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TMSJ publishes original researches, interesting case reports and reviews regarding all fields of medicine. All of the published articles are open-access and reachable in our website. The primary aim of the journal is to publish original articles with high scientific and ethical quality and serve as a good example of medical publications for stimulating students, doctors, researchers. Our mission is to feature quality publications that will contribute to the progress of medical sciences as well as encourage medical students to think critically and share their hypotheses and research results internationally.

The Editorial Board and the Publisher adheres to the principles of International Council of Medical Journal Editors (ICMJE), Committee on Publication Ethics (COPE).

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Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992.p.1561-5.

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EDITORIAL

Dear readers,

As the Hungarian biochemist Albert Szent-Györgyi, who won the Nobel Prize in Physiology or Medicine in 1937, said: “Research is to see what everybody else has seen and to think what nobody else has thought.” Inspired by the same thought, our former editor-in-chief Aslı Nur Özkan thought of investigating the effect of spider silk on tumor cells, as she became aware of the traditional knowledge that spider silk heals wounds. Thus, she carried out a brilliant research regarding the effect of spider silk on prostate cancer cells and found out that it induces apoptosis of prostate cancer cells by using intrinsic pathways. With the findings of her study, she won the first place in the National Patent Competition organized by Turkish Patent and Trademark Office. We congratulate her not only because of her success but also serving as a model for young researchers.

As TMSJ editors, we attended many medical student congresses to represent our journal and reach more readers, while contributing to the scientific atmosphere built by young passionate researchers. Two editors of our editorial board, Kubilay Elmacı with a case of a spontaneous coronary artery dissection and Berfin Tan with a research focusing on the risk of hepatitis B virus reactivation in patients receiving immunosuppressive therapies, won the second place in their sessions in Bukovinian International Medical Congress (BIMCO, 4-6 April 2018). We also congratulate them for their success believing that they will do great contributions to the scientific world in the years ahead.

In this issue, you can find 4 original articles and 2 case reports. Acet et al. investigated the relationship between chronotypes and physical activity in healthy young medical students, as controversial results exist in the literature on the topic. Öner et al. shared their data regarding the resistance rates of Mycobacterium tuberculosis complex isolates to major antituberculous drugs, as they investigated 4752 clinical samples from the region Edirne, Turkey; since the increase in the rates of drug resistance has become one of the major problems in the management of many infectious diseases. Considering medical students constitute a part of the population at risk in terms of internet addiction, Güzel et al. carried out a research focusing on the impact of internet addiction on physical health in medical students by using Internet Addiction Scale. Çıfırcıbaşı et al. reported a case, whereby they investigated the efficiency of Next-generation sequencing to portrait a detailed genetic profile of patient, investigating for any mosaicism or other risk alleles.

One of the goals of our journal in this year has been to increase the diversity of the editorial board, in order to reach more readers and evaluate manuscripts more efficiently. A new editor from New South Wales University Faculty of Medicine has joined our editorial board. We are grateful to him for adjusting to our teamwork in a very short time with great motivation. We still plan on including more qualified editors from other countries to our team, so I kindly suggest to the interested readers to follow our announcements and contact us with any questions.

Hope to meet you again in the next issue.

Koray DEMİRCİ
Editor-in-Chief



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THE RELATIONSHIP BETWEEN CHRONOTYPES AND PHYSICAL ACTIVITY IN HEALTHY YOUNG MEDICAL STUDENTS

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ABSTRACT

Aims: The aim of this study is to determine the relationship between circadian rhythm and physical activity in students of Trakya University School of Medicine ranging from 1st to 5th grade.

Methods: Horne & Östberg's Morningness-Eveningness questionnaire and International Physiological Activity Scale were used to compare physical activity and chronotype features of 1st to 5th grade students of Trakya University School of Medicine. Pearson Chi-Square and Kruskal-Wallis tests were used to evaluate the results of the study.

Results: This study included 351 medical students, of whom 143 were male and 208 were female. The mean age of the study population was 20.79 ± 1.9 . There were 32 (9.1%) morning-type, 234 (66.5%) intermediate-type and 85 (24.4%) evening-type volunteers. Out of all, 102 (29.0%) were inactive, 177 (50.3%) minimal active and 73 (20.7%) active. There was no significant relationship between physical activity and chronotype differences between the study groups.

Conclusion: The findings of this study showed no relationship between physical activity and chronotype in healthy young medical students. Circadian preference may not be considered as an effective factor for daily physical activity.

Keywords: Exercise, circadian rhythm, medical student

INTRODUCTION

The circadian rhythm is defined as the changes in daily physiological and biological processes in an organism. Sleep-wake cycle is a basic and determinative element of circadian rhythm in humans (1). It has been shown that circadian rhythm effects physiological conditions (2). The relationship between circadian rhythm, sleep-wake cycle and health conditions such as mood disorders were demonstrated in various studies (3-6). However, in literature, there are contradictory results regarding the relationship between physical activity and circadian preferences, as several studies did not reveal any effect of circadian rhythm to physical activity (7, 8).

Due to contradictory results from existing studies, this study was planned to further investigate the effect of circadian preferences on physical activity levels. Thus, in

this study, it is aimed to analyze the relationship between physical activity and circadian preferences in medical students of Trakya University School of Medicine. To the best of our knowledge, there are no studies investigating this relationship in medical students.

MATERIAL AND METHODS

This cross-sectional survey study was approved by Scientific Research Ethics Committee of Trakya University School of Medicine. The research was carried out between April and May 2017 involving 1st to 5th grade students of Trakya University School of Medicine. Participants who reported any physical or mental illness were not included in the study.

The groups were determined as morning-type, intermediate-type and evening-type by using Horne & Östberg's Scale to find out their circadian rhythm characteristics in terms of chronotypes (9). Participants who have 16-41 morningness-eveningness score were accepted as evening-type, scores of 42-58 as intermediate-type, scores of 59-86 as morning-type.

Two types of International Physical Activity Questionnaire (IPAQ) forms are used to evaluate physical activity levels: IPAQ short form and IPAQ long form. In our study, IPAQ short form was used to determine physical activity levels of participants (10). Participants with less than 600 points were accepted as inactive, between 600 and 3000 were minimal active and more than 3000 were accepted as physically active.

Demographic and anthropometric values including gender, age and Body Mass Index (BMI) of participants were also determined by questionnaires. All questionnaires were filled out by the participants under the researcher's surveillance. The questionnaires were collected right after they were completed for evaluation. Surveys with missing data were excluded from the study. After recording the data, statistical analysis was performed.

As for statistical analysis, Pearson Chi-Square test and Kruskal-Wallis test were used to evaluate the categorical data. Numbers, percentages, mean $\pm$ standard deviation were used as descriptive statistics. A p value of <0.05 was set for statistical significance.

RESULTS

The study included 351 students of Trakya University School of Medicine, 27 were excluded due to missing data and 29 due to health conditions. Out of all participants, 208 were female and 143 of them were male. The mean age of the study group was 20.79 ± 1.94 years. The mean age of female participants was 20.69 ± 1.84 years and of male participants was 20.95 ± 2.08 years. The mean value of BMI was 22.33 kg/m^2 .

There was no statistically significant difference regarding the demographic data among the chronotype groups ($p=0.858$ for age and $p=0.788$ for BMI). The mean value of the Horne & Östberg's score for morning-type was 62.25 ± 4.02 , intermediate-type was 49.52 ± 4.48 , and evening-type was 36.26 ± 3.68 . There were 32 (9.11%) morning-type, 234 (66.6%) intermediate-type and 85 (24.21%) evening-type volunteers. Among

all morning-type volunteers, 22 (68.75%) of them were female and 10 (31.25%) were male morning-type, while among intermediate-type participants 146 (70.19%) were female and 88 (29.81%) were male intermediate-type. Also out of all evening-type subjects, 40 (47.15%) of them were female and 45 (52.85%) were male evening-type.

In this study, the groups were compared regarding their physical activity scores based on IPAQ classification. Of the morning-type volunteers, 4 (12.5%) were inactive, 19 (59.4%) were minimal active and 9 (28.1%) were found as physically active. Of the intermediate-type volunteers 74 (31.6%) were inactive, 116 (49.6%) were minimal active and 44 (18.8%) were active. Of the evening-type volunteers, 24 (27.9%) were inactive, 42 (48.8%) were minimal active and 20 (23.3%) were active. Considering all study population, 102 (29.0%) were inactive, 177 (50.3%) were minimal active and 73 (20.7%) were active. However, there were no statistically difference between the chronotype groups and the physical activity levels ($p=0.222$).

Comparison of chronotype preferences and physical activity levels with gender groups brought no statistically significant difference ($p>0.05$).

The relationship between circadian rhythm and physical activity of subjects was evaluated separately regarding their grades ranging from 1 to 5. No significant difference was shown between circadian rhythm groups in terms of physical activity levels in the 1st grade ($p=0.667$), 2nd grade ($p=0.298$), 3rd grade, ($p=0.591$) and 5th grade ($p=0.780$) students. There was a significant difference between circadian rhythm groups in terms of physical activity levels in the 4th grade students ($p=0.026$). The distribution of different chronotype preferences among students from each grade is shown in Table 1.

Table 1: Distribution of chronotype preferences among students from each grade.

Grade	Chronotype Preference	Number
1	Morning-type	11
	Intermediate-type	79
	Evening-type	41
	Total	131
2	Morning-type	9
	Intermediate-type	53
	Evening-type	7
	Total	69
3	Morning-type	3
	Intermediate-type	42
	Evening-type	18
	Total	63
4	Morning-type	3
	Intermediate-type	20
	Evening-type	5
	Total	28
5	Morning-type	6
	Intermediate-type	40
	Evening-type	15
	Total	61

DISCUSSION

The results of this study showed no correlation between chronotype that were determined with Horne & Östberg's scale and physical activity in healthy young medical students. The subjects were more likely to be intermediate-type. They were mostly minimally active.

The circadian rhythm characteristics of volunteers were classified as morning-type, intermediate-type and evening-type using Horne & Östberg's scale (9). Every movement that is done by using skeletal muscles and requires energy is described as physical activity (11). Physical activity is associated with whole body system. IPAQ can be used to evaluate physical activity as in our study (10). Likus et al. (12) found that even though future healthcare professionals are aware of the importance of physical activity, they do not prefer doing physical activity regularly. Besides, Stanford et al. (13) found that physicians and medical students do more physical activity compared to the general population. Results from studies concerning this topic were contradictory, and review of the literature did not locate any studies specifically involving medical students. The mean age of the study population as 20.79 ± 1.94 pointed out that the population consists of young volunteers and this population has homogenous demographic data.

The analysis did not reveal any statistically significant relationship between physical activity and chronotypes ($p=0.222$). Similarly, a separate assessment regarding the grades of students did not reveal any statistically significant relationship with an exception for the 4th grade students ($p=0.026$). Since there were only 28 participants from the 4th grade, further studies are needed to be performed with a greater population. Evaluation methods for physical activity might be changed and physical activity monitoring like acti-graph can be used instead of questionnaires.

The relationship between chronotype and physical activity has been investigated in several studies. Vardar et al. (2) and Schall et al. (3) found that morning-type students are more active than the others. Wennman et al. (4) showed in their study that evening-type people are less physically active and are more likely to live a sedentary life compared to the morning-types. It is also shown that there is a positive correlation between chronotype score and free time physical activity (5). Schaal et al. (3) found out that physical activity levels are higher in morning-type German adolescents. Similarly, the study results of Haraszti et al. (6), Vitale et al. (14), Schaal et al.

(3) and Urban R et al. (15) showed a correlation. Haraszti et al. (6) found that working-women who are prone to morningness have higher physical activity levels. Moreover, Urban R et al. (15) described eveningness as a risk factor for physical inactivity. In contrast to these findings, Laborde et al. (7) and Whitlier et al. (8) did not find any statistical correlation between physical activity and circadian rhythm, which is consistent with the findings of our study.

In conclusion, the results of this study showed no relationship between physical activity and circadian types in healthy young medical students. Thus, endogenous control of circadian rhythms may not be accepted as an important factor for daily physical activity in medical students.

Ethics Committee Approval: This study was approved by Scientific Researches Committee of Trakya University School of Medicine.

Informed Consent: Written informed consent was obtained from the participants of this study.

Conflict of Interest: The authors declared no conflict of interest.

Author contributions: Concept: ÇG, OA, ŞK, NS, SAV. Design: ÇG, OA, ŞK, NS, SAV. Supervision: ÇG, OA, ŞK, NS, SAV. Resources: ÇG, OA, ŞK, NS, SAV. Materials: ÇG, OA, ŞK, NS, SAV. Data collection and/or processing: ÇG, OA, ŞK, NS, SAV. Analysis and/or Interpretation: ÇG, OA, ŞK, NS, SAV. Literature Search: ÇG, OA, ŞK, NS, SAV. Writing Manuscript: ÇG, OA, ŞK, NS, SAV. Critical Review: ÇG, OA, ŞK, NS, SAV.

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RESISTANCE RATES OF MYCOBACTERIUM TUBERCULOSIS COMPLEX ISOLATES OBTAINED FROM CLINICAL SAMPLES TO MAJOR ANTITUBERCULOUS DRUGS: A STUDY IN EDİRNE, TURKEY

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ABSTRACT

Aims: The aim of this study is to reveal the rates of the Mycobacterium tuberculosis complex resistance to major antituberculous drugs (streptomycin, isoniazid, rifampicin, ethambutol) by the evaluation of the specimens that are sent to Trakya University Hospital Microbiology Laboratory.

Methods: In this study, laboratory data of the cases that were pre-diagnosed with tuberculosis between 11/02/2016 and 31/12/2017 were scanned retrospectively. To compare the annual data descriptive statistics as arithmetic mean, numbers and percentages were used.

Results: Out of 4752 samples, 133 (2.79%) were culture positive. 120 isolates were identified as Mycobacterium tuberculosis complex, while other 13 were defined as Mycobacterium other than tuberculosis. Antimycobacterial susceptibility tests showed that 9 (7.5%) isolates were resistant to streptomycin, 10 (8.33%) isolates to isoniazid, 4 (3.33%) isolates to rifampicin, 4 (3.33%) isolates to ethambutol. 5 (4.16%) isolates were multidrug resistant.

Conclusion: Antituberculous drug resistance is still a threat for an effective treatment of tuberculosis and streptomycin resistance has increased. However, it is also pointed out that presence of Mycobacterium other than tuberculosis in isolates has increased.

Keywords: Drug resistance, tuberculosis, streptomycin

INTRODUCTION

Tuberculosis (TB) is an infectious disease that is caused by Mycobacterium tuberculosis complex bacilli which enter the body through the respiratory route and reside in the lungs (1). Atypical isolates such as Mycobacterium other than tuberculosis (MOTT) can also rarely cause the disease. TB is one of the most fatal diseases all around the world (1). Ehrlich-Ziehl-Neelsen (EZN) staining of sputum in order to identify acid-resistant bacteria (ARB), bacterial cultures, clinical history and chest X-ray are utilized for the diagnosis (2, 3). Major anti-TB drugs are streptomycin (SM), isoniazid (INH), rifampin (RIF), ethambutol (EMB) and pyrazinamide (PZA). Other anti-TB drugs are minor ones such as para-aminosalicylic acid, ethionamide, cycloserine, kanamycin, capreomycin, amikacin, thioacetazone, fluoroquinolones (ofloxacin, ciprofloxacin), rifabutin. Major drugs have stronger effects, fewer side

effects than minor drugs. Nevertheless, minor drugs are preferred for multidrug-resistant TB (MDR-TB).

For the treatment, a combination of at least four types of anti-TB drugs, mostly INH, RIF, EMB, SM, and PZA, are used for the first two months (3). This is known as the bactericidal phase which has the maximum amount of bacteria and maximum risk for resistance. Then, maintenance phase follows the bactericidal phase that lasts four or seven months and in this period at least two drugs that contain isoniazid are given to the patient (3). Drug resistance should be monitored before designing the treatment plan if the drug resistance rates for SM, INH, RIF, and EMB in the region are higher than estimated percentages determined by World Health Organization (4). A long period of time is necessary for the treatment and follow-up (1, 3, 4).

In the last twenty years, anti-tuberculosis drug resistance increased significantly all around the world

due to inappropriate use of drugs, insufficient treatment and incomplete adherence (5, 6). Although the incidence of TB decreases over the years, the number of patients infected with resistant strains increases greatly (7). The drug resistance is measured by antimycobacterial susceptibility tests. There are several studies about drug resistance demonstrating the continuous change of the percentages (8, 9). The reason for the multitude of studies concerning drug resistance is that the treatment regimens are developed according to the drug resistance and the problem directly targets the public health.

There are 5 types of drug-resistant TB: Mono-Drug Resistant TB, Poly-Drug Resistant TB, MDR-TB, Extensively Drug Resistant TB and Extremely Drug Resistant TB (10). MDR-TB, a disease originated from *Mycobacterium tuberculosis* complex which is resistant to at least two drugs (especially INH and RIF), is a global threat, as it brings a great challenge in the management of TB. In 2015 there were 4.6% MDR-TB cases among an estimated 10.4 million TB cases worldwide (11). MDR-TB is a crucial problem for the TB control because it completely changes the direction of the treatment. Preventing the development of drug resistance, providing an early detection and proper treatment play an important role to prevent MDR-TB (12).

The aim of this study is to reveal the rates of the *Mycobacterium tuberculosis* complex bacilli resistance to major anti TB drugs (SM, INH, ETB, RIF) by evaluating the specimens that are sent to Trakya University Hospital Microbiology Laboratory in Edirne, Turkey and to compare the annual results.

MATERIAL AND METHODS

This study was approved by Scientific Research Ethics Committee of Trakya University School of Medicine. In this study, laboratory registers of the cases that were pre-diagnosed with tuberculosis between 11/02/2016 and 31/12/2017 were scanned retrospectively. The study was carried out with data from Trakya University Hospital.

Samples of sputum, pleural fluid, urine, peritoneal fluid, tissue, cerebrospinal fluid, bronchial lavage, selective lavage, synovial fluid, endotracheal aspirate, early morning gastric washings and abscess were investigated with EZN staining. Bacterial culture examination and antimycobacterial susceptibility tests were carried

out on BACTEC MGIT 960 (Becton Dickinson Diagnostic, USA) automated system. Tests were performed for the antimycobacterial drugs; SM, INH, RIF, EMB as suggested by National Committee Clinic Laboratory Standards (13). Positive cultures were also identified using the immunochromatographic assay (BD MGIT TBc Identification Test, Becton Dickinson Diagnostic, USA). If there was more than one culture positivity of the same patient, the patient's initial culture was used for drug susceptibility.

Along with the drug susceptibility test results, data including patient's age and obtaining date of the samples were retrieved using laboratory registers.

The results are recorded and grouped according to the year obtained. To compare annual results descriptive statistics as arithmetic mean $\pm$ standard deviation, numbers and percentages were used.

RESULTS

This retrospective study included 4752 different specimens from the patients of Trakya University Hospital. Most of the specimens were sputum (2907) followed by bronchial lavage (628), urine (286) and pleural fluid (174). The mean age of the patients was 49.51 ± 19.40 in 2016 and 53.73 ± 16.54 in 2017. 111 of the specimens were identified as positive in EZN staining and 234 of the specimens were culture positive. These 234 samples belonged to 133 different patients, therefore antimycobacterial susceptibility tests were performed on their initial samples. 133 (2.79%) of these samples showed growth of ARB. *M. tuberculosis* complex was found in 120 isolates, while MOTT was identified in the other 13. Antimycobacterial susceptibility tests showed that 9 (7.5%) isolates were resistant to SM, 10 (8.33%) isolates to INH, 4 (3.33%) isolates to RIF, 4 (3.33%) isolates to EMB. Results also revealed that 5 (4.16%) isolates were multidrug-resistant, as one of them to INH and RIF, one to INH and EMB, two to INH and SM, while another one to all anti TB drugs that we had tested (SM, INH, RIF, EMB). Resistance to SM was 5% in 2016 but was found to be increased to 10% in 2017. On the contrary, INH resistance was 10% in 2016 and it decreased to 6.66% in 2017. Another annual data showed that percentage for MOTT among the isolates were 3.22% in 2016 but it was increased to 15.49% in 2017. Yearly distribution of the results is shown in Table 1.

Table 1: Annual values of the results.

	2016 Number (%)	2017 Number (%)
SM resistance	3 (5)	6 (10)
INH resistance	6 (10)	4 (6.66)
RIF resistance	3 (5)	1 (1.66)
EMB resistance	2 (3.33)	2 (3.33)
INH+RIF resistance	1 (1.66)	0
INH+EMB resistance	1 (1.66)	0
INH+SM resistance	0	2 (3.33)
INH+RIF+EMB+SM resistance	1 (1.66)	0
Total MDR-TB	3 (5)	2 (3.33)
<i>M.tuberculosis</i> complex	60 (96.78)	60 (84.51)
MOTT	2 (3.22)	11 (15.49)
Total isolates	62	71

INH: Isoniazid, RIF: Rifampin, EMB: Ethambutol, SM: Streptomycin, PIR: Pyrazinamide, MDR-TB: Multidrug-Resistant Tuberculosis, MOTT: Mycobacterium Other Than Tuberculosis

DISCUSSION

Tuberculosis is one of the most important chronic infectious diseases with its high global rates of morbidity and mortality, especially in developing countries such as Turkey (14). Therefore, preventing and therapeutic strategies against this disease are of crucial importance especially in countries where tuberculosis is endemic. Early diagnosis, proper and regular treatment of patients and patient follow-ups after treatment are essential components of tuberculosis control programs (15). Evaluation of the success of this treatment strategies can be made by analyzing the epidemiological data (7, 9).

Limited availability of antituberculosis drugs and the development of resistance against these drugs are not only public health concerns for developing countries, but also for the developed countries (8, 16, 17). Among the causes of resistance development, the most important ones are noncompliance to medication and misapplication strategies. Also, inadequate drug dosing and/or absorption contribute to the resistance development (8, 14, 17, 18). The incidence of tuberculosis decreases, whereas the rate of resistance increases (7).

In our study, SM (7.5%) and INH (8.33%) resistances showed an increase compared to other anti-TB drugs. Previous studies in Edirne identified the resistance rates as 8.1%, 9.7% and 8.2% for SM, 11.5%, 12.6% and 14.4% for INH in 2005, 2006 and 2007, respectively. They also revealed the MDR as 6% (13). Percentages for INH resistance (8.33%) and MDR (4.16%) decreased in our study. Another study on anti TB drug

resistance was carried out by Tansel et al. (9) on 139 isolates between 1999 and 2001 in Edirne. Findings of the study for INH, RIF, and EMB were similar to our study. Although the percentages were consistent with our study, resistance for SM (2.2%) was quite lower at that time. Comparison with this study indicates an increase in SM resistance.

Another study carried out in Sivas revealed that resistance to RIF (10.4%) and EMB (9.1%) were higher than INH (5.2%) and SM (2.6%) (19). MDR's value also surpassed the value in our study (4.16%) with 14.3%. In our study, resistance to RIF (3.33%) and to ETH (3.33%) were lower. On the other hand, resistance to SM (7.5%) was higher.

For the surveillance in Ankara, another study was carried out by Sezen et al. (20). They detected the resistance to INH as 3,8%, to RIF 0,9%, to SM 3,8%, EMB to 0,5% (20). All of the resistance rates were lower than those in our study. Considering these results, the location may have a role in drug resistance.

This was a retrospective study carried out using data drawn from the laboratory registers, however, patient files were not used during the study. This was a limitation of our study.

In conclusion, this study revealed that anti TB drug resistance remains a problem for the proper treatment of tuberculosis and resistance to SM has increased. Another aspect to point out is that the presence of MOTT in the isolates has increased over the years. Therefore, follow-up studies are needed to be carried out.

Ethics Committee Approval: This study was approved by Scientific Researches Committee of Trakya University School of Medicine.

Informed Consent: Written informed consent was obtained from the participants of this study.

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Author contributions: Concept: OÖ, CE. Design: OÖ, İEÖ, KE, CE. Supervision: OÖ, İEÖ, KE, CE. Resources: OÖ, İEÖ, KE, CE. Materials: OÖ, İEÖ, KE, CE. Data collection and/or processing: OÖ, İEÖ, KE, CE. Analysis and/or Interpretation: OÖ, İEÖ, KE, CE. Literature Search: OÖ, İEÖ, KE, CE. Writing Manuscript: OÖ, İEÖ, KE, CE. Critical Review: OÖ, İEÖ, KE, CE.

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INTERNET ADDICTION AND ITS IMPACT ON PHYSICAL HEALTH

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ABSTRACT

Aims: Internet addiction, a recently emerged term in medical literature, has significant physical effects on the young generation. In this research, controversial effects of internet addiction on physical health have been investigated among the students of Trakya University School of Medicine, who constitute a part of the population at risk.

Methods: The study included 327 medical students. The correlation between internet addiction and physical complaints associated with internet usage and its relation with gender, purpose and duration of internet usage were investigated. The data were obtained by using surveys and Internet Addiction Scale. To evaluate the data; descriptive statistics, Correlation, Mann-Whitney U tests, Cronbach alpha methods and survey with 16 questions were used for statistical analysis.

Results: There is a statistically significant difference in terms of Internet Addiction Scale score between internet addiction and physical complaints such as headache, feeling of stiffness, backache, neck pain and insomnia. Internet Addiction Scale score and time spent on the internet showed a statistically significant correlation.

Conclusion: Increase in internet usage leads to many physical health problems, which may cause serious and permanent damage to physical health. Therefore, the required attention must be given to this subject especially for the benefit of younger generations.

Keywords: Internet, medical student, headache, neck pain

INTRODUCTION

Computers and internet, substantial technological developments of the 21st century, constitute an indispensable part of daily life. They are used mostly for education, communication, entertainment, gaming, shopping also for access to current news. The easy accessibility during every hour of the day may be both advantageous and disadvantageous for the young generation (1, 2).

Bratter T.E and Forrest G.G. (3) defined addiction as a behavioral pattern of compulsive drug use characterized by overwhelming involvement with the use of a drug and the securing of its supply, as well as a strong tendency to relapse after completion of withdrawal. Traditionally, the term “addiction” has been associated with psychoactive substances such as alcohol and tobacco. Features of internet addiction were initially

proposed by Young (4) in 1998 based on the criteria of pathological gambling, later adapted and included in The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-V). Before this, the term “internet addiction” was first proposed by psychiatrist Dr. Ivan Goldberg to describe the pathological usage of internet (5).

Inspired by these, in this research, controversial effects of internet addiction on physical health problems have been investigated among the students of Trakya University School of Medicine, who constitute a part of the population at risk (2).

MATERIAL AND METHODS

This study cross-sectional descriptive survey study was approved by Scientific Research Ethics Committee of Trakya University Medical Faculty. The study was

carried out in Trakya University Hospital between September 2017 and March 2018 including participants as medical students from Trakya University School of Medicine from 1st to 6th grades. Among medical students of Trakya University a sample group was formed by using layered and random sampling methods. The Internet Addiction Scale (IAS) and a questionnaire were applied to the participants. The questionnaire consisted of questions regarding the demographical data of subjects, their purpose of internet use (education, communication, entertainment, gaming, shopping, access to current news), behaviors and problems of subjects that might be associated with internet use such as physical complaints, weight gain, snacking during internet usage. The physical complaints consisted headache, feeling of stiffness, backache, neck pain, insomnia, dizziness, dry-eyes, wrist pain and stomachache. The questionnaires were distributed to the predetermined participants and collected after the questions were answered.

The Internet Addiction Scale developed by Selim Güneş and Murat Kayri (6) was used in our study. All of the 35 items on the scale, were positive and scaled by a five-point Likert scale. Attitudes in the Likert form are rated as “I definitely do not agree”, “I do not agree”, “Neutral”, “I agree” and “I completely agree”. It was found that the discrimination levels of the items varied between 0.420 and 0.681. The scale consists of 4 sub-items, the first factor is called “Withdrawal”, the second factor is “Controlling Difficulty”, the third factor is “Disorder in Functionality” and the fourth factor is “Social Isolation Dimensions”.

Taking S. Aslan and R. Aylaz’s (1) study titled “Evaluation of internet addiction levels and possible health problems related to the academicians” as a reference and considering the incidence of neck pain which is the most common physical problem, as 11.3% and the tolerable difference as 5%; it is estimated that 393 cases should be taken with 0.05 probability of error and 80% power. All students in Trakya University School of Medicine were randomly selected according to their stratified and random sampling methods by classifying their strata according to their study year and gender. 78 students from the 1st year; 81 students from the 2nd year; 80 students from the 3rd year; 79 students from the 4th year; 64 students from the 5th year; 55 students from the 6th year were selected. Of these, 56 students from the 1st year; 65 students from the 2nd year; 79 students the 3rd year; 51 students from the 4th year; 47 students from the 5th year; 29 students from the 6th year were reached. As a result, although the study was planned to be conducted with 437 subjects, only 327 of those could be reached.

Research data were entered in the Excel sheet. The analysis was done using SPSS version 19.0 (SPSS Inc. Chicago, IL, USA). The internal consistency reliability of the IAS was assessed by calculating Cronbach’s alpha. Normal distribution suitability is tested with Shapiro Wilk test. Kruskal Wallis Variance Analysis and Mann-Whitney U test with Bonferroni correction were used to compare the differences in subscales of the questionnaire between students from different study years. Spearman’s rho correlation coefficient was calculated between subscales of the questionnaire and the time spent on the internet. Descriptive statistics were calculated for the categorical and numeric variables [frequency and percentages and mean $\pm$ standard deviation, median (min-max)]. A p value of <0.05 was considered statistically significant and all hypothesis tests were evaluated two-sided.

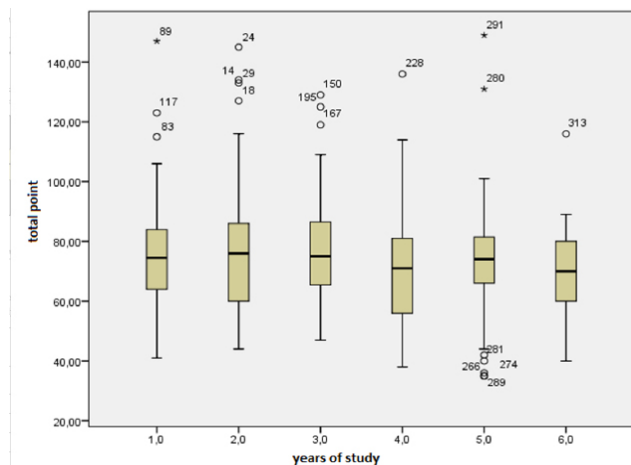


Figure 1: Normal distribution of the total scores of the subjects from different study years.

Since the results did not fulfill the parametric assumptions, they were later analyzed by using nonparametric tests (Mann-Whitney U, Kruskal Wallis). The corrected p value for different study years was set at 0.0033.

RESULTS

All 327 students from each 6 curricular years of Trakya University School of Medicine, including 177 female and 150 male subjects participated in this research. Their ages varied between 18 and 26.

Cronbach alpha (α) reliability scores of the IAS were calculated. The reliability of the first subscale

(withdrawal) consisting of 11 items was found to be 80.3%, the reliability of the second subscale (controlling difficulty) consisted of 10 items was 85.1%, the reliability of the third subscale (disorder in functionality) consisted of 7 items was 90.4% and the reliability of the fourth subscale (social isolation dimensions) consisted of 7 items was 89.6%. Total reliability score was calculated as 93.7%.

The average time spent on the internet was found as 3.9 hours per day. There was a statistically significant and low correlation between the time spent on the internet and the internet addiction subscale withdrawal and total internet addiction scale score ($r=0.308$, $p<0.001$; $r=0.303$, $p<0.001$).

The distribution of total IAS scores among grades of participants is demonstrated in Figure 1. A statistically significant difference was found between the groups in terms of withdrawal subscale of the IAS ($p=0.010$), particularly between the 3rd and 4th year students ($p<0.001$) (Table 1A). Although the difference between the 1st and 4th year students ($p=0.09$) was not statistically significant, 1st year students had higher withdrawal scores. No statistically significant difference was found between the groups and the subscales (controlling difficulty, disorder in functionality, social isolation dimensions) also the total IAS scores ($p=0.509$, 0.306, 0.338, 0.309).

Despite the IAS scores had no statistically significant difference between the male and female students in terms of the Social Isolation Dimensions subscale ($p=0.91$), the scores regarding the males were higher (Table 1B). Furthermore, there was no statistically significant difference among settlement groups in terms of total IAS scores (Table 1C).

Table 1: Results of IAS and nonparametric tests (Mann-Whitney U, Kruskal Wallis) distributed in years of study (A), gender (B) and settlement (C).

A	Years of Study						P-value
	1	2	3	4	5	6	
Withdrawal Score							
M±SD	31.18±8.33	29.92±6.43	31.46±6.14	26.92±6.29	28.34±8.36	28.51±6.76	0.010*
Md(Min-Max)	31(14-55)	31(17-44)	31(19-48)	27(14-39)	29(11-46)	31(15-51)	
Controlling Difficulty Score							
M±SD	21.42±6.76	21.49±7.12	21.30±6.15	20.33±7.05	22.27±6.71	19.65±5.72	0.509*
Md(Min-Max)	21(12-46)	20(11-44)	22(10-42)	21(10-39)	23(10-42)	20(10-33)	
Disorder in Functionality Score							
M±SD	13.14±4.89	14.21±6.58	12.86±4.60	12.17±5.91	13.10±5.69	11.65±3.75	0.306*
Md(Min-Max)	13(7-31)	14(7-33)	12(7-28)	10(7-33)	13(7-33)	12(7-23)	
Social Isolation Dimensions Score							
M±SD	9.96±3.34	11.83±5.56	10.64±4.35	11.27±5.44	10.59±5.25	9.89±3.32	0.338*
Md(Min-Max)	9(7-22)	10(7-35)	10(7-35)	10(7-33)	9(7-32)	9(7-17)	
Total Score							
M±SD	75.71±19.08	77.46±21.33	76.26±17.47	70.70±19.74	74.31±22.22	69.72±16.49	0.309*
Md(Min-Max)	74.50(41-147)	76(44-145)	75(47-129)	71(38-136)	74(35-149)	70(40-116)	

B	Female	Male	P-value
Withdrawal Score			
M±SD	29.71±6.89	29.65±7.51	0.670**
Md(Min-Max)	30(11-48)	30(14-55)	
Controlling Difficulty Score			
M±SD	20.88±6.68	21.58±6.58	0.460**
Md(Min-Max)	21(10-44)	21.50(10-46)	
Disorder in Functionality Score			
M±SD	12.62±5.20	13.44±5.64	0.267**
Md(Min-Max)	12(7-33)	13(7-33)	
Social Isolation Dimensions Score			
M±SD	10.54±4.79	11.07±4.64	0.91**
Md(Min-Max)	9(7-35)	10(7-35)	
Total Score			
M±SD	73.77±19.30	75.75±19.92	0.473**
Md(Min-Max)	74(35-149)	74(39-147)	

C	House	Private dormitory	Public dormitory	P-value
Withdrawal Score				
M±SD	29.28±7.24	30.79±6.81	29.98±7.29	0.142*
Md(Min-Max)	29(11-55)	31(14-52)	31(11-44)	
Controlling Difficulty Score				
M±SD	20.81±6.52	21.95±6.29	21.69±7.43	0.459*
Md(Min-Max)	21(10-46)	21(12-37)	21.5(10-39)	
Disorder in Functionality Score				
M±SD	12.84±5.26	12.73±5.56	13.87±5.79	0.419*
Md(Min-Max)	12(7-33)	12(7-33)	13(7-32)	
Social Isolation Dimensions Score				
M±SD	10.43±4.51	10.82±4.13	12.01±5.89	0.114*
Md(Min-Max)	9(7-35)	10(7-30)	10(7-33)	
Total Score				
M±SD	73.32±19.56	76.31±17.57	77.57±21.79	0.154*
Md(Min-Max)	72(35-149)	78(41-127)	77.5(35-136)	

*Kruskal Wallis Analysis of Variance, **: Mann-Whitney U Test, ‡: Statistically Significant M: Mean, SD: Standard Deviation, Md: Median, Min: Minimum, Max: Maximum

As a result of the research, it was found out that students use the internet mostly for communicational purposes (94.5%) followed by educational purposes (68.9%). The study also revealed common problems and behavioral features associated with internet addiction (Table 2).

Table 2: Behaviors and problems associated with internet addiction.

Variable	Present (number/%)	Absent (number/%)	Total (number/%)
* Physical complaint	269 (82.3)	58 (17.7)	327 (100.00)
Snacking during internet usage	215 (65.7)	112 (34.3)	327 (100.00)
Weight gain	65 (19.9)	262 (80.1)	327 (100.00)
Interview With a Doctor	11 (3.4)	316 (96.6)	327 (100.00)

* Most common physical complaint was dry-eyes(40.1%).

In terms of total IAS score, there was a statistically significant difference between the subjects, who reported complaints such as headache, feeling of stiffness, backache, neck pain, insomnia and the ones who did not ($p=0.005, 0.020, 0.004, 0.012, 0.004$). These complaints were more common in the subjects with higher total score of IAS.

In terms of total IAS score, there was no statistically significant difference between the subjects, who reported complaints such as dizziness, dry-eyes, wrist pain and stomachache and the ones who did not ($p=0.085, 0.375, 0.090, 0.066$).

DISCUSSION

Internet addiction and excessive computer usage are gaining importance day by day and it affects mostly young adults which medical students are also a member of. Therefore, this study carries an important role in understanding the recently emerged term, internet addiction.

As shown in Table 1A, 4th year students reported lower internet usage than 1st year students. The reason for this may be that the internet addiction of the new generation is increasing compared to the old generation.

Computer and internet usage are most common in 16-24 age group (7). This research was conducted among subjects between the ages of 18 and 26. Data obtained from Turkish Statistical Institute shows that the subject pool of this study consists of those in the risk group according to previous studies (7).

The factors that cause internet addiction have been the subject of various studies. Previous researches show that the gender factor is an important determinant of internet addiction and male students have a higher tendency for internet addiction during their education compared to their female counterparts (8, 9). In addition, Shao et al's (10) study showed a statistically significant difference in the internet addiction detection rates between male students (16%) and female students (8%). Similarly, in this research, the tendency of male participants to use the internet was found higher than female participants. However, this difference was not statistically significant ($p=0.473$).

Gün et al. (11) conducted a research on 83 subjects who worked as a secretary at Erciyes University Medical Faculty Hospital, evaluating the effects of computer use on health problems. 77.1% of subjects complained of neck pain. In our research, the rate of neck pain was found to be 33%. Additionally, the subjects, who presented neck pain complaint, had significantly higher total IAS scores ($p=0.012$).

In the research of S. Aslan and R. Aylaz (1), the most common health problem due to internet use was neck pain (11.3%, $p=0.01$) in terms of total IAS scores. In our research, the most common complaint of those who stated that they had a physical complaint was dry-eyes. However, no statistically significant difference was found between the subjects who complained of having dry-eyes and the ones who did not ($p=0.375$). The reason for the high prevalence of dry-eyes might be the constant stimulus exposure to the eyes, rather than internet usage. This may also be related to insomnia.

Subjects stated that they used the internet frequently for educational purposes. Reason for this could be the easier accessibility to education materials on the internet.

The withdrawal score increased with the increase of the internet usage time ($r=0.308, p<0.001$). Cut-off symptoms are expected in those who use the internet for longer time periods when they cannot reach internet connection.

According to Shao et al. (10), the most important point should be to help people forming a reasonable understanding of internet addiction and changing unhealthy lifestyles. As a result of the obtained data, the dimension of this health problem was evaluated in the Trakya University School of Medicine. The next step should be taken in the light of the recommendation of Shao et al (10).

In conclusion, students of Trakya University School of Medicine, who constitute a part of the young population were found to suffer from several physical effects of internet addiction. It is thought that this may lead to permanent physical pathologies in the future. Considering that internet usage can lead to addiction, it is essential to take measures to control internet usage in order to prevent the health problems that may arise.

Ethics Committee Approval: This study was approved by Scientific Researches Committee of Trakya University School of Medicine.

Informed Consent: Written informed consent was obtained from the participants of this study.

Conflict of Interest: The authors declared no conflict of interest.

Author contributions: Concept: GNV. Design: GNV. Supervision: GNV, VT. Resources: GNV. Materials: GNV. Data collection and/or processing: GNV, VT, VV. Analysis and/or Interpretation: GNV, VT, VV. Literature Search: GNV, VT, VV. Writing Manuscript: VT, VV. Critical Review: GNV, VT, VV.

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THE IMPORTANCE OF INDIVIDUAL CLINICAL AND LABORATORY INDICATORS IN THE DIFFERENTIAL DIAGNOSIS OF POSTPARTUM SEPTIC COMPLICATIONS

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ABSTRACT

Aims: To perform a comparative analysis of individual clinical and laboratory indicators in the differential diagnosis of conditionally limited and generalized forms of postpartum septic complications.

Methods: The study included 34 patients at Gynecology Department of the Zaporizhzhia Regional Clinical Hospital from 2013 to 2016 with postpartum purulent-septic diseases. Patients were divided into 2 groups. Group I consisted of 15 women who were diagnosed with a conditionally limited postpartum purulent-inflammatory disease (endometritis). Group II included 19 women with generalized forms of postpartum purulent-inflammatory diseases (peritonitis, sepsis). For the diagnosis of Multiple Organ Failure due to sepsis, we used the Sequential (Sepsis-Related) Organ Failure Assessment and quick Sequential (Sepsis-Related) Organ Failure Assessment. The differences between the first and second group were assessed by using the Mann-Whitney U test and STATISTICA Version 10.

Results: Body temperature was increased in all 34 patients. The average heart rate in group I was 91.6 ± 8.35 beats/min and 102.26 ± 16.42 beats/min in group II. The average respiratory rate was 19.07 ± 2.49 breaths/min in group I and 24.16 ± 5.09 breaths/min in group II. In group I, none of the patients scored a total of two or more points on the Sequential (Sepsis-Related) Organ Failure Assessment and quick Sequential (Sepsis-Related) Organ Failure Assessment scales; in group II, there were 5 (26.32%) patients who had scored two points or more on the Sequential (Sepsis-Related) Organ Failure Assessment scale; and 2 (10.53%) patients had scored 2 points or more in the quick Sequential (Sepsis-Related) Organ Failure Assessment scale.

Conclusion: Clinical cases of postpartum period with inflammation of uterus and signs of multiple organ failure should be regarded as a septic state, assessed by the Sequential (Sepsis-Related) Organ Failure Assessment scale as they require urgent medical help.

Keywords: Postpartum period, endometritis, sepsis, peritonitis, multiple organ failure

INTRODUCTION

With the implementation of regulations and guidelines set by WHO, the global maternal mortality ratio decreased from 385 to 216 deaths per 100,000 live births from the year 1990 to 2015, but still conditions need to be moderated (1). According to authors Lapinsky and Slynko et al. (2, 3) complications of infections occupy the third place among the causes of maternal mortality with a rate up to 10%.

In the United Kingdom, despite significant advances in diagnostics, medical management and use of

advanced capabilities of antimicrobial therapy, postpartum sepsis remains as an important cause of maternal mortality and is responsible for about 14/100.000 deaths per year (4). Jawad et al. (5) defined a mortality rate of 20-40% for potentially life threatening complications of acute infection as severe sepsis with acute organ dysfunction which increased to 60% if septic shock develops. Additionally, Netto et al. (6) found that 17% of cases involving septic complications were diagnosed during pregnancy, 36% during childbirth and 47% of septic complications developed in the postpartum period.

In 1991, the first recommendations to identify sepsis as a result of a systemic inflammatory response to infection (systemic inflammatory response syndrome) were given, reflecting the orders of the report by Ministry of Health of Ukraine which identified it as septic shock (7). The diagnosis of systemic inflammatory response syndrome (SIRS) is formulated in the presence of two of the four initial criteria for sepsis. It effects only the inflammatory response and is regarded as an extremely infectious process (8). The criteria include systemic inflammation, organ dysfunction, organ failure and cytokine storm (9). However, the validity of SIRS as a descriptor of sepsis pathobiology was challenged. The main reason for this is that the researches on the mechanism of sepsis revealed that it involved the activation of both pro-inflammatory and anti-inflammatory response. Significant changes occur not only in the immune system, but also in cardiovascular, nervous, hormonal, metabolic and coagulation systems. Changes in each of the systems have clinical significance (10, 11).

Based on these, in 2014, the Congress of the European Society of Intensive Care Medicine and Society of Critical Care Medicine decided to review the concept of sepsis. According to the new concept, sepsis was revised as the life threatening condition due to organ dysfunction and was defined by the changes in Sepsis-related Organ Failure Assessment (SOFA) score (12). Additionally, the recommendations by the Ministry of Health of Ukraine are currently being regulated and current national protocols suggest using Glasgow Coma Scale to determine the level of consciousness, that is also a variable in SOFA score (6).

Hospitalization due to sepsis generally occurs from the emergency department due to its acute severity and its number has been rapidly increasing. Since it is accounted for 215.000 deaths alone in the United States, management of its complications are of crucial importance (13). Despite the development of new methods in sepsis assessment such as Acute Physiology and Chronic Health Evaluation, Mortality Probability Model and Simplified Acute Physiology Score, SOFA score remains as the traditional means of individual assessment and manual evaluation method for sepsis (14, 15).

The aim of this study is to perform a comparative analysis of selected clinical, laboratory parameters, also the use of SOFA scores in the differential diagnosis of sepsis between relatively limited and generalized forms of postpartum septic complications.

MATERIAL AND METHODS

This retrospective study was approved by Scientific Research Ethics Committee of Zaporozhye State Medical University. The study included 34 patients who were hospitalized with a diagnosis of postpartum sepsis and pyo-septic diseases between 2013 and 2016 at the Gynecological Department of Zaporizhzhia Regional Clinical Hospital (ZRCH), which is the clinical base of the Department of Obstetrics and Gynecology, of Zaporizhzhia State Medical University. Patients were divided into two clinical groups. The first group consisted of 15 women who were all (according to clinical and laboratory examination) given the confirmed diagnosis of relatively limited postpartum inflammatory diseases (endometritis). The second group consisted of 19 women with generalized forms of postpartum inflammatory diseases (peritonitis, sepsis). The reproductive function of the clinical groups is summarized in Table 1.

Table 1: Reproductive function in clinical groups.

Reproductive function	Group 1 (n=15)		Group 2 (n=19)	
	Number of patients	%	Number of patients	%
Nulliparic women	1	6.67	1	5.26
Women who had a history of one childbirth	7	46.67	11	57.89
Women who had a history of two births and more (multiparity)	7	46.67	7	36.84

The average age of the patients was 27.18 ± 7.62 years; 23.94 ± 4.29 years in the first group and 30.06 ± 8.81 years in the second group respectively.

Of the first group, 12 patients lived in rural parts and 3 patients lived in the urban part of Zaporizhzhia, whereas of the second group 12 patients lived in the countryside of the city and 7 in the urban part and cities around the region.

The clinical examination and laboratory results were obtained from patients' files. The data regarding the time of diagnosis of postpartum inflammatory disease, the cause and the management of postpartum septic complication and patients' follow-ups were recorded. Clinical and laboratory parameters including body temperature ($^{\circ}\text{C}$), hearth rate (beats/min), mean respiratory rate (breaths/min), the level of leukocytes were noted, that are mandatory parameters to be monitored during the general clinical examination of patients with postpartum purulent-inflammatory complications according to the orders of the Ministry of Health of Ukraine (7).

To evaluate the diagnostic criteria of sepsis, we used SOFA and quick SOFA (qSOFA) scores in accordance with the recommendations of the Third International Consensus Definitions for Sepsis and Septic Shock (12). SOFA score used in the study consisted of 6 variables: partial pressure of oxygen, platelet count, level of consciousness set by Glasgow Coma Scale (6), bilirubin level, mean arterial pressure, serum creatinine level and urine output; while qSOFA scale based on 3 parameters: mean systolic arterial pressure, level of consciousness and mean respiratory rate. Total score of SOFA ranges from 0 to 24 points, whereas qSOFA from 0 to 3 points assigning one point for low systolic blood pressure (≤ 100 mmHg), high respiratory rate (≥ 22 breaths/min) and altered state of consciousness (Glasgow Coma Scale < 15). The presence of qSOFA scores 2 points or more is associated with the high risk of death and extended intensive care unit length of stay (12). The necessary information to assess SOFA and qSOFA scores were obtained from patients' laboratory results.

Investigated values were interpreted as mean $\pm$ standard deviation, numbers, and percentages. To assess the differences between selected clinical, laboratory parameters, SOFA and qSOFA scores of two independent groups, Mann-Whitney U test was used. All statistical procedures were performed with the use of STATISTICA Version 10.0 and Microsoft Excel 2010. P value of < 0.05 was considered statistically significant.

RESULTS

Patients belonging to the first clinical group were transferred to a tertiary referral hospital with a diagnosis of postpartum endometritis on an average of 11.0 ± 7.45 days after birth. The earliest diagnosis was given 3 days after birth (cesarian section) and the latest diagnosis was 27 days after birth. In 3 (20%) cases complications arose after surgical cesarean section, 7 (46.67%) cases had clinical and ultrasound data from placental tissue remains in the uterus, in 4 (26.67%) cases SIRS was diagnosed.

All patients in the first group were administered a course of comprehensive anti-inflammatory, antibiotic therapy, which lasted an average of 7.0 ± 2.0 days. 8 (53%) patients were administered with fluoroquinolones (ofloxacin, levofloxacin) in combination with metronidazole (ornidazole); for 3 (20%) patients diagnosed with SIRS, antibiotic therapy was carried out using preparations of carbapenems (imipenem, meropenem) in combination with metronidazole (ornidazole).

From the clinical and ultrasound data it is evident that 7 (46.67%) patients had placental residual remnants in the uterus which were removed using vacuum extraction, while in 2 (28.57%) cases, the operation was carried out twice. With the comprehensive anti-inflammatory therapy, clinical data (Table 2), ultrasound and laboratory follow-up, the patients in the first group were discharged in satisfactory condition after an average of 11.8 ± 5.25 days of hospitalization and transferred to their permanent place of residence.

Patients belonging to the second clinical group were transferred to a tertiary referral hospital with various forms of generalized postpartum inflammatory disease on an average of 9.16 ± 5.07 days after delivery (cesarean section). In 6 (31.58%) patients, complications arose after a late miscarriage, the average gestational period was 16.75 ± 3.77 weeks. In 5 (83.33%) cases, septic complications developed associated with the background of missed pregnancy, in one (16.67%) case after an incomplete spontaneous miscarriage. Overall the cause of the postpartum or postabortion sepsis was infected uterus in all 19 patients, as confirmed by pathomorphological examination. In 13 (68.42%) cases, the generalized septic complication was developed in the postpartum period, while in 8 (61.54%) patients after surgery (caesarean section) in 5 (38.46%) patients after delivery. After clinical and laboratory examination (Table 2), in all cases, sepsis was diagnosed as a complication with a pan-metritis background. In all 8 patients who underwent delivery by cesarean surgery, postoperative failure of sutures was described according to clinical and laboratory tests and ultrasound results, which was confirmed intraoperatively. Also, in 4 (21.05%) patients belonging to the second clinical group, sepsis occurred associated with the background of the manifestations of multiple organ failure syndrome (pneumonia, acute kidney injury) and 5 (26.32%) patients were diagnosed with peritonitis.

Table 2: Clinical and laboratory parameters in the differential diagnosis of postpartum septic complications.

Vital signs during hospitalization in Zaporizhzhia Regional Clinical Hospital (ZRCH)	Group 1 (n=15) Mean $\pm$ Standard Deviation	Group 2 (n=19) Mean $\pm$ Standard Deviation	p
Body temperature, °C	38.19 $\pm$ 0.52	38.15 $\pm$ 1.1	p> 0.05
Heart rate (beats /min)	91.6 $\pm$ 8.35	102.26 $\pm$ 16.42	p=0.00078
The frequency of breathing (breaths/min)	19.07 $\pm$ 2.49	24.16 $\pm$ 5.09	p=0.0164
The number of leukocytes ($\times 10^9/L$)	9.08 $\pm$ 5.1	10.6 $\pm$ 7.4	p> 0.05

All patients in the second group underwent hysterectomy including the fallopian tubes as an urgent procedure followed by antibiotic group therapy with carbapenems (imipenem, meropenem) in combination with vancomycin or metronidazole and linezolid (or-nidazole). After the surgery and complex anti-inflammatory therapy, 18 (94.74%) patients with generalized postpartum septic complications were discharged with sufficient condition and placed under active ambulatory care in permanent place of residence. Average period of inpatient treatment was 17.84 ± 8.39 days. Despite a comprehensive anti-inflammatory and intensive care and three surgical procedures, one (5.26%) patient died, associated with septic complications (severe sepsis, syndrome of multiple organ failure, iridocorneal endothelial syndrome) and diffuse peritonitis.

Fever was noted in all 34 (100%) patients included in the study; $38.19 \pm 0.52^{\circ}\text{C}$ in the first group; $38.15 \pm 1.1^{\circ}\text{C}$ in the second group ($p > 0.05$). Febrile values (over 38°C) were measured in 10 (66.67%) patients belonging to the first group and in 11 (57.89%) patients belonging to the second group.

The data regarding the evaluation of heart rate obtained during the hospital stay of patients with suspected septic complications in the postpartum period showed following results: The group of patients with a mean heart rate of 91.6 ± 8.35 beats/min were hospitalized with a clinical diagnosis of postpartum endometritis (group I) and the group of patients with a mean heart rate of 102.26 ± 16.42 beats/min had suspected generalized form of septic complications (group II) ($p=0.00078$).

Mean respiratory rate in the first clinical group was 19.07 ± 2.49 breaths/min during hospitalization in ZRCH and it was significantly lower than the second clinical group's rate which was recorded as 24.16 ± 5.09 breaths/min ($p=0.0164$).

Concerning the level of leukocytes; significant values of standard error of the mean and the lack of reliable difference on indicators of leukocytes in both clinical groups are noteworthy. In the first group, leukocyte level was $9.08 \pm 5.1 \times 10^9$ cells per liter and in the second clinical group, it was $10.6 \pm 7.4 \times 10^9$ cells per liter ($p > 0.05$).

During the hospitalization of the patients in the admission department, the condition of patients

were pre-evaluated with the qSOFA score to decide whether they should have been hospitalized at the intensive care unit and if there was a difference between the groups.

Analyzing the results in both clinical groups with regard to the qSOFA score, there was no significant difference in all three indices between the groups ($p > 0.05$). Meanwhile, in the second clinical group, 2 (13.33%) patients scored a total of 2 points on the qSOFA score (Table 3). They had been admitted to the intensive care unit for further treatment.

Table 3: Results of clinical examination of patients with the qSOFA score.

Indicators	Group 1 (n=15)		Group 2 (n=19)		p
	Mean $\pm$ Standard Deviation(min-max)	qSOFA=1 (Number of patients)	Mean $\pm$ Standard Deviation (min-max)	qSOFA=1 (Number of patients)	
Systolic blood pressure ≤ 100 mm Hg	121.33 $\pm$ 13.16 (110-160)	0	116.05 $\pm$ 13.9 (90-130)	4	$p > 0.05$
Respiratory rate ≥ 22 /min	17.9 $\pm$ 0.32 (17-18)	0	21.46 $\pm$ 6.46 (14-36)	5	$p > 0.05$
Altered mental status (Glasgow Coma Scale) ≤ 15 points	14.93 $\pm$ 0.26 (14-15)	1	14.24 $\pm$ 1.44 (10-15)	5	$p > 0.05$
qSOFA ≥ 2 points (Number of patients)	0		2		

Min: Minimum Max: Maximum

During the first day of the hospitalization of the patients, regardless of their subsequent stay (in the intensive care unit or in the Department of Gynecology), SOFA score was used for the diagnosis of septic organ failure (Table 4). A SOFA score of 2 or more points indicates a multiple organ failure of the septic genesis.

Table 4: Results of examination of patients in clinical groups on the SOFA scale.

Indicator	Group 1 (n=15)		Group 2 (n=19)		p
	Mean $\pm$ Standard Deviation(min-max)	SOFA ≥ 1 (Number of patients)	Mean $\pm$ Standard Deviation(min-max)	SOFA ≥ 1 (Number of patients)	
PaO ₂ /FiO ₂ *	-	-	-	-	
Platelets ($\times 10^9/\mu\text{L}$)	360.0 $\pm$ 120.93 (210-497)	0	259.0 $\pm$ 148.84 (72-504)	2	$p > 0.05$
Bilirubin ($\mu\text{mol/L}$)	12.79 $\pm$ 2.89 (9-20)	0	11.08 $\pm$ 2.94 (6-16)	0	$p > 0.05$
Mean arterial pressure (mm Hg)	91.11 $\pm$ 7.45 (83.3; 106.7)	0	86.23 $\pm$ 11.95 (63.3-103.9)	3	$p > 0.05$
Glasgow Coma Scale score	14.93 $\pm$ 0.26 (14-15)	1	14.23 $\pm$ 1.44 (10-15)	5	$p > 0.05$
Creatinine ($\mu\text{mol/L}$)	108.78 $\pm$ 41.19 (60-179)	4	80.61 $\pm$ 44.31 (32-223)	1	$p > 0.05$
Urine output (mL/day)	1277.33 $\pm$ 84.8 (1170-1450)	0	1323.68 $\pm$ 513.3 (170-2600)	2	$p > 0.05$

Min: Minimum Max: Maximum

* The ratio of PaO₂ / FiO₂ in relation to invasive risks (catheterization of the arterial vessel), was determined in patients of the second clinical group (n = 3) without further statistical processing of the results and without taking these values into account in the overall assessment of the number of points SOFA scale.

DISCUSSION

In our study, the patient group with relatively limited postpartum inflammatory diseases and the group with generalized forms of postpartum inflammatory diseases were compared in terms of four indicators (body temperature, heart rate, respiratory rate and the number of leucocytes) with the data of Zaporizhzhia Regional Clinical Hospital, that were selected in accordance with clinical protocols of the Ministry of Health of Ukraine (7). The group of patients with a generalized form of postpartum sepsis had significantly higher mean heart rate (102.26 ± 16.42 beats/min) and mean respiratory rate (24.16 ± 5.09 breaths/min) ($p=0.00078$, $p=0.0148$). Considering these results, monitoring heart and respiratory rates may be crucial in the differential diagnosis of postpartum sepsis.

Alan Jones et al. (16) involved a clinical setting of 248 subjects in their study, suggested that compared to many outcome predicting models available in the everyday clinical practice, SOFA scale is simple, easy to interpret and ready to use in the patient bedside assessment. Their results validated the utility of the SOFA score for patients admitted to the emergency department.

In a study by Roberto Ceriani et al. (17) including 218 patients who underwent cardiothoracic surgery, the accuracy of SOFA score in describing the severity of complications was identified. They were unable to evaluate the scores in dying patients with the neurological parameter of SOFA score. They supported the accuracy of SOFA score and described it as a useful analytic scale for the evaluation of patients who need to be admitted to the intensive care unit or critical care unit. Their study concluded that this system should be included for a group analysis and not just being as a clinical scale, which is a making decision on individual patients.

Harrison et al. (18) validated the use of a computer program for the calculation of SOFA score provided an easy and accessible method for the clinical setting. They indicated the necessity of real-time calculation of the SOFA score to evaluate the patients in the intensive care unit.

Considering these results in the literature, in this study we aimed to investigate the efficiency

of SOFA and qSOFA scales in the differential diagnosis of postpartum sepsis. However, SOFA and qSOFA score assessment results of the two patient groups indicate a lack of a significant difference in all indicators ($p>0.05$). Despite this result it is found out that none of the patients in the first group received a total of two or more points in the SOFA score. In the second clinical group, there were 5 (26.32%) patients who had 2 or more points on the SOFA scale. Out of which 2 (10.53%) patients had 7 points on the SOFA scale and 3 (15.79%) patients had 2 points on the SOFA scale, which allowed, in combination with other indicators, to evaluate their condition as sepsis. Moreover, only the second group had patients who had 2 points or more on the qSOFA scale, that is associated with high risk of death and extended intensive care unit length of stay (12).

Based on our results, we concluded that it is necessary to comprehensively assess the status of the patients according to the definition of sepsis based on SIRS criteria in combination with the SOFA score and qSOFA in order to timely diagnose postpartum septic complications (6, 7). Besides, patients with clinical and/or laboratory signs of postpartum septic complications must be transferred to a tertiary referral hospital within the first 24 hours. Moreover, all clinical cases within the postpartum period, demonstrating inflammatory processes of the uterus and signs of multiple organ failure should be regarded as a septic state. These cases may require urgent surgical intervention with hysterectomy and salpingectomy. We believe this clinical approach will allow an early differential diagnosis including localized and generalized forms of septic complications and ensure the clinical diagnosis of sepsis can be made at an optimal time with the subsequent provision of adequate treatment.

Ethics Committee Approval: This study was approved by Scientific Researches Committee of Zaporozhye State Medical University.

Informed Consent: Written informed consent was obtained from the participants of this study.

Conflict of Interest: The authors declared no conflict of interest.

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EFFECTIVE USE OF NEXT GENERATION SEQUENCING FOR GENETIC DIAGNOSIS OF A PATIENT WITH A MOSAIC TSC2 VARIANT

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ABSTRACT

Aims: Tuberous sclerosis complex is a genetic disorder characterized by mutations in Tuberous Sclerosis Complex 1 (* 605284) or Tuberous Sclerosis Complex 2 (* 191092) genes. PALB2 (* 610355) gene has long been known to be associated with increased breast and pancreatic cancer risk. Its association with risk of stomach and lung cancers has also been established recently. In this case report, it is aimed to present a case of a 24-year-old female patient, who has been diagnosed with both novel mosaic Tuberous Sclerosis Complex 2 pathogenic variation and pathogenic PALB2 variation at the same time.

Case Report: A 24-year-old female patient was admitted to Trakya University Genetic Diseases Center with suspected tuberous sclerosis complex. Her primary complaints were a continuous headache and fatigue. She had no history of convulsion and seizure. There were bilateral facial angiofibromas around her nose. When genomic DNA was isolated, both novel mosaic Tuberous Sclerosis Complex 2 pathogenic variation and pathogenic PALB2 variation were observed.

Conclusion: This case report shows that in cancer predisposing syndromes, Next-generation sequencing is a powerful technique to portrait a detailed genetic profile of patient, investigating for any mosaicism or other risk alleles.

Keywords: Tuberous sclerosis, mosaicism, mutation

INTRODUCTION

Tuberous sclerosis complex (TSC) is a genetic disorder characterized by mutations in TSC1 (* 605284) or TSC2 (* 191092) genes (1). TSC1 gene (* 605284) encodes hamartin protein while TSC2 gene (OMIM) encodes tuberin protein (1, 2). Heterozygous mutations in these two genes are found in about 75%-90% (31% of mutations are found in TSC1 gene and 69% of mutations are in TSC2 gene) according to the TSC clinical diagnostic criteria (1). The overall incidence of TSC is 1/6,000 to 1/10,000 live births (2).

Diagnosis of TSC is mainly based on clinical findings, including the formation of hamartomas in different organs. Tubers and nodules in brain and retina, facial angiofibromas, hypomelanotic macules and fibromas of the skin, cardiac rhabdomyomas, renal angiomyoli-

pomas, and pulmonary lymphangiomyomatosis are also other common clinical manifestations of TSC (2).

Located in 16p12, PALB2 (*600185) gene, whose product colocalizes with BRCA2 gene in nuclear foci, has recombinational repair and checkpoint functions. The association between PALB2 gene and risk of breast and pancreatic cancer has long been recognized. Moreover, PALB2 gene has recently been suggested to be associated with increased risk of stomach and lung cancers (3, 4).

Next-generation sequencing (NGS) is a practical and cost-effective method for screening mutations in large genes and many genes at the same time. The other advantage of this technique is its ability to detect mosaic variants. Next-generation panels contain different genes that can be analyzed in a single reaction. These genes can be responsible for overlapping clinical mani-

festations, like neurofibromatosis and TSC (5).

In this case report, a 24-year-old female patient is presented who has been diagnosed with having both novel mosaic TSC2 pathogenic variation and pathogenic PALB2 variation at the same time.

CASE REPORT

A 24-year-old female patient was admitted to Trakya University Genetic Diseases Center with TSC as a differential diagnosis. The patient was the only child of a non-consanguineous Turkish couple. Patient's primary complaints were a continuous headache and fatigue. The patient had no history of convulsion and seizure. There were bilateral facial angiofibromas around her nose (Figure 1). Hyperintense foci were found in her left temporal region in T2A and fluid-attenuated inversion-recovery sequences of magnetic resonance imaging scan, which are compatible with cortical tubers. The patient also had angiomyolipoma on her right kidney.

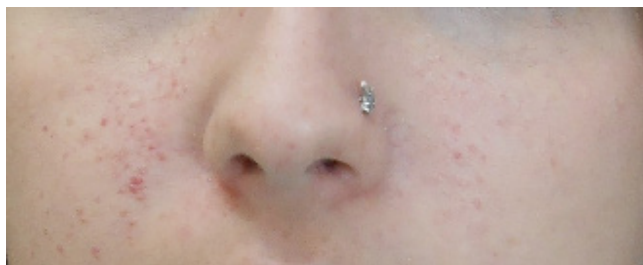


Figure 1: Bilateral facial angiofibromas on the nasolabial folds.

After obtaining written informed consent, genomic DNA was isolated using EZ1 automated DNA isolation system (Qiagen) from peripheral blood samples of the patient and patient's family members. DNA Quantification was performed with Qubit® dsDNA HS Assay Kit (Invitrogen) according to the instructions of the manufacturer. TruSight Rapid Capture Kit (Illumina) was used for target enrichment of 94 genes (TruSight Cancer Kit, Illumina) including both TSC1 and TSC2. 150 bp paired-end reads were sequenced and aligned on Miseq System. Variant calling and analysis was performed on Genomize-Seq (Turkey) platform. Because of the probability that TSC1 and TSC2 variants might be mosaic in the patient, fastq files were analyzed on base space with Cancer Variant Caller (Illumina) and visualized data on IGV (Broad Institute). Mutation confirmation and segregation analysis was made by Sanger Sequencing on ABI 3130 XL. Variants have

been analyzed in silico by using Varsome and classified according to the ACMG 2015 criteria (6).

A mosaic TSC2 in-frame deletion encompassing 9 bp around the splice site of exon 34 was found (NM_000548.4(TSC2):c.4006-2_4012delAGTCGTCCT) (Figure 2A). The frequency of the mutated allele was about 10% (38/300 coverage). In addition, the patient was heterozygous for NM_024675.3(PALB2):c.1704_1707delAAAA (p.Lys569Argfs) variation (Figure 2B) which has been reported as "pathogenic" in ClinVar database previously.

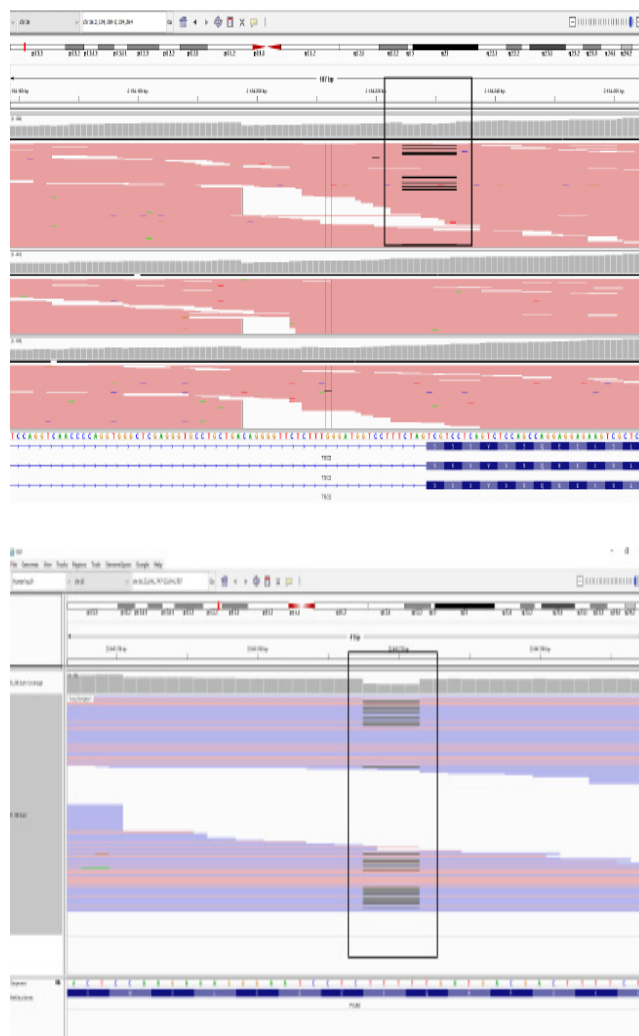


Figure 2: A mosaic TSC2 in-frame deletion encompassing 9bp around the splice site of exon 34(NM_000548.4(TSC2):c.4006-2_4012delAGTCGTCCT) (A), Heterozygous NM_024675.3(PALB2):c.1704_1707delAAAA (p.Lys569Argfs) variation (B).

On the contrary, based on results from sequencing, a mutation in TSC2 gene was not present in genome of the patient's parents. However, the patient had some small raw peaks near the base of the sequencing baseline and these raw peaks were compatible with the deleted allele of the patient. On the other hand, the patient's mother was a carrier of PALB2 pathogenic variation, whereas her father did not have any mutation in this region (Figure 3). Her mother does not have any cancer

history or familial history of cancer. Close clinical follow-up was offered to both the patient and her mother, in particular assessment of any features of cancer.

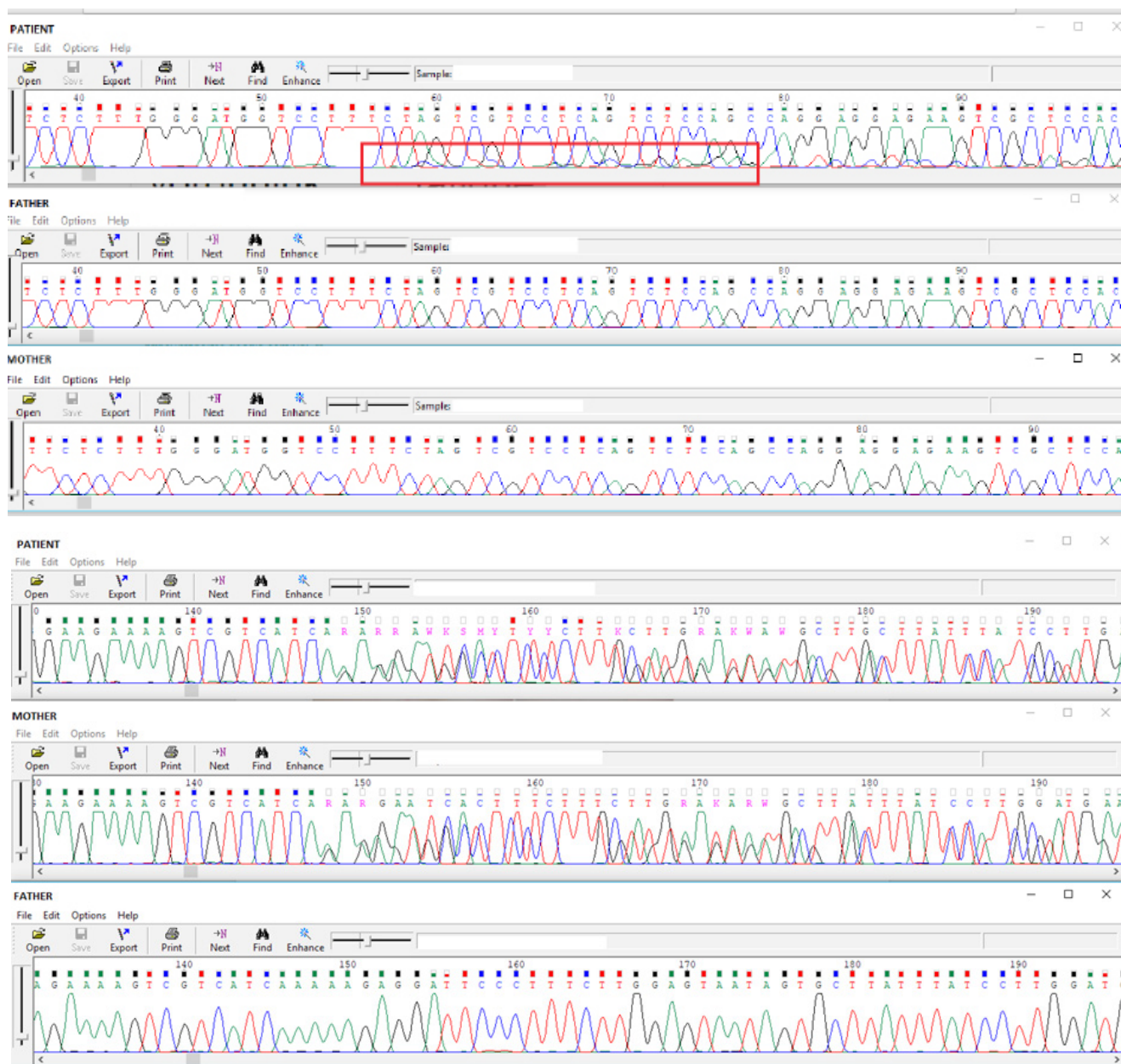


Figure 3: Small raw peaks near the base of the sequencing baseline and these raw peaks (red framed region) were compatible with the deleted allele and normal electropherogram of parents, mother was carrying the PALB2 pathogenic variation, whereas the father is normal for this region.

DISCUSSION

A number of mutations in TSC1 and TSC2 genes have been reported in the literature, including somatic pathogenic variants in patients who are clinically diagnosed with TSC (1). The patient reported in the present case report was diagnosed with mosaic TSC2 in pathogenic variant. She was also heterozygous for a previously described pathogenic PALB2 gene variation. To the best of our knowledge, this is the first case report in the literature that identified a patient with concurrent mosaic pathogenic TSC2 variant and pathogenic PALB2 gene variant at the same time.

Mosaic variants in TSC1 and TSC2 genes are known to be associated with a milder phenotype of TSC. Clinical manifestations of TSC differ among patients, depending on the degree of the mosaic variant. Milder clinical phenotype of our patient may be attributed to the low level of mutated allele ratio. It is difficult to determine low frequency mosaic mutation by conventional methods like Sanger sequencing. In comparison, NGS is an easier and faster method to detect mosaic variations (1). The precise determination of mosaic variant in our patient with NGS supports the effectiveness of this technology for the diagnosis of clinically suspected TSC.

Incidental findings should be reported to the patients in case of identifying any pathogenic variant at an important locus (7). The finding of PALB2 mutation by NGS when searching for TSC in our patient is described as an incidental finding. Because PALB2 is an important cancer predisposing gene, the patient and the patient's mother are given a detailed genetic counseling and referred to close clinical follow-up for assessing and monitoring risk of cancer.

In conclusion, we suggest that in cancer predisposing syndromes, NGS is a powerful technique to portray a detailed genetic profile of patient, investigating for any mosaicism or other risk alleles.

Ethics Committee Approval: N/A

Informed Consent: Written informed consent was obtained from the patient of this study.

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A RISING CONCERN: A CASE OF PERFORATION OF THE FLOOR OF THE MOUTH CAUSED BY TONGUE PIERCING

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ABSTRACT

Aims: The aim of this study is to present a case of an infection in the oral cavity due to tongue piercing perforated into the floor of the mouth, thus to raise concern over the increasing popularity of tongue piercing in spite of its risks including perforation in the oral cavity and oral ulcers.

Case Report: A sixteen-year-old female patient presented to the clinic with lesions and extreme pain in her oral cavity. The thorough examination showed displacement of the piercing through the tongue, causing a perforation of the floor of the mouth. The piercing was surgically removed. The ulcers were treated with medication. The patient was advised to get professional help and was instructed to pay close attention to oral hygiene in case of reiterated demand for tongue piercing.

Conclusion: It is important to ensure that piercing is inserted by a specialist under sterile conditions to prevent complications. If a surgical operation is needed to treat the complications occurred, the clinicians must be aware of the critical veins and nerves that are located in the oral cavity and they should be very careful not to cause any harm during the operation.

Keywords: Tongue, inflammation, ulcer

INTRODUCTION

Piercing is a type of jewelry that is permanently inserted into the body. Lately, tongue piercings are gaining increasing popularity and mostly preferred by young people (1). Piercings may cause problems such as pain, inflammatory reactions, edema and dental problems if inserted in unsanitary conditions by unqualified people (2, 3).

A biofilm is a thick mucoid matter that contains and promotes the development of the bacteria around itself (4). Even in case of appropriate oral hygiene habits, a piercing inside the mouth is often covered with biofilm containing various bacteria such as normal flora, opportunistic and/or inflammatory. The biofilm that covers the piercing acts as a reservoir for bacteria and causes complications by infecting the piercing channel, which is located inside the oral soft tissues (2, 3, 5). This report presents a case of an infection in the oral cavity caused by tongue piercing, which was embedded in the tongue and also led to a rare case of perforation of the floor of the mouth.

CASE REPORT

A sixteen-year-old female patient presented to the Department of Otolaryngology in Private Keşan Hospital with severe pain and lesion on the underside of her tongue and at the base of her mouth. A barbell-shaped tongue piercing with a bead on each end was inserted two months ago on her median lingual sulcus. The patient's medical history was insignificant and she was not taking any medications. During the physical examination, it was noted that the upper bead of the barbell-shaped piercing, which was supposed to be seen on top of the tongue, was not visible. It was embedded in between the muscles of the tongue but was not fully covered by mucosa. At the bottom of the tongue, piercing with the bead was still screwed on. It was visible under the tongue and it perforated the floor of the mouth. The incision being 12 mm in width and 16 mm in length, caused infections and ulcers in both undersides of the tongue and floor of the mouth. (Figure 1). Since all information was collected from the patient, no further investigations were needed. The patient was taken to the operating room and lidocaine spray was

applied for local anesthesia. In the operation, the bottom bead of the tongue piercing was carefully screwed off and rest of it was drawn completely out from the surface of the tongue while avoiding any contact that may harm the veins, nerves and muscles located nearby (Figure 2-3). For post-op treatment, the patient was given chlorhexidine oral rinse and tablets containing paracetamol and propyphenazone. A week later, in the follow-up appointment, the lesions on the floor of the mouth and underside of the tongue were found to be healed and the patient had no complaints. To prevent the recurrence of this condition, the patient was informed about the importance of having the piercing inserted by a specialist under sterile conditions.



Figure 3: The removed barbell shaped tongue piercing.



Figure 1: The perforation of the floor of the mouth caused by the barrel-shaped tongue piercing.



Figure 2: The removal of the barbell shaped tongue piercing.

DISCUSSION

The popularity of tongue piercing is growing day by day along with its complications (6). The case control study by Ziebolz et al. (7) showed that the most popular type of tongue piercing among the young people between the ages of sixteen and twenty-four was the barbell-shaped piercing.

A tongue piercing is embedded in the soft tissue of the tongue and runs through its muscles vertically (8). A tongue piercing's location, angle and firmness determine the risk of infection. A tight tongue piercing could cause necrosis due to pressure and may lead to surgical operations as shown in this very case (9).

In a case series by López-Jornet et al. (4) conducted on 70 patients who had oral and facial piercings, 60% of the subjects reported pain and 34.3% had inflammatory reactions associated with piercing.

Oral hygiene is a significant determinant of inflammation. Bacteria that are contained in the oral cavity contaminate the piercing tract and cause inflammation. More bacteria proliferate as the oral hygiene diminishes (10).

As shown in all three cases in the study of Shacham et al. (9) tongue piercing can cause swelling of both the tongue and the floor of the mouth. The case report of Bryan et al. (11) has shown that edema causes the barbell to slip and be relocated in between the tongue muscles that are later on covered over with mucosa creating ulcers in oral cavity. This case was also supported

by the reports of Dayakar et al. (6), Farah et al. (12), Shinohara et al. (13) and Escuardo-Castaño et al. (14).

With the treatment, the healing process begins immediately and the piercing tract proceeds to close within an hour (15).

Complications can be preventable by informing young people about sterilization conditions and recommending consultation to specialists (7, 12).

In conclusion, it is important to ensure that piercing is inserted by a specialist under sterile conditions. Oral hygiene is essential to prevent any risk of bacterial colonization that might cause infection in the oral cavity, mostly around the perforation line caused by the piercing. To prevent further harm, tongue piercing should be fixed in the tongue firm enough not to let it move around yet loose enough to avoid any necrosis due to its tightness. If a surgical operation is needed, the clinicians must be aware of the critical veins and nerves that are located in the oral cavity and they should be very careful not to cause any harm during the operation.

Ethics Committee Approval: N/A

Informed Consent: Written informed consent was obtained from the participants of this study.

Conflict of Interest: The authors declared no conflict of interest.

Author contributions: Concept: FÖ, YCÖ, KE. Design: FÖ, YCÖ, KE. Supervision: FÖ. Resources: FÖ, YCÖ, KE. Materials: FÖ, YCÖ, KE. Data collection and/or processing: FÖ, YCÖ, KE. Analysis and/or Interpretation: FÖ, YCÖ, KE. Literature Search: FÖ, YCÖ, KE. Writing Manuscript: FÖ, YCÖ, KE. Critical Review: FÖ.

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*If you are the corresponding author, and neither you nor your co-authors have any disclosures to declare under Sections 2, 3, or 4 below, you can check "Nothing to disclose" (see Section 1, line 7, page 2). In this case only, the disclosure applies to all authors, and the form is complete.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party—that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation, or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations, or academic institutions, need not be disclosed here (but can be acknowledged on the title page of the manuscript). For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

*If you are the corresponding author, and neither you nor your co-authors have any disclosures to declare under Sections 2, 3, or 4 below, you can check "Nothing to disclose" (see Section 1, line 7, page 2). In this case only, the disclosure applies to all authors, and the form is complete.

Section 1. Identifying Information

Complete by providing the requested information in the white boxes.

1. Given Name (First Name):		2. Surname (Last Name):		3. Current Date:	
4. Are you the corresponding author?	☐ Yes	☐ No	If "No", name of corresponding author:		
5. Manuscript Title:					
6. Manuscript Identifying Number (if you know it):					
7. If you are the corresponding author, and neither you nor your co-authors have any disclosures to declare, check here:				☐ Nothing to Disclose	

Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information in the white boxes. Add rows as needed.

The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments
1. Grant					
2. Consulting fee or honorarium					
3. Support for travel to meetings for the study or other purposes					
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like					
5. Payment for writing or reviewing the manuscript					
6. Provisions of writing assistance, medicines, equipment, or administrative support					
7. Other					

*This means money that your institution received for your efforts this study.

Section 3. Relevant financial activities outside the submitted work.

Please indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions.

You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information in the white boxes.

Relevant Financial Activities Outside the Submitted Work

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments
1. Board membership					
2. Consultancy					
3. Employment					
4. Expert testimony					
5. Grants/grants pending					
6. Payment for lectures including service on speakers bureaus					
7. Payment for manuscript preparation					
8. Patents (planned, pending or issued)					
9. Royalties					
10. Payment for development of educational presentations					
11. Stock/stock options					
12. Travel/accommodations/meeting expenses unrelated to activities listed**					
13. Other (err on the side of full disclosure)					

*This means money that your institution received for your efforts.

**For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section 4. Other Relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

___ No other relationships/conditions/circumstances that present a potential conflict of interest.

___ Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, we ask that you update your disclosure statements if anything has changed. On occasion, we to disclose further information about reported relationships.



CONSENT FORM for CASE REPORT

Title of Project: _____

1. I have read, and understood the Participant Information Sheet dated _____
2. I freely agree to the use of my medical records for the purpose of this study.
3. I understand that the case report will be published without my name attached and researchers will make every attempt to ensure my anonymity. I understand, however, that complete anonymity cannot be guaranteed.
4. I have been given a copy of the Participant Information Sheet and Consent Form to keep.

Name of Participant _____

Signature of Participant _____ Date _____

The participant was informed through phone call and a verbal consent was obtained.

The following section regarding the witness is not essential but may be appropriate for patients where the research teams feel that the participant should have a witness to the consent procedure.

Name of witness (if appropriate) _____

Signature of witness _____ Date _____

Name of Researcher _____

Signature of Researcher _____ Date _____

Name of Researcher _____

Signature of Researcher _____ Date _____

