a mass effect on adjacently located bowels. Small bowel leiomyomas can appear as a homogenous focal round-shaped mass that has intense, constant enhancement. The tumor also shows uniform enhancement that is greater than that of the adjacent bowels when shown on post-gadolinium images (18). On T2-weighted images, leiomyoma is displayed as hypo-intense (low signal) round and smooth mural defect that is demarcated by sharp angles to the walls of the intestine (Figure 11).

Carcinoid tumors, however, cause focal and asymmetric bowel wall thickening while manifesting as a nodular thickening of the wall. In other cases, it can manifest as a smooth sub-mucosal mass. The primary tumors display contrast enhancement and can range from 2 to 4 cm (20). Typically, the tumors are hypo-intense (low signal) to muscle on T2-weighted images (Figure 12). The mesentery changes in response to tryptophan and serotonin secretion. The diagnosis for carcinoid tumors involves MR imaging, serum chromogranin A levels, and 5-hydroxyindoleacetic acid (5-HIAA) urinary excretion levels.

Desmoid tumors are benign myofibroblastic neoplasms that originate from deep fibromatoses. Although they are associated with aggressive local infiltration and Gardener syndrome, the tumors do not possess metastatic potential. However, the hostile local permeation and compression of nearby structures have a high rate of relapse (10). Desmoid tumors display a low SI on T2-weighted MR images, which are often influenced by the tumor's fibrous nature (Figure 13).

Gastrointestinal lymphomas form between one and two percent of gastrointestinal malignancies. The tumors can have various gross appearances such as diffusely infiltrating tumors producing full-thickness mural thickening, polypoid tumors protruding into the lumen, as well as large, fungating, and exophytic masses that are highly prone to fistula formation and ulceration (22). The walls of the bowel can appear dilated if the tumors are diffuse infiltrating because of interfer-

ence with the usual regulation of smooth bowel muscles. Bowel masses and dilatation that do not have proximal bowel obstruction suggest lymphoma. Lymphomatous invasion and damage of muscle layers result in aneurysmal dilatation of small-sized bowels that have lymphoma, which is caused by the loss of muscle tone where the tumor is attached to the intestinal wall. When viewed on T2-weighted images, the tumors have intermediate low SI (22).

CONCLUSION

MR imaging defines a well-developed technique that is used to examine tumors. MR imaging allows identification of tumor characteristics such as location, size, and content. In other cases, the imaging technique allows identification of the tumor's stage of development as well as whether it is benign or malignant. T2-weighted images involve presentation of basic MR imaging sequences that are determined by two key parameters of the spin echo, such as the time of repetition and the relative time taken to echo. Structures that have a short T2 relaxation time appear as hypo-intense (low signal) on T2-weighted images while those with a long time appear as hyper-intense (high signal).

Hypo-intense (low signal) tumors presented on T2-weighted images are generated when the T2 relaxation time is shortened. The shortening often transpires as a result of the effect of paramagnetic substances including blood, contrast medium, melanin, and mineral substances or the absence of excited protons such as rapid turbulent flows and air-containing spaces. Other causes can involve a high viscosity of protein and colloid material concentration as for protein and mucous-containing tumors or reduced extracellular concentration of fluid such as in highly cellular tumors. Identifying the location and morphology of pathological modifications that result in T2-hypointensity makes it possible to narrow the differential diagnosis. Similarly, having knowledge of such aspects enhances the possibility of making the final and correct diagnosis based solely on an MR imaging examination.

Abbreviations

MR — Magnetic resonance
SI — Signal intensity
TCCs — Transitional cell carcinomas
pRCCs — Papillary cell carcinoma
RCCs — renal cell carcinomas
cRCC — clear renal cell carcinoma
AML — Angiomyolipoma

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Sažetak

TUMORI BUBREGA, KARLICE I MEZENTERIJUMA SA NISKIM INTENZITETOM SIGNALA NA T2 PONDERISANOJ MR SLICI: PREGLED

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Magnetna rezonanca (MR) intraabdominalnih tumora je neophodna za kliničku praksu. MR omogućava optimalnu evaluaciju masa zbog svojstvenog kontrasta mekih tkiva i mogućnosti multiplanarnog skeniranja. Tumori T2 niskog signala nisu česti, i specijalisti treba da budu pažljivi prilikom njihovog interpretiranja.

Tumori koji sadrže glatke mišiće, visok nukleus-citoplazma odnos ili su papilarne građe, imaju tendenciju da prikažu nizak intenzitet signala na T2 ponderisanoj slici. Kao rezultat toga, postaje esencijalno otkriti i znati razne karakteristike koje definišu svaki tumor. Identifikacija tumora i svesnost o niskom intenzitetu signala na T2 ponderisanoj slici, pomažu radiolozima da postave finalnu dijagnozu.

Ključne reči: magnetna rezonanca, dijagnoza, tumor, signal niskog intenziteta.

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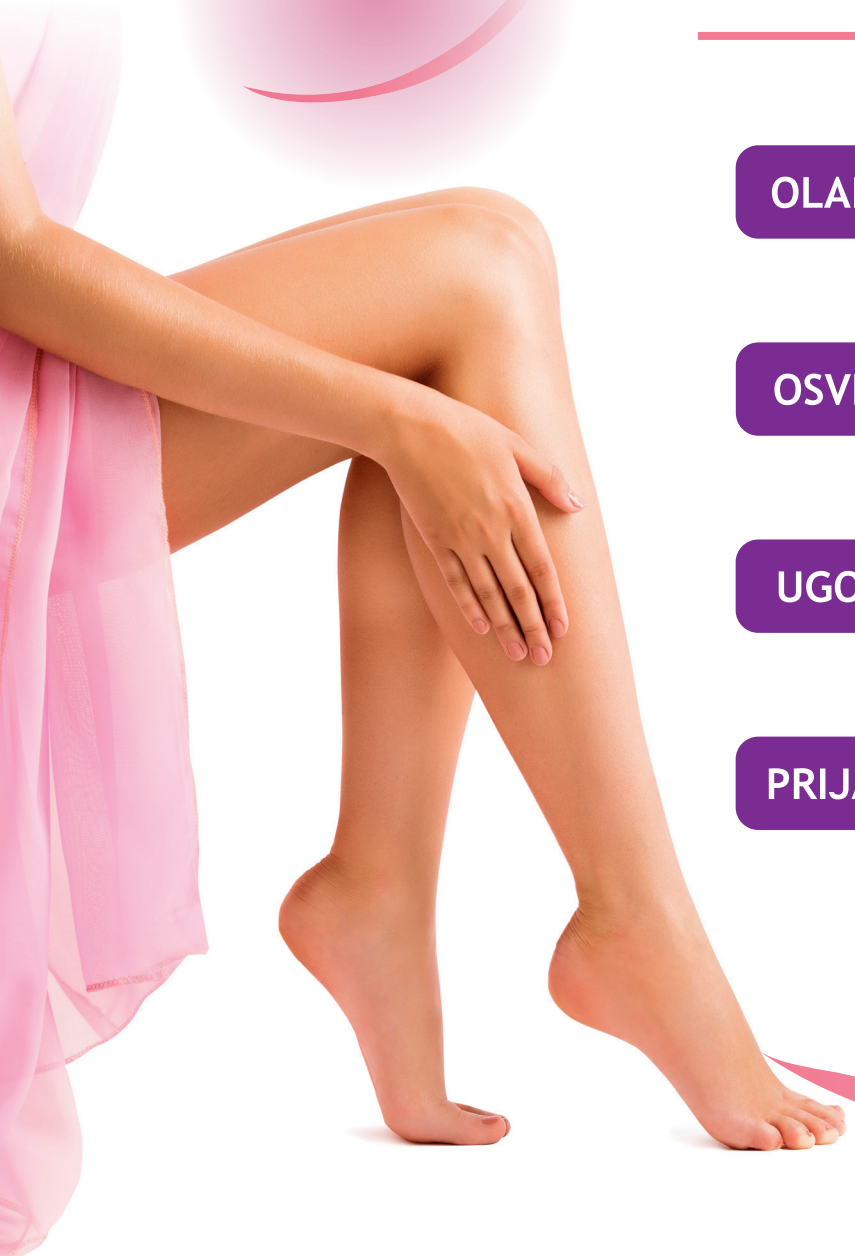

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