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The Middle Black Sea Journal of Health Science, which is international journal, is published by Ordu University Institute of Health Sciences on behalf of the Middle Black Sea Universities Collaboration Platform

Aims and Scope

Middle Black Sea Journal of Health Science is an international journal that publishes original clinical and scientific research. Middle Black Sea Journal of Health Science, published by Ordu University, publishes basic innovations in health education, case reports, reviews, letters to the editor, case reports and research articles.

The aim of the journal is to contribute to the international literature with clinical and experimental research articles, case reports, reviews and letters to the editor in the field of health sciences.

The target audience of the journal is all scientists working in the field of health, graduate students and researchers in this field.

Middle Black Sea Journal of Health Science is an open access, independent and impartial, international journal based on double-blind peer-reviewed principles.

The publication language of the journal is English. The journal is published every four months, in April, August and December, and three volumes are completed.

Middle Black Sea Journal of Health Science - adheres to the standards of publication ethics in health science research, Higher Education Council's Scientific Research and Publication Ethics Directive, Committee on Publication Ethics (COPE), Directory of Open Access Journals (DOAJ), Open Access Scholarly Publishers It also adopts the ethical publishing principles published by the Association (OASPA) and the World Association of Medical Editors (WAME).

No fee is charged from the authors for the evaluation and publication of the article.

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- All submitted studies go through pre-evaluation, language editor, statistical editor and referee evaluation processes. The evaluation process is carried out by the editor of the journal.

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• Can direct the article to the referees and initiate the referee evaluation process.

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Ethics Committee Approval: Ethics committee approval was received for this study from ……. Clinical Research Ethics Committee of …… University (No…….).
Author Contributions: Concept: …….., Design: …….., Literature search:……..... Data Collection and/or Processing: ……..., Analysis and/or Interpretation:……, Writing - …….
Acknowledgements:
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Levine WC, Pope V, Bhoomkar A, Tambe P, Lewis JS, Zaidi AA, et al. Increase in endocervical CD4 lymphocytes among women with nonulcerative sexually transmitted diseases. J Infect Dis. 1998;177(1):167–174.
Chapter in Edited Book: Hornbeck P. Assay for antibody production. In: Colign JE. Kruisbeek AM, Marguiles DH, editors. Current Protocols in Immunology. New York: Greene Publishing Associates; 1991. p. 105-32.
Book with a Single Author: Fleiss JL. Statistical Methods for Rates and Proportions. Second Edition. New York: John Wiley and Sons; 1981. p. 105-32.
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Conference Paper: Entrala E, Mascaro C. New structural findings in Cryptosporidium parvum oocysts. Eighth International Congress of Parasitology (ICOPA VIII); October 10-14; Izmir-Turkey: 1994. p. 1250-75
Thesis: Erakinci G. Searching for antibodies against parasites in donors. Izmir: Ege University Health Sciences Institute. 1997.
Article in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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Structure
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Abstract should be structured with subheadings (Objective, Methods, Results, and Conclusion) (average 200-400 word)
Key words
Introduction
Methods
Results
Discussion

Conclusion
Acknowledgements
References (most 40)
Whole text should not exceed 4500 words except for resources and English summary.

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Conclusion
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Discussion
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The compilation text also including appropriate sub-headings,
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Abstract
Key words
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Title
Abstract (average 200-400 word)
Key words
Surgical technique
Conclusion
References (most 15)

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Structure
Cover Letter
Title
Abstract (average 100-150 word)
Key words
Topics related to the subject.
Conclusion
References (3-5 inter)

h) Original Images: Rarely seen annotated medical images and photographs in the literature.
Structure
300 words of text and original images about the subject
References (3-5 inter)

ı) What is Your Diagnosis? Are the articles prepared as in questions and answers about rarely seen diseases which differ in the diagnosis and treatment?
Structure
Topics related to the subject.
References (3-5 inter)

i) Questions and Answers: Are the texts written in form of questions and answers about scientific educative –instructive medical issues.

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EDITORIAL

We are together with a new issue.

In this issue, Internal Medicine, Anatomy, General surgery, Neurosurgery, Pediatric Neurology, Chest Diseases, Thoracic Surgery, Anesthesiology and Reanimation, Neurology, Child and Adolescent Psychiatrist, Nursing, Mental Health and Diseases, Plastic and Reconstructive Surgery, Gynecology, Physical Therapy and Rehabilitation, there are very interesting studies.

We would like to thank all the authors, referees and those who contributed to the publication process of our journal.

I wish you healthy and happy days…

PhD, Assoc. Prof. Ülkü KARAMAN

Editor

August – 2021 REFEREES INDEX In Our Journal Publications Process, Extend Our Thanks To Article Assessment Referees.	
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RESEARCH ARTICLE

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Evaluation of Vitamin D levels of patients with Type 2 Diabetes Mellitus taking oral antidiabetic drugs

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Abstract

Objective: The aim of this study was to evaluate the vitamin D levels of type 2 diabetes Mellitus (T2DM) patients taking oral antidiabetic drugs.

Methods: The data of 276 T2DM patients who applied to the internal medicine outpatient clinic of our hospital between January-2020 and March-2021, and the control group consisting of normoglycemic individuals in the same age group, as well as the data of 130 patients, were retrospectively reviewed from archive records. Patients with serum 25-hydroxyvitamin D (25(OH)D) level below 30 ng/mL were accepted as vitamin D deficiency and insufficiency, and patients with serum 25(OH)D levels above 30 ng/mL were accepted as normal vitamin D adequacy. The data of T2DM patients taking oral antidiabetic drugs and the data of normoglycemic control group patients were statistically compared.

Results: 60.8% (n=168) of T2DM patients taking 276 oral antidiabetic drugs included in the study were female and 39.2% (n=108) were male. The mean age of the patients was 52.5±4.2 years. The mean serum 25(OH)D level of the T2DM group patients taking oral antidiabetic drugs was 9.6±4.3 ng/mL. Of the 130 patients taken as the normoglycemic control group, 65.3% (n=85) were female and 34.7% (n=45) were male. The mean age of these patients was 53.6±4.4 years. Mean serum 25(OH)D level of the control group was 16.1±4.6 ng/mL. When the 25(OH)D levels, HOMA-IR, fasting blood glucose, HbA1c and BMI ratios of the T2DM group patients taking oral antidiabetic drugs were compared statistically compared to the normoglycemic control group patients, significant differences were found between the groups (respectively; $p < 0.01$; $p < 0.01$; $p < 0.01$; $p < 0.01$; $p < 0.01$).

Conclusion: The fact that vitamin D levels were found to be significantly lower in T2DM patients taking oral antidiabetic drugs compared to the normoglycemic control group suggests that vitamin D deficiency has an important place in the formation of T2DM. We think that early vitamin D replacement therapy in these patients may be a preventive factor in the formation of T2DM.

Key words: Vitamin D, Oral antidiabetic drugs, Type 2 diabetes mellitus

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Introduction

Diabetes mellitus (DM) is the most common endocrinological disease. Today, it is considered an epidemic disease in many developed and developing countries and ranks fourth among the top five causes of death in most developed countries. DM is a chronic, hyperglycemic, metabolic disorder that causes disorders in carbohydrate, protein and fat metabolism as a result of a series of pathological events caused by genetic and immune structure, the absolute or relative insufficiency or ineffectiveness of the insulin hormone secreted from pancreatic beta cells, cataking complications in almost all systems. is a disease (1).

Type 2 DM is often characterized by a strong genetic load. Family history is present in almost all of them. Three important factors play a role in its pathogenesis: Disruption of pancreatic beta cell insulin secretion, insulin resistance and increased liver glucose production. It is mostly seen in elderly people, sedentary people and obese people. However, although it is known to be seen in non-obese patients, this becomes important in etiological classification. Accordingly, while insulin resistance is more important in obese type 2 DM, insulin secretion disorder is in the first place in non-obese ones (2).

Endogenous vitamin D status is determined by the serum 25-hydroxy vitamin D (25(OH)D) level. 25(OH)D level is the best indicator for defining vitamin D deficiency and insufficiency. There is no clear consensus regarding vitamin D deficiency, insufficiency and optimal 25(OH)D levels. Vitamin D deficiency is defined as the lowest serum 25(OH)D level (20 ng/ml) that prevents secondary hyperparathyroidism, increased bone formation-destruction and bone mineral loss. Serum 25(OH)D level below 12 ng/ml was associated with a decrease in muscle strength. Serum 25(OH)D levels are recommended to be above 30 ng/ml for maximum calcium absorption and optimal health (3).

Although DM, which is among the causes of secondary osteoporosis, is a heterogeneous group of disorders with different causes, it is characterized by hyperglycemia, absolute or relative insulin insufficiency or insulin resistance, and a tendency to develop some long-term complications (4).

Vitamin D can affect insulin secretion and fat breakdown. The genetic diversity of the vitamin D receptor (VDR) is widespread, and its relationship with bone mineral density and type 2 DM has been demonstrated in many studies. Although the relation of VDR gene diversity with high rate of obesity and early onset type 2 DM has been shown, the pathophysiological mechanism has not been explained (5).

Vitamin D reduces insulin resistance in surrounding tissues, thereby reducing excess insulin secretion that occurs in response to the increase in blood sugar due to insulin resistance and increases insulin sensitivity. It has been shown that vitamin D deficiency is a risk factor for metabolic syndrome and type 2 DM, and that vitamin D deficiency is associated with insulin resistance and-cell dysfunction (6,7).

The aim of this study was to evaluate vitamin D levels in type 2 DM patients taking oral antidiabetic drugs. Thus, we think that adding vitamin D prophylactically to type 2 DM patients will be beneficial in the patient's clinic and in preventing complications that may develop in the patient.

Methods

The data of 276 patients with Type 2 DM who applied to the internal medicine outpatient clinic of our hospital between January-2020 and March-2021, and the control group consisting of normoglycemic individuals in the same age group, were retrospectively reviewed from archive records. The data of the patients (age, gender, serum 25(OH)D level, biochemical parameters, parathyroid hormone) were retrospectively reviewed from file records. Serum 25(OH)D levels were studied in Abbott Architect i2000-SR autoanalyzer in our hospital. Patients with serum 25(OH)D level below 30 ng/ml were accepted as vitamin D deficiency and insufficiency, and patients with serum 25(OH)D levels above 30 ng/ml were accepted as normal vitamin D adequacy. The data of T2DM patients taking oral antidiabetic drugs and the data of normoglycemic control group patients were statistically compared.

Exclusion Criteria

Patients receiving vitamin D and immunosuppressive drug therapy, patients with bone metabolism disease, cancer patients, breastfeeding and pregnant patients, patients diagnosed with osteoporosis and osteomalacia, patients with primary hyperparathyroidism, patients with chronic renal failure, patients taking alcohol and smoking and archive records are insufficient. and missing patients were excluded from the study.

Statistical Analysis

All data were uploaded to SPSS 22.0 program. In the evaluation of the data, number(n), percentage (%), mean and standard deviation were used for

descriptive statistics. Data were analyzed by Kolmogorov-Smirnow test. Student-t test was used to compare the groups. Pearson and Spearman tests were used for correlation analysis. P value less than 0.05 was considered significant.

Results

60.8% (n=168) of T2DM patients taking 276 oral antidiabetic drugs included in the study were female and 39.2% (n=108) were male. The mean age of the patients was 52.5±4.2 years (men 51.7±11.4 years, women 53.5±12.1 years). The mean serum 25(OH)D level of the T2DM group patients taking oral antidiabetic drugs was 9.6±4.3 ng/ml. Of the 130 patients taken as the normoglycemic control group, 65.3% (n=85) were female and 34.7% (n=45) were male. The mean age of these patients was 53.6±4.4 years (men 53.5±10.4 years, women 52.6±11.7 years). Mean serum 25(OH)D level of the normoglycemic control group was 16.1±4.6 ng/ml.

When the 25(OH)D levels, HOMA-IR, fasting blood glucose, HbA1c and BMI ratios of the T2DM group patients taking oral antidiabetic drugs were compared statistically compared to the normoglycemic control group patients, significant differences were found between the groups (respectively; p <0.01; p < 0.01; p <0.01; p <0.01; p <0.01) (Table 1).

Table 1. Demographic and laboratory findings of the groups.

PARAMETERS	T2DM (n=276)	Control group (n=130)	*P value*
	Mean±SD	Mean±SD	
Age (year)	52.5±4.2	53.6±4.4	0.862
Gender (F/M)	168/108	85/45	0.142
25(OH)D (ng/ml)	9.6±4.3	16.1±4.6	**< 0.01**
Ca (mg/dl)	8.2±0.4	8.9±0.6	0.178
P (mg/dl)	3.2±0.2	3.3±0.5	0.243
PTH (pg/ml)	55.3±24.6	53.2±23.5	0.451
Albumin (g/dl)	4.6±0.3	4.5±0.2	0.315
HOMA-IR	5.3±3.5	1.9±0.8	**< 0.01**
FBG (mg/dl)	186.4±72.5	88.4±6.7	**< 0.01**
HbA1c (%)	8.7±2.3	5.6±0.8	**< 0.01**
BMI (kg/m^2)	30.6±3.8	27.3±4.2	**< 0.01**

BMI: Body mass index, **FBG:** Fasting blood glucose, **HbA1c:** Hemoglobin resistance, **Ca:** Calcium, **P:** Phosphorous, **PTH:** Parathyroid hormone, **25(** deviation, **M:** Male, **F:** Female, **n:** number.
T2DM: Type 2 Diabetes Mellitus.

Discussion

It has been reported that the incidence of diabetes has been increasing rapidly in dangerous proportions in recent years. According to WHO, it is estimated that there are more than 180 million diabetic patients in the world and this figure is expected to increase more than double in 2030 (8). In our study, when vitamin D levels of the normoglycemic control patient group and T2DM patients taking oral antidiabetic drugs were compared, vitamin D levels were found to be significantly lower in the T2DM patient group.

Studies have suggested that vitamin D may have an effect on insulin resistance by regulating both calcium metabolism and insulin receptor gene expression (9).

Vitamin D has an important role both in the pathogenesis of bone diseases and calcium homeostasis and in the development of various chronic diseases. It has been suggested that vitamin D deficiency is a risk factor in the development of DM. Knekt et al. (10) supports the hypothesis that high vitamin D levels are protective against T2DM.

Shankar et al. (11) found a positive relationship between low vitamin D levels and diabetes. In this study, it is emphasized that vitamin D treatment is effective in protecting against diabetes and the importance of vitamin D in diabetes.

Another study Modi et al. (12). In this study, they found that the vitamin D levels of diabetic patients were statistically lower than the control group. Targher et al. (13) found in their study that DM patients with low vitamin D levels had high HbA1c levels. They attributed this to the healing effect of vitamin D on beta cell functions. In this study, we found that as the HbA1c level increases in diabetic patients, the vitamin D level decreases.

However, Giorelli et al. (14) found low levels of vitamin D in both the diabetic group and the control group without a statistically significant difference between them. These different results may be due to seasonal difference, skin pigmentation difference and ethnic group difference.

Chiu et al. (6) found that there was a positive correlation between 25(OH)D levels and insulin sensitivity and the negative effects of vitamin D deficiency on beta cell function in 126 individuals without diabetes, with glucose intolerance, by adjusting parameters such as age, gender, and alcohol. It has been shown to be. As a result, individuals with vitamin D deficiency seemed to be at risk in terms of insulin resistance and diabetes development.

In a similar study, Baynes et al. (15) found a statistically significant difference between increased fasting plasma glucose and decreased vitamin D levels in their study, which included 126 people without DM disease.

However, Davidson et al. (16), in the study they conducted with diabetic patients with low vitamin D levels, showed that keeping vitamin D levels normal

with vitamin D supplements for 1 year had no effect on insulin secretion, insulin sensitivity and diabetes development.

Conclusion

The relationship between vitamin D levels and the development of diabetes has been demonstrated in many studies. Vitamin D deficiency is thought to trigger insulin resistance and is one of the reasons leading to T2DM. In our study, the fact that vitamin D levels were found to be significantly lower in T2DM patients taking oral antidiabetic drugs compared to the normoglycemic control group suggests that vitamin D deficiency has an important place in the formation of T2DM. We think that early vitamin D replacement therapy in these patients may be a preventive factor in the formation of T2DM.

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The Effect of Leg Strength and Jump Performance on Balance in Handball Players

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Abstract

Objective: The purpose of this study was to examine the effect of leg strength and jump performance on balance in handball players.

Methods: It involved the evaluation of balance, leg strength, and jump performance of licensed handball players in our region. Athletes' balance measurements were collected under three parameters (static balance with eyes open, static balance with eyes closed, and bipedal dynamic balance) using a CSMI-Tecnobody PK-252 isokinetic balance measuring device. Vertical jump was measured on a splash mat, horizontal (forward) jump on a flat surface, and leg strength with a back-leg dynamometer. Athletes' anaerobic strengths were calculated based on the Lewis formula, and all data were analyzed on SPSS 22.0 V software. At statistical analysis, a test of normality (Shapiro Wilk) was applied to determine whether data were normally distributed ($p>0.05$). Pearson correlation analysis was applied for values exhibiting normal distribution in the test results, and Spearman correlation (r) for non-normally distributed values.

Results: Negative correlation was observed between athletes' vertical jump values and bipedal average track error (ATE) and stability indicator values. Negative correlation was observed between horizontal jump and bipedal ATE values, and between leg strength data and closed-eye average medial lateral speed values. Anaerobic strength values were also negatively correlated with closed-eye average forward-backward velocity, closed-eye PM, and bipedal ATE values ($p<0.05$). Examination of the analysis results showed that balance values decreased as vertical jump, horizontal jump, leg strength, and anaerobic strength increased.

Conclusion: We concluded that an athlete would acquire better balance performance through jump, strength, strength, and anaerobic strength developing training.

Key words: Handball, Static Balance, Dynamic Balance, Leg Strength, Vertical Jump, Horizontal Jump

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Introduction

Handball is a performance sport with millions of fans and players and the subject of considerable global interest. It is highly popular with young people as one of the branches of sport that is enjoyable and easy to play, and that improves group dynamics. This interest in developed countries and Turkey has made handball a part of life, bringing it to schools and clubs (1). The sport involves movements such as jumping, running, sprinting, shooting, blocking, and pushing. Maximum muscle strength, power, and balance on one leg are especially important during jumping and shooting for the development of technical and tactical skills in handball. Improving these performance skills that affect the neuromuscular system bestows a major advantage on players (2).

Handball being a sport requiring the combined use of various motor skills means that muscle power, muscular-nervous system compatibility, endurance, speed, flexibility, mobility, anaerobic capacity, and performance reaction time in anaerobic capacity are all important components of success in dynamic and static balance (3). Scientific and technological progress has led to major advances in handball-player performance, together with all branches of sport. Research in the field of sport is aimed at improving performance and success. Individuals obliged to adapt to different situations may sometimes experience difficulty in adapting to changes around them. Corrective steps and lurch-like movements are required to prevent falls when the limit of balanced posture is exceeded. Nerve-muscle coordination and adaptation are particularly important at this point (4).

Balance occupies an important place in gymnastics, sport, dance, and games. It is essential in order to avoid accidents and to perform daily activities (5). Balance is the key to mobility and is important at all ages. Impairment of balance occurs with age, representing a risk for falls (6). Balance serves an important function in the ability to maintain bodily integrity, essential to success in sporting activities. It therefore represents the basis of dynamic sports involving sudden changes in movements (7).

Due to the multifaceted nature of handball, the purpose of the present study was to examine the effect of leg strength and jump performances of licensed handball players on balance. Measurements were performed on handball players, and the relationships and effects of parameters capable of affecting their performance were investigated. Despite an increase in professionalization in handball, research investigating the characteristic performances of elite plays is insufficient, and the number of studies evaluating handball players' performances over the entire season is very low (8).

Due to the multi-directional movement involved in handball and the absence of sufficient studies in this area, the purpose of the present research was to examine the effects of leg strength and jumping performances of licensed handball players on their static and dynamic balance. Accordingly, we performed measurements of handball players and investigated the relationships and effects of parameters affecting their performances.

Methods

Research Group

Ethical committee approval was granted once the research had been designed. Informed consent and voluntary participation forms were obtained from athletes before the tests were performed. The study was then performed with 40 male licensed handball players ranging in age between 16 and 26. Inclusion criteria were being an active and licensed player, with no disability, and no long-term ban on sporting activity.

Bulgay's (2017) study titled 'An examination of the relationship between top-rank wrestlers' leg strength and balance performance' was adopted to determine the sample size; power and sample size analysis at α (alpha) =0.05 and a test power of 95% determined a total sample size of 20 individuals five for each group. A sample size of 40 individuals was determined in the present study.

The simple random sampling method was employed to select from among athletes meeting the determined criteria and playing handball in the province of Ordu.

Data Collection

Athletes' height, weight, and birth dates were recorded before the tests commenced.

During height measurements, athletes were asked to remove their shoes and to stand in the anatomical position. The distance between a line parallel to the floor and touching the head was measured to a sensitivity of 0.1 cm.

Weight was measured before training, with the athletes wearing standard shorts and t-shirts, and without having eaten, to a sensitivity of 0.1 kg.

The information on athletes' identity documents was used to determine their ages.

The devices used in the study were a Jawon Body Composition Analyzer Model X-Scanplus II, a Holtain stadiometer, a tape measure, a digital back-leg dynamometer, a CSMI-TecnoBody PK-252

isokinetic balance system measuring device, and a Microgate jumping system-compatible jump mat

Balance Test

Balance test measurements were performed after the participants' age, surname, height, and weight values and date of birth information had been recorded onto a CSMI-TecnoBody PK-252 isokinetic balance system measuring device.

1. Static balance test: Before the measurements took place, the participants completed a 10-min warm-up consisting of a 5-min low tempo run, warm-up movements, and expansion-contraction movements. All participants were allowed to perform a trial before the test began. The athletes were placed on a platform and subjected to open-eye and closed-eye static balance measurement tests. The measurements were taken with the patient's feet at shoulder width on the CSMI-TecnoBody PK-252 balance device platform, and with the feet on lines representing the x and y axes of the platform and equidistant from the point of origin. Tests lasted 30 sec, and maintenance of body position and the participant's position were monitored from the screen. The test was recorded automatically at the end of 30 sec. The closed-eye test was then applied, with participants undergoing the same test with their eyes shut. A 1-min rest period was allowed between the tests (10).

2. Dynamic balance test: The importance of not using the support rail was emphasized during this test, which was performed with the patient in the double foot stance. Participants were instructed that the test should be completed using only the feet, in order to reduce upper body movements to a minimum. Bipedal mode was selected on the CSMI-TecnoBody PK-252 balance device, and key sensors were immobilized to allow the platform to move. Stabilometer pressure was set to a difficulty level of 5 in this test. The test was completed by following the circular route on the screen within 60 seconds and rotating the platform by five turns clockwise. The test was stopped and restarted in the event of inability to maintain balance during measurement, measurement being affected by environmental factors, or the hands making contact with the device. In the event of a participant being unable to complete the test within the specified time, the best performance up to that time was recorded as the test result (10).

The distribution of errors made during the track according to the regions on the platform are shown in the Track Errors chart, and the distribution of the participant's center of gravity by sectors is shown on the Force Variance chart. The isokinetic balance device platform was divided into eight sectors, a margin of error being calculated for each. Figure 1 shows that the highest margin of error is in the S3 sector. All sectors can be separately examined in this way. If the sector proportion exceeds 20% the device offers protocol options ranging between 2 and 88 degrees of difficulty in order to overcome the problem there or to improve balance, and participants are enabled to perform applications improving their balance skills (10).

Jump Test

Jump force can be defined can be defined as the individual jumping as far as possible in the horizontal plane or as high as possible in the vertical plane (11). Vertical jumping is particularly important in handball for blocks or for shooting toward the goal over blocks.

1***. Horizontal jump test:*** The standing long jump technique was employed to measure participants' horizontal jump performances, using a measuring tape. Participants were asked to jump forward from the start line using both legs, and the distance was measured between the start line and the closest point of contact on landing. The test was repeated twice for each individual, and the best value was recorded.

2. Vertical jump test: The vertical jump test protocol described in previous studies was applied (12). Vertical jump measurements were performed on a mat compatible with the Microgate system. Participants were asked to jump at full power, also swinging their arms, on a plastic mat, the procedure being repeated twice. The highest vertical jump distance was recorded in cm.

Leg strength test

The participant arranged his feet with the knees bent on the dynamometer bench, with the arms tensed, the back straight, and the trunk slightly inclined forward. Leg strength measurements were then performed with the participant holding the dynamometer bar and using his legs to raise it to the highest possible vertical position. The test was repeated twice, and the measurement was completed with the best data being elicited for each participant (13).

Anaerobic strength calculation: Anaerobic strength was calculated in the form of kg-m/s using the Lewis formula based on vertical jump and body weight values.

$P = (\sqrt{4,9} \times (BW) \times \sqrt{V}$

Where P = strength (kg-m/s)
V = Vertical Jump Distance (m) and
BW = Body Weight (kg)

Statistical analysis

Statistical analyses were performed on SPSS version 22.0 software (demo version). Pearson's correlation test was applied for normally distributed descriptive statistic data, and Spearman's correlation test for non-normally distributed data. Data analysis was performed at a 95% confidence interval and at a significance level of $p < 0.05$.

Correlation coefficients were calculated between -1 and +1. Positive correlation (+) indicates that variables move in the same direction, while negative correlation (-) indicates that they move in opposite directions.

Zero correlation indicates no relationship between increases and decreases in variables. r<0.2-0.4 is interpreted as weak correlation, r=0.4-06 as moderate correlation, r=0.6-08 as high correlation, and r=>0.8 as very high correlation (14).

Results

The mean age of the athletes in the study was 18.83±2.59 years, mean body weight was 70.78±10.30 kg, and mean height was 176.48±7.26 cm. Quantitative data were expressed in tables as mean, standard deviation, minimum, and maximum values.

Examination of the descriptive statistic values in Table 1 shows a mean research group vertical jump value of 38.16±7.11, a mean horizontal jump value of 208.19±22.75, a mean leg strength value of 140.87±29.60, and a mean aerobic leg strength value of 96.06±14.81.

In table 2 analysis of static balance values for the Examination of the descriptive statistic values shown in Table 3 revealed a mean dynamic balance bipedal balance error of 53.03±16.73 in the research group, mean bipedal strength variance of 2.07±1.17, and a mean stability indicator of 1.70±0.58. research group revealed a mean open-eye center of pressure X value of -2.15±4.47, a mean open-eye center of pressure Y value of -3.70±12.01, mean open-eye anterior-posterior deviation of 5.95±3.52, mean closed-eye standard right-left deviation of 3.73±1.52, mean open-eye forward-backward velocity of 10.20±3.30, an open-eye mean right-left velocity of 9.48±3.76, a mean open-eye area used of 377.85±262.02, a mean closed-eye circumference of 477.40±150.11, a mean closed-eye center of pressure X value of -415±8.30, a mean closed-eye center of pressure Y value of -3.53±14.73, mean closed-eye standard anterior-posterior deviation of 6.80±3.06, mean closed-eye right-left deviation of 5.23±1.62, mean closed-eye forward-backward velocity of 13.68±4.20, mean closed-eye right-left velocity of 12.00±3.94, mean closed-eye area used of 642.90±382.55, and mean closed-eye circumference of 605.18±169.28.

Analysis of the results in Table 4 revealed significant negative (-) correlation between the research group vertical jump values and bipedal mean balance error and stability indicator values, significant negative (-) correlation between horizontal jump values and bipedal mean balance error values, significant negative correlation (-) between leg strength values and closed-eye mean right-left velocity values, and significant negative (-) correlation between anaerobic strength values and closed-eye mean forward-backward velocity, closed-eye circumference used, and bipedal mean balance error values ($p<0.05$).

Open- and closed-eye values for static balance were determined separately. Standard anterior-posterior deviation and standard right-left deviation values were expressed as arithmetical mean plus standard deviation. The groups' mean balance was interpreted as poor as arithmetical mean plus standard deviation increased, and as good as arithmetical mean plus standard deviation decreased. The value obtained from the mean balance error in athletes' dynamic balance measurements shows the distance that the participant needs to traverse. Athletes' total dynamic balance mean balance error was expressed as a percentage (%) value. A low mean balance error percentage was interpreted as indicating good dynamic balance, and a high value as indicating poor dynamic balance (10).

Table 1. Correlation analysis results between statistic and dynamic balance measurements and vertical jump, horizontal jump, leg strength, and anaerobic strength values

	DB		HJ		LS		AS	
Measurements	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Open-eye- Mean center of pressure X *	0.211	0.191	0.122	0.453	-0.042	0.797	0.127	0.433
Open-eye - Mean center of pressure Y *	-0.013	0.936	-0.027	0.866	-0.007	0.966	0.100	0.538
Open-eye -Standard anterior-posterior deviation	0.031	0.851	0.130	0.425	0.256	0.111	-0.267	0.096
Open-eye -Standard right-left deviation	0.240	0.135	-0.022	0.892	-0.147	0.367	-0.046	0.779
Open-eye –Mean forward-backward velocity (mm/sec)	0.118	0.469	-0.067	0.683	0.030	0.856	-0.188	0.246
Open-eye – Mean right-left velocity (mm/sec)	0.249	0.121	0.116	0.478	-0.302	0.058	-0.052	0.748
Open-eye – Area used (mm²)	0.152	0.349	0.000	0.998	0.038	0.818	-0.211	0.191
Open-eye – Circumference used (mm)	0.232	0.149	0.012	0.943	-0.227	0.159	-0.131	0.422
Closed-eye – Mean center of pressure X *	0.168	0.299	0.302	0.058	0.012	0.944	0.043	0.792
Closed-eye – Mean center of pressure Y *	-0.045	0.783	0.030	0.856	-0.124	0.447	-0.048	0.768
Closed eye –Standard anterior-posterior deviation *	-0.262	0.102	-0.152	0.348	-0.267	0.096	-0.283	0.076
Closed-eye –Standard right-left deviation	-0.209	0.196	-0.157	0.333	-0.270	0.092	-0.218	0.177
Closed-eye – Mean forward-backward velocity (mm/sec)	-0.195	0.229	-0.173	0.286	-0.197	0.222	-0.375	**0.017***
Closed-eye – Mean right-left velocity (mm/sec)	-0.071	0.662	0.023	0.889	-0.357	**0.024***	-0.294	0.066
Closed-eye – Area used (mm²)	-0.143	0.379	0.000	0.998	-0.267	0.096	-0.309	0.053
Closed-eye – Circumference used (mm)	-0.132	0.418	-0.088	0.589	-0.292	0.067	-0.390	**0.013***
Bipedal – Mean balance error (%)	-0.495	**0.001***	-0.315	**0.047***	-0.260	0.105	-0.313	**0.049***
Bipedal – Mean strength variance (kg)	0.182	0.261	0.045	0.783	0.100	0.541	0.270	0.092
Stability indicator (°)	-0.444	**0.004***	-0.141	0.387	-0.073	0.652	-0.015	0.927

* Since open-eye mean center of pressure X, open-eye mean center of pressure Y, and closed-eye standard anterior-posterior deviation measurements were not normally distributed, Spearman rank correlation coefficients were used to analyze levels of correlation for these.
*p<0.05.

Table 2. Group static and dynamic balance data analysis

		N	Mean	SD
Static Balance (SB) (FBSD+MLSD)	Open eye (OE)	40	4.84	2.92
	Closed eye (CE)	40	6.01	2.56
Dynamic Balance (DB)	Average track error %	40	53.03	16.73

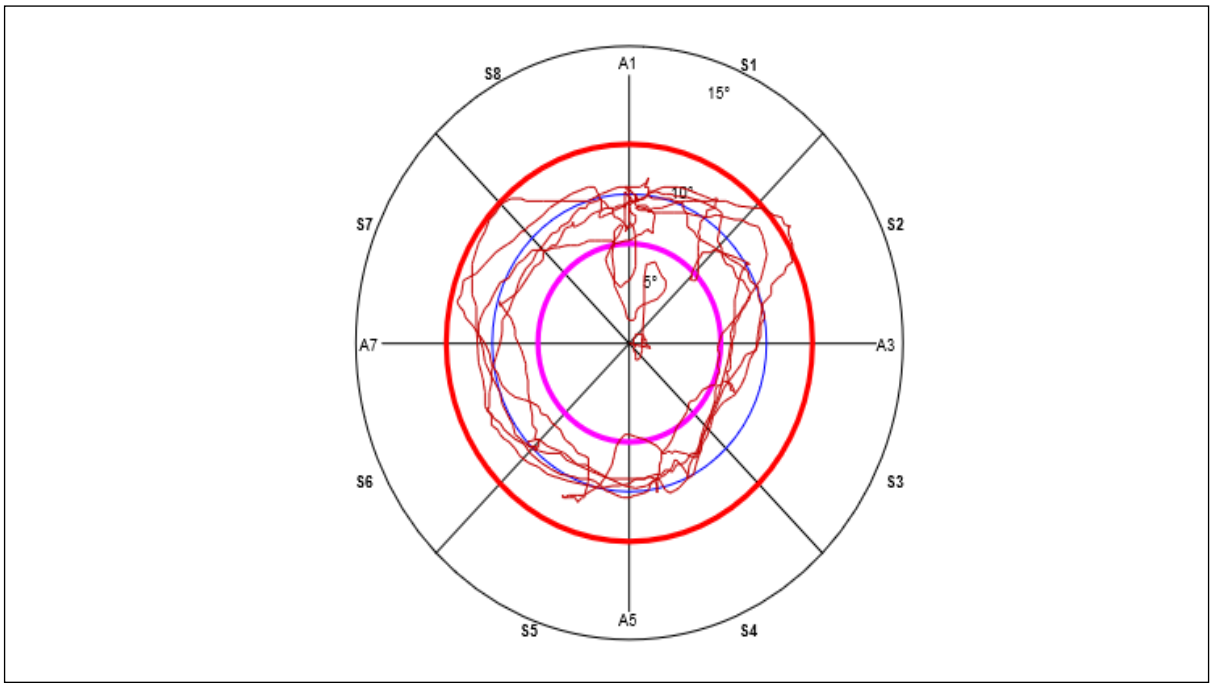

Figure 1. The track followed by the athlete inside the circle

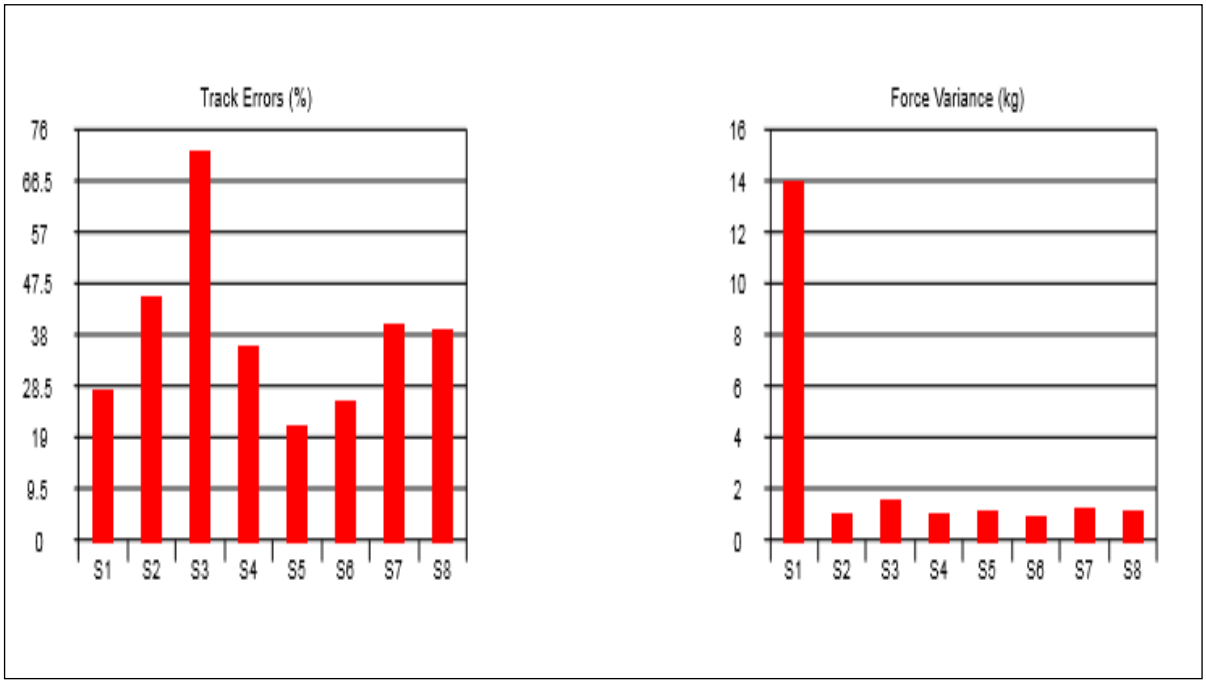

Figure 2. Measurement result charts

Discussion

This study examined the effect of handball players' leg strength and jump performance on balance. Balance is thought to impact positively on physical development involving motor skills and is a significant factor in differentiating individuals with successful sporting skills from those without (15).

In addition to technical skills and tactics, physical characteristics and powerful throwing abilities are very important in falling, jumping, twisting shots, and deceptions, all of which are frequently employed in handball. Shots involving vertical and horizontal jumping play an important role in both team victories and individual performance (16).

Yildirim (1997) reported a mean vertical jump height among elite handball players of 41.583±5.38

cm, and Gökdemir (1997) a height of 59.20±5.20 cm. Oxyzoglou et al. (2008) reported a mean vertical jump height among top-rank handball goalkeepers of 57.7±6.09 cm, compared to 56.44±5.5 cm among midfielders, and 55.71±4.48 cm among pivotal players. In their study of top-rank handball players, Yildirim and Ozdemir (2010) reported vertical jump values of 48.86±2.12 cm among players aged 17-21, and 53.07±2.27 cm among players aged 22-27. Eler (1996) reported and handball player vertical jump value of 50.66 cm, while Albay et al. (2008) measured a mean vertical jump value among university handball players of 53.80±9.07 cm. Tutkun (1995) reported a mean vertical jump height of 58.75±6.43 cm in university handball players and of 56.38±8.01 cm in top-rank national-level players. Cherif et al. (2012) reported a mean vertical jump height of 38.05±4.69 cm among elite Tunisian handball players. The mean vertical jump height among handball players in the present study was 38.16±7.11 cm (Table 1).

The vertical jump values were lower than the results generally reported in the previous literature. These differences may possibly be attributable to variations in explosive strength in the leg muscles, jumping technique, the elasticity of the muscles employed in jumping, training differences, and length of time as athletes.

One previous study investigated the relationship between balance and triple jump, vertical jump, and balance performance among footballers. The authors found no correlation between footballers' balance performances and triple jump or vertical jump distances (24).

Analysis of relationships between vertical jump data and open- and closed-eye static balance and bipedal dynamic balance values in the present research revealed negative (-) correlation between vertical jump and dynamic balance mean balance error and stability indicator values ($p<0.01$). It may therefore be concluded that dynamic balance values will decrease as vertical jump performance increases, and that dynamic balance will be positively affected (Table 1).

Oxyzoglou et al. (2008) reported a mean horizontal jump distance of 206.62±16.23 cm among top-rank foreign handball goalkeepers, 208±22 cm among wingers, 201.21±11.79 cm among midfielders, and 202.21±11.79 cm among pivotal players.

The mean horizontal jump distance among the handball player group in the present research was 208.19±22.75 cm. This was compatible with previously reported horizontal jump distances in the literature.

Significant negative (-) correlation was observed between horizontal jump data and dynamic balance mean balance error ($p=0.047$). A decrease in dynamic balance mean balance error may therefore be expected as horizontal jump performance increases. It may therefore be concluded that dynamic balance is positively affected with increased horizontal jump performance (Table 1).

Zorba et al. (2014), reported leg strength of 127.65±4.51 kg in 2nd league handball players, The mean leg strength of the handball players in the present study was 140.87±29.60 kg (Table 1).

One previous study examined the relationship between leg strength and balance performance among top-rank wrestlers. The authors reported significant correlation between left leg hamstring and quadriceps strength and left leg posterolateral and posteromedial balance performances (9). Tekin (2016) investigated the relationship between balance and strength and reported that both parameters can support one another and that this can be effective in training models. One study investigated increases in muscle and strength balance following balance training concluded that balance training contributed to the acquisition of muscle strength, and that muscular inequalities could be eliminated following balance training (27). Akcesme and Aktug (2018) reported positive correlation between isokinetic leg strength and balance performance, leg volume, and leg mass in football players.

Soyuer et al. (2006) reported a correlation between lower extremity muscle strength and balance. In a study of young male athletes, Mohammadi et al. (2012) also reported improvement in static and dynamic balance together with an increase in leg strength following six-week strength training involving the leg muscles. Siriphorn and Chamonchant (2015) reported improvement of balance skills following Wii board balance exercises among weightlifters and an increase in lower extremity muscle strength. In a study of healthy individuals from different age groups, Muehlbauer et al. (2005) reported significant correlation between lower extremity muscle strength and balance. A study investigating the effect on dynamic balance of quadriceps and hamstring muscle strength in children aged 12-14 reported significantly greater right-left extension peak strength in boys than in girls. However, no correlation was observed between quadriceps and hamstring strength and dynamic balance for male and female participants either

independently of gender or when gender was considered (34).

Consistent with the previous literature, negative (-) correlation was determined in the present research between leg strength data and static balance closed-eye right-left velocity (p=0.024). Better static balance may therefore be expected with an increase in leg strength (Table 1).

Albay et al. (2008) reported mean aerobic strength values of 119.06±13.26 kg-m/sn in footballers, 133.39±15.41 kg-m/sn among handball players, and 146.05±16.67 kg-m/sn in volleyball players, and concluded that handball players possessed, and also volleyball players, possessed significantly greater aerobic strength than footballers (p<0.01). The mean aerobic strength value in the present study was 96.06±14.81 kg-m/sn. The anaerobic strength values in the present study being lower than the results from the previous literature may be attributed to differences in training, the lack of activity aimed at improving aerobic strength, and the age of the athletes.

Erkmen et al. (2009) measured balance performance before and after resistance training and observed a significant decrease in balance performance in line with fatigue. Bove et al. (2005) also reported a decrease in balance performance and an increase in body oscillation following induction of fatigue. Wilkins et al. (2004) induced fatigue using a seven-station circular jogging route and observed a subsequent decrease in balance performance. Waterman et al. (2004) also detected negative changes in balance test results following fatigue caused by sporting matches.

Significant negative (-) balance was observed in the present study between anaerobic strength values and static balance closed-eye forward-backward velocity, static balance closed-eye area used, and dynamic balance mean balance error (Table 2). In the light of these findings, it may be concluded that fatigue will develop later as anaerobic strength increases, and that static and dynamic balance scores will decrease with movement, and that balance will therefore be positively affected.

Aslanoğlu et al. (2018) determined no relationship between leg strength-aerobic capacity and leg strength-anaerobic capacity in footballers. No relationship was determined between aerobic and anaerobic capacity and leg strength measured using an isometric leg dynamometer in football players.

Open- and closed-eye static balance values were determined separately in the present. Arithmetical mean and standard deviation values were calculated for standard anterior-posterior deviation and standard right-left deviation. We assumed that athletes' mean balance would be poorer as standard deviation and arithmetical means increased, and better as standard deviation and arithmetical means decreased. The value obtained from the mean balance error in athletes' dynamic balance measurements shows the distance that the participant needs to traverse. Athletes' dynamic balance was expressed as the percentage (%) of the arithmetical means of total mean balance error (Table 2). A low research group mean balance error percentage was interpreted as good dynamic balance, and a high percentage as poor dynamic balance (6). Accordingly, the data in the present study suggest that the dynamic balance of the research group was poor in the light of the high balance error percentage.

Conclusion

Examination of the relationships between vertical jump data and open- and closed-eye static balance and bipedal dynamic balance values revealed significant negative correlation between vertical jump performance and dynamic balance and stability. It may therefore be concluded that dynamic balance values will decrease as vertical jump performance increases, and that dynamic balance will be positively affected.

Significant negative correlation was also determined in this study between horizontal jump data and dynamic balance values. Accordingly, a decrease in dynamic balance values may be expected as horizontal jump performance increases. It may therefore be concluded that dynamic balance will be positively affected by an improvement in horizontal jump performance.

In agreement with the previous literature, leg strength data in this study were significantly negatively correlated with closed-eye static balance values. Accordingly, it may be concluded that static balance values will be better with an increase in leg strength.

Significant negative correlation was also determined between research group anaerobic strength values and closed-eye static and dynamic balance values. In the light of these findings, it may be concluded that static and dynamic balance scores will decrease with an increase in aerobic strength, and that balance will be positively affected. On the basis of these findings, it may be concluded that a high mean balance error percentage (ATE) indicates poor research group dynamic balance.

The findings and data from the present research show that leg strength and jump training have a positive impact on balance. We think that training

aimed at increasing anaerobic strength will be useful in the improvement of balance. We therefore think that the positive contributions to balance of the methods aimed at improving strength, jump performance and balance in handball, in which these factors are exceedingly important, will result in improved success as a result of improved performance. Our study can also be applied to other areas in which these parameters are significant, to other performance criteria, and to other athlete characteristics.

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In Vitro Interactions of Antibiotics with Drugs Used in Chronic Diseases

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Abstract

Objective: In this century, with the prolonged life expectancy, chronic diseases have become the most important cause of mortality and morbidity in the world and in our country. Frequent drug-drug interactions have made it necessary to update the doses of drugs in multiple drug use. In our study, we aimed to observe how the drugs that are frequently prescribed by physicians in the treatment of chronic and infectious diseases, together with standard bacteria and fungi strains in *in vitro* environment, change the effects of each other.

Methods: By combining antibiotic discs and drugs that are commonly used in chronic diseases (acetylsalicylic acid, amlodipine, atorvastatin, warfarin, metoprolol and clopidogrel) in *in vitro* environment, we determined the drug interactions (synergy/antagonism) by Kirby Bauer disk diffusion method.

Results: While most of the discs placed on the culture of *Candida albicans* through impregnation of drugs showed potentiation synergism with itraconazole and fluconazole, other microorganisms showed synergistic and sometimes antagonistic interactions with different drugs and antibiotics, whereas some of the drugs did not show any interaction with antibiotic discs.

Conclusion: Due to the strong relationship between advanced age and the number of prescribed drugs and the frequency of possible drug-drug interactions, the elderly people especially are susceptible to this situation. Infections caused by resistant bacteria cause an increase in disease/death rates and treatment costs. With the awareness that the only difference between drug and poison is the dose, all health professionals especially doctors and pharmacists and patients have a responsibility towards the rational use of drugs.

Key words: Antibiotics, chronic diseases, disk diffusion method, drug interactions

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Introduction

The World Health Organization (WHO) estimates the non-contagious diseases (NCDs), including cancer, cardiovascular diseases, stroke, chronic lung diseases and diabetes to be responsible for approximately 70% of deaths worldwide (1). With the increase in life expectancy and the changing burden of diseases, the NCD prevalence and its share in the causes of death are increasing day by day in our country, as in the whole world (2).

The frequency and incidence of chronic diseases increase with old age, and this process requires the use of multiple drugs. Since geriatric patients are particularly sensitive to interactions, possible drug-drug interactions can be seen frequently in those patients. Drug-drug interactions can lead to positive or negative consequences. Unwanted drug-drug interactions ought to be considered as they cause 10-20% of drug reactions that require hospitalization, and this process can be prevented (3).

Elderly patients are at higher risk of infection compared to adults, and the rational use of antibiotics can be lifesaving for them. For proper antibiotic use, correct antibiotic should be administered after correct diagnosis in the most appropriate way, at effective dose, at optimal intervals, and for the appropriate duration. The most common bacterial infections in the elderly are urinary tract infections, pneumonia, skin, and soft tissue infections. Unnecessary antibiotic use may cause drug toxicity, allergic reactions, secondary infections, and antibiotic resistance. Antibiotics, in terms of problems caused by irrational drug use, not only affect the person, but they differ from other drugs by affecting the society, environment, and new generations as well (4).

Considering the fact that our country ranks first among 46 countries in the WHO European Region in terms of antibiotic consumption) and one third of the society is exposed to chronic diseases, it is inevitable that drug-drug interactions will occur as a result of the combined use of antibiotics and drugs that are used for chronic diseases. Drug interaction can be seen as an antagonistic as well as a synergistic interaction (5).

In this study, we aimed to examine the drug interactions in detail using the disk diffusion method by combining microorganisms that frequently cause infectious diseases, the antibiotics kept in *in vitro* environment and drugs used extensively in chronic diseases. By this way, we aimed to reduce the duration and costs of treatment and contribute to the rational drug use by trying to enlighten the drug-drug interactions, which are among the factors determining the effectiveness of the treatment.

Methods

S. aureus ATCC 29213, Methicillin-resistant *S. aureus* (MRSA) ATCC 43300, *E. faecalis* ATCC 29212, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *A. baumannii* ATCC 19606, *K. pneumoniae* ATCC 700603 and *C. albicans* ATCC 10231 strains were provided by Malatya Inonu University Faculty of Pharmaceutical Microbiology laboratory. Amoxicillin-clavulanic acid (AMC 30), Sulbactam-ampicillin (SAM 20), Ciprofloxacin (CIP 5), Penicillin (P 10), Clarithromycin (CLR 15), Trimethoprim-sulfamethoxazole (SXT 25), Meropenem (MEM 10), Colistin (CT 10), Tigecycline (TGC 15), Vancomycin (VA 30), Levofloxacin (LEV 5), Tetracycline (TE 30), Ceftriaxone (CRO 30), Cefazolin (CZ 30), Cefuroxime (CXM 30), Teicoplanin (TEC 30), Linezolid (LNZ 30), Gentamicin (CN 10), Amikacin (AK 30), Amphotericin B (AMB 100), Fluconazole (FLU 25) and Itraconazole (ITR 10) discs were used in this study.

Mueller Hinton Agar (MHA) medium (Merck, Germany), Mueller Hinton Broth (MHB) medium (Merck, Almanya), Sabouraud Dextrose Agar medium (Merck, Germany) and Tryptic Soy Agar medium (Merck, Germany) were prepared as described and were sterilized at 121°C for 15 minutes in an autoclave and, thus, the petri dishes to be used in our study were prepared for the cultivation purposes.

In this study, acetylsalicylic acid (aspirin 100mg tablet/bayer), warfarin (coumadin 5mg tablet/zentiva), amlodipine (vazkor 5mg tablet/deva), atorvastatin (ator 10mg tablet/sanovel), metoprolol (beloc zok 25mg tablet/astrazeneca), clopidogrel (plavix 75mg tablet/sanofi), as well as the dual combinations of all above-mentioned drugs, were powdered using porcelain mortar, dissolved in distilled water and were made to be absorbed into sterile blank paper discs. We dissolved each tablet in distilled water and absorbed the mixture on blank discs. Each of the discs, which we prepared by absorbing the drug or dual combinations of drugs, contained different concentrations of the drugs (Acetylsalicylic acid 1000µg, warfarin 50µg, amlodipine 50µg, atorvastatin 100µg, metoprolol

250µg and clopidogrel 750µg were absorbed on paper discs).

The standard microorganisms were incubated in liquid medium (Mueller Hinton Broth) for 2 hours at 37°C. A standard turbidity was prepared by adjusting the medium according to 0.5 McFarland standard (1.5×10^8 microorganisms/ml). This suspension was cultivated using a sterile swab with the spreading technique in petri dishes containing MHA prepared beforehand.

Each of the bacteria was placed on the agar surface with the help of sterile forceps, using all the standard antibiotic discs, in such a way that the disc which impregnated the relevant drug was in the middle of the petri dish. We placed ready-made antibiotic discs around the discs that were prepared by absorbing drugs into sterile blank paper discs.

Then, the media were incubated for 18-24 hours at 35°C in the incubator and the resulting inhibition zones were evaluated (6-8)

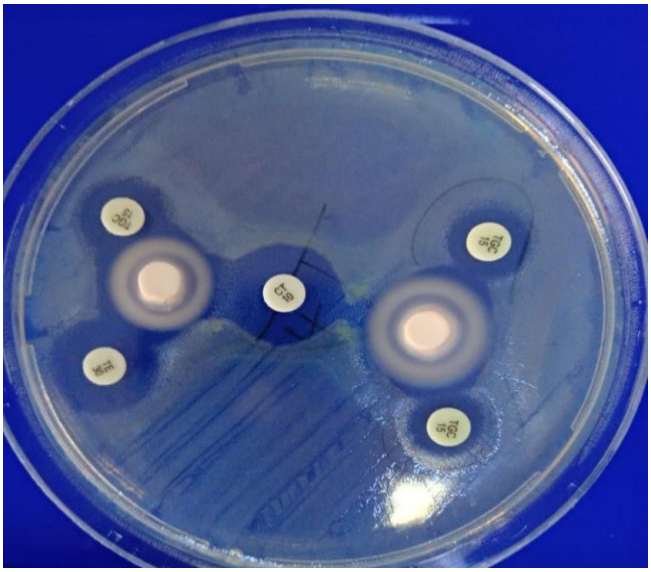

Figure 1. Synergism between TGC and Plavix in *P. aeruginosa* cultivated plate

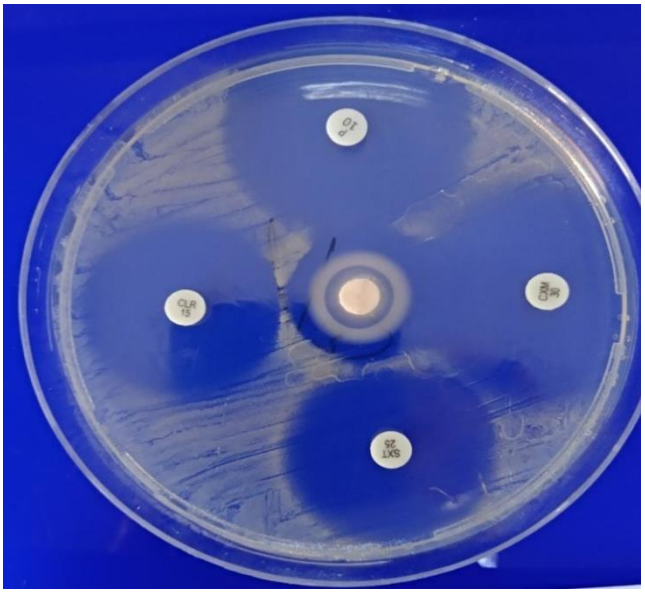

Figure 2. Antagonism between CLR and Plavix in *S. aureus* cultivated plate

Results

In our study, we used acetylsalicylic acid, warfarin, amlodipine, atorvastatin, metoprolol and clopidogrel, which are drugs commonly used in chronic diseases. We impregnated these drugs one by one and in combinations of two on our empty discs. We placed the discs on the plates we prepared and recorded the interactions seen as antagonism and synergism. In Figure 1 there is synergism between TGC antibiotic disc and Plavix disk (which prepared by us) in P. aeruginosa cultivated plate. In Figure 2 there is antagonism between CLR antibiotic disk and Plavix disk in S. aureus cultivated plate.

The highest interaction was observed with Plavix. All the interactions that took place were gathered in Table 1. The photos of some interactions are as follows;

Table 1. All interactions that took place as antagonism and synergism.

	S. aureus	*E. faecalis*	*E. coli*	*P. eruginosa*	*C. albicans*	*A. baumannii*	*K. pneumoniae*	MRSA
aspirin	TEC, TGC				FLU, ITR			
vazkor			CXM, TGC, CLR		FLU, ITR		LEV	
ator					FLU, ITR			
beloc			CT			CLR		
coumadin		CLR			FLU, ITR			
plavix	TEC, TGC, CIP, CLR	MEM, VA, TGC,P, CLR	CXM, TGC	TGC, AK	FLU, ITR	AMC, TGC, CLR	TE, CT, LEV	TEC, CXM
vazkor+aspirin				TGC	FLU, ITR	TE, CT, CLR	TE, CZ	
ator+aspirin				LEV	FLU, ITR			SXT
beloc+aspirin			CZ		FLU, ITR	TGC		
coumadin+aspirin				CT	FLU, ITR		CT	CIP
plavix+aspirin	CXM	TGC, P, SXT		CT	FLU, ITR	CT, AK, TGC, CLR		
ator+vazkor	AMC		CRO, LEV, AMC		FLU, ITR			LNZ, SXT, MEM
beloc+vazkor				CZ	FLU, ITR	TGC, LEV, TE	TE, CRO	
coumadin+vazkor		CN			FLU, ITR			
plavix+vazkor	MEM, AMC	LNZ, AMC		CZ	FLU, ITR		CT	CIP, MEM
beloc+ator	AMC			LEV	FLU, ITR			
coumadin+ator	AMC	AMC			FLU, ITR			
plavix+ator	AMC	AMC, LNZ			FLU, ITR			
coumadin+beloc	CIP, CN	LNZ, SAM			FLU, ITR			LNZ
plavix+beloc			CXM, TGC	CZ	FLU, ITR, AMB			CXM
plavix+coumadin	AMC, LNZ	AMC, SXT			FLU, ITR			

Note: Among the antibiotic symbols used in the table, black symbols show synergistic and red symbols show antagonistic interactions.

Discussion

Irrational drug use is a common public health problem. According to WHO data, it is known that more than 50% of all drugs are improperly prescribed, supplied or sold worldwide. Furthermore, 50% of the patients do not use their medication correctly. Also, unfortunately, one third of the world population is unable to have access to essential drugs. Due to the increase in the elderly population worldwide, the use of multiple drugs in the treatment of chronic diseases has become an important economic problem both in terms of public health and an increase in health costs (9).

As people get older, the reactions and transmissions occurring in the brain and the body suffer from malfunctions due to the loss of function of the related tissues. As a result of human aging, the function of homeostasis mechanism, which is one of the most important factors affecting the pharmacokinetics of drugs and the progression of diseases, decreases and the sensitivity of the receptors towards related chemicals changes. It is the duty of clinicians to know how drug-drug interactions occur and how to manage these interactions (10).

The search for combinations of non-antibiotic drugs with antimicrobial agents currently in clinical use has recently regained interest and is a promising approach with many advantages. Information regarding the pharmacological properties (both safety and pharmacokinetics) of non-antibiotic drugs that

are approved by the Food and Drug Administration (FDA) is widely available in pre-clinical and clinical studies. Therefore, the time loss and economic costs associated with repositioning these drugs for other therapeutic applications such as the treatment of bacterial and fungal infections are expected to be minimized (11,12).

In such a time when new antimicrobial drugs are becoming increasingly difficult to be found, it is critical to understand the antimicrobial effects of non-antibiotic drugs and their potential clinical consequences. Antipyretic drugs in particular have been known to have direct and indirect antimicrobial effects for more than 30 years. Among these drugs, studies on the most commonly used acetylsalicylic acid (ASA) are quite abundant (13).

In our study, while Aspirin often showed antibacterial activity alone, it interacted synergistically with the antibiotic discs containing teicoplanin and tigecycline in the plates where we cultivated *S. aureus*, whereas it did not show any antifungal effect alone in the plate where we cultivated *C. albicans*. It showed potentiation synergism on *C. albicans* which are resistant to fluconazole and itraconazole. In other words, while there were no effects of individual drugs alone, they started to show antifungal effect when they came together.

Again, in our study on amlodipine, a widely used Ca channel blocker, it was found that the drug alone did not show any antimicrobial activity. However, when we placed the discs that we impregnated with Vazkor on the plates where we had cultivated *E. coli*, a synergistic interaction occurred with CXM, TGC and CLR. Vazkor showed potentiation synergism with FLU and ITR in *C. albicans* cultivated plates. LEV and amlodipine interacted synergistically in *K. pneumoniae* cultivated plates.

In our study on atorvastatin, which is frequently used as an antihyperlipidemic, we observed that Ator did not have any antimicrobial activity alone, but it created a potentiation synergism with FLU and ITR on *C. albicans* cultivations.

Another drug that we used was Metoprolol, which is commonly used as a β1-adrenergic receptor blocker. It did not show antibacterial and antifungal activity alone in different samples where we applied disk diffusion method. The discs that we impregnated with Beloc created synergism with CT in the *E. coli* cultivated plates and with CLR in the *A. baumannii* cultivated plates.

Warfarin, an anticoagulant drug, stands out with its narrow therapeutic range. It is used with INR follow-up. In our study, coumadin impregnated discs showed synergism with CLR in *E. faecalis* cultivated plates and with FLU and ITR on *C. albicans* cultivated plates.

Among the 7 drugs we used, Plavix with clopidogrel active ingredient showed the most interaction. Plavix showed synergistic interaction with TEC and TGC in *S. aureus* cultivated media, with MEM, VA, TGC and P in *E. faecalis* cultivated plates, with CXM and TGC in *E. coli* cultivated media, with TGC in *P. aeruginosa* cultivated plates, with FLU and ITR in *C. albicans* cultivated plates, with AMC and TGC in *A. baumannii* cultivated media, with TE and CT in media cultivated with *K. pneumoniae* and with TEC and CXM in our *S. aureus* MRSA cultivated plates. And it showed antagonistic interaction with CIP and CLR in our *S. aureus* cultivated plates, with CLR in *E. faecalis* cultivated media, with AK in *P. aeruginosa* cultivated plates, with CLR in *A. baumannii* cultivated media, and with LEV in *K. pneumoniae* cultivated media.

Aspirin has been shown to induce efflux-mediated resistance against quinolones in some *E. coli* strains (14). High concentrations of salicylicacid have been shown to reduce the production of flagellin, a virulence factor in *E. coli* which is responsible for motility, and alter the expression of more than 144 genes (15).

Rosner showed that aspirin and salicylic acid reduce the susceptibility of *E. coli* to ampicillin, cephalosporin, chloramphenicol, fluoroquinolones, nalidixic acid and tetracycline antibiotics (16). Aumercier et al. showed that the sensitivity of *E. coli* to aminoglycosides increased with salicylate (17).

P. aeruginosa is an opportunistic and hospital-acquired cause of infection, especially in immuno-compromised patients. It is associated with a high rate of antibiotic resistance and biofilm formation. In studies on *P. aeruginosa*, it has been shown that the use of SAL and ASA alters the expression of more than 331 genes, reduces the production of hemolysin, elastase, protease and pyocyanin by approximately 55%, and effectively inhibits quorum sensing, which is an important virulence factor, motility, biofilm, and toxin formation (18,19).

Bazyleu and Kumar showed that salicylate regulates the expression of porins, and efflux pumps and increases the sensitivity of *A. baumannii* to ceftriaxone, ciprofloxacin, gentamicin and imipenem antibiotics by comparing MIC values (20).

In a study conducted by Domenico et al. on *K. pneumoniae*, it was found that salicylate decreased the sensitivity of *K. pneumoniae* to aztreonam, cefazolin, cefoperazone, ceftizoxime, clindamycin, doxycycline, norfloxacin, and trimethoprim-sulfamethoxazole antibiotics, whereas it increased the sensitivity of *K. pneumoniae* to amikacin, gentamicin, and tobramycin (21).

Chan et al. showed that aspirin alone is not as effective as commonly used antibiotics. However, when it is used along with cefuroxime and chloramphenicol, it can resist more effectively against MRSA by having a synergistic interaction (22). In their study on *S. aureus* in Australia, Gustafson et al. showed that salicylate and acetylsalicylate increased the resistance of ciprofloxacin, a fluoroquinolone used in the treatment of staphylococcal infections. According to a study, *E. coli, K. pneumoniae, P. aeruginosa* and *P. cepacia* are some of the bacteria that cause increased resistance to quinolones in the presence of disalicylate (23).

In different studies conducted on *Candida* species, the use of aspirin alone or combined with amphotericin B and azoles in treatment has been shown to increase the activity against biofilm-related infections by showing antibiofilm properties (4, 24, 25).

In a study conducted on calcium channel blockers called cinnarizine, verapamil, nifedipine, nimodipine against C. *albicans*, it was found that the use of drugs alone and combined with ketoconazole showed antifungal activity at high concentrations and the effect of verapamil alone was detected to be higher than the others (26).

In their study, Liu et al. investigated the combined use of calcium channel blockers and fluconazole on *Candida*. They also showed that the combined use of amlodipine with fluconazole caused a synergistic interaction against resistant *C. albicans* by causing downregulation in some genes (27).

In an *in vitro* study conducted by Hu et al. on *A. baumannii*, one of the common agents of nosocomial infections, it was reported that the combined treatment of amlodipine and imipenem showed synergistic antimicrobial activity against 64 strains of *Acinetobacter* by inhibiting some genes belonging to efflux pumps (28).

In another study conducted on *A. baumannii*, Li et al. showed that the combined use of imipenem and amlodipine, which is frequently preferred in treatment, increased the antibiotic activity of carbepem in 52 strains compared to the effectiveness of the drug alone (29).

Statins have been found to have bacteriostatic activity in *in vitro* studies at doses exceeding normal serum concentration levels during statin treatment against clinically important bacteria such as *S. aureus, E. coli* and *P. aeruginosa* (30).

In their studies on *S. aureus, E. coli, P. aeruginosa* and *C. albicans* in 2008, Kruszewska et al. reported that clopidogrel showed antibacterial activity against *S. aureus* (31).

In a study conducted by Chen et al. in 2020, it was shown that the INR of patient streated in combination with warfarin and azole derivative antifungal agents increased by more than 20% as compared to patients using warfarin alone. According to this study, as the inclusion of azole group drugs in the treatment of patients undergoing warfarin treatment increases the anticoagulant efficacy of warfarin, the INR values need to be closely monitored in these patients (32).

In their *in vitro* study using six statins, Lima et al. determined that statins show high selectivity for fungal cells as compared to bacteria, and also that some statins when combined with azoles show synergistic interactions. According to this study, statins show antifungal activity *in vitro*, whereas they show anti-inflammatory activity *in vivo* (33).

Conclusion

We may observe many interactions when we use drugs either alone or combined with other drugs. When all these interactions are evaluated, we understand that drug-drug interactions can never be ignored. Our study in particular shows that an important reason for the infection related high mortality and morbidity in more sensitive, comorbid patients who need to use more drugs, patients receiving immunosuppressive therapy etc, may be antagonisms or synergisms that may result from combined use of drugs. It is the duty of all healthcare professionals to prevent possible undesirable drug interactions from occurring. Healthcare professionals should train themselves well on this issue and they should constantly follow up-to-date information. It is desirable to prevent these interactions before they take place. The need for further studies on this issue continues to increase. This research was supported by Inonu University Scientific Research Projects Unit with the Project Number TDK-2018-1376.

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Recurrence of Hepatic Hydatidosis: How and Why?

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Abstract

Objective: For recurrence of hepatic hydatid, cysts overlooked during surgery, secondary cysts due to the spread of cystic fluid, late postoperative hydatid cyst formation and inadequate treatment are recommended. Factors affecting recurrence were investigated in cases with recurrence. In this retrospective study, data on 199 patients with hepatic hydatid disease treated by surgery in our hospital, between January 1993 and December 2018 were reviewed.

Methods: In this study, patients who were operated for hepatic hydatid disease; The relationship between cyst diameters, cyst stages, number of cysts and recurrence was investigated.

Results: 84 patients were male and 115 were female. Most of the cases (189 patients- 88.06 %) treated by conservative surgical methods. Remaining's (8 patients-4.3 %) had total cystectomy or segmental hepatectomy. Recurrence rate was found 5.47%. In that cases, primary operations were done by us, there was no significant differences between cysts' stages and recurrences. There was not significantly differences between cysts' number and recurrences, except the patients had 2 cysts ($z=2.17$, $p=0.03$).

Conclusion: The best way of prevention of the recurrence of hepatic hydatid cysts are complete diagnosis of cysts' classification, localization, and medico-surgical combination. Perioperative medical treatment must be start three days ago before the operation and should be continued for at least 6 months.

Key words: Hepatic Hydatidosis, Recurrence, Overlooked cysts

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Introduction

Hydatid cyst causes infection in the liver with the ingestion of parasite eggs, which are thrown into the external environment by the host, by human digestion (1,2). Hepatic hydatid, which is diagnosed serologically and radiologically, is usually treated with surgical methods (3). Recurrence may occur despite surgical treatment. Recurrence may have many reasons such as insufficient drainage, overlooked cysts, spread into the abdomen during surgery, and lack of medical treatment. Even postoperative cystic cavity collections may cause false recurrence diagnosis (4-7).

Recurrence of hepatic hydatid cysts is the most common and serious complication of hydatid surgery. Although perioperative or single albendazole treatment is effective as high as 77-97 % and better results with praziquantel combination, it still remains controversial (8-10).

On the other hand, enlargements of hepatic hydatid cysts are not clear. In most of reports that growth rate has recommended 1-2.5 mm per month (10-12). Also, some authors have reported enlargement 4-5 cm per year. Also, it has been reported that cystic growth one centimeter in diameter during the first six months and then it is strictly related to host immunity and the surrounding tissue resistance (13). Roaming has reported that about 30 %,45% and 11% of cyst grew about 1-5 mm, 6-15 mm and mean 31 mm per year respectively. The cysts and the sizes did not change or got lesser in 16% (14). Our aim in this report was to investigate the factors affecting recurrence in hepatic hydatidosis.

Methods

In this retrospective study, data on 199 patients with hepatic hydatid disease treated by surgery and dual benzoimidazole derivate treatment in Ondokuz Mayis University Medical Faculty Department of General Surgery, between January 1993 and December 2018 were reviewed.

Patients

All the records were evaluated retrospectively. The histories of the cases were investigated as preoperative hydatid procedures and recurrences.

Diagnoses were done by ultrasonography (US), computed tomography (CT) and/or magnetic resonance investigation (MRI). Also, serological analyses (including IHA and/or echinococcosis Ig G) were done. Since 1996, intraoperative ultrasonography (IOUS) was used routinely for the diagnosis of probably "overlooked cysts" (15).

Medical treatment protocol

Perioperative benzoimidazole therapy was started immediately and continued in postoperative period for 6-12 months as monthly cure application. Because of no albendazole drug for human was in sale in that time in Turkey, the former 11 cases (5.53 %) had mebendazole (50 mg/kg/d) therapy. By the time, albendazole (10-12 mg/kg/d) used in the laters (188 cases, 94.47 %).

In operation, benzoimidazole solutions in concentration of 2% mgr, were used for cystic cavity disinfection, have been reported previously (9,16-18).

Surgical procedure

All the cysts were treated by surgically. In 189 cases (94.97 %) conservative procedures such as drainage, evacuation, omentoplasty were the method of choice. The remaining's (10 cases-5.03%) were treated by total cystectomy with or without hepatectomy.

Postoperative follow-up

The patients were evaluated by serological tests and either US and/or CT-scan on the fifth to seventh day and at the first, sixth and twelfth months in the post-operative period. Patients were evaluated on an annual basis by US after the first year of follow-up.

If suspected lesions were found in US and/or radiological imaging, percutaneous transhepatic cystic liquid sampling was done. Then, protoscolices were examined by light microscopy. If protoscolices were seen, it was recommended recurrence. So, it was determined as golden rule: *"no protoscolices no recurrence"*

Evaluations of recurrences

The recurrences were evaluated as four forms as "overlooked cyst", "insufficient/incomplete drainage of cystic cavity", "secondary hydatidosis" and "re-infestation"; depending on diagnostic times, cysts' sizes and natural cyst growth in human livers (1-2.5 cm per year) (Table 1) (15,19,20).

Statistical analysis

Statistical analysis was done by using "Z Test for proportion" on pc.

Results

84 patients were male and 115 were female. Mean age was 47.74±16.463 years (range 18-84 years). Most of the patients (115 cases, 57.79 %) had one cyst. The others had two or more cysts. Most of the cases (189 patients - 88.06 %) treated by conservative surgical methods. (Either cystic evacuation with or

without omentoplasty or capittonage). Remaining's (8 patients - 4.3 %) had total cystectomy or segmental hepatectomy.

Nineteen recurrences (9.45%) were found in whole patients in 12th -360th postoperative months. But only eleven of these cases (5.47%) have been operated by our team. The mean recurrence time was 72.55±57.327 months (range 12-192 months). So, totally 20 recurrences (10.05%) were investigated. Diagnosis of recurrences established in 12th -360th postoperative months.

Only eleven cases of recurrences (5.47 %) had been operated by our team. All of them had been treated by conservative surgery. In those cases, the mean recurrence time was 72.55±57.327 months (range 12-192 months). The remaining's (9 cases – 4.52 %) have been treated at other hospitals. Eight of them had treated by surgical procedures and one had been percutaneously drainage. The mean recurrence time was 144.5±145.334 months (range 16-360 months).

So, recurrence rate of our study was found 5.47%. According to table 1, three of them were re-infestations. The intervals of recurrences were 154±36.166 months (range 120-192 months). Eight cases were probably overlooked cysts (mean time was 42±20.284 months, range 12-60 months). In that cases, primary operations were done by us, there was no significant differences between cysts' stages and recurrences (Table 2). On the other hand, there was not significantly differences between cysts' number and recurrences, except the patients had 2 cysts (z=2.17, p=0.03) (Table 3).

Table 2. Recurrence rates according to cysts' stages. (Z Test for proportion)

Stage	n			z- p	
	Whole cases	Recurrences	%	z	p
I	38	3	7.89	-0.64	0.520
II	71	3	4.23	0.17	0.869
III	76	2	2.63	0.89	0.372
IV	48	3	6.25	-0.42	0.676
V	-	-	-		

Table 3. Recurrence rates according to cysts' number (Z Test for proportion)

Number of Cysts	n			z- p	
	Whole cases	Recurrences	%	z	p
1	138	13	9.42	-0.08	0.933
2	43	1	2.33	2.17	0.030
3	7	1	14.29	-0.31	0.765
4	5	2	40	-1.41	0.158
≥5	6	1	16.67	-0.74	0.461

Table 1. Causes of hepatic hydatidosis recurrence.

	Cyst's diameter	Time of diagnosis after operation	Localisation
Overlooked cyst	> 1-2.5 cm p.y.	Close (Commonly in first postoperative year)	Liver
Insufficient drainage of cystic cavity	Similar with preoperative diameter	Commonly second postoperative years	Liver
Secondary hydatidosis	1-2.5 cm p.y.	Commonly in 3 years	Extrahepatic peritoneal cavity
Re-infestation	<1-2.5 cm p.y.	Commonly 5 years or more after surgical treatment	Anywhere in whole body (Also liver)

All of these patients were treated by conservative surgery and has got off follow-up and albendazole treatment started at least perioperative 4 days preoperatively and in second postoperative days for 6 months in cyclic form.

In early stages of this study, 2 cases (1.08 %) *"overlooked cysts"* were found at post-operative 3rd and 5th days and treated by PAIR. After those cases, IOUS was used. In those cases, four centrally localised hydatid cysts of high risk of vasculary and ductal injuries were determined. So, they were treated by puncture and injection of albendazole solution.

There were 2 deaths (0.99 %) due to hydatidosis. A 71-year-old female patient has died due to cardio-pulmonary insufficiency (died on 18th hours after hepatic hydatid surgery). Another male patient aged 74 years old has died on second month because of *"brain hydatid cyst*".

In late postoperative period, there were 22 (10.95%) deaths unrelated to hydatid diseases). One hundred seventy-seven patients were followed up for 24-297 months (164.62±79.108).

Discussion

As a term of "recurrence" means, "the return of a sign, symptom or disease after a remission. If a treated infectious/parasitic disease re-occurs after long time symptom-free interval, it may be result of reinfection or re-infestation. It is necessary that new terminology must explain whether infection due to relapse in deficiently treated/non symptomatic patients or just new one.

"Recurrence" of hydatid cysts of the liver is one of the most serious complications in surgery. This pathology which is generally investigated under the title of recurrence may be arranged in four different titles as true recurrence, secondary hydatidosis, insufficiency of drainage or evacuation and overlooked cysts. On the other hand, in post-operative period, cystic cavity collections commonly imitate recurrence, cause false diagnosis.

Recurrence rates in the literature vary with the time of the study and treatment methods. Eventually, the recurrence rates in the literature are between 1.1 and 24% (19-25). Some of the recurrence rates are unacceptably high. However, cases accepted as recurrence have different characteristics.

Reports on the development of hepatic hydatidosis makes the recurrence problem controversial. That is: the cyst diameter grows ≥1 mm monthly. Therefore, the growth of the cyst diameter in one year is about 1-2.5 cm. Is it true to refer one or more small cysts located centrally in the liver may be found in shorter postoperative period than expecting developing time? It is hard to talk "recurrence". It must be considered an "overlooked" or "missed" liver hydatid cyst (15,20).

Recurrence rates, change with the performance of medical treatment, the type of surgical treatment and the experience of the surgeon. It is not possible to say that complications of surgical treatment are completely prevented (25-27). Medical treatment applied by surgical methods to prevent or minimize dissemination, may be effective in preventing recurrence.

Of course, in the cases of multiple hydatid and/or satellite cysts risk of overlooked cyst arises. So, IOUS is very helpful (15). But the benefit of IOUS is not absolutely. The quality of ultrasonic equipment and experience of staff will affect the results. If a cyst is lesser then 1 cm diameter it may be undetected easily.

The main reasons for overlooked cases are the presence of multiple cysts, satellite cysts, centrally localized non-palpable, of lesser diameter cysts. In spite of preoperative assessment by US, CT, and MRI, overlooked cysts continue to be problems in surgery. So, IOUS must be used especially in the case of multiple cysts, routinely.

In literature, it is clearly shown that, radical surgical procedures are with lower recurrence rates than conservative surgery (27,28); but never explained "why". In conservative methods such as "evacuation with or without omentoplasty", "capittonage", "drainage", recurrences can be explained by "overlooking", "satellite cysts", "incompetent evacuation-sterilization of communicated cysts", "spreading" or "re-infestation". But these are not enough, in the cases of treated by radical surgery such as "totally cystectomy, "anatomical" or "non anatomical hepatectomy" with "no cystic perforation and/or spreading of cystic liquid". So, the causes of recurrences still remain controversial (24,26,27).

"On the other hand, comparing the treatment results (also morbidity-mortality and recurrence rates) of different patient groups from the same center leads to false results. Patients presenting to any center are grouped according to disease and personal characteristics and different treatment methods are applied. How realistic is it to compare the results of surgical methods? Can the results of percutaneous drainage be the same in early and late-stage cysts? Can the results of video laparoscopic treatment in posteriorly localized or multicystic lesions be as good as applicable cases? Is it correct to compare the results of cases performed by selecting convenient cases for radical interventions and inconvenient cases in which conservative treatment was applied?" (20).

It is necessary that:

a. All cysts found in the patients should be identified pre-and intraoperatively.

b. Being aware of, in 30% of liver hydatid cysts, there is more than one cyst. Satellite and multiple and closed location cysts.

c. In the early postoperative period, the operation site and the liver should be definitely investigated by CT or MRI for overlooked cysts and/or cystic cavity collections.

d. Prevention of cystic liquid or spreading vesicles into the peritoneal cavity. It is the cause of "s*econdary hydatidosis".*

About hepatic hydatid cyst recurrences, there are some questions need discussion:

1. How to establish diagnosis of recurrence?

Cystic cavity collections and/or infections are eliminated. So, if US, CT, MRI investigations suggest of doubt, percutaneous transhepatic sampling and investigation of protoscolices must be done.

2. Effectiveness of medical treatment:

The success rate of albendazole treatment alone is about 77-97%. Currently, peri-operative medical treatment decreases the recurrence rate. It is reported that, preoperative albendazole treatment for at least 3-4 days is sufficient for sterilization of the cyst content. Current reports are shown that albendazole-praziquantele combination is more effective than albendazole is alone. In this study, perioperative medical treatment was used when the diagnosis is done.

The cysts' stage and number are not clearly shown that effectiveness on recurrences. In this study, the cases had two cysts were found lesser recurrence rate than had one. It is thought that the cases of two or more cysts -especially lesser than 1 cm diameter- diagnosed had single cyst. So overlooked cysts, detected as of single cyst. Those cases had overlooked cysts and recommended as recurrence.

On the other hand, the cases of recurrences who had primary operations at other clinics are not included and evaluated in this study.

Conclusion

1. The best way of prevention of hepatic hydatid cysts recurrences are complete diagnosis of cysts' classification, localization, and medico-surgical combination.
2. Serological tests are valuable in diagnosis but because of false positivity, never in follow-up.
3. Perioperative medical treatment must be done and start 3 days ago before the operation at least.
4. Medical treatment must be continued 6 months, at least.
5. Cystic cavity collections are more common than reported. If seen, percutaneous aspiration and search of protoscolices must be done absolutely.

Ethics Committee Approval: This study was conducted with approval from our hospital's ethics committee (approval number: 2020/651; approval date: January 26.11.2021).
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Management of Stabil Vertebra Fractures in Patients Underwent Liver Transplantation

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Abstract

Objective: Bone mineral density decreases after liver transplantation, and the incidence of vertebral fracture concerning this increase. Vertebral fractures due to bone mineral density increase mortality due to pain, spinal deformity, neurological deficit, and immobility. This study discussed the patients with a vertebral fracture who underwent liver transplantation and received kyphoplasty and conservative treatments to reference clinical treatments.

Methods: Among the 2200 patients who underwent liver transplantation between 2002-2020, 65 of the 110 patients underwent spinal Magnetic Resonance Imaging (MRI), and computed tomography (CT) due to back and low back pain had vertebral fractures. Of these 65 patients, 48 were unstable, and 17 were stable vertebral fractures. Patients with stable vertebral fractures were grouped as conservative (n=9) and balloon kyphoplasty (n=8), as these groups compared the following parameters: age, sex, bone densitometry, laboratory findings (Ca, P), vertebral fracture levels, cigarette, high blood pressure, alcohol use, pre-operation, and post-operation 20th-day Visual Analogue Scale scores.

Results: While there were no significant differences between the VAS score and the VAS score after 20 days in the patients who received conservative treatment, a significant difference was found between the VAS score and the VAS score after 20 days in the patients who received kyphoplasty.

Conclusion: It disrupts patient compliance in treating the primary disease due to pain and immobilization in patients who received organ transplantation, and increases the complications due to immobilization. Therefore, performing kyphoplasty is recommended in symptomatic vertebral fractures that do not require stabilization after organ transplantation regardless of the VAS score.

Key words: Liver Transplantation, Osteoporosis, Kyphoplasty, VAS score

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Introduction

The incidence of vertebral fractures observed in patients who need liver transplantation is higher in the post-transplantation period than the pre-transplantation period. The bone mineral density decreases in the first three months after transplantation in patients who underwent liver transplantation, and it reaches the pre-transplantation level after two years. Thus, fractures after liver transplantation are generally observed within the first two years. Although fractures are observed at different patients' levels, the fractures are often occurred together at more than one vertebrae and rib levels. The incidence of this unification is between 15-27% (1-3).

Although age, sex, type of liver disease, and menopause in female patients are regarded as risk factors for the increase in fractures observed after liver transplantation, no consensus is reached (4). The presence of cirrhosis in diseases requiring liver transplantation increases the risk of osteoporosis two times; thus, the osteoporosis prevalence in cirrhotic patients in the 6th and 7th decades is observed between 12-55% (4, 5). Monegal et al. investigated 58 patients with cirrhosis due to viral hepatitis and reported that the risk of osteoporosis highly increased (6).

Vertebral fractures developed after liver transplantation cause severe pain in patients regardless of etiologic reasons and disrupt the compliance and comfort of the patient in the treatment of the primary disease, with additional complications emerging due to immobilization performed on the follow-up and treatment periods (7). Vertebral fractures due to bone mineral density increase mortality due to pain, spinal deformity, neurological deficit, and immobility. Kyphoplasty and nonsurgical treatments are used in these types of fractures. However, there are differences regarding which treatment to apply. The number of studies on these treatments in patients who underwent organ transplantation is limited. The triple column theory, defined by Denis in 1983, is used in practice in vertebral fractures. Front column; 2/3 anterior part of the vertebral body, middle; the back 1/3 of the vertebral body, the back column contains the other bone structures of the spine. It is considered stable only if there is a fracture in the anterior and posterior column and unstable if there is a middle column fracture with one of these fractures (8). In diagnosis, the presence of hyperintensity in the T2 stir sequence in Magnetic Resonance Imaging (MRI) and the evaluation of the vertebral bone structure in computed tomography (CT) (Figure 1).

This study discussed the patients with stable vertebral fractures who were consulted at the neurosurgery clinic after liver transplantation at the İnönü University Organ Transplant Institute and received kyphoplasty and/or conservative treatment in line with the literature and aimed to be a reference for clinical treatment

Methods

Among 2200 patients who underwent liver transplantation in the Inonu University Liver Transplantation Institute between 01.01.2002-01.01.2020, 65 of 110 patients underwent T2 stir sequence MRI (Siemens Magneto 3 tesla MRI) and spinal CT (Toshiba Astetion 4 CT) due to back and back pain detected vertebral fractures were. According to Denis' triple column theory, 48 of these 65 patients were diagnosed with an unstable fracture, tumor metastasis, and spinal infection and were not included in the study. Conservative treatment was applied to 9 patients with a Visual Analogue Scale (VAS) score below 5 five among 17 patients with stable vertebral fracture included in the study, and balloon kyphoplasty was applied to 8 patients VAS score above 5.

Patients with stable vertebral fractures were grouped as conservative (n=9) and balloon kyphoplasty (n=8), as these groups compared the following parameters: age, sex, bone densitometry, laboratory findings (Ca, P), vertebral fracture levels, cigarette, high blood pressure, alcohol use, pre-operation, and post-operation 20th-day Visual Analogue Scale scores.

Statistical analysis

Quantitative data were given as median (min-max) or mean (standard deviation), while qualitative data were given as numbers (percentage). The suitability to normal distribution was assessed using the Shapiro-Wilk test. Mann-Whitney U test, Fisher's exact chi-square, and Wilcoxon paired samples tests were used in the statistical analyses. The statistical significance level was $p<0.05$. IBM SPSS Statistics 26.0 program was used in the analyses.

Results

The total number of vertebral fractures was 65 (3%). The number of patients with stable vertebral fractures was 17 (0.77%). The number of patients with a stable vertebral fracture who received conservative treatment was 9 (52.9%), while the number of patients who received balloon kyphoplasty (average 4-5 ml cement application was made) was 8 (47.1%). Of the 17 patients, five were female

(29.4%), and 12 were male (70.6%). Of the patients, 13 (76.5%) smoked, and 4 (23.5%) did not smoke. Of them, 11 (64.7%) had a history of DM, and 6 (35.3%) did not. Among the patients, 4 (23.5%) had HT, and 13 (76.5%) did not. The number of patients who used alcohol was 10 (58.8%), and 7 (41.2%) patients did not use alcohol (Table 1).

While the variables of age, DEXA, the lowest CA value, the lowest P-value, and VAS score after 20 days showed normal distribution (Shapiro-Wilk; p>0.05), the variable of VAS score in the first examination did not. The mean age of 17 patients was 61.00 ± 9.09 years, and the mean age of the females was 60.60 ± 12.52 years, and the mean age of the males was 61.17±7.94 years. The mean DEXA was -3.19±0.93; the mean lowest CA value was 6.74±0.74; the mean lowest P-value was 14.59 ± 7.12, and the mean VAS score after 20 days was 3.82±2.04, and the median (min-max) VAS score in the first examination was 5.00 (4.00-9.00) (Table 2).

Of the patients, 2 (11.7%) had a thoracic vertebral fracture, 9 (52%) had a lumbar vertebral fracture, 6 (35%) had a thoracolumbar vertebral fracture, and 9 (52%) had multiple level vertebral fractures. No costa fractures were detected. 6 (75%) of the patients who received balloon kyphoplasty had multiple level fractures. Six of the patients who were followed up had a single-level vertebral fracture. No complications occurred in the patients who received kyphoplasty.

No statistical differences were found between the patients who received conservative treatment and/or kyphoplasty in terms of age, DEXA, the lowest CA value, the lowest P-value, and VAS score after 20 days (Mann-Whitney U test; p>0.05) while there was a significant difference in terms of VAS score (Mann-Whitney U test; p=0.001) (Table 3).

No significant differences were found between the patients who received conservative treatment and kyphoplasty in terms of the history of smoking, DM, HT, and alcohol use (Fisher's Exact Chi-Square Test; p>0.05).

While there were no significant differences between the VAS score and the VAS score after 20 days in the patients who received conservative treatment (Wilcoxon Paired Two Sampling test; p=0.472), a significant difference was found between the VAS score and the VAS score after 20 days in the patients who received kyphoplasty (Wilcoxon Paired Two Sampling test; p=0.011).

Table 1. Distribution of sex, cigarette, DM, HT, alcohol

Variable	Variable Categories	n	%
Condition	Conservative treatment	9	52.9
	Receiving Kyphoplasty	8	47.1
Sex	Female	5	29.4
	Male	12	70.6
History of Smoking	No	4	23.5
	Yes	13	76.5
History of DM	No	11	64.7
	Yes	6	35.3
History of HT	No	13	76.5
	Yes	4	23.5
Alcohol use	No	7	41.2
	Yes	10	58.8

Table 2. Age, DEXA, CA, P, VAS Scores of All Patients

Variables	Mean ± Standard Deviation [Median (Min-Max)]
Age	61.00±9.09 [62.00 (40.00-77.00)]
DEXA	-3.19±0.93 [-3.30 (-4.90--1.40)]
Lowest CA Value	6.74±0.74 [6.80 (5.70-8.00)]
Lowest P Value	1.62±0.54 [1.70 (0.70-2.50)]
VAS Score in the first examination	6.06±1.68 [5.00 (4.00-9.00)]
VAS Score after 20 days	3.82±2.04 [4.00 (0.00-7.00)]

Table 3. Age, DEXA, Ca, P, VAS scores between the two groups

Variable	Conservative Treatment Median (min-max) (n=9)	Receiving Kyphoplasty Median (min-max) (n=8)	p*
Age	62 (40-77)	61 (47-69)	0.562
DEXA	-3.6 (-4.2--2)	-2.9 (-4.9--1.4)	0.175
Lowest CA Value	6.8 (5.7-8)	6.85 (5.7-7.1)	0.287
Lowest P Value	1.7 (0.9-2.4)	1.7 (0.7-2.5)	1.000
VAS Score in the first examination	5 (4-6)	7.5 (5-9)	0.001
VAS Score after 20 days	4 (3-7)	4 (3-5)	0.766

*: Mann-Whitney U test

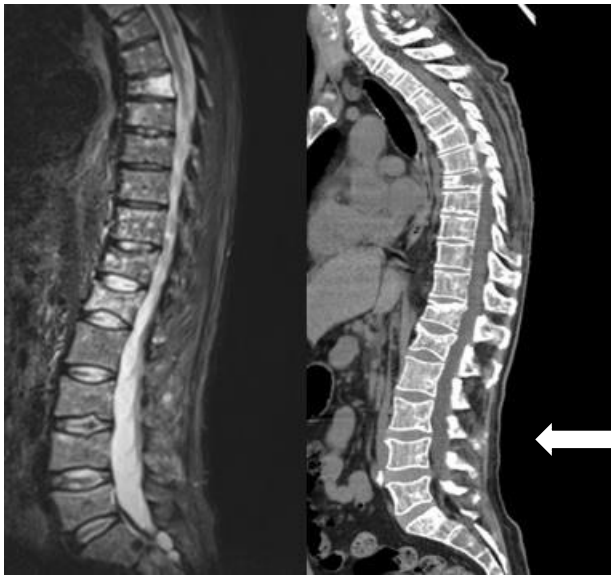

Figure 1: sagittal whole spinal CT on the right, sagittal T2 streak sequence MRI on the left

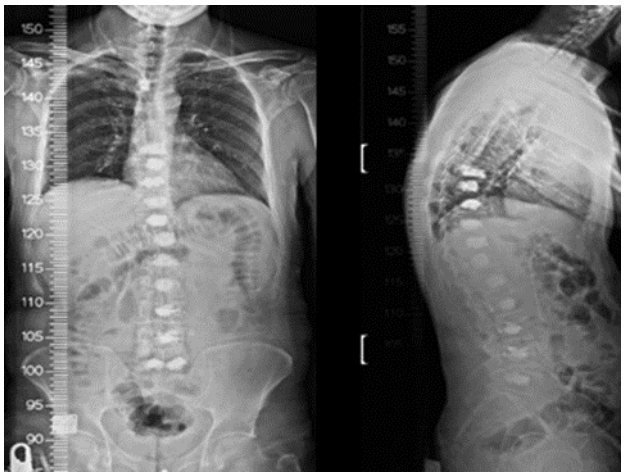

Figure 2: AP and Lateral scoliosis radiographs after kyphoplasty procedure

Discussion

The osteoporosis prevalence in cirrhotic patients in the sixth and seventh decades who need liver transplantation is known to be between 12-55% (4, 5). In line with the literature, the mean age of all patients in the present study was 61.00±9.09, of the patients who received conservative treatment was 62 and of the patients who received kyphoplasty was 61. It is known that chronic liver diseases cause bone loss, and it was revealed that female sex, menopause, long-term alcohol use, cigarette, chronic diseases, immobilization, malnutrition, and low body mass index cause osteoporosis (4, 9). Butin S. et al. conducted a study on 115 patients and found that the risk of vertebral fracture was higher after transplantation (10). The trabecular bone score calculated in DEXA measurements reflects the trabecular structure of the vertebrates. Bone densitometer performed on various patient groups such as low T scores gives information about pre-and post-menopausal kidney disease, diabetes mellitus gives information about the trabecular structure. The lumbar vertebra and thigh bone densitometry screenings are recommended in patients with hepatic cirrhosis regardless of the cause and severity of the disease (11-15). In the present study, the results of T score in bone densitometry were found to be severe osteoporosis (-2.95> T) and are in line with the literature. In our series, the results obtained after age, alcohol, and cigarette use in patients with vertebral fractures are parallel with the literature, and there are no differences between the groups. Female sex is at the forefront in the sex-based evaluation but there is no similar opinion in the literature (4). Male sex is at the forefront of our series. The occurrence of severe osteoporosis explains the multiple levels of fractures. According to Leidig-Bruckner et al., vertebral fractures after transplantation are observed in the lower thoracic and lumbar regions. Vertebral fractures are usually seen at multiple levels and with rib fractures (1-3). Vertebral fractures were most often in the thoracolumbar region in the present study, and the incidence rate of multiple level fractures was 52%, but there was no rib fracture unity.

When considering the vertebral corpus, a 4-6 ml cement application was regarded as fit (16, 17). Approximately 4-5 ml cement application was performed in 8 patients who received balloon kyphoplasty (Figure 2). The treatment protocols applied in the osteoporotic vertebral fractures are resting, analgesia, corset, and kyphoplasty. Studies reported that patients with osteoporotic vertebral fractures did not benefit much from analgesics and that the treatment duration was long. Balloon kyphoplasty performed on these patients is a minimally invasive procedure, and it is an effective method preventing the development of deformity due to providing rapid analgesia and achieving normal vertebral corpus height (18-21).

On the other hand, some studies report that balloon kyphoplasty provided better results only in the first month in the one-year follow-up of the patients and that there is no significant difference in the change in the VAS score at the end of the year compared to the patients who received conservative treatment. Therefore, instead of emergency balloon kyphoplasty, balloon kyphoplasty is recommended in patients who did not benefit from conservative treatment after three weeks (20). The presence of pain due to vertebral fractures and facet degeneration in elderly patients creates difficulties in evaluating pain scales.

It is the reason why the pain is reduced but does not pass completely after kyphoplasty (22). Most of the literature studies present the comparative results of the treatments on osteoporotic vertebral fractures; however, the number of studies on vertebral fractures and organ transplantation is limited. While no significant differences were found between the VAS score and VAS score after 20 days of the patients who received conservative treatment, there was a significant decrease in the post-operative 20th day VAS score of the patients who received balloon kyphoplasty compared to the pre-operation VAS score. This indicates that the pain experienced by the patients who received kyphoplasty significantly decreased

Conclusions

Osteoporotic vertebral fractures in patients who underwent liver transplantation are limited. Therefore, the management of these vertebra fractures is still controversial. Conservative treatment in patients who received liver transplantation disrupts patient compliance in treating the primary disease due to pain and immobilization and increases the complications due to long-term immobilization. Therefore, we recommend performing balloon kyphoplasty in the presence of symptomatic vertebral fractures that do not require stabilization after organ transplantation regardless of the VAS score.

Ethics Committee Approval: Ethics committee approval was received for this study from Clinical Research Ethics Committee of Inonu University (92040931-045.99).
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Etiological Factors in Pediatric Pseudotumor Cerebri Cases

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Abstract

Objective: Pseudotumor cerebri (PTC) is the presence of the signs and symptoms of intracranial pressure increase in the absence of a tumoral, structural or vascular mass-occupying lesion. This study aimed to investigate the etiological factors involved in childhood PTC cases.

Methods: Data of the patients presented to the Private Medical Park Samsun Hospital, pediatric neurology outpatient clinic with the preliminary diagnosis of PTC between June 2015 and December 2020 were retrospectively reviewed. Demographic data, presentation symptoms, neuro-ophthalmological examination findings, laboratory data, and radiological imaging (brain magnetic resonance imaging, magnetic resonance venography) findings. The female (i.e., Group 1) and male (i.e., Group 2) children were compared concerning the etiological factors.

Results: The study cohort included 45 patients. There were 24 patients in Group 1 (i.e., female children) and 21 patients in Group 2 (i.e., male children). Among the 45 patients, 41 (91.1%) had an overt etiological factor. Mean age of the study patients were 9.06 year [2,5 months-18 years]. The most common symptom was headache (64.4%). Two groups were similar concerning mean patient age, pubertal stage, and rates of vitamin B12 deficiency, iron deficiency anemia, vitamin D deficiency, abnormal brain magnetic resonance imaging, and magnetic resonance venography findings. However, the obesity rate was significantly higher in Group 2 than Group 1 (32,7% vs. 12,5%, $p<0.05$).

Conclusion: A thorough investigation concerning etiology is crucial in pediatric PTC cases regardless of patient gender. Timely investigations regarding etiology will lead to timely treatment of this clinical condition and prevent irreversible devastating complications such as permanent hearing loss.

Key words: Pseudotumor cerebri, Intracranial pressure, etiology

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Introduction

Pseudotumor cerebri (PTC) is defined as the presence of the signs and symptoms of intracranial pressure increase in the absence of a tumoral, structural or vascular mass-occupying lesion (1). It is classified as idiopathic intracranial hypertension (IIH) or primary PTC and secondary PTS. While secondary PTC develops due to underlying clinical conditions leading to an increase in the intracranial pressure, the etiology of IIH is still unclear (2). The most important complication of PTC is irreversible visual loss. Therefore, its timely recognition and treatment by elimination of the underlying clinical conditions are crucial. This study aimed to investigate the etiological factors involved in childhood PTC cases.

Methods

This study followed the Helsinki Declaration, and informed consent was taken from the caregivers of all children. It was approved by the Ethical Review Committee of the Samsun Training and Research Hospital (101864/01.10.2020). Data of the patients presented to the Private Medical Park Samsun Hospital, pediatric neurology outpatient clinic with the preliminary diagnosis of PTC between June 2015 and December 2020 were retrospectively reviewed. These patients were subsequently diagnosed with PTC as per the diagnostic criteria previously reported in the literature (Table 1) (3). A second lumbar puncture was performed in all patients to see the response to the treatment and to evaluate the need for additional treatment. The procedure was repeated for the third time in patients with high cerebrospinal fluid pressure. No patient required more lomber puncture.

Demographic data, presentation symptoms, neuro-ophthalmological examination findings, laboratory data (i.e., complete blood count, blood biochemistry, acute phase reactants, thyroid function tests, iron, vitamin B12 and D levels, thrombophilia panel, cortisol, and parathormone levels), radiological imaging (brain MRI, magnetic resonance venography) findings and data regarding treatment were retrieved from electronic patient folders. The female (i.e., Group 1) and male (i.e., Group 2) children were compared concerning the etiological factors. All patients had undergone funduscopic examination, Snellen visual acuity test, and Goldmann visual field testing. Children younger than twelve were considered prepubertal, while those older than twelve were considered pubertal or postpubertal. Patients with body weight at or above the 95th percentile of children of the same age and gender were considered obese.

Table 1. Daignostic criteria for PTC

1. Criteria for PTC diagnosis	
A	Papilledema
B	Normal neurological examination findings except for cranial nerve anomalies
C	Neuro-imaging: -Typical patients (i.e., female and obese): Normal brain parenchyma with no hydrocephaly, mass or structural lesion and no abnormal meningeal contrast enhancement in the magnetic resonance imaging (MRI) with or without gadolinium injection -Other patients: MRI or MR venography with or without gadolinium injection; computerized tomography with contrast medium injection can be performed if MRI is unavailable or contraindicated
D	Normal cerebrospinal fluid (CSF) content
E	High lumbar puncture opening pressure; 250 mmCSF in adults and 280 mmCSF in children (250 mmCSF if the child is not sedated or obese)
PTC diagnosis is 'definite' if the criteria A-E are all fulfilled. *PTC diagnosis is 'probable' if the A-D criteria are fulfilled but the lumbar puncture opening pressures are lower than the levels required for a definitive diagnosis.*	
2. Criteria for PTC diagnosis in patients without papilledema	
-In the absence of papilledema, the diagnosis is PTC if the criteria B-E are fully met and if there is unilateral or bilateral abducens muscle paralysis *-In the absence of both papilledema and abducens muscle paralysis, PTC diagnosis is considered if the criteria B-E are fully met and if 3 of the neuro-imaging critera mentioned below are met.*	
i.	Empty sella
ii.	Posterior ball flattening
iii.	Distention of the perioptic subarachnoid space (optic nerve tortuosity may accompany may be present or absent)
iv.	Transverse venous sinus stenosis

Statistical analysis

The Statistical Analysis for Social Sciences Software (SPSS v17.0, Chicago, IL, US) was used for all statistical analyses. Descriptive statistics were used, and data were given as percentages (%) and means±standard deviations. The p value was considered significant when it was lower than 0,05.

Results

A retrospective review of patient data revealed that 58 patients were evaluated during the study period with the provisional diagnosis of IIH. However, three patients with brain tumors and ten patients with normal CSF pressures were excluded. Therefore, the study cohort included 45 patients. There were 24 patients in Group 1 (i.e., female children) and 21 patients in Group 2 (i.e., male children). Among the 45 patients, 41 (91.1%) had an overt etiological factor. Two patients in Group 1 (8,3%) and one patient in Group 2 (4,8%) had utterly typical results, and these patients were diagnosed with primary PTC. The etiological factors are presented in Table 2.

Mean age of the study patients was 9.06 year [2,5 months-18 years]. Two groups were similar regarding mean patient age (9,3 years in Group 1 [2,5 months-18 years] and 8,7 years in Group 2 [9 months-16 years]).

Ten (22%) patients were obese. Among these patients, 3 (12.5%) were in Group 1, and 7 (32.7%) were in Group 2. There was a significant difference between the two groups in this regard ($p< 0.05$).

Among 45 study patients, 28 were pubertal-postpubertal, while 17 were prepubertal. In Group 1, 66,6% of the patients were prepubertal, and 33,3% were pubertal, while in Group 2, 57% of the patients were prepubertal, and 43% were pubertal. There was no significant difference between the groups concerning the pubertal stage.

The most common symptom was headache (64.4%). Our analysis revealed that 62,5% of the patients in Group 1 and 66,6% of Group 2 presented with headaches. The chief complaints of the patients who did not present with a headache but were diagnosed with PTC are displayed in Table 3.

A review of the patients' visual fields (VF) revealed that 21 (46,6%) patients had narrowing of the VF. Seven patients (15,5%) had normal VF. The VF tests could not be performed in 17 (37.7%) cases. In Group 1, 11 patients had narrowing of the VF, four patients had normal VF, and 9 patients could not undergo VF testing. In Group 2, 10 patients had narrowing of the VF, 3 patients had normal VF, while 8 patients could not undergo VF testing. The two groups were not different regarding the results of VF assessments. In both groups, 1 patient with VF narrowing was diagnosed with PTC in the absence of headache. All patients except for 4 aged younger than 18 months (91.1%) had bilateral papilledema.

Mean CSF pressure was 33,2 mmCSF [25-60] in the entire cohort. Fourteen (31,1%) patients underwent lumbar puncture once, while 21 (46.6%) underwent it twice, 7 underwent for three times, and 3 (6.6%) underwent for four times.

A review of the laboratory data revealed that 10 (22.2%) patients had normal vitamin levels while 35 (77,8%) patients had a deficiency of one or more types of vitamins. In Group 1, 11 patients had vitamin B12 deficiency, 7 patients had iron deficiency anemia, and 16 patients had vitamin D deficiency. In Group 2, 12 patients had vitamin B12 deficiency, 6 had iron deficiency anemia, and 15 had low vitamin D levels. The two groups were similar in this regard.

The brain MRIs showed anomalies in 7 (29.1%) patients in Group 1 and 6 (28.5%) patients in Group 2.

In Group 1, two patients had arachnoid cysts, 4 had mastoiditis, and 1 patient had a slit ventricle and a cyst anterior to the mesencephalon. In Group 2, one patient had cortical atrophy, three patients had mastoiditis, one patient had pituitary adenoma, and one patient had pansinusitis. The two groups were not statistically different in this regard.

All MRV images were reviewed, and this analysis revealed that 19 (42.2%) patients had abnormal MRV findings. In Group 1, 11 (45.8%) patients and Group 2, 8 (38.1%) patients had sinus vein thrombosis. There was a significant difference between the two groups regarding the rates of abnormal MRV findings ($p<0.05$).

In patients with sinus vein thrombosis, all potential prethrombotic risk factors were investigated. The results of this analysis are displayed in Table 4. This analysis revealed that some of these patients had multiple risk factors.

All patients were given acetazolamide (10-30 mg/kg/day) as first-line medical treatment. Patients with persistently high pressures at the post-treatment LP were given topiramate (2-3 mg/kg/day) treatment and furosemide (1-2 mg/kg/day) if topiramate treatment fails. In Group 1, 12 (50%) patients were given acetazolamide treatment, 11 (45.8%) patients received acetazolamide and topiramate treatments, while 1 (4.1%) patient was given acetazolamide, topiramate, and furosemide treatments. Eleven patients received low molecular weight heparin (1 mg/kg, twice a day). In Group 2, 9 (42.8%) patients were given acetazolamide treatment, 8 (38%) patients

received acetazolamide and topiramate treatments, while 4 (19%) patients were given acetazolamide, topiramate, and furosemide treatments. Eight patients received low molecular weight heparin treatment. None of the study participants were given steroid treatment nor surgical treatment.

Table 2. Etiological factors

Etiology	Group 1 (n=24)	Group 2 (n=21)	Total (n=45)
Sinus vein thrombosis	11 (%45.8)	8 (%38)	19 (%42.2)
Hypovitaminosis D	2 (%8.3)	7 (%32.7)	9 (%20)
Hypervitaminosis D	-	1 (%4.72)	1 (%2.2)
Hypervitaminosis A	1 (%4.16)	-	1 (%2.2)
Miller-Fisher syndrome	1 (%4.16)	-	1 (%2.2)
Hypovitaminosis B12 and D	3 (%12.5)	3 (%14.2)	6 (%13.3)
Low serum iron level and hypovitaminosis B12 and D	3 (%12.5)	1 (%4.72)	4 (%8.8)
Idiopathic	3 (%12.54)	1 (%4.72)	4 (%8.8)

Table 3. Chief complaints of the patients who did not present with headache

Complaints	Group 1 (n=24)	Group 2 (n=21)	Total (n=45)
Strabismus or diplopia	4 (16.6%)	3 (14.28%)	7 (15.5%)
Gait disturbances	1 (4.16%)	1 (4.76%)	2 (4.4%)
Macrocephaly	-	2 (9.5%)	2 (4.4%)
Bulging fontanelle	-	1 (4.76%)	1 (2.2%)
Seizure	1 (4.16%)	-	1 (2.2%)
Vomiting	1 (4.16%)	-	1 (2.2%)

Table 4. The prothrombotic risk factors determined in patients with sinus vein thrombosis

Group 1 (n=24)		Group 2 (n=21)	
Hyperhomocysteinemia	1	Hiperhomocysteinemia	1
PAI-1 heterozygote	1	High lipoprotein a level	1
MTHFR homozygote	1	PAI-1 and MTHFR heterozygote	1
MTHFR homozygote + FV Leiden heterozygote	1	PAI-1 and MTHFR heterozygote+Protein S deficiency	1
MTHFR and PAI-1 homozygote+FV Leiden heterozygote	1	MTHFR heterozygote+ Protein S deficiency	1
FMF variant (Trabss syndrome)	1	Mastoiditis	3
MTHFR heterozygote+Antithrombin III deficiency	1		
Mastoiditis	4		
Total	11		8

PAI-1: Plasminogen activator inhibitor-1
MTHFR: Methylenetetrahydrofolate reductase
FV Leiden: Faktor V Leiden mutation
FMF: Familial Mediterrenean Fever

Discussion

Although PTC is usually called IIH, it is not usually "idiopathic". It is termed secondary PTC if an etiological factor is determined and primary PTC or IIH if an overt underlying reason is not detected (4). Loss of vision is its most serious complication of both primary and secondary PTC. On the other hand, the etiopathogenesis of secondary PTC has not been clearly understood yet, and it is more common in children than in adults (5). The most frequent causes of PTC are summarized in Table 5 (6). It was hypothesized that the mineralocorticoid receptors in the choroid plexus were activated, sodium-potassium ATPase pumps were stimulated, and subsequently, the CSF secretion and CSF pressure were both increased (7). It was reported that non-obese, young and male patients frequently had overt etiological reasons (8). While overt etiological factors were not usually identified in adults, they can be detected in 53-77% of the pediatric patient population (4). In our study, 91,1% had specific etiological factors, and this rate is higher than the rates reported in the literature. We believe that our study's relatively low mean patient age contributed to this difference.

Although PTC is primarily diagnosed in fertile-aged women, it can be encountered at any age (9). Obesity is considered a risk factor. It was suggested that an increase in the obesity incidence led to an increase in the PTC rate in our country (10). However, most of the post pubertal (i.e., older than 12) children with PTC have risk factors such as obesity and female gender, the rate of obesity is relatively lower, and there is an even gender distribution in prepubertal children. While PTC

incidence is 1/100000, this rate increases 13 to 15-fold if there is 10% weight gain and 19-fold if there is 20% weight gain (11). A study reported that the rate of obesity was 43% in PTC cases aged between 3 and 11 and 91% in those aged between 12 and 18 (10). The same study also concluded that the association of obesity and PTC got stronger with increasing age. It was also reported that the rate of PTC got higher among older women than those at younger ages. In our study, there was a relatively lower rate of obesity in prepubertal children. This finding was consistent with the literature.

The most common symptom of PTC is headache; it is encountered in 84-92% of these patients (12). Although its features, such as being diffuse, getting more severe at night, suggest that it is associated with the tension of the meninges and cerebral veins, its characteristics are not specific to PTC. Several studies reported in the literature stated that characteristics of the headache might vary, but it was usually a chronic daily, an acute repetitive, or a chronic repetitive type of headache. In our cohort, the rate of headache was 64,4%. This rate is lower than the rates reported in the literature. This difference can be explained by the fact that most of our patients were at prepubertal age, and some of them were so young that they could not express their complaints. Visual complaints such as blurred vision, strabismus, diplopia, and decreased visual acuity constitute the second group of complaints in these patients (13). Temporary visual complaints accompany the clinical picture in 68-72% of the patients. It is known that the types and severities of the temporary visual complaints are not correlated with the severity of PTC, and they do not predict visual loss (14). It was reported that visual complaints were more dominant in patients with prepubertal PTC (15). Also, it was stated that 12-22% of the PTC cases were asymptomatic, and they were diagnosed incidentally by the detection of papilledema (16). This fact highlights the importance of a careful funduscopic examination. Bilateral papilledema is the most common finding in symptomatic cases ((17). It is detected in 86-100% of these patients.

Assessment of the VF provides essential data regarding PTC in children who can cooperate; however, it should be considered that this assessment is not easy (6). In our study, 46% of the patients had VF defects, and 91% had bilateral papilledema. Nausea, vomiting, dizziness, bulging of the fontanelles, seizure, tinnitus, gait disturbances, macrocephaly, and behavioral disorders are the other potential manifestations of PTC. In our study, one patient presented with vomiting, one with seizure, two with macrocephaly, one with fontanelle swelling, and two with gait disturbance.

Recently, critical values were determined for CSF opening pressures (3). Contrary to the old criteria, the new criteria did not include clinical signs and symptoms of intracranial pressure increase, and they consider some radiological findings as specific for PTC. As per these new criteria, a CSF opening pressure of higher than 28 cmH2O is considered positive for obese and sedated patients, while the threshold was 25 cmH2O for non-obese and non-sedated patients (3). On the other hand, in a study that considered CSF pressures in the range of 21-27 cmH2O as significant, the authors noted that the opening pressure could be affected by the depth of sedation during lumbar puncture, excessive hyperventilation, pain, and stress (8). This study concluded that the CSF opening pressure should be measured again in patients whose opening pressures were normal, but the clinical pictures were consistent with PTC (8). In our study, the mean CSF opening pressure was 33,2 mmCSF, and this figure was consistent with the literature.

There are several reported regarding the association between infections and PTC (18,19). These reports state that the reason for relatively higher rates of PTC in winter might be related to higher rates of respiratory viral infections in this season. Also, it was denoted that sinus vein thrombosis detected in 9-14% of the patients with PTC could be associated with a middle ear infection or mastoiditis (18,19). On the other hand, it was suggested that hypervitaminosis A could lead to PTC via mineralocorticoid pathways (20). While some studies suggest that hypervitaminosis and hypovitaminosis D could be the underlying reason for PTC, some suggest that they can accompany PTC without a cause-and-effect relation (21). Anemia is another potential culprit, as per the published literature (22). It was stated that the tissue hypoxia stemming from anemia could lead to cerebral hemodynamic changes, increase the capillary permeability and cause an increase in the intracranial pressure. Iron deficiency anemia, megaloblastic anemia, and hemoglobinopathies are associated with increased risk of PTC (22). In this study, we detected sinus vein thrombosis, anemia, mastoiditis, hypervitaminosis A and D, and hypovitaminosis D in our patients.

Brain MRI and MRV are essential diagnostic methods in PTC cases (6). They are used for diagnosing or eliminating neoplastic, vascular, or structural mass occupying lesions, sinus vein thrombosis, and other potential causes of secondary

PTC. In our study, all patients had undergone contrast enhanced MRG and MRV. These imaging methods showed sinus vein thrombosis in 42,2% and abnormal MRI findings in 28,8% of the patients. The abnormal MRI findings included arachnoid cyst, mastoiditis, slit ventricle, anterior mesencephalon cyst, cortical atrophy, pituitary adenoma, and pansinusitis. Our study did not investigate the secondary radiological findings, and we consider this fact a weakness of our report.

The treatment regimens for PTC vary from center to center (23). The aim of treatment is to lower the intracranial pressure, prevent visual loss, and relieve headaches. Acetazolamide is the first-line medical treatment agent. It inhibits the carbonic anhydrase enzyme, decreases CSF production in the choroid plexus, and reduces pressure. The other medications are topiramate, furosemide, and steroids. The surgical treatment methods include lumboperitoneal and ventriculoperitoneal shunts, endoscopic fenestration of optic nerve sheaths, and stenting of dural sinuses. Although the standard approach is giving medical treatment first and saving the surgical treatment methods for medical treatment-unresponsive cases, surgical treatments can be considered the first-line treatment in patients with progressive and severe visual impairment. It was reported that 37-76% of patients responded to acetazolamide treatment (12). In a study including 31 pediatric patients with PTC, 19% had a permanent visual loss (24). Two studies reported from our country reported permanent visual loss rates of 11% and 7,1% (25,26).

These studies reported an acetazolamide treatment response rate of 46%. In our study, we did not perform any surgical treatments, and none of our patients experienced permanent visual loss.

Conclusion

We believe that this result is due to comprehensive investigations regarding etiology performed at an early stage. Our findings indicate that a thorough investigation concerning etiology is crucial in pediatric PTC cases, regardless of patient gender. Timely investigations regarding etiology will lead to timely treatment of this clinical condition and prevent irreversible devastating complications such as permanent hearing loss.

Ethics Committee Approval: It was approved by the Ethical Review Committee of the Samsun Training and Research Hospital (101864/01.10.2020).
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Trans-Sphenoidal Surgery for "Growth Hormone-secreting adenoma; Revisiting Surgical Outcome

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Abstract

Objective: The purpose of this research is to review our clinical experience in transsphenoidal surgery for pituitary adenomas performed by Recep Tayyip Erdogan University Faculty of Medicine, Department of Neurosurgery and contribute to the literature in this way.

Methods: This is a case review of Growth Hormone secreting pituitary adenoma operated in the Recep Tayyip Erdogan University Faculty of Medicine Department of Neurosurgery from January 2014 to May 2021. All patients underwent a microscopic transnasal approach. It was aimed gross total excision of adenoma. For functioning adenomas, hormonal assessment was done on follow-up (8 weeks) and remission was said to be achieved if normal hormonal levels were achieved along with gross total tumor removal. Surgical complications were evaluated, and postoperative follow-up with laboratory and imaging studies were performed.

Results: 78 patients were operated by trans nasal route in our hospital between January 2014-June 2021. Of these 78 pituitary tumors, 22 were growth hormone secreting adenoma. The study population consisted of 22 people, 11 men and 11 women, and the average age of the population was calculated as 60.45 years ± 18.4. Statistical analysis showed that the difference between the pre-operative and post-operative somamedine and growth hormone level was statistically significant

Conclusions: Microscopic Trans-Sphenoidal Surgery for Acromegalic patients is a minimally invasive, safe, and efficacious choice

Key words: Adenoma, Surgery, Trans-sphenoidal, Pituitary.

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Introduction

Pituitary gland locates in an area of complex anatomical structures, but it holds a very important physiological role to maintain all body function (1). The most common type of pituitary tumor is a benign pituitary adenoma, which occurs in the sellar and suprasellar regions (2). These tumors are referred to as those atypical tumors, which are not only benign slowly developing, but also show development of the pituitary gland (3). 12% of all cerebral tumors are pituitary adenoma (PA)(4). It is the third primary brain tumor to be common. (5). While most of them are not symptomatic, they may cause a wide range of signs which depend on their hormone function (3). PA's primary clinical signs include endocrinologic syndrome characteristic, whether because of hormone hypersecretion or deficiencies, compressive symptoms or unusually acute or subacute pituitary apoplexy (6). PA can be of various subtypes depending on the source cell or the corresponding hormones (non-functioning PA, prolactinoma, somatotropinoma, corticotropinoma, thyrotropinoma, and gonadotropinoma) (7). Functioning PA is relatively more morbid and mortal due to the associated hormone hypersecretion syndromes (7). Functional PA diagnosis is determined using biochemical hormone hypersecretion confirmation and imaging pituitary lesion (7). The treatment of functioning pituitary tumors consists of one or more of the following 3 modalities: surgery, radiation therapy (RT) and medical therapy (7). In the late 1960s, pituitary surgery evolved from a craniotomy approach toward less invasive approaches, in particular microscopic and endoscopic (8,9). All tumor tissue (i.e. gross total resection) should be removed, pressures should be alleviated and the risk of relapse reduced (10). Currently, surgical procedure can be carried out by two different techniques: microscopic or endoscopic (7). The trans-sphenoidal route (both the sublabials and cross-nasals)– with the advent of the operative microscope in the 1960s – became the gold standard for approaching the sellar area lesions (11). The first-line treatment of most types of tumors is transsphenoidal surgical resections, except for prolactinomas, in which the treatment is preferred with dopamine agonists (7), because these adenomas' surgical approaches have higher risk of complications (4). Other options for managing PA are RT and medical therapy (7). Growth hormone (GH)-secreting PA is an insidious disease with an estimated incidence of 30 to 50 cases/1 million population annually (12). Acromegaly is caused by an excess of GH, most commonly caused by a somatotroph PA, and is associated with significant metabolic changes that have a negative impact on quality of life (13). Uncontrolled acromegaly patients experience a lower life expectancy of 10-15 years and suffer from multimorbidity (14).

Methods

Recep Tayyip Erdogan University Non-Invasive Clinical Research Ethical Committee approved the study. Preoperative and postoperative medical records of the patients were evaluated. Data collection involved examination of the clinical and surgical notes, including indications for surgery, histopathology, pituitary magnetic resonance imaging (MRI) findings, cerebrospinal fluid (CSF) leak grade, complications. Hormonal and visual status were also evaluated. According to pre-operative hormonal and clinical features, tumors were classified into clinically ‘functioning’ and ‘non-functioning’. Pre- and post-operative somatomedin and GH levels were compared. The postoperative results were evaluated in terms of the control of hormone hypersecretion and safety of surgical procedure.

Neuroimaging evaluation

Traditional MRI sequences, such as contrast-enhanced (CE), T1 weighted image (WI), and T2WI, are commonly used to assess adenoma characteristics such as invasion and size (15). All patients in this study were evaluated with a 1.5 T magnetic resonance imaging (MRI) unit before surgery, using T1- and T2-weighted spin echo before and after the addition of gadolinium-based contrast. This radiological model was used to assess the configuration and size of tumors, as well as their extensions into the suprasellar, infrasellar, or parasellar region. Preoperative MRI are presented in Figure 1.

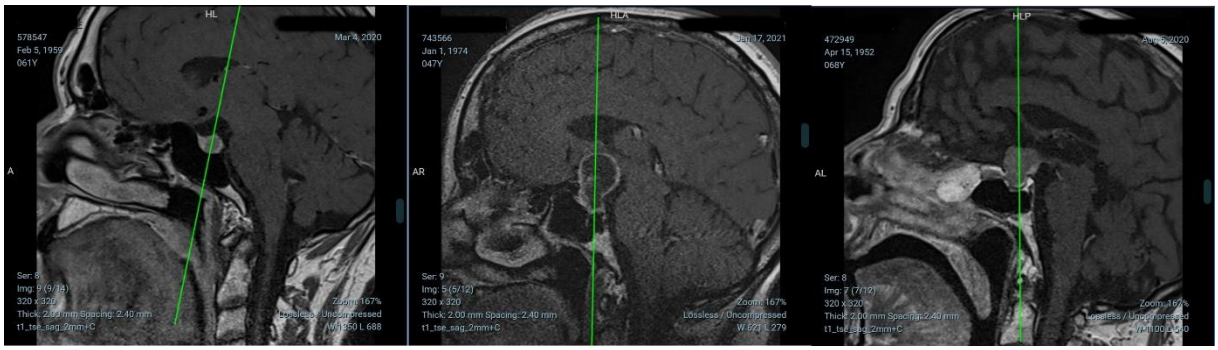

Figure 1. Preoperative MRI of patients

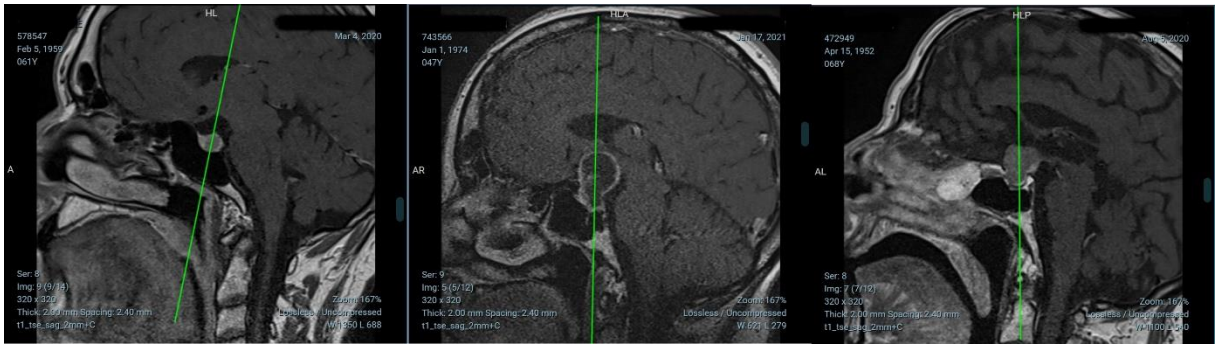

Figure 2. Postoperative MRI of patients

Surgical Procedure

The transsphenoidal approach was performed using an endonasal transseptal microsurgical technique. The patient was positioned semi-sitting, with the head rotated 15° to the right and tilted to the left. The sphenoid sinus is about 20 mm deep, 70 – 90 mm deep to the nasal spine, and has a 30° angle to the nasal cavity floor (9). Irrigation was used to control venous bleeding after removing the sphenoid sinus mucosa. The sellar floor was removed sufficiently, and the dura was opened. The tumor was resected. The arachnoid layer has been closely watched. Hemostasis was meticulously maintained in the tumor cavity, and hemostatic agents such as a gelatin sponge (Spongostan; Ferrosan, Seborg, Denmark) were used, when necessary, in the cavity. The dura was opened in a cruciate fashion from laterally to medially to prevent inadvertent injury to the sinuses. The nasal bony septum, sphenoidal rostral bone fragments, cellulose, and an autologous abdominal adipose graft were used to reconstruct the sella turcica floor. As in Villar-Taibo et al's study, surgical complications were classified as intraoperative (during surgery), immediate postoperative (within the first week after surgery), and late postoperative (within the first month after surgery) (6).

Follow-up

Follow-up monitoring included postoperative MRI, endocrinological and neurological evaluations, performed at 3 months after surgery as in the study of Asioli et al. (16). The patients were followed for a period of 61 months. MRI scans were obtained 3 and 6 months after surgery. Postoperative MRI are presented in Figure 2.

Statistical analysis

SPSS 20.0 for Windows (SPSS, Inc, Chicago, Illinois, USA) was used to perform statistical calculations. When describing sociodemographic variables, frequencies, means, standard deviations and median were used. Normality for continuous variables was tested by using Shapiro–Wilk test. Wilcoxon sign rank test was performed because preoperative and postoperative somatomedin and GH level were not normally distributed. Significance was set at $p < 0.05$.

Results

78 patients were operated by trans nasal route in our hospital between January 2014-June 2021 in the Neurosurgery Department of Recep Tayyip Erdogan University University Faculty of Medicine. All operations have been conducted in collaboration with 2 neurosurgeons. Of these 78 PA, 22 were GH secreting adenoma. The tumors were classified as microadenomas (0–10 mm; n:2), macroadenomas (10–29 mmn:15), large adenomas (≥30 mmn:4), and giant adenomas (≥40 mmn:1) based on their diameter. Acromegaly was present in 22 cases. There were 11

women and 11 men in this group, with a mean age of 60,45 years ± 18.4. All 22 patients underwent a single surgical procedure. The surgical goal was gross total resection and hormonal cure, which have been achieved in the majority of patients. Median hospitalization duration was 4 days. Demographic and operative data are given in table 1. Early period CSF fistulas were observed in 3 patients. Diabetes insipidus occurred in 3 patients. Reoperation for recurrent adenoma was required only in 3 patients.

Table 1. Demographic and Operative Data

Age (year, mean±SD)	60.45±18.4
Gender (female/male) N	11/11
BMI (kg/m2, mean±SD)	26.49 ± 4.75
Tumor classification	**N**
Microadenoma	2
Macroadenoma	15
Large Adenoma	4
Giant Adenoma	1
Operation duration (minute, mean±SD)	98.12±22.35
Hospitalization duration (day, median)	4±1,37

BMI: Body Mass Index

Postoperative assessments

Every single patient was closely followed up for the development of complications. At the 8th week and 3rd month, after surgery, routine follow-up was performed in the outpatient clinic. A full hormonal test was performed to assess pituitary function in depth. An MRI was routinely performed at 6 months to assess a tumor remnant as well as to establish a baseline measurement for future recurrence assessments. There was no death in this series. The mean pre- and post-operative 8th week somatomedin levels were 342,19 ng/mL and 144,77 ng/mL respectively. The difference of pre-operative and post-operative level of somatomedin was statistically significant (P=0.002, <0.01). Mean pre-operative growth hormone level was decreased from 2,6 ng/mL to 0.7 ng/mL. The difference was also statistically significant (p=0.003, <0.01) (Table 2).

Table 2. Pre and postoperative somatomedine and growth hormone levels

Hormonal parameters	Preoperative (mean±SD)	Postoperative (mean±SD)	p
Somatomedin, ng/mL	342.19±303.96	144.77±93.37	0.002**
Growth hormon, ng/mL	2.6±3.99	0.75±1.23	0.003**

Wilcoxon sign rank test,**p<0.01

Discussion

Acromegaly is the result of unrestricted GH secretion, which is a serious medical disorder. (17). Although typically benign under a histological point of view, PAs can exhibit an aggressive clinical and radiological behavior, characterized by quick growth, along with resistance or early recurrence, with the gross invasion of the surrounding tissues after treatment. (16). As the pituitary adenoma is the most common cause of acromegaly pituitary MRI may be helpful in the diagnosis of acromegaly. Enlarged pituitary gland with gadolinium uptake and extend of adenoma to the suprasellar region are observed on MRI. Findings on MRI for spine are hypertrophy of spinal ligaments and cartilaginous structures and osteoarthritis. In addition to these findings, joints MRI shows ligamentous and cartilaginous hypertrophy and crystal deposition (18). The long-term effects of chronic GH excess on metabolism and the cardiovascular system are negative, and include diabetes mellitus, arterial hypertension, heart disease, and an increased risk of cancer (17). In acromegaly, somatostatin receptor ligands (octreotide, lanreotide, pasireotide), dopamine agonists (cabergoline) and GH receptor antagonist (pegvisomant) are used for medical treatment (19). The surgical treatment of these adenoma is aimed at restoring GH levels as soon as possible (13), we noted a statistically significant decrease of GH levels in this study.

Pituitary adenomas are tumors of extra-arachnoidal origin, so usually grow outside the confines of CSF (20). As the tumor lies in close relationship to the diaphragm sellae and subarachnoid space, there is always a risk of iatrogenic arachnoid breach (20). As a result, CSF leak is a common complication of this surgery (20) among several transsphenoidal chirurgical complications. Apart from CSF leak, transient diabetes insipidus, permanent diabetes insipidus, minor nasal bleeding, and hyposmia can be seen after microsurgical surgery (21). The optimal treatment for GH secreting PA is trans-sphenoidal pituitary surgery (22). The first treatment option in acromegaly is surgical removal of the adenoma. Patients with severe mass effects, such as vision loss or double vision, require immediate surgical treatment. Medical treatment can be applied before surgical treatment in patients at risk of anesthesia such as cardiomyopathy, uncontrolled diabetes mellitus, severe hypertension and sleep apnea. Following the application of medical treatment for 3-6 months, surgical intervention can be performed for patients whose anesthesia and surgical risks are reduced. After successful adenoma resection, clinical improvement begins within days (19). The anatomy of the pituitary fossa's roof varies greatly (23). A "barrier" of three anatomical structures exists between the adenoma and the CSF (23). This tripartite structure progressing from the cephalad to the cauda consists of arachnoid, dura

mater (ie sellar diaphragm) and pituitary gland tissue. Of these three elements, only the arachnoid is found in every human (23). In the literature, CSF leaks have been reported varying from 0.5% to 10.3% (20). We had a total of 3 (13,6%) cases with postoperative CSF leak. Three cases needed re-exploration. Potential morbidities following CSF leaks include meningitis, prolonged hospitalization, tension pneumocephalus and additional operations (24).

Outcomes of Surgery

Surgical procedure outcomes are frequently reported in the literature in a clinician-centered manner (25). Traditional surgical outcome studies concentrate on efficacy measures like remission rates and gross total resection (25). An important aim of treatment of patient with PA is to improve or preserve health-related quality of life (26). The recovery of pituitary function is much less than that of vision (27). Re-emergence of symptoms of acromegaly with re-increased GH and IGF-1 levels is defined as recurrence after surgical control (28). According to the literature, the recurrence rate ranges from 0% to 31% (28). In this study, the patients were followed for 6±1 months. Recurrence was observed in 3 patients. Although we are aware that the postoperative timing of MRI following PA surgery is still controversial, MRI scans of patients were obtained at the third and sixth months after surgery (29). Follow-up of asymptomatic residual tumor should be following up (29). Early evaluation is frequently difficult in the setting of acute postoperative changes such as hemorrhage, packing, and, in some cases, undescended residual tumor (29). The rationale for early postoperative imaging is to give surgeons a chance to intervene earlier for residual tumor (29). Important predictors of surgical outcome of GH-secreting PA are tumor size, invasiveness, duration of acromegaly, and preoperative GH levels (13). GH-secreting PA, the predominant cause of acromegaly, is associated with a standardized mortality rate of 0.72–1.13(28). No mortality was seen in this series.

Conclusion

This study indicates that patients undergoing surgery for acromegaly can have excellent outcomes. Low complication rates and high resection rates were noted in the present study. The length of stay in hospital was not long. Although it is considered a relatively safe procedure in transsphenoidal pituitary surgery, postoperative complications should be expected. Knowing about these complications is the first step in preventing them (1). Timely diagnosis and effective treatment to control hormone hypersecretion and relieve mass effects along with replacement of deficient hormones are crucial to reduce these associated health risks (7), because PA invasion of local structures on MRI is associated with postoperative outcomes following surgical resection (15). We recommend the transsphenoidal surgery for GH secreting PA as a safe and effective approach.

Ethics Committee Approval: This study was conducted with the approval of the ethics committee of Recep Tayyip Erdogan University Faculty of Medicine, Non-Invasive Clinical Research Ethics Committee. (Ethics Committee date and Decision no: 26.04.2021 2021/75)
Peer-review: Externally peer-reviewed.
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Conflict of Interest: The authors do not declare any conflict of interest.
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Thoracic Spinal Stenosis: Surgical Approaches and Outcomes

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Abstract

Objective: Thoracic spinal stenosis (TSS) develops as a result of decreased spinal canal volume in the thoracic spine. The prevalence of TSS is low as when compared with cervical or lumbar spinal stenosis, and conservative treatment is not effective. The present study aimed to present all surgical methods employed and their outcomes in patients diagnosed with TSS in our clinic.

Methods: In this study, the data of 14 patients including three patients with single-level, nine patients with two-level, one patient with three-level, and one patient with multilevel TSS and hypophosphatemic rickets who underwent surgery due to TSS, were retrospectively evaluated using the discharge summary, surgical reports, and preoperative and postoperative radiological images.

Results: The age of the patients ranged from 53 to 68 years. Of the patients included in the study, one underwent hemilaminectomy, two underwent total laminectomy, six underwent laminoplasty, and five underwent total laminectomy with fusion and posterior instrumentation. A dramatic improvement was observed in the neurological deficits existing in the preoperative period in patients who were diagnosed in the early period and underwent surgery with adequate decompression before the development of severe neurological deficits and who continued postoperative rehabilitation added to the treatment.

Conclusion: Patients with TSS have an insidious clinical course manifested by upper motor neuron symptoms. Although the prevalence of TSS is low, early diagnosis and treatment are important. The results of surgery are satisfactory when adequate decompression is achieved before the clinical condition worsens.

Key words: Spinal stenosis, ossification, dura mater, ligamentum flavum

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Introduction

Thoracic spinal stenosis (TSS) is a clinical condition in which neurological dysfunction characterized by a reduction in the volume of the thoracic spinal canal occurs, leading to compromise of the spinal cord and/or nerve roots (1). According to the location of TSS, it can be divided into two as ventral and dorsal stenosis. Ventral stenosis is caused by broad-based thoracic intervertebral disc protrusion and ossification of the posterior longitudinal ligament. Dorsal stenosis is caused by the ossification of the ligamentum flavum (OLF) or facets joint hypertrophy (2). The most common cause of TSS, especially in East Asian countries, is the OLF (3). The OLF usually occurs at the lower thoracic spine, especially at the T10-T12 levels (4-6), followed by the upper thoracic spine at the T1-T4 (7) levels, due to increased biomechanical stress. The prevalence of TSS is lower than that of cervical or lumbar spinal stenosis (8); moreover, if neurological symptoms occur, conservative therapy is not effective and early decompressive surgery is required (2,8,9). Since neurological symptoms mostly affect the lower extremities, TSS can be confused with lumbar spinal pathologies and patients may be clinically misdiagnosed (2,10). Generally, patients present to the clinic with symptoms of progressive thoracic myelopathy, back pain, and/or signs of acute severe paraparesis or paraplegia after minor trauma (4-6,11).

The present study aims to present all surgical methods employed and their outcomes in patients diagnosed with TSS in our clinic.

Methods

In this study, the data of 14 patients who were operated with the diagnosis of TSS were retrospectively evaluated using the discharge summary, surgical reports, and preoperative and postoperative radiological images. The study was approved by the ethics committee of Kocaeli Derince Education and Research Hospital (project number 2020/42).

Of the patients included in the study, one underwent hemilaminectomy, two underwent total laminectomy, six underwent laminoplasty, and five underwent total laminectomy with fusion and posterior instrumentation.

In patients undergoing bilateral decompression with unilateral hemilaminectomy (Figure 1, 2), paravertebral muscles were unilaterally stripped from the spinous processes and vertebral bones through a midline incision. Under the microscope, hemilaminectomy was performed with ultrasonic bone cutter and high-speed drills, while remaining medial to the facet joint. Then, the junction of the lamina and the spinous process was thinned with a drill. The thinned lamina in some areas was removed with the help of a curette and a rongeur. This technique was used in one patient. By performing unilateral muscle dissection in this technique, operation time is shortened, perioperative bleeding is reduced, and spinal instability is avoided by sparing the facet joints. Therefore, the use of a corset in the postoperative period is no longer needed. However, failure to achieve the appropriate angle may cause insufficient contralateral decompression.

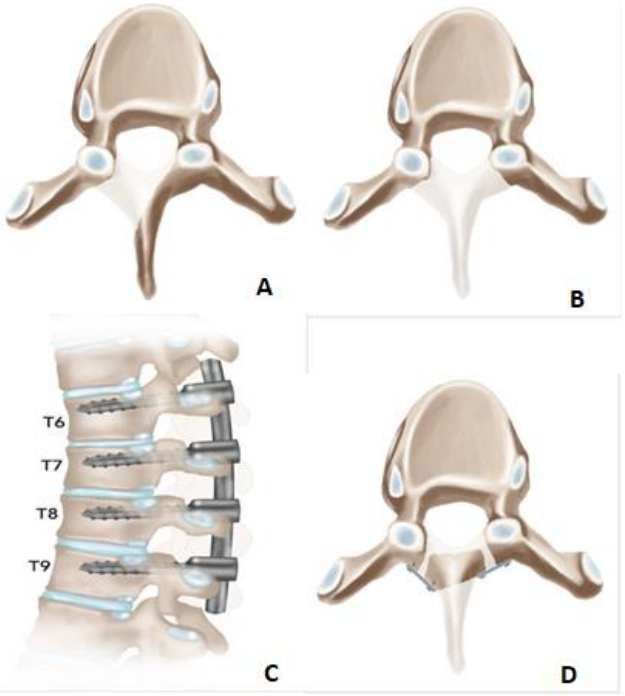

Figure 1. A: Bilateral decompression with unilateral hemilaminectomy, B: Total laminectomy, C: Total laminectomy with fusion and posterior instrumentation, D: Laminoplasty

In patients undergoing total laminectomy (Figure 1, 3), the paravertebral muscles were stripped from the spinous processes and vertebral bones after performing a midline incision. The dissection was advanced to the medial aspect of the facet joints and care was taken not to damage the facet joint capsule. The lamina and OLF were dissected off the dura using an ultrasonic bone cutter and a high-speed drill while preserving the facet joints. This technique was used in two patients. A clearer view of the borders of the central canal and neural foramen was achieved compared to hemilaminectomy. Similar to that in hemilaminectomy, the risk of spinal instability was reduced as the facet joints were preserved. The use of corsets in the postoperative period was not required in both patients. However, the removal of more posterior elements than hemilaminectomy and the

disruption of the integrity of midline tension band structures caused postoperative pain. Also in this technique, preserving the facet joints to avoid instability may cause inadequate decompression.

In five patients undergoing total laminectomy with fusion and posterior instrumentation Figure 1, 4), the paravertebral muscles were stripped from the spinous processes and vertebral bones through a midline incision. Then, pedicle screws were inserted, and total laminectomy was performed at the levels of stenosis by removing the facet faces using a Kerrison rongeur and rongeur. Since stabilization was achieved using the pedicle screws, the margin of laminectomy was widened to include the facet joints. Extensive decompression was achieved. Since a wide incision is made with this technique and the muscles are retracted, perioperative bleeding and postoperative pain may be more common in patients, and screw malposition may be observed.

In six patients undergoing laminoplasty, the laminoplasty technique that we applied was a modification of the previously described classical laminoplasty technique (Figure 1, 5). Z-laminoplasty, open-door laminoplasty, double-door laminoplasty methods were not used in this technique. In one of the cases in which we applied this technique, there was severe multiple stenosis. Absolute stenosis was detected in the patient at T3, T4, T6, T7, T8, T9, T11, T12 levels. If laminectomy was performed by fusion with posterior instrumentation, it would have been necessary to apply a very long-segment stabilization from the cervicothoracic junction, including the thoracolumbar junction. Instead, total laminectomy was performed at eight levels of stenosis in this patient using Kerrison rongeur, rongeur, and high-speed drills. Posterior stabilization was achieved by fixing the removed spinous part to the facet joints and transverse processes with a mini-plate screw in a horizontal position. Since long-segment posterior instrumentation was not performed in this patient, the operation time was very short, there was no screw malposition problem, and perioperative bleeding was minimal. However, the use of a corset in the postoperative period was required in this patient as the technique employed may cause stabilization problems.

Figure 2. Images of computerized tomography (CT) axial and sagittal sections in a patient who underwent bilateral decompression with unilateral hemilaminectomy (R) **A**. Preoperative **B.** Postoperative

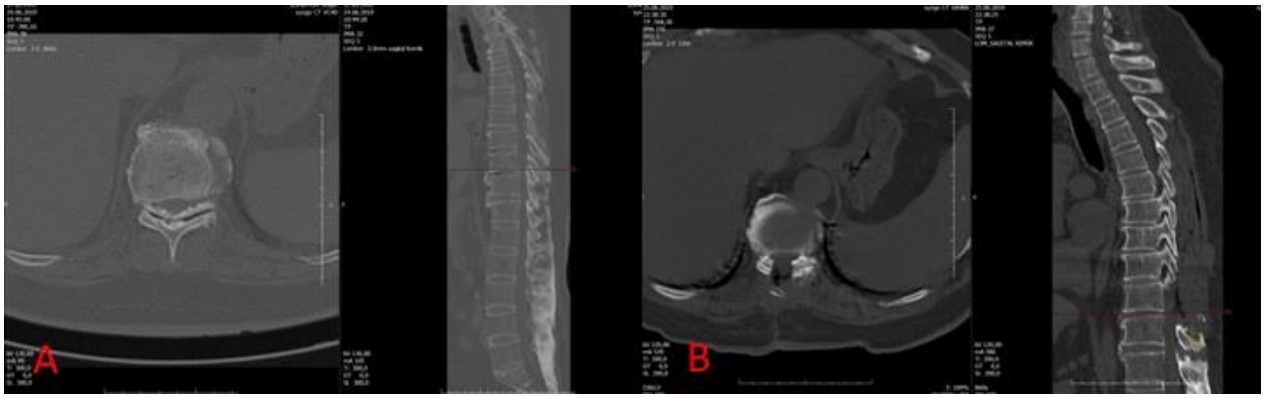

Figure 3. Images of computerized tomography (CT) axial and sagittal sections in a patient who underwent total laminectomy **A**: Pre-operative **B:** Post-operative

Figure 4. Images of computerized tomography (CT) sagittal and axial sections in a patient who was previously operated on with the diagnosis of lumbar spinal stenosis and underwent total laminectomy with fusion and posterior instrumentation **A**: Pre-operative **B:** Post-operative

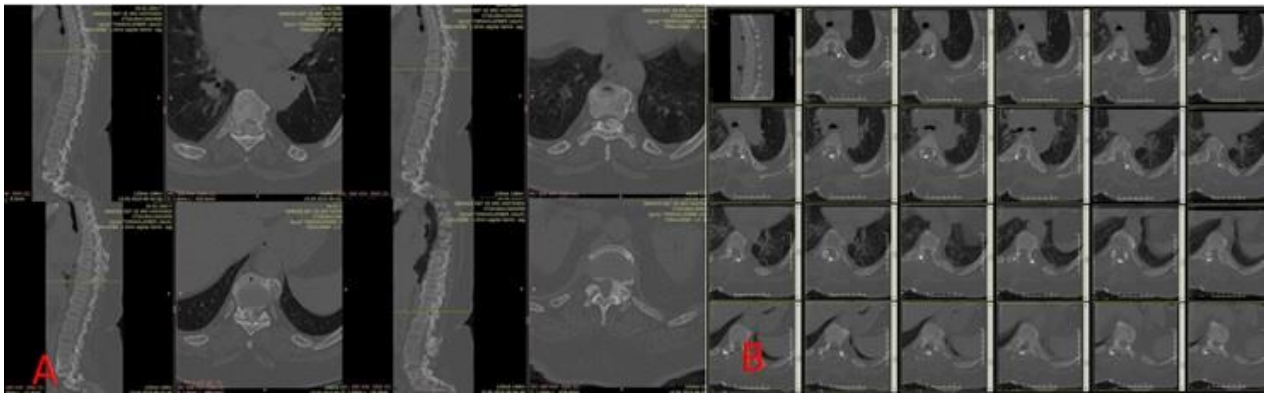

Figure 5. Images of computerized tomography (CT) sagittal and axial sections in a patient with eight levels of thoracic spinal stenosis who underwent laminoplasty **A**: Pre-operative **B:** Post-operative

Results

A total of 14 patients were included in the study, including three patients with single-level, nine patients with two-level, one patient with three-level, and one patient with stenosis at eight levels and with a diagnosis of X-linked hypophosphatemia (XLH). Of the patients, five had type 2 diabetes mellitus and four had chronic renal failure. The age of the patients ranged between 53 and 68 years. Of patients undergoing surgery, two underwent repeat surgery after the observation of inadequate decompression on control computed tomography (CT) examination of the spine in the postoperative period. Two patients developed dural defects due to the presence of severe dural ossification (DO). Dural repair with fascia graft was performed in these cases. In the early postoperative period, the cases were followed up for possible acute complications. Among 14 patients with paraparesis in the preoperative period, complete recovery of paraparesis was observed in seven patients in the postoperative period. The other seven cases were referred to the Physical Medicine and Rehabilitation clinic due to partial persistence of paraparesis. A neurological rehabilitation program, which was planned to include stretching and strengthening exercises, weight-bearing, balance, proprioception, and ambulation training, daily living activities, and splinting program, was applied to these cases. It was observed that there was a dramatic improvement in the existing neurological deficits of the patients with the rehabilitation applications added to the program after surgery. One patient was able to ambulate with a walker and the other six patients were able to ambulate independently without support. During an extended follow-up duration of 1-3 years, the patients did not develop re-stenosis and instability (Table 1).

Table 1: Presentation of patients

Patient number	Age	Gender	Level of stenosis	Pre-op clinic	Pre-op calcification	Operation	Post-op clinic	Post-op complication
1	58	Female	T4	Paraparesis	OLF	Total laminectomy	Decrease of paraparesis	-
2	57	Male	T5	Paraparesis	OLF+DO	Total laminectomy	Decrease of paraparesis	Dura defect
3	61	Male	T4	Paraparesis	OLF	Right hemilaminectomy	Completely improvement	-
4	56	Female	T10, T11	Paraparesis	OLF+DO	Posterior instrumentation+ total laminectomy	Completely improvement	-
5	54	Female	T9, T11	Paraparesis	OLF	Posterior instrumentation+ total laminectomy	Decrease of paraparesis	-
6	53	Male	T10, T12	Pain+ paraparesis	OLF	Posterior instrumentation+ total laminectomy	Completely improvement	-
7	54	Male	TT9, T10, T12	Pain+ paraparesis	OLF+DO	Posterior instrumentation+ total laminectomy	Completely improvement	-
8	61	Female	T9, T10	Pain+ paraparesis	OLF	Laminoplasty	Completely improvement	-
9	62	Male	T10, T11	Paraparesis	OLF	Laminoplasty	Decrease of paraparesis	-
10	62	Female	T10, T12	Pain+ paraparesis	OLF	Laminoplasty	Completely improvement	-
11	64	Male	T11, T12	Pain+ paraparesis	OLF	Laminoplasty	Completely improvement	-
12	66	Male	T11, T12	Paraparesis	OLF	Laminoplasty	Decrease of paraparesis	-
13	68	Female	T4, T5, T7, T8, T9, T10, T11, T12	Paraparesis	OLF+DO	Laminoplasty	Decrease of paraparesis	Dura defect
14	65	Male	T10, T12	Paraparesis	OLF	Posterior instrumentation+ total laminectomy	Decrease of paraparesis	-

T: thoracic, OLF: ossified ligamentum flavum, DO: dural ossification, pre-op: preoperative, post-op: postoperative

Discussion

Since the thoracic spine is relatively stable, myelopathy caused by pathologies developing in the thoracic spine is less common than myelopathy caused by pathologies developing in the cervical and lumbar spine (12). The diameter of the spinal canal is narrower in the thoracic region as compared to the other parts of the spinal canal. Therefore, any compression that occurs at this level causes severe neurological symptoms in patients (9). For this reason, when TSS is diagnosed, decompression surgery should be performed early in symptomatic cases. TSS may be caused by the OLF, ossification of the dura, herniation of the thoracic disc, and ossification of the posterior longitudinal ligament (2). Since TSS can often be associated with cervical and lumbar spinal canal diseases, its diagnosis and treatment may be delayed (1,2). Of the patients with TSS and OLF included in this study, three had DO. In all cases, the entire spinal column was examined preoperatively using magnetic resonance imaging (MRI) and CT.

OLF is shown as the primary cause of thoracic myelopathy (13-16). The studies have reported that OLF is more common in the fifth and sixth decades of life, its incidence increases with age, and it is seen at a higher rate in East Asian countries, especially in Japanese people (4,14,17-19). In many studies, factors such as genetics, dietary habits, mechanical stress, and cytokine production in the ligamentum flavum have been implicated in the etiology of OLF, and no definitive etiological factor has been reported (7). Histological studies have shown that fibroblastic proliferation contributes to endochondral ossification (20). It has been reported that thoracic OLF is most frequently seen at the lower thoracic spine at T10-T12, followed by the upper thoracic spine at T1-T4, and rarely at T5-T9 (21,22). This is due to the fact that because the mid-thoracic region is located posterior to the thoracic cage, and thus more stable, while the other regions are located in the cervicothoracic and

thoracolumbar transition regions and are more exposed to mechanical stress (7). In the cases with OLF in this study, it was observed that the lower thoracic region was the most commonly affected region, and the middle thoracic region was rarely affected.

One of the other causes of thoracic myelopathy is DO, which can be seen in patients with OLF. In the literature, the incidence of DO has been reported to be ranging between 11% and 66.6% (19,23-25). CT is considered superior than to MRI in the diagnoses of DO. It has been reported that the etiology of DO is unclear and inflammatory reactions may be involved in its pathogenesis (17). In 2009, Muthukumar et al. defined two radiological signs for DO in preoperative CT imaging, tram trace sign and a comma sign (26). In this study, DO was detected in three cases (21.4%).

In our clinical series, it was shown that severe DO did not manifest as a comma, or a tramway mark as described in the literature and that dural calcification expanded similar to the expansion of an intradural extramedullary mass and pushed the spinal cord (Figure 6).

Figure 6. Intradural view of dural ossification

In one of our cases who presented to our clinic with symptoms of back pain, spasticity, and severe paraparesis had been diagnosed with XLH. In imaging studies, TSS was detected at multiple levels in the thoracic spinal canal (Figure 5, 6). XLH is the most common form of hereditary rickets and is characterized by renal phosphate loss. In affected patients, hyperplasia of fibrochondrocytes occurs in tendons and ligaments, causing thickening and ossification of the structures (27,28). In the literature, there are a few reported cases with a diagnosis of XLH, who developed stenosis due to calcification in the thoracic spinal canal causing myelopathy and/or paraplegia (29,30).

The earliest symptom of TSS is an ataxic gait. As the stenosis worsens, spasticity and muscle atrophy occur, the patient experiences difficulties in standing balance and climbing stairs, numbness and hypoesthesia begin, and bladder and bowel disorders occur in the late stage (7,11,17,25). The patients may rarely present with back pain. Conservative approaches have no place in the treatment of symptomatic cases (17,31). Satisfactory outcomes can be achieved by adequate decompression with early treatment and employing appropriate surgical methods (18,32,33). Hemilaminectomy, total laminectomy, laminectomy with fusion and posterior instrumentation, and laminoplasty are the surgical techniques employed. In the literature, the addition of fusion to decompression surgery is controversial, and some studies argue that fusion should be added to prevent the development of early instability and kyphotic deformity (11,20,26). In cases where the posterior longitudinal ligament is ossified, some authors consider that only decompression is appropriate (11,20), while many authors have reported that laminectomy alone will not be sufficient, and fusion should be added (34,35). In

2019, Barath et al. reported that they performed decompression with fusion and instrumentation for the treatment of a patient with recurrent stenosis after undergoing posterior decompression (4). The addition of fusion to surgery is a more appropriate option, especially in pathologies in the thoracolumbar junction that have caused TSS. The facet joints can be adequately removed by both laminoplasty and laminectomy with fusion and posterior instrumentation, and thus the risk of re-stenosis can be minimized.

In spinal surgery applications, there are studies in which three-dimensional navigation systems are used instead of classical fluoroscopy (o-arm). There are studies Studies are showing that anatomic structure can be located precisely, and the placement of pedicle screws can be controlled more easily using these navigation systems (36,37). In this study, classical fluoroscopy was used to determine the level, and two patients were re-operated after inadequate decompression was observed in control thoracic CT examination in the postoperative period.

In the literature, ultrasonic bone curettes have been shown to reduce cerebrospinal fluid (CSF) leakage in spinal surgeries, and the incidence of CSF leakage has been reported as 1.6%–9.8% (5,17,38). In this study, ultrasonic bone cutter and high-speed drills were used; by adjusting the cutting depth of the ultrasonic bone cutter, the laminae could be cut smoothly near the border of the bilateral facet joints and safely removed in an en-bloc manner. This technique was used in cases with only OLF without DO. In cases with DO, the DO was thinned with a high-speed drill until a thin layer remained and left as a thin lamella. Dural defect was observed in two patients, and duraplasty was performed using fascia graft in these cases. In one case, it was observed that the dural defect was caused by the bone cutter, and the other dural defect was caused by the intradural thickening.

Rehabilitation programs after surgery should be an integral part of the treatment in order to maximize independence in the mobilization of the patients and daily life activities, such as self-care and home-work-social life management. The management of rehabilitation programs in patients with myelopathy due to ligamentum flavum pathology is very similar to the management of traumatic spinal cord injuries. The Conventional rehabilitation program should mainly consist of in-bed mobility of the patient, transfers, mobility with a wheelchair, sitting, sitting/standing, balance-coordination and walking exercises with or without an assistive device and re-training the patient about daily activities while considering the clinical condition of the patients in the postoperative period. In the postoperative period, prevention of complications, such as skin deterioration, deep venous thrombosis, and pulmonary embolism, pain management, spasticity, bowel, and bladder management should be handled appropriately (39,40).

In this study, it was observed that the patients who were diagnosed in the early period and operated with adequate decompression before the onset of symptoms of severe myelopathy and who were included in the rehabilitation program in the early postoperative period, showed a significant and rapid clinical recovery.

Conclusion

It should be kept in mind that TSS causes slowly progressing thoracic myelopathy and minor traumas may accelerate the onset of symptoms. The outcomes of surgical treatment in the early period before the deterioration in clinical condition are satisfactory. In symptomatic cases, follow-up with conservative treatment is not appropriate. The authors consider that among the surgical methods employed, laminectomy with fusion and posterior instrumentation and laminoplasty will provide better decompression in these patients.

Ethics Committee Approval: The study was approved by the ethics committee of Kocaeli Derince Education and Research Hospital (project number 2020/42).
Peer-review: Externally peer-reviewed.
Author Contributions:
Concept: A.G; ***Design:*** A.G, M.S; ***Literature Search:*** A.G, M.S, T.G, ***Data Collection and Processing:*** A.G, M.S, T.G; ***Analysis or Interpretation:*** A.G, M.S, T.G; ***Writing:*** A.G, M.S, T.G.
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The effect of minimal-flow and high-flow hypotensive anesthesia on oxidative stress

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Abstract

Objective: The main objective of this study was to compare the effects of minimal and high gas flow-controlled hypotension applications on IMA and thiol/disulfide balance, which are indicators of oxidative stress.

Methods: Patients undergoing elective tympanoplasty were randomized to two groups as minimal-flow and high-flow anesthesia groups. Minimal flow anesthesia was performed with 5L/min fresh gas flow reduced to 0.4 L/min. High flow was administered as 2 L/min fresh gas. Preoperative and intraoperative SpO2, StO2, EtCO2, mean arterial pressure and heart rate values were recorded. Preoperative and intraoperative IMA, total thiol, native thiol, disulfide, disulfide/native thiol and disulfide/total thiol values were recorded and compared between the two groups.

Results: The mean intraoperative arterial pressure was statistically notably higher in the high flow group (p=0.048). The mean intraoperative SPO2 value was remarkably higher in the minimal flow group (p=0.032). The mean EtCO2 value was notably lower in the minimal flow group at 5 minutes and 15 minutes of the operation (p=0.029; p=0.048). The mean preoperative and intraoperative IMA values were statistically notably higher in the minimal flow group compared to the high flow group (for both, p=0.001). There was no remarkable difference between the groups in terms of the other monitored parameters (for all, p>0.05).

Conclusion: IMA value was found to be significantly higher with minimal-flow anesthesia. However, no notable difference was found in terms of thiol/disulfide homeostasis, indicating the need for further comprehensive studies in order to draw a definitive conclusion.

Key words: Minimal flow, high flow, anesthetics, oxidative stress, thiols

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Introduction

To be considered controlled hypotension, one must lower one'adjusted systolic or mean arterial pressure (MAP) to 50-65 mmHg, or reduce one's basal MAP by 30 percent (1). Controlled hypotension provides better visualization of surgical site during surgery, and thus decreasing blood loss, operational time and the incidence of complications (2). Some studies have proposed that decreased platelet activity during hypotension protects against postoperative consumptive coagulopathy (3). Numerous agents can be used for controlled hypotension including direct vasodilators, beta blockers, alpha blockers, and combined alpha-beta blockers. The ideal agent to be used for this purpose should be easily applied with dose-dependent effects, rapid onset and minimal side effects (1). On the other hand, hypotensive anesthesia is associated with decreased perfusion to vital organs such as the brain, heart and kidneys. Therefore, when performing hypotension contraindications such as cerebrovascular disease, liver dysfunction and renal dysfunction that suggest low organ perfusion in the patient should be taken into account (4). In addition, general anesthetic agents, postoperative analgesic regimen and anesthesia-induced hypotension may lead to oxidative stress related to surgical stress.

The imbalance between reactive oxygen species (ROS) and antioxidant defense mechanisms is referred to as oxidative stress (OS). OS is involved in ageing, inflammation, cancer and expose to drugs such as anesthetic agents. Contribution of anesthetic procedures to surgical stress and postoperative complication has been associated with increased oxidative stress and release of inflammatory cytokines (5). Anesthesia-induced oxidative stress may affect proteins, lipids and DNA. Surgical patients can undergo surgeries that may cause inflammation, surgical trauma, and ischemia-reperfusion injury all of which are resulted from oxidative stress (6).

Anesthesia can be performed with both minimal and high fresh gas flow. Minimal gas flow (≤ 0.5 L/min) has several advantages. These include reduction in the use of inhalational anesthetics, improved body temperature and humidity homeostasis, decreased environmental pollution and significance cost saving (7). However, high gas flow between 2L/min and 6L/min is still being used. Both methods have specific advantages and disadvantages. Controlled anesthetic hypotension applications with these two forms of flow were thought to have different effects on oxidative stress parameters. There is no study on the literature on this subject. Therefore, the purpose of this research was to compare the effects of minimal and high gas flow-controlled hypotension applications on IMA and thiol/disulfide balance, which are indicators of oxidative stress.

Methods

A number of 89 patients aged between 18-60 years with an American Society of Anesthesiologists (ASA) status I or II, who underwent elective tympanoplasty operation under hypotensive anesthesia between August 2018 and December 2018 were participated in the study. Three patients were excluded from the study because their blood samples were coagulated and two patients since they developed hypotension that required short-term inotropic support, and finally the study was completed with 84 patients. Patients with uncontrolled hypertension, diabetes mellitus, cerebrovascular disease, morbid obesity (BMI ≥ 35 Kg/m2), anemia, pregnancy, renal disease, carotid artery stenosis and those who used antioxidant drugs, smokers, and patients with alcohol and drug addiction were excluded from the study. All operations were performed by the same otorhinology surgical team.

Patients were randomly assigned to one of two groups. In the group to be administered minimal flow anesthesia Group MF, a fresh gas flow of 5L/min (50% oxygen and 50% air) was provided for 10 minutes following intubation. After the tenth minute, oxygen support was provided so that the inspiratory oxygen fraction (FiO2) would not fall below 50% and the fresh gas flow was reduced to 0.4 L/min. Whereas in the high flow anesthesia group (Group HF) was administered 2 L/min fresh gas flow (50% oxygen, 50% air) continuously.

Monitoring and Anesthesia Management

The same perioperative monitoring procedure was applied in all patients. A 20-gauge intravenous (iv) cannula was placed on the dorsum of the left hand of the patients 30 minutes before the operation and 5 mL/Kg isotonic fluid was given. Venous blood samples were collected via an 18 Gauge iv cannula inserted into the right brachial vein.

All patients were followed-up with routine monitoring including three-derivation electrocardiogram (ECG), peripheral oxygen saturation (SpO2) and non-invasive arterial blood pressure. Evaluation of anesthesia depth and sedation was analyzed by bispectral index (BIS) using the mean frequency of electroencephalography (EEG). BIS provides conversion of the EEG recording to integers in the range of 1-100, and its value decreases as anesthesia deepens. Values of BIS between 40 and 60 indicate the appropriate depth of anesthesia. With

BIS monitoring, the control of the depth of anesthesia becomes objective (8). The bispectral index was also measured with an electrode with four leads placed on the patient's forehead. (Covidien, Boulder, CO, USA). Peripheral tissue oxygen saturation (StO2) was monitored via a probe inserted to the thenar region of the left hand through InSpectraTM StO2 Spot Check Model 3000 (Hutchinson Technology, INC., Hutchinson, MN, USA) device, which measures with NIRS technology. In all patients, Dräger Primus (Dräger Medical, Lübeck, Germany) was used as the anesthesia device and CLIC Absorber 800+ (Dräger Medical, Lübeck, Germany) as the soda lime. All patients were received 0.02 mg/Kg iv midazolam as premedication and preoxygenation was applied with 5L/min 100% oxygen. For induction, 1 µg/Kg iv remifentanil was administered over 60 seconds as the loading dose followed by 1 mg/Kg iv lidocaine ve 2 mg/Kg iv propofol. Neuromuscular block was provided with 0.6 mg/Kg iv rocuronium bromide. In the maintenance of anesthesia, desflurane and 0.25-0.75 µg/Kg/min iv remifentanil was used. The BIS value was maintained between 40% and 60%. Following endotracheal intubation, 6 ml/Kg tidal volume and 5 cm H2O positive end-expiratory pressure were applied according to the ideal body weight in volume-controlled mode with the Dräger Primus anesthesia device. Respiratory frequency was adjusted to be in the range of EtCO2 35-40.

Controlled hypotension was achieved in patients by reducing the MAP by 30% from the baseline value or by maintaining it to be 60-65 mmHg during the operation. A mean arterial pressure <50 mmHg was considered as hypotension, a HR <45 bpm as bradicardia, and remifentanil infusion was stopped, and ephedrine (5 mg) and atropine (0.5 mg) doses were added for the treatment.

Fifteen minutes before the end of the surgery, 100 mg iv tramadol was administered for postoperative analgesia and 8 mg iv ondansetron for antiemetic purposes. When it was reported that there was 10 minutes to the end of the surgery, the fresh gas flow was increased to 5 L/min and desflurane was discontinued in both groups. 100% oxygen support was initiated. Infusion rate of remifentanil was lowered to 0.2 µg/Kg. When the BIS value exceeded 80% and the patient began to obey verbal commands, 15 µg/kg iv atropine and 50 µg/kg iv neostigmine was administered and extubation was performed. All patients were taken to the postoperative recovery room. If the Aldrete score was 9-10, the patient was sent to the service.

Data Collection

EtCO2, inspiratory oxygen fraction (FiO2), inspiratory desflurane fraction (FiDESF) values were measured and recorded before anesthesia induction, at 5-, 15-, 30- and 60-minutes following intubation. The heart rate (HR), mean arterial blood pressure (MAP), SpO2 and StO2 values were recorded 10 minutes before the induction of anesthesia and at 60 minutes of the operation.

Biochemical Analysis

Ten minutes before the induction of anesthesia and at 60 minutes of the operation, 2 milliliters of venous blood samples were taken into biochemistry tubes containing coded anticoagulant and serum separator, centrifuged at 1500 rpm for 10 minutes and stored frozen at -80° C. The spectrophotometric was used to measure the thiol/disulfide homeostasis which method developed by Erel and Neselioglu (9). This was accomplished by first reducing disulfide bonds in order to produce free functional thiol groups that included sodium borohydride. The unused reducing sodium borohydride was depleted with formaldehyde to prevent reduction of 5,5'-dithiobis- (2-nitrobenzoic) acid (DTNB). After reaction with DTNB, all thiol groups including the reduced "disulfide", "native thiol" and "total thiol" groups were determined. Following the determination of native and total thiols, the amounts of disulfide were calculated as Disulfide/native Thiol ratio, Disulfide/Total thiol ratio and Native thiol/Total thiol ratio.

IMA levels were determined with the rapid colorimetric method developed by Bar-Or et al. using an autoanalyzer (Mindray BS 2000, Mindray Bio-Medical Electronics Co. Ltd., Shenzhen, China) (10). In brief, 200 µL patient serum was added to 50 µL 1 g/L cobalt chloride solution and after mixing vigorously, the mixture was left in the dark incubation for 10 minutes. Then, 50 µL dithiothreitol (DTT; 1.5 g/L) was added and mixed. After incubation for 2 minutes, 1 mL was added to 9 g/L NaCl solution. The absorbance of test mixtures was read at 470 nm and the results were calculated as the absorbance unit (AU).

Ethics Considerations

Before the beginning, the necessary approval was received from the Non-interventional Clinical Research Ethics Committee of our hospital with the 2018/64 decision. All patients gave written consent, and the study was conducted in line with the ethical principles of the Declaration of Helsinki.

Statistical Analysis

For statistical analysis of data, NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software was used. Descriptive statistics (mean ± standard deviation, minimum, maximum) were used to express the results. Normality of the variables was tested with the Shapiro-Wilk method. To compare normally distributed quantitative variables across three or more time periods, the Repeated Measure test was used. The Friedman test was used for the comparison of non-normally distributed quantitative variables between three or more periods. The Mann-Whitney U test was used for comparing non-normally distributed qualitative variables between two groups. The student t test was used for the comparison of normally distributed qualitative variables between two groups. $p<0.05$ values were considered statistically significant.

Results

Of all patients included in the study, 38 (45.2%) were female and 35 (54.8%) were male. The patients aged between 18-60 years with a mean age of 32.96±13.09 years. The mean body mass index (BMI) was calculated as 24.61±3.94 (min-max: 16.61-34.25) Kg/m2. Forty-six patients (53.6%) were in the minimal flow (MF) group and 39 (46.4%) in the high flow (HF) group.

When routine anesthetic monitoring parameters were evaluated; the mean preoperative tissue hemoglobin index (THI) value was 10.56±1.67 in Group MF, while this value was 12.09±2.33 in Group HF. The difference between two groups in terms of preoperative THI was significant (p=0.003). The mean intraoperative arterial pressure was statistically significantly higher in Group HF (63.72±4.59) compared to Group MF (61.53±4.87) (p=0.048). The mean intraoperative SpO2 value was 98.49±1.16 in Group MF and 99.03±1.09 in Group HF. The difference between both groups was statistically notable (p=0.032). However, hypoxia was not observed in any patient. No statistically notable difference was found between the two groups in terms of the BIS parameters followed in the intraoperative period (p>0.05). No statistically significant difference was found between the two groups in terms of the other monitored parameters (for all p>0.05). Comparison of the routinely monitored parameters between the groups is given in Table 1.

When intraoperative anesthesia monitoring data were examined; the mean EtCO2 value was significantly lower in Group MF at 5 minutes (32.73±3.12 vs 34.33±3.49) and 15 minutes (31.16±5.68 vs 33.31±3.78) compared to Group HF (p=0.029 and p=0.048; respectively). The mean FiO2 value was significantly higher in Group MF at 5 minutes (68.36±18.37 vs 53.44±11.94) and 15 minutes (53.76±15.08 vs 42.69±8.12) compared to Group HF (for both p=0.001). The mean FiDESF value was statistically remarkably higher in Group MF (6.07±1.22) compared to Group HF (4.94±1.24) at intraoperative 5 minutes (p=0.001). The mean FiDESF value was statistically significantly lower in Group MF (4.40±1.16) compared to Group HF (5.13±1.12) at intraoperative 30 minutes (p=0.004). No statistically notable difference was observed

Table 1. Anesthesia monitoring parameters according to the groups

Parameter	Group	Mean±SD	Min-Max	p
Preoperative StO_2	**MF**	77.31±7.94	55-93	[a] 0.602
	HF	78.08±6.76	63-91	
Intraoperative StO_2	**MF**	87.82±6.37	63-95	[b] 0.227
	HF	86.15±6.15	75-97	
Preoperative THI	**MF**	10.56±1.67	7.3-13.8	[a] **0.003****
	HF	12.09±2.33	7.1-17.2	
Intraoperative THI	**MF**	11.71±2.03	8.2-16.3	[a] 0.067
	HF	12.46±2.26	7-16.6	
Preoperative HR	**MF**	85.38±14.64	52-120	[a] 0.753
	HF	83.28±13.11	48-110	
Intraoperative HR	**MF**	64.67±10.61	51-96	[b] 0.388
	HF	62.82±8.59	48-88	
Preoperative MAP	**MF**	91.27±12.66	56-120	[a] 0.943
	HF	90.46±11.74	59-112	
Intraoperative MAP	**MF**	61.53±4.87	51-72	[a] **0.048***
	HF	63.72±4.59	55-76	
Preoperative SPO_2	**MF**	98.96±1.3	95-100	[b] 0.293
	HF	98.54±2.25	90-100	
Intraoperative SPO_2	**MF**	98.49±1.16	95-100	[b] **0.032***
	HF	99.03±1.09	95-100	

Abbreviations: StO_2: tissue oxygen saturation; THI: tissue hemoglobin index: HR: heart rate; MAP: mean arterial pressure; SpO_2: oxygen saturation, Mann Whitney Testi (a) . Student T Testi (b) *p<0.05 **p<0.01

between both groups in terms of the other monitored intraoperative parameters (for all p>0.05) (Table 2).

Table 2. Intraoperative anesthetic parameters according to the groups

		Mean±SD	Min-Max	p
5 minutes	**MF**	32.73±3.12	23-38	[b] **0.029***
$EtCO_2$	**HF**	34.33±3.49	28-42	
15 minutes	**MF**	31.16±5.68	0-39	[b] **0.048***
$EtCO_2$	**HF**	33.31±3.78	21-41	
30 minutes	**MF**	31.87±3.56	23-44	[b] 0.495
$EtCO_2$	**HF**	32.36±2.92	26-38	
60 minutes	**MF**	31.93±4.06	24-48	[b] 0.483
$EtCO_2$	**HF**	32.46±2.5	27-38	
5 minutes	**MF**	68.36±18.37	36-93	[b] **0.001****
FiO_2	**HF**	53.44±11.94	32-87	
15 minutes	**MF**	53.76±15.08	29-88	[b] **0.001****
FiO_2	**HF**	42.69±8.12	33-72	
30 minutes	**MF**	41.07±8.72	29-66	[b] 0.078
FiO_2	**HF**	38.13±5.86	31-55	
60 minutes	**MF**	35.91±6.49	29-55	[b] 0.349
FiO_2	**HF**	37.13±5.16	30-55	
5 minutes	**MF**	6.07±1.22	2.4-8.1	[a] **0.001****
FiDESF	**HF**	4.94±1.24	2.1-7.8	
15 minutes	**MF**	5.15±1.53	1.06.2009	[a] 0.557
FiDESF	**HF**	4.91±1.17	2.07.2008	
30 minutes	**MF**	4.4±1.16	1.4-6.4	[b] **0.004****
FiDESF	**HF**	5.13±1.12	2.07.2004	
60 minutes	**MF**	4.58±1.29	1.7-6.9	[b] 0.145
FiDESF	**HF**	4.96±1.01	2.07.2001	

Abbreviations: EtCO2: end tidal carbon dioxide; FiO2: fraction of inspired oxygen; FiDESF: fraction of inspired desflurane, Mann Whitney Testi (a) . Student T Testi (b) *p<0.05 **p<0.01

Table 3. Preoperative and intraoperative oxidative stress parameters of the groups

		Mean±SD	Min-Max	*p*
Albumin	**MF**	4.83±0.13	4.49-5.03	[a] 0.637
	HF	4.84±0.13	4.58-5.09	
Ischemia Modified	**MF**	0.74±0.08	0.56-0.97	[a] ***0.001****
Albumin 1	**HF**	0.58±0.09	0.4-0.82	
Native Thiol 1	**MF**	343.66±52.18	249.9-475.4	[a] 0.360
	HF	330.48±51.6	206.7-432.9	
Total Thiol 1	**MF**	385.81±54.56	288.79-516.29	[a] 0.358
	HF	370.58±54.99	240.6-484.5	
Disulfide 1	**MF**	21.07±4.07	11.56-32.2	[a] 0.177
	HF	20.05±3.8	10.5-28.55	
Disulfide Native	**MF**	6.23±1.33	3.02-9.12	[b] 0.784
Thiol 1	**HF**	6.15±1.31	4.06-11.14	
Disulfide Total	**MF**	5.52±1.05	2.85-7.71	[a] 0.518
Thiol 1	**HF**	5.46±1.01	3.76-9.11	
Native Thiol /	**MF**	88.97±2.1	84.58-94.3	[a] 0.510
Total Thiol 1	**HF**	89.09±2.02	81.77-92.49	
Albumin 2	**MF**	4.69±0.13	4.43-4.96	[a] 0.939
	HF	4.69±0.16	4.31-4.96	
Ischemia Modified	**MF**	0.9±0.12	0.66-1.4	[a] ***0.001****
Albumin 2	**HF**	0.72±0.13	0.51-1	
Native Thiol 2	**MF**	255.62±56.14	125.6-376.9	[a] 0.979
	HF	252.48±63.33	79.4-342.7	
Total Thiol 2	**MF**	296.5±56.48	166.51-412.29	[a] 0.600
	HF	289.68±61.02	138.5-386.2	
Disulfide 2	**MF**	20.44±6.43	12.71-49.49	[b] 0.162
	HF	18.6±5.34	12.75-38.45	
Disulfide/ Native	**MF**	8.58±5.15	4.35-39.4	[b] 0.943
Thiol 2	**HF**	8.49±6.53	4.49-37.22	
Disulfide /Total	**MF**	7.09±2.75	4-22.04	[b] 0.753
Thiol 2	**HF**	6.87±3.57	4.12-21.34	
Native Thiol /	**MF**	85.82±5.5	55.93-91.99	[b] 0.754
Total Thiol 2	**HF**	86.26±7.13	57.33-91.76	

Mann Whitney Testi (a) . Student T Testi (b) *p<0.05 **p<0.01

Figure 1 presents a visual depiction of the intraoperatively monitored anesthetic parameters. Oxidative stress parameters were compared between Group MF and Group HF in the preoperative and intraoperative periods. Accordingly, there was a statistically notable difference between the groups in terms of the preoperative and intraoperative ischemia modified albumin (IMA). The mean preoperative IMA value was statistically significantly higher in Group MF (0.74±0.008) compared to Group HF (0.58±0.09) (p=0.001). Similarly, the mean intraoperative IMA value was statistically remarkably higher in Group MF (0.90±0.12) compared to Group HF (0.72±0.13) (p=0.001). In Group MF, the mean IMA value increased by 21.6% at intraoperative 60 minutes compared to the baseline value, while this rate was 24.1% in Group HF. No statistically remarkable difference was found between the two groups in terms of the mean total thiol, native thiol, disulfide, disulfide/native thiol, disulfide/total thiol and native thiol/total thiol values both in the preoperative and intraoperative periods (for all p>0.05). Table 3 shows oxidative stress parameters of both groups and Table 4 shows the changes in oxidative stress parameters.

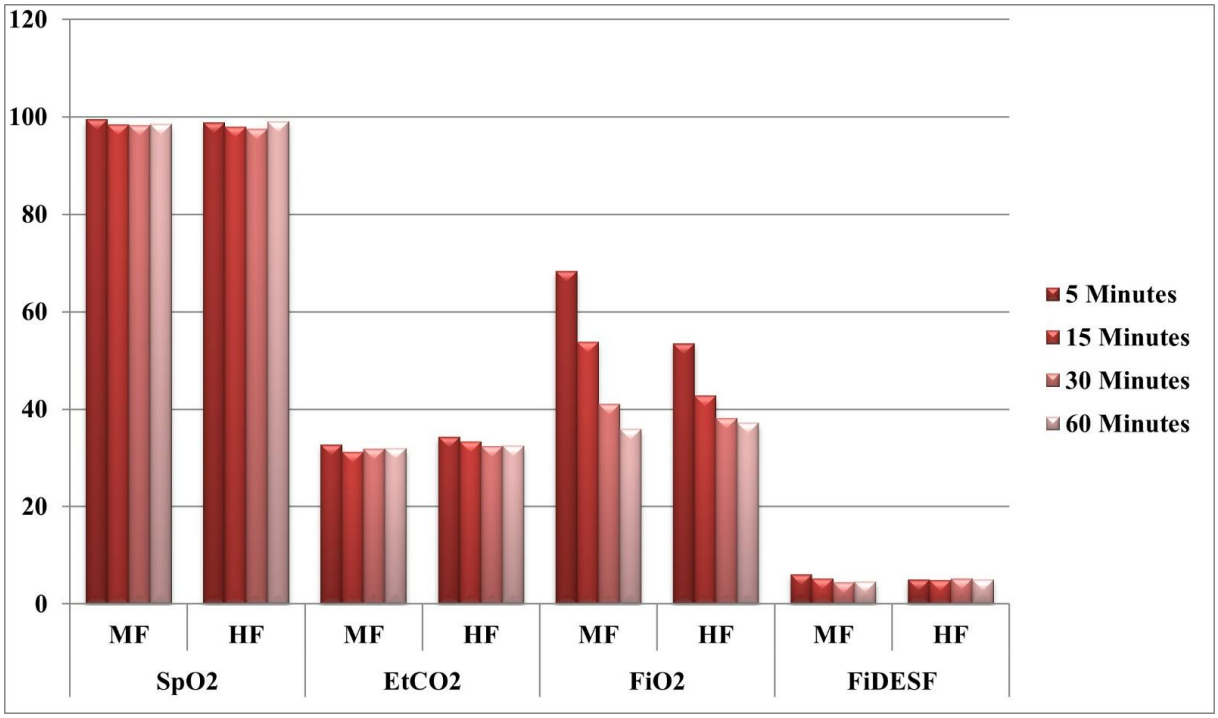

Figure 1. Changes in the monitored anesthetic parameters in the intraoperative period

Table 4. The changes in the oxidative stress parameters according to the groups (%)

	Minimal Flow			High Flow		
	Pre-op	**Intra-op**	**Change (%)**	**Pre-op**	**Intra-op**	**Change (%)**
IMA	0.74	0.9	21.62	0.58	0.72	24.14
NT	443.66	255.62	-42.38	330.48	252.48	-23.60
TT	385.81	296.5	-23.15	370.58	289.68	-21.83
DIS	21.07	20.44	-2.99	20.05	18.6	-7.23
DIS/NT	6.23	8.58	37.72	6.15	8.49	38.05
DIS/TT	5.52	7.09	28.44	5.46	6.87	25.82
NT/TT	88.97	85.82	-3.54	89.09	86.26	-3.18

Abbreviations: IMA: ischemia modified albumin; NT: native thiol; TT: total thiol; DIS: disulfide

Discussion

Controlled hypotension is defined as keeping systolic blood pressure in the range of 80-90 mmHg or mean arterial pressure (MAP) in the range of 50-65 mmHg (1, 11). Intravenous anesthetics, inhalation anesthetics, opioids, calcium channel blockers, beta blockers and nitrate derivatives are often used for this purpose (12). Pharmacokinetic and pharmacodynamic properties of these agents are quite different. Anesthetic agents used for hypotensive anesthesia are known to have effects on oxidant-antioxidant balance of the body, and thus oxidative stress. Anesthesia-induced oxidative stress may affect lipids, proteins and DNA (13). Therefore, it is important to determine oxidative stress induced by anesthetic stress in individuals who are exposed to anesthetic agents for a long time or to anesthesia applications. Both duration and nature of the anesthetic procedures may affect the degree of oxidative stress (13).

In our study, in the anesthetic management of the patients undergoing tympanoplasty, controlled hypotension was provided by keeping MAP in the range of 51-76 mmHG. Respiratory frequency was adjusted to be in the range of EtCO2 35-40. Anesthetic management was performed with remifentanil loading dose followed by lidocaine and propofol as intravenous agents. Anesthesia maintenance was provided by desflurane as the inhalation anesthetic and remifentanil as the intravenous agent.

Safety of anesthetics has drawn attention in terms of toxicity and potential side effects for a long time (14). Inhalation of volatile anesthetics mechanical ventilation triggers an inflammatory response, which increases systemic oxidative stress, impairing oxidant-antioxidant balance. Multiple chronic diseases such as neurodegenerative diseases, cardiovascular diseases, and cancer are caused by oxidative stress accumulation (15, 16).

The effects of desflurane, which was used as the inhalation agent, and propofol, which was used as the intravenous agent in our study have been investigated in several studies. Intravenous anesthetics including propofol directly remove reactive oxygen species (ROS) and inhibit lipid peroxidation (17). On the contrary, inhalation anesthetics such as desflurane have been shown to produce ROS (18). In an animal study by Allaouchiche et al., it was reported that the concentrations of MDA, one of the oxidative stress markers, and consumption of GPx, which is among the antioxidant defenses, were increased in both serum and lavage samples of the pigs exposed to desflurane. Conversely, MDA levels and the consumption of GPx were decreased in the animals exposed to propofol (19). Thus, the authors demonstrated the presence of local and systemic oxidative stress in mechanically ventilated animals during desflurane exposure. One of the factors that may be responsible for desflurane anesthesia related oxidative stress is the increase in the expression of proinflammatory cytokines in macrophages (20). Propofol has similar chemical properties with alpha-tocopherol, which is an endogenous antioxidant.

General anesthesia performed to create controlled hypotension can be performed with minimal and high fresh gas flow. Minimal flow anesthesia is considered as a subtype of low flow anesthesia with the lowest possible volume and full rebreathing. This method can be performed safely with modern anesthesia devices (21). Desflurane has a low blood/gas solubility and is preferred as an ideal and safe inhalation anesthetic for minimal-flow anesthesia. In a study by Ceylan et al., considering hemodynamic data, minimal-flow anesthesia technique was reported to be a hemodynamically safe and stable method (22). Some advantages of minimal-flow anesthesia include less impairment of pulmonary function, better protection of the respiratory system, reduced cost and decreased environmental pollution (23).

In our study, we observed the effects of minimal flow and high flow anesthesia on anesthesia monitoring parameters and oxidative stress. In this study, the difference between the intraoperative SPO2 values at 5, 15 and 30 minutes was not significant, but the 60-minute SPO2 values were notably lower in the minimal flow group (98.49%) compared to the high flow group (99.03%). Kilic et al. In the study performed by Abdominal surgery, the difference between intraoperative SPO2 values reached a significant level at the 45th minute of the operation and the mean SPO2 value was found to be 98.85 in the low flow group and 99.40% in the high flow group (24). The results of these two studies support each other.

IMA has been shown to increase as a result of oxidative stress (25). Changes in the binding capacity of albumin to transit metals as a result of oxidative stress during ischemia/reperfusion lead to the formation of IMA (10, 26). In our study, we compared the effects of minimal and high flow anesthesia techniques on oxidative stress through IMA. In our study, the mean intraoperative IMA value was notably higher in the minimal flow group compared to the high flow group. However, the change in the IMA values was higher in the high-flow group.

In cells, sulfhydryl group-containing chemical compounds such as thiol play a critical function in the protection of oxidative stress (27). Between thiols and their oxidized forms, disulfides, there is a balance known as dynamic thiol/disulfide homeostasis. Increased disulfide/native thiol and disulfide/total thiol ratios in favour of disulfide can be considered as an indicator of oxidative stress. In our study, native and total thiol values were decreased in both minimal flow and high flow groups. However, the decreases in intraoperative native thiol and total thiol values were higher than the decrease in disulfide values in both groups. This indicates oxidative stress with both flow techniques, but no notable difference was found between the groups in terms of thiol/disulphide homeostasis.

Study Limitations

This study has many limitations. First, it was conducted in a single center with a relatively small number of patients. Second, we could not directly compare our results since there was no study in the literature comparing minimal and high flow techniques in terms of oxidative stress parameters. Finally, different oxidative stress parameters could be included in the study. However, this is the first study in the literature investigating the effects of different flow techniques on oxidative stress, and we think that our results will guide future studies.

Conclusion

There was no significant difference was found between minimal-flow and high-flow anesthesia techniques in terms of their effects on oxidative stress. Only IMA values were higher with minimal-flow anesthesia. However, since no notable difference was found in terms of thiol/disulfide homeostasis, evaluation of IMA alone may not be meaningful. This subject is relatively new in the literature, and further comprehensive prospective studies are needed on this subject.

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Frequency and Causes of False Negative Diffusion-Weighted Imaging in Acute Ischemic Stroke

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Abstract

Objective: The high sensitivity of diffusion-weighted magnetic resonance imaging (DWI MRI) has led to its frequent use in the diagnosis of acute ischemic stroke (AIS). However, false negative DWI MRI results have been obtained for some patients diagnosed with stroke, which led us to initiate this study. Our aim was to determine the prevalence of false negative DWI MRI scans and prevent the clinician from making a late diagnosis or misdiagnosis by relying on MRI results only.

Methods: In a retrospective file screening conducted between February 2017- February 2019, after the patients hospitalized with a diagnosis of ischemic stroke who couldn't have an MRI or who were diagnosed with transient ischemic attack were excluded, the frequency of patients with a normal initial cranial DW MRI scan whose follow up scans revealed acute diffusion restriction was identified, and vascular anatomical localization of stroke was classified according to OCSP (Oxfordshire Community Stroke Project).

Results: Of 235 patients admitted to our clinic with a diagnosis of ischemic stroke, 21 couldn't have a DWI MRI, and of 214 stroke patients who had a DWI MRI, 23 were admitted with a transient ischemic stroke attack. Of the remaining 191 patients, 14 had initially negative DWI MRI images but their clinical findings lasted longer than 24 hrs so they had a follow up MRI, which revealed an ischemic lesion in brain diffusion. In our clinic, the percentage of false negative diffusion MR images was 7.3% (14/191). The distribution of ischemia in the aforementioned 14 patients was as follows: 6 patients with posterior circulation ischemia (POCI), including 4 in brain stem and 2 in cerebellum, 2 patients with lacunar stroke (LACI), 5 patients with partial anterior circulation ischemia (PACI) and 1 patient with total anterior circulation ischemia (TACI).When the time of symptom onset was questioned, data could be derived from only 8 patients' files, and DWI MR images were obtained within the first 6 hours according to the onset of the symptoms.

Conclusion: In acute stroke patients, if symptoms of the patient are consistent with stroke during physical examination, the diagnosis of stroke should not be automatically ruled out even if brain DWI MRI is negative. The decision of urgent thrombolytic or endovascular intervention that can be taken for eligible patients should not be overlooked based on false negative DWI MRI findings. With this study, we aim to help clinicians avoid misdiagnosis or delays in diagnosis.

Key words: Diffusion magnetic resonance, Imaging, Stroke, False negative

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Introduction

Early and rapid thrombolytic or endovascular therapy has been shown to increase recovery in the long term. Acute ischemic stroke (AIS) is a clinical diagnosis based on sudden focal neurological deficits (1, 2).

Accordingly, the inclusion criteria for the landmark 1995 National Institute of Neurological Disorders and Stroke study of IV tissue plasminogen activator (tPA) for AIS included a neurological deficit measurable on NIH Stroke Scale (3). The guide published by the American Academy of Neurology (AAN) in 2010 says "DWI needs to be done for the most accurate diagnosis of acute ischemic stroke"(4).

Recently, there has been a significant increase in the use of brain MRI in the evaluation of patients with AIS (5). DWI MRI has a significantly higher sensitivity (96.7%) and specificity (93.4%) than CT in detecting acute ischemia (6). It's recommended that brain CT, one of the imaging methods, is used as soon as possible to rule out intracranial hemorrhage, tumor or abscess contraindicated to thrombolysis (7-9). Non-contrast CT is an easily accessible, versatile and rapid procedure, making it a better choice than MRI in imaging of acute ischemia when considering thrombolytic therapy, and it's also cost-effective (10).

With increasing DWI MRI use over the years, evidence showing that it cannot identify AIS albeit in a small group of patients has emerged. Causes of diffusion-negative cases are classified into 3 categories. The first group is posterior circulatory system ischemia, the second group is minor ischemia (especially in the brain stem), and the third group consists of those who present in the hyperacute period and may be overlooked in DWI MRI (11-17).

The conflicts between clinical and radiological findings in AIS patients forced us to investigate the reasons for such conflicts. We aimed to detect false negative DWI MRI prevalence in our clinic, bring to the attention of the clinicians that there may also be diffusion negative AIS cases and help them avoid misdiagnosis or delays in diagnosis by relying on MRI results only.

Methods

After consent of the local ethics committee was obtained, the patients admitted with a diagnosis of ischemic stroke to the Neurology Clinic of Ahi Evran University in Kirsehir between February 2017-February 2019 were included in the study by retrospective file screening. After the patients who couldn't have an MRI or who were diagnosed with transient ischemic attack were excluded, the frequency of patients with a normal initial DWI MR image whose follow up images revealed acute diffusion restriction was identified, and these patients were classified according to OCSP (Oxfordshire Community Stroke Project). MR images of the study patients with a negative DWI MRI were assessed by a radiologist who has no knowledge of their clinical presentation and 2 neurologists who have knowledge of their clinical examinations. In our hospital, DWI sequences; a 5-mm thick cross-section area, b value 1000 s. mm-², 1.5 Tesla MR are used.

Statistical Analysis: Statistical analyzes of the study were performed using Statistical Package for Social Sciences version 25.0 software for Windows (IBM SPSS Statistics for Windows,Version 25.0. Armonk, NY: IBM Corp., USA). In the study, descriptive statistics are given as mean∓standard deviation and n (%).

Results

Of 235 patients admitted to our clinic with a diagnosis of ischemic stroke, 21 couldn't have a DWI MRI, and of 214 AIS patients who had a DWI MRI, 23 were admitted with a transient ischemic stroke attack. Of the remaining 191 patients, 14 had initially negative DWI MRI images but their clinical findings lasted longer than 24 hours, so they had a follow up MRI, which revealed an ischemic lesion in brain diffusion (Figure 1).

In our clinic, the percentage of false negative diffusion MR images was 7.3% (14/191). The distribution of ischemia in the aforementioned 14 patients was as follows: 6 patients (42.8%) with posterior circulation ischemia (POCI), including 4 in brain stem and 2 in cerebellum. 2 patients (14.2%) with lacunar stroke (LACI), 5 patients (35.7%) with partial anterior circulation ischemia (PACI) and 1 patient (7.1%) with total anterior circulation ischemia (TACI) (Figure 2). When the time of symptom onset was questioned, data could be derived from only 8 patients' files, and DWI MRI were obtained within the first 6 hours according to the onset of the symptoms.

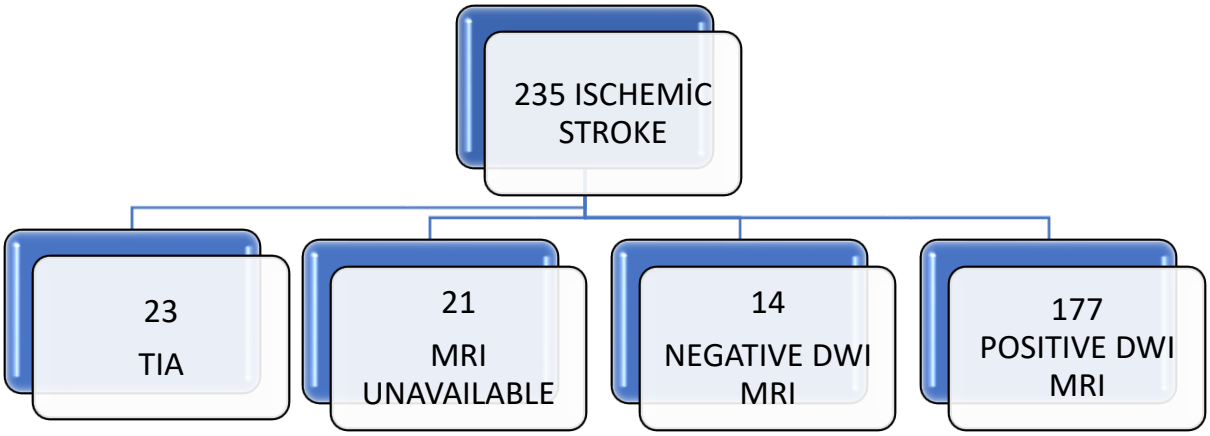

Figure 1. Distribution of Ischemic Stroke Patients

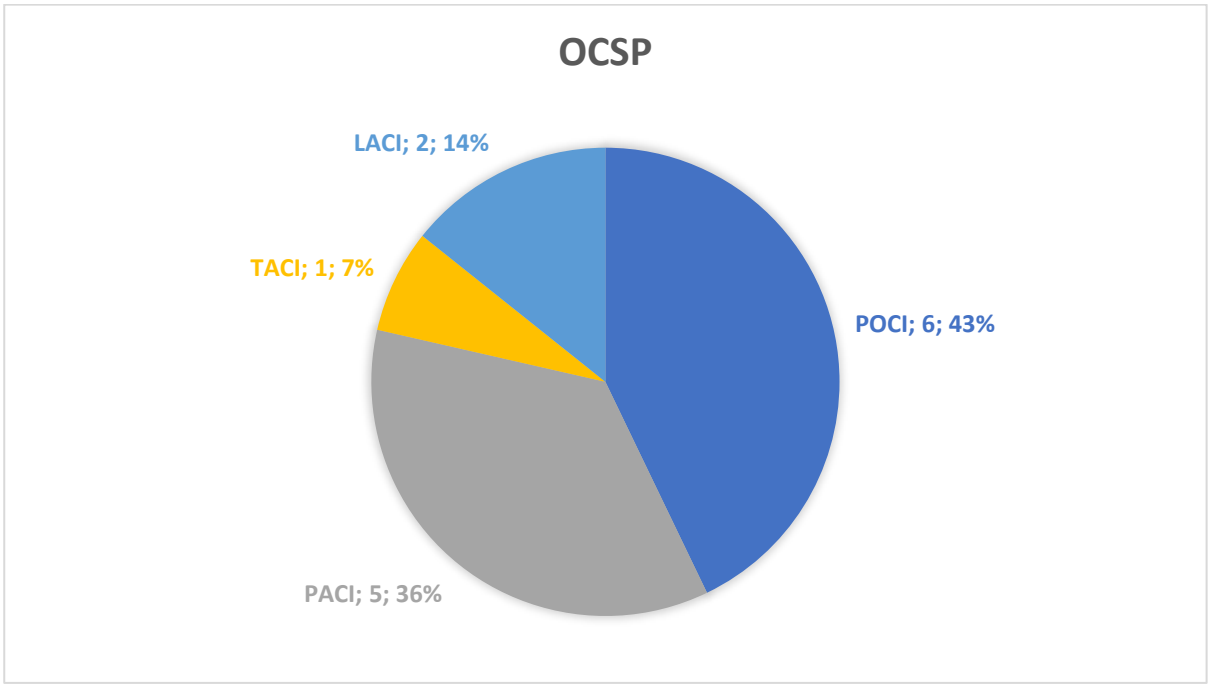

Figure 2 Clinical Classification According to OCSP (Oxfordshire Community Stroke Project)

Discussion

MRI diffusion negativity is an expected finding in patients presenting with transient ischemic stroke and stroke-like clinical presentation (seizures, migraine, vertigo). However, although examination findings of such patients were consistent with the clinical symptoms of stroke, their DWI MRI at admission didn't reveal diffusion restriction. Their follow up DWI MRI revealed diffusion limitation, which forced us to investigate the reasons for this observation and question the diagnostic criteria again.

Among stroke and TIA admissions 15.7 % of cases had initial DWI-negative scans at the beginning of follow-up (18). Edlow et al.'s review reported a false negative DWI MRI percentage of 6.8% (1.1-17.4) (9). We found a similar false negative DWI MRI percentage in AIS patients in our clinic (7.4% (14/191)).

Only 2 studies evaluated the percentage of negative DWI MRI by comparing the DWI MRI scans performed in the first 6 hours of stroke with the scans performed 6 hours later (19, 20). In the first study, the rate of negative DWI MRI scans performed in the first 6 hours of stroke onset was 5.9% (2 of 34 patients) and 13.7% (16 of 117 patients) performed 6 hours later (19). In the second study, the rate of negative DWI MRI scans performed in the first 6 hours of stroke onset time was 14.3% (2 of 14

patients) and 2.2% (1 of 45 patients) performed 6 hours after the stroke onset time (20). Some studies made comments about DWI MRI time and the rate of negativity although they did not use the 6-hour threshold value. Chalela et al. found that diffusion negativity was strongly associated with DWI MRI scan (OR (95% CI) 5.8 (2.3–14.9)) performed in the first 3 hours(21). Similarly, Simonsen et al. reported that DWI-negative AIS patients underwent DWI MRI sooner after symptom onset than DWI-positive AIS patients, an average of 109 minutes versus 120 minutes, respectively ($p<0.05$) (22). All of our patients whose records were accessible presented within the first 6 hours and diffusion positivity was detected within 24 hours in repeated scans. But data about the duration could be obtained from only 8 patients' files.

10% of AIS cases are brainstem ischemia and observed in pons, medulla oblongata and the mesencephalon. The main arterial supply of the brain stem is provided by the vertebral artery, anterior spinal artery, posterior inferior cerebellar artery and posterior cerebral artery. A study by Phillippe et al. reported that of 155 brainstem ischemia patients, ischemia was localized in mesencephalon in 12 patients, pons in 115 patients and medulla oblongata in 31 patients. Standard axial (5 mm) and thin-section coronal (3mm) DWI MRIs were performed for each patient. 3 (1.9%) patients had ischemia in the medulla oblongata, which could only be viewed in thin-section coronal (3mm) DWI MRI. In comparison, 35 (22.6%) patients had ischemic lesions, which were more prominent with coronal imaging than axial imaging and found to be significantly smaller (0.06 cm3, $p <0.001$) (23). If the lesion is small, high-resolution DWI MRI combining thinner axial and coronal sections increases sensitivity in identifying these lesions (13, 24).

In a meta-analysis of 5 studies in the literature, the odds ratio (OR) of posterior circulatory ischemia relative to the anterior system was found to be 5.1 (9). However, in our study, the ratio of posterior system to anterior system was 8/6, whereas Bulut et al. found an equal ratio (25).

There's limited number of studies investigating the relationship between DWI MRI false negativity and small stroke volume. One study reported an average infarct size ± standard deviation of 0.19 ± 0.16 cm^3 (range 0.05–0.5 cm^3) (26).

False negative conditions can occur especially in the vertebrobasillary region and in lacunar ischemia due to its small size or anisotropic sensitivity artefacts (6, 13, 26). 3.0 Tesla MRI is more advantageous due to higher signal to noise ratio (SNR) but has larger sensitivity artifacts (27, 28). Despite the high SNR of 3.0 T MRI, DWI contrast was 18% lower compared to 1.5 T MRI, which surprisingly led to the finding that diffusion changes in acute AIS are less visible in 3 T MRI, which also has lesser diagnostic power. In the diagnosis of AIS, the sensitivity of 1.5 T MR DWI was 99.1% and that of 3.0 T MR was 92.5%, and the specificity decreased from 97.8% at 1.5 T to 84.1% at 3.0 T (6).

In addition, as the magnetic force area increased, image distortion artifacts became heavier (27, 29, 30). These bright artifacts may mask some early ischemic changes, especially in the skull base. This is particularly worrisome at the very early stage of stroke (in the first 2 hours) when there are certain DWI findings. In other words, false negativity increases with early imaging and 3 T MRI (6).

After it was understood that there might be negative DWI MRI scans, various techniques were tried to increase the sensitivity of MRI. Primary approaches included perfusion-weighted MRI (PWI) scans incorporating gadolinium-based and arterial-spin-labeled techniques or increasing the spatial resolution of DWI MRI sequences, reducing geometric distortion or a second coronal section scan from the posterior fossa were applied (9). In another study compared imaging methods to help the clinical detection of cerebral infarction(DWI was 97% (33/34) , DTI was 94% (32/34), SWI was 88% (30/34), T2WI was 79% (27/34)) and found that combined imaging is better than single imaging (31).

Addition of a PWI scan may increase DWI sensivity from 92% to 97.5% (22). However, its disadvantages include time and contrast agent side effects.

To increase the DWI sensitivity, the 'b value', which is a value that reflects the strength and duration of the diffusion gradients applied to water molecules in the brain, can be increased. It is argued that the increase in the b value (1000 s. mm^{-2}) in diffusion-weighted scans may increase the sensitivity to minor ischemia (9, 32, 33).

Currently, neither complementary MRI sequences such as PWI nor high b-value DWI techniques have gained wide recognition in the clinical evaluation of patients with AIS (9).

The study has some limitations. First, it is necessary to validate these findings with a larger cohort to reach a more definitive conclusion. Second, this study was retrospective. Third, MRI’s were not always performed by the same technician.

Conclusion

These results show that in AIS cases, if the patient's symptoms are consistent with stroke on examination, the diagnosis of stroke should not be immediately excluded, even if DWI MRI is negative. The decision of urgent thrombolytic or endovascular intervention that can be taken for eligible patients should not be overlooked based on false negative DWI MRI findings. We recommend that the clinician should rule out conditions that cause contraindication to brain CT in all patients with suspected AIS during examination and assess such patients in terms of the suitability of IV tissue plasminogen activator treatment without delay.

Future studies should focus on methods to increase DWI MRI sensitivity, the hour at which diffusion-negative patients develop diffusion positivity, and its relationship with the volume of ischemia.

Ethics Committee Approval: This study was approved by the Ethical Committee of Kirsehir Ahi Evran University School of Medicine number of 2019-04/56.

Peer-review: Externally peer-reviewed.

Author Contributions*:*

Concept, Design, Literature search, Data Collection and Processing, Analysis or Interpretation, Writing – BES

Conflict of Interest: No conflict of interest was declared by the authors.

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Quality of Life, Emotional and Behavioral problems in Full-Term Small for Gestational Age Infants at Preschool Age

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Abstract

Objective: To determine the emotional, behavioral, and developmental problems and quality of life of children born as Term Small for Gestational Age (SGA) in the preschool period, and to compare them with children born as term appropiate for gestational age (AGA).

Method: This study conducted as a prospective case control study. Term SGA babies who were followed up in the Neonatal Intensive Care Unit were taken in the study group, while babies born with term AGA were taken in the control group. All participants' parents filled the Sociodemographic form, Child Behavior Checklist (CBCL) and Pediatric Quality of Life Scale (PedsQL) and were asked questions to complete the ADSI by expert psychologists.

Results: 20 SGA (63 months ± 7 months) born term and 20 AGA (59 months ± 8 months) born term children were taken in the study group. There was no significant difference between the groups in terms of gestational age, gender, and age at the outpatient clinic. Social problems were significantly higher in the SGA group ($p = 0.014$). The school functionality score (SchFS) was found to be significantly lower in the SGA group ($p <0.01$). In the developmental evaluation, there was no statistically significant difference between the two groups.

Conclusion: The long-term follow-up of term SGA patients is important, as inadequate recognition or inadequate treatment of the disorders that may arise may cause impairment not only in the quality of life and psychiatric condutions of the patients, but also in their ability to adapt to the society.Key words: Chondroblastoma, lower extremity, pain.

Keywords: SGA, behavioral, developmental, emotional, quality of life

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Introduction

Small for gestational age (SGA) newborn according to the gestational week is defined as a baby with birth weight below the 10th percentile for the gestational age (1,2). SGA is reported in 3%–10% of all newborns (3). It is widely accepted that SGA newborns are more likely to experience adverse neurodevelopmental and behavioral outcomes than newborns classified as appropriate for gestational age (AGA). Studies have shown that children born as SGA are associated with higher risk of poor neurodevelopmental and behavioral outcomes including minor to major deficits than those with AGA (2,3). SGA babies are more likely to have behavioral problems, low social competence and poor academic performance later in life (4).

Most studies in the literature include preterm, low birth weight SGA infants (5,6) or evaluate SGA infants in terms of behavioral problems in school age and adolescence (7,8). The preschool period is a quite challenging time where multiple factors are involved to recognize and measure psychiatric symptomatology. To the best of our knowledge, only two studies examined behavioral problems of term SGAs in preschool period. In these studies, SGA and control AGA groups have been evaluated in preschool period and it has been determined that behavioral problems were not higher in SGA children (9,10).

Academic performance and functioning expectations are higher for school-age children compared with those for preschool-age children. Therefore, more comprehensive tests can be used to determine a child's developmental level, academic success, cognitive level, and intelligence level compared with those conducted in preschool age. Accordingly, preschool assessment of developmental differences between children born as SGA and AGA may not be reflected in their entire life. In a study investigating preterm and term SGAs and AGAs, Tanis et al. showed that though there was no statistically significant difference, SGA children at school age had an average of 3 points lower IQ (8). In addition, long-term adverse outcomes on language and speech development, fine and gross motor skills have been reported in children born as SGA (5,11,12). However, the developmental outcomes for full-term SGAs are not fully understood yet.

Quality of life (QoL) is a subjective term that is defined as a person's social, emotional, and physical well-being and ability to perform the usual tasks of daily life (13,14). There are relatively few published studies on the health-related quality of life (HRQoL) of babies born as SGA. It is difficult to assess and determine the quality of life in young children. Therefore, in the absence of self-report in pediatric cases, valid and safe parent reports are required (15). In the literature, QoL has mostly been evaluated in preterm and low birth weight children (16). In a national study conducted in Finland, HRQoL has been found to be significantly lower in very low birth weight children compared with full-term controls at 5 years old (16). However, evidence about the QoL of term SGA in at the preschool period is quite insufficient.

To the best of our knowledge, there is no previous study comparing full-term SGA children and AGA children in terms of QoL, emotional and behavioral problems, and developmental levels in the preschool period. For this reason, our aim in this study is: 1) Whether full-term SGA children are at higher risk for emotional and behavioral problems in preschool period compared to AGA children, 2) To determine the quality of life of term SGA children in the preschool period and to compare them with AGA children, 3) To determine whether there are developmental differences in term SGA and AGA children in the preschool period

Methods

Procedure and participants

Our study was planned as a prospective case–control study. Full-term SGA (gestational age≥37 weeks) babies born between January 1, 2011 and January 1, 2014 and followed up in Gazi Yaşargil Training and Research Hospital Neonatal Intensive Care Unit were planned to be included in the study. Gazi Yaşargil Hospital ethics committee approval was obtained.

Inclusion / Exclusion Criteria

The criteria for inclusion in the study group were;

1) To be born after completion of 37 weeks of gestation,
2) To be Small for Gestational Age,
3) Hospitalized, and followed up in the neonatal intensive care unit,
4) Who had accessible medical records of hospital stay, and agreed to take part in the study

The criteria for inclusion in the control group were.

1) To be born after completion of 37 weeks of gestation,
2) To be Appropiate for Gestational Age,
3) Had no history of hospitalization in the neonatal period or chronic disease.

Term baby was defined as a newborn born at the 37th or above gestational week. Fenton curve was used to evaluate birth weight according to gestational age (17). According to the Fenton curve, babies with birth weight below the 10th percentile were evaluated as SGA, whereas those between the 10th and 90th percentile were evaluated as AGA. Having a history of congenital and/or chromosomal anomalies, intrauterine infection, perinatal asphyxia, intracranial hemorrhage, periventricular leukomalacia, ventricular dilatation, hydrocephalus, and microcephaly were excluded from the study. After obtaining approval from the ethics committee, the patients who met the criteria were identified from the hospital database and the patient files were examined. Week of gestation, birth weight, mode of delivery, gender, hospitalization diagnosis and hospitalization periods were examined from the patient files. After examining 65 files, 20 patients who could be contacted and informed about the study were included in the study group. Simultaneously, it was intended to include 20 aged-matched term AGA children who were allowed to the pediatric outpatient clinic for different reasons. Consent was obtained from the families. All cases were planned to be evaluated by a child and adolescent psychiatrist.

Evaluation Tools

Sociodemographic Form

The sociodemographic characteristics of the participating children were obtained using the sociodemographic data form developed by the researchers. The child's age, gender, sibling presence, demographic information of the mother and father, the duration of breastfeeding, and the presence of psychiatric disease in the family were evaluated in the form.

Child Behavior Checklist

The Child Behavior Checklist (CBCL) was developed by Achenbach and Edelbrock (1983) to evaluate emotional and behavioral problems in children aged between 4–18 years in line with the information obtained from parents (18). Adaptation studies of the scale to Turkish children were conducted by Erol et al. (19). The questions in the scale are answered and rated by the parents using a 3-point Likert scale. Options are scored "Not true" as "0", "somewhat or sometimes true" as "1" and "very true or often true" as "2". The scale consists of eight subscales: somatic complaints, withdrawn, anxiety/depression, thought problems, social problems, attention problems, delinquent behavior, and aggression. "i

Internalizing problems" and "externalizing problems." scores are obtained in the scale as two distinct behavioral symptom scores. "Total problem score" is obtained from the sum of subscale scores. Test–retest reliability and internal consistency values were found to be 0.84 and 0.88, respectively (19). In our study, a cut-off points of 65 was established for the scores obtained from the CBCL.

Pediatric Quality of Life Inventory for Ages 5–7 (PedsQL™ 4.0)

The PedsQL™ was developed in 1999 to evaluate the HRQoL in children and adolescents aged in 2–18 years (13). There is only a parent form for ages 2–4 years and both parent and Child/Adolescent forms for ages 5–18 years. The 23-item scale allows for assessment of both healthy children and pediatric patients. The scoring ranges from 0 to 100. "Never" corresponds to 100 points, "rarely" to 75 points, "sometimes" to 50 points, "often" to 25 points, and "almost always" to 0 points. The scores obtained from the items are summed up and then divided by the number of filled items to obtain the total scale score. Scale scoring is presented as total scale score (TSS), psychosocial health total score (PsychoSS), physical health score (PSS). PsychoSS (15 items) is formed by calculating the mean scores of social functioning subscale score (SFS), emotional functioning subscale score (EFS), and school functioning subscale score (SchFS) (13). The Cronbach alpha coefficient was determined as 0.93 for both parent and children's reports (13,14). Üneri et al. performed the study of Turkish validity and reliability for ages 2–4 and 5–7 years (20). The validity of the parental reports was sufficient for both age groups, and the validity of the self-report scale was found to be low for the 5–7 age group (20). In our study, a parent-filled form of the scale for preschool children aged 5–7 years was used.

Ankara Developmental Screening Inventory

Ankara Developmental Screening Inventory (ADSI), developed in 1992, is a screening inventory that is often used in Turkey to assess the developmental status of children between the ages of 2 and 66 months (21). ADSI is based on the assessment of 154 items and 4 developmental fields (self-care and social skills, language-cognitive, gross and fine motor development, and general development) answered in the form of "yes" or "no" by mothers. Results for each field are expressed in months and/or years. The Cronbach alpha coefficient were 0.98 for 0–12 months and 0.88 for 13–44 months as well as 45–72 months (21).

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (SPSS, Chicago, IL, USA). Kolmogorov–Smirnov and Shapiro–Wilk tests were used to determine data distribution. Mann–Whitney U-test was used to analyze the continuous nonparametric variables; chi-squared or Fisher's exact test was used to compare categorical variables. Normally distributed variables are presented as mean SD, whereas nonparametric continuous variables are presented as median (IQR). Categorical variables are presented as n (%). $P < 0.05$ was considered statistically significant.

Results

Twenty children born as SGA (68±4.4 months) and 20 children born as AGA (64±6.8 months) at term participated in our study. Approximately 65% (13) of the patients in the SGA group and 60% (12) of the patients in the AGA group were male. There was no significant difference between the SGA and AGA groups in terms of gestational age, gender and age of outpatient evaluation. According to SGA group case report forms, the mean birth weight was 1862±142 g, gestational week was 37.6±1.3 weeks, mode of delivery was 50% (n: 10) normal spontaneous vaginal delivery, median length of stay was 9 (30) days There was no difference between the sociodemographic findings of the SGA and AGA groups. The sociodemographic data of the groups are given in Table 1

The mean scores of the CBCL subscales were compared between the groups. Subscale mean scores of withdrawn was 58±8.4, somatic complaints was 58.2±12, anxiety/depression was 61±11, social problems was 57±8.7, thought problems was 58±7.5, attention problems was 58±9.5, delinquent behavior was 55±7.1, and aggressive behavior was 56.7±8.3 in the SGA group and 54±5.6, 56±6.5, 56±7, 52±4.1, 55±6.6, 54.5±5.1, 55±7.3, 54±6.2 in the AGA group, respectively.

Approximately 30% of children born as SGA had internalizing problems and 25% had externalizing problems. Although not statistically significant, 30% had anxiety-depression problems, 25% had aggressive behavior problems, 20% had attention problems, and these rates were higher than the AGA group. In the social problems subscale, the SGA group scored 57.10 ± 8.74 points, the AGA group 52.10±4.12 points, and social problems were determined to be significantly higher in the SGA group (p:0.01). CBCL assessments of SGA and AGA groups are given in Table 2.

When the PedsQL scale was evaluated, SchFS was found to be significantly lower in the SGA group (70.35±26.92) compared with that in the AGA group (91.76±11.17) (p:0.01). There was not a statistically significant difference between the SGA and AGA groups with regard to TSS, physical PSS, PsychoSS, EFS, and SFS (Table 3).

The evaluation of ADSI showed no statistically significant differences between the groups in terms of developmental retardation in ADSI subtests (p:0.10). (Table 4)

Table 1. The Demographic Characteristics of the SGA and AGA Groups

	SGA (n:20)	AGA (n:20)	p
Admission age to the polyclinic	68±4.4	64±6.8	0.06
Male gender	13(%65)	12(%60)	0.51
Cesarian delivery	10(%50)	10(%50)	1
Gestational age	37.6±1.3	38.1±0.87	0.18
Maternal age	32± 6.2	33.6± 5.5	0.53
Educational status of the mother			0.09
Pre-high school	15(%75)	11(%55)	
High school and beyond	5(%25)	9(%45)	
Mother working status			0.09
Not working	18(%90)	14(%70)	
Working	2(%10)	6(%30)	
Mother health condution			1
Healthy	18(%90)	18(%90)	
Chronic illness	2(%10)	2(%10)	
Paternal age	35±4.9	36±6.1	0.42
Educational status of the father			0.09
Pre-high school	18(%90)	14(%70)	
High school and beyond	2(%10)	6(%30)	
Father working status			0.49
Not working	2(%10)	0	
Working	1818(%90)	20(%100)	
Mother health condution			0.18
Healthy	16(%80)	19(%95)	
Chronic illness	4(%20)	1(%5)	
Sibling existence	11(%55)	13(%65)	0.56
Consanguineous marriage	12(%60)	6(%30)	0.05
Breast milk time			0.71
<6 months	6(%30)	4(%20)	
≥ 6 months	14(%70)	16(%80)	
Family history of psychiatric illness	5(%35)	2(%10)	0.23

Table 2. CBCL mean scores of the SGA and AGA groups

	SGA group	AGA group	p
CBCL Total Problems	57±13	52±11	0.19
Internalizing Scale	58±13	53±11	0.15
Externalizing Scale	53±11.5	50±11.4	0.38
Withdrawn	58±8.4	54±5.6	0.10
Somatic Complaints	58.2±12	56±6.5	0.46
Anxious/Depressed	61±11	56±7	0.10
Social Problems	57±8.7	52±4.1	0.02
Thought Problems	58±7.5	55±6.6	0.29
Attention Problems	58±9.5	54.5±5.1	0.18
Delinquent Behaviour	55±7.1	55±7.3	0.86
Aggressive Behaviour	56.7±8.3	54±6.2	0.25

CBCL: Child Behaviour Check List

Table 3. PedsQL mean scores of the SGA and AGA groups

	SGA group	**AGA group**	**p**
PSS	67±27	77±17	0.23
EFS	77±15	81±15	0.47
SFS	82±19	89±14	0.21
SchFS	70±26	91±11	0.01
PsychoSS	77±15	82±21	0.45
TSS	73±19	83±12	0.84

PedsQL: Pediatric Quality of Life Inventory. *PSS:* Physical health summary score. *EFS:* Emotional functioning score. *SFS:* Social functioning score. *SchFS:* School functioning score. *PsychoSS:* Psychosocial health summary score. *TSS*:Total scale score.

Table 4. ADSI mean scores of SGA and AGA groups

	SGA group	AGA group	p
Language-cognitive	59±11	62±10	0.32
Fine motor	56±11	62±10.5	0.28
Gross motor	57±7.7	53.9±6.4	0.17
Social skills/Self-Care	57.8±9.4	55.3±8.5	0.42
General development	61.9±9.8	63.8±8.7	0.38
ADSI total score (developmental delay)*	4 (%20)	0	0.10

ADSI: Ankara Developmental Screening Inventory

Discussion

In our study, children at preschool period between the ages of 4–6 who were born as SGA at term and children who were born as AGA at term in the same age group were compared in terms of behavioral problems, QoL, and developmental levels. It was found that social problem scores were higher, and school functioning scores were lower in children with SGA. In the CBCL assessment of full-term SGA children, 30% of the children had internalizing problems and 25% had externalizing problems. Studies of children born as SGA show conflicting results. In the literature, there are many studies conducted with preterm and low/ very low birth weight (LBW, VLBW) SGA children in various age groups (5-7). These studies have shown that SGA children compared with AGA children have behavioral and emotional problems at various levels and their academic success is lower.

On reviewing the literature, it was shown that SGA is associated with various psychiatric problems, including attention deficit disorder symptoms, learning difficulties, social problems, anxiety-depression and aggression (3,16,22-24). In some studies, SGA delivery has not been found to be associated with higher risk of behavioral problems and psychiatric symptoms (9,10). A large sample study conducted in Canada did not find any statistically significant results for internalizing problems and externalizing problems in SGA-born infants at the age of 4–16 years (23). Children born preterm were not included in our study. It has been shown that children born LBW/VLBW or preterm are at least two times more at risk for emotional and behavioral problems than children born term (4).

In our study, anxiety-depression problems were found in 30% of SGA children, aggressive behavior in 25%, and attention problems in 20%, and although these rates were higher than those in the AGA group, no statistically significant difference was identified. In a study using CBCL, attention deficit, delinquent behaviors and low social competence were found in adolescents born SGA (25). In a large sample sized study evaluating the behavior of full-term children aged 6.5 years, SGA birth was found to negatively affect social development (26). School is the first environment in which children need to concentrate on specific tasks for a long time and have continuous social interaction within a group. Most externalizing findings are more pronounced in school-age children. The low sample size in our study and the fact that the participants were still in the preschool period may explain these results.

In our study, the SGA group were found to have higher social problems than the AGA group. Low social competence has been reported in children born SGA (25). In a study by Yang et al. SGA was found to negatively affect social development (26). The presence of social problems causes low social competence and may be associated with neurocognitive problems and/or impairment in school functioning at school age (25,27). We can assume that parents who have a baby born SGA are more anxious than parents with AGA children. Therefore, when these children are raised, problems such as parents' concerns about the health status of the child may cause the children to be raised in a more protective environment. Growing up in a more protective environment can affect both the child's social skills and their coping skills. Although there is no consensus about why social problems may be more common in children born with SGA, we think that it could theoretically be one of the effects of growing up in a more protective family environment. Although it is not statistically significant, the presence of anxiety and depression problems in 30% of the SGA group may support this situation.

Because the children participating in the study were in preschool period, the QoL was determined by the parents. In our study, the SchFS was found to be significantly lower in the SGA group compared to the AGA group. We considered that in the SGA group with more social problems, school functionality might be lower in relation to this. The literature is rich in evaluating HRQoL in preterm and/or LBW/VLBW children (16,28,29). It has been found that the QoL in preschool ages and adolescence is often lower in preterm children (29). Zubrick et al. found that SGA children were more likely to have lower academic skills in school (24). In another study, a 10%–15%

increase in school-related problems has been found in SGA cases (22). Term SGA children at ages 12 and 18, was associated with poorer school performance (30). It has also been concluded that SGA infants may have relatively mild disorders that are easily overlooked but may have a significant impact on their QoL later in adulthood (28). However, as much as we know, there is no study comparing children born SGA at term with those born AGA in terms of QoL in the preschool period. We considered that in the SGA group with more social problems, school functionality might be lower in relation to this.

Parents' knowledge of child development, combined with their cultural, social, and educational situation, may lower HRQoL compared with children's self-reports, and/or parents' expectations may affect the HRQoL rating. It is also possible that defining emotional and psychosocial problems requires incorporating more detail than found in the structure of PedsQL. Therefore, we can assume that our results may underestimate HRQoL in SGA children.

ADSI evaluation showed four children (20%) with general developmental retardation in the SGA group, but no statistically significant difference was found compared with that in the AGA group in terms of general development and ADSI subtests. According to a meta-analysis released in 2020, it term SGA children were shown to have cognitive disadvantages from infancy to middle childhood compared with AGA children (27). Lower school success and lower IQ scores have been reported in SGA children (3). However, preterm SGAs were also included in the study sample in which low IQ scores were determined in the aforementioned study. In a study involving preterm and term SGAs and AGAs, interestingly, AGA children exhibited more borderline skills than SGA in terms of motor skills, although this was not statistically significant (8). Arcangeli et al. have reported in a meta-analysis study that neurodevelopmental scores were lower in full-term babies with SGA than full-term babies with AGA (2). In the literature, it has been shown that full-term SGAs have lower motor skills and language development and have poorer cognitive outcomes compared with those in full-term AGAs (5,12). However, it is not known exactly whether all children born SGA are at the same risk. In contrast, the small size of the groups requires careful interpretation of negative findings. While evaluating the harmful effects of born as SGA on development, it should be distinguished from other risk factors such as premature birth, perinatal complications, and serious socioeconomic differences.

Our study has some limitations. The low sample size is one of the limitations of our study. Because 45 of the 65 full-term SGA children born between January 1, 2011 and January 1, 2014, who were supposed to become involved in this study, could not include, the number of cases was limited to 20. Although preschool behavioral problems predict some behavioral problems at school age (9), certain behavioral problems such as inattention may not be detected definitely before starting school. Although the absence of an in-depth psychiatric examination made it difficult to detect emotional and behavioral problems, the use of the CBCL scale, which has been shown to be a valid measure for behavioral and emotional problems, has largely overcome this limitation. QoL assessment was based solely on parent reports, as our sample was not of school age. At the same time, intelligence quotient test could not be added to the developmental assessment because there was no applicable test to this age group in the study center. However, the use of valid and reliable psychometric tests and the inclusion of the control AGA group have largely overcome these limitations. When the results of this study are evaluated, future studies are needed to examine the effects of parental attitude on the quality of life with emotional and behavioral problems in children.

Conclusions

We think that being SGA (among term babies) may negatively affect the behavior, quality of life and developmental characteristics of the child in the long term. The findings of this study show that routine screening is needed in order to determine preschool children in terms of psychiatric symptoms and quality of life perspective and to prevent problems in later childhood.

Ethics Committee Approval: Ethics committee approval was received for this study from Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee. (Ethics Committee date and number: 2017/97)

Author Contributions:

Concept: Y.G, K.Ç; ***Design:*** Y.G.,O.O. D, N.O.; ***Literature Search:*** Y.G.,O.O.D, N.O.; ***Data Collection and Processing:*** Y.G.,O.O. D, N.O. ***Analysis or Interpretation:*** K.C,G.Y.A.; ***Writing:*** Y.G

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An Analysis of Personal Indecisiveness and Problem Solving in Women with Premenstrual Syndrome: A Cross-Sectional Study in Turkey

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Abstract

Objective: Premenstrual syndrome (PMS) is a cyclical disorder that emerges at the luteal stage of the menstrual cycle, cognitive, emotional, and behavioral changes. This study was conducted to determine the relationship between premenstrual syndrome (PMS), personal indecisiveness, and problem solving among female university students.

Methods: This cross-sectional study was conducted with 1,157 female students in a university in the eastern region of Turkey. Data were collected using the Introductory Information Form, Premenstrual Syndrome Scale, Personal Indecisiveness Scale, and Problem-Solving Inventory. Students were classified as those who had PMS and those who did not based on the results of the Premenstrual Syndrome Scale.

Results: Of the students in this study, 70.4% were found to have PMS. According to the logistic regression analysis, it was determined that the rates of indecision (OR:1.062), being impetuous while making decisions (OR:1.063), and being exploratory while making decisions (OR:1.055) were higher in students with PMS than students without PMS. Moreover, the rates of insufficient self-perception in solving problems (OR:.952), being avoidant in solving problems (OR:1.084), no self-confidence in solving problems (OR:1.066), and acting without thinking while solving problems (OR:1.091) were higher among students with PMS compared to those who did not have the condition.

Conclusion: The results of this study indicate that PMS was an important risk factor for indecisiveness and inadequacy in problem solving.

Key words: Premenstrual syndrome, personal indecisiveness, problem solving, menstruation

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Introduction

Premenstrual syndrome (PMS) is a cyclical disorder that emerges at the luteal stage of the menstrual cycle, which regresses as menstruation begins and shows itself through bodily, cognitive, emotional, and behavioral changes (1). PMS may emerge at any age following menarche and is quite common among women. According to reports, approximately 80% of women experience at least one mild PMS symptom (2), 20–50% experience moderate symptoms (3), and approximately 5% experience severe symptoms that negatively affect their lives (1-4). Mood and behavioral changes are among the most common PMS symptoms. The most frequent mood change symptoms include indecisiveness, tension, irritability, impatience, attention deficit, and forgetfulness (3, 5, 6).

The decision-making process is performed by recognizing and defining a decision-requiring case, collecting information and determining the options, examining and assessing the options, selecting and implementing the option that will yield the most positive and effective results, performing a selection once again after assessing the results, and receiving feedback regarding the selection (7-9). The decision-making process can be regarded as a process of establishing balance in one's internal world (7, 8). Indecisiveness, however, can delay the process of conducting an action (10). Therefore, it may adversely affect people's daily routines and cause them to become doubtful or even neurotic (11). It is known that some stimuli triggered by daily events also trigger PMS in women with doubtful and neurotic (12).

The decision-making process is also required for solving problems. A problem is mainly an event that prevents one from reaching one's goals (7, 8, 11). Problem solving is a process in which cognitive and psychological tools are employed to terminate any sorts of difficulties encountered on the way to reaching certain goals that require certain efforts (13). Both the decision-making process and problem-solving skills consist of different dimensions and are affected by different cases. When studies involving PMS were examined in the literature, it was found that many dimensions related to PMS were evaluated, but no studies could be found on how PMS affects both of these cognitive processes. Healthcare professionals need to learn more about emotional distress in women with PMS, including indecision and difficulty in solving problems. For this reason, ıt is important to investigate the relationship between PMS, indecisiveness, and problem-solving efficiency. Therefore, this study aimed to determine the prevalence of personal indecision and problem-solving difficulties in students with PMS to contribute to the relevant literature.

Methods

Research Design and Sample

This cross-sectional study was performed with female students studying at an university, which is located in the eastern part of Turkey. There were 15 faculties at the time at which the study was conducted, and there were 18,800 female students studying in these faculties. A statistical program, which was the publicly available OpenEpi version 3, was used to calculate the sample size (http://www.openepi.com). In the power analysis, when the prevalence of PMS was accepted as 62% (14), the sample size was calculated to be at least 1,157 students, with two-way significance level, 97% confidence interval and 80% power to represent the population.

The number of students from each faculty was determined in proportion to the weighted figures for faculties in the entire population. The faculties whose students were included were as follows: Faculty of Education (n=165; 1,910 students in total); Faculty of Science and Letters (n=126; 1,458 students in total); Faculty of Economics and Administrative Sciences (n=163; 1,886 students in total); Faculty of Divinity (n=76; 880 students in total); Faculty of Engineering (n=75; 868 students in total); Faculty of Health Sciences (n=265; 3,067 students in total); Faculty of Medicine (n=38; 440 students in total); Faculty of Pharmacy (n=15; 174 students in total); Faculty of Dentistry (n=27; 312 students in total); Faculty of Fine Arts, Design, and Architecture (n=36; 417 students in total); Faculty of Law (n=38; 440 students in total); Faculty of Communication (n=44; 510 students in total); Faculty of Sports Sciences (n=50; 579 students in total); Faculty of Agriculture (n=13; 151 students in total); and Faculty of Nursing (n=26; 301 students in total). The students in these faculties were listed using the simple random sampling method—a probability sampling method—and students within the samples were determined using a random number table. The inclusion criteria were being between 18 and 49 years of age, being single or married, and having no children. Students who did not have any diagnosed psychiatric disorder, declared that they had regular menstrual periods (every 22-35 days), did not have any diagnosed somatic diseases or gynecological or hormonal disorders and were not using any medication or contraceptive pills were included in the study. Participants' verbal consent

was obtained before the initiation. The researchers stated to the participants that the data obtained would be published for scientific purposes, without using their names, and that they could leave the study at any time. The study was assessed by the Ethics Committee of Health Sciences, and their consent was obtained (Decision no: 2018/13-1).

Measures

The data were collected between May and July 2018 using an Introductory Information Form, the Premenstrual Syndrome Scale, the Personal Indecisiveness Scale, and the Problem-Solving Inventory. The questionnaire forms were personally filled out by the students. The Introductory Information Form was created by the researchers and included items examining certain sociodemographic and menstrual cycle characteristics of the students. With respect to the sociodemographic characteristics, questions on the student's age, place of residence, and department were asked, and the menstrual cycle characteristics questions targeted information such as the menarche age, and duration of menstrual flow.

Premenstrual Syndrome Scale (PMSS)

The PMSS was developed by Gençdoğan (2006) with the aim of measuring the severity of premenstrual symptoms. This 5-point Likert-type scale has 44 items. The scale has nine subdimensions for PMS syndromes, such as depressive feelings, anxiety, fatigue, irritability, depressive thoughts, pain, changed appetite, changed sleep, and swelling. The total PMSS score is obtained from the total score of the nine subdimensions. The lowest score that could be obtained on the scale is 44, while the highest score is 220. The higher the score is, the more severe the PMS symptoms are. While assessing the results of the PMSS, the presence of PMS is evaluated in terms of whether the score is higher than 50% of the highest possible score on the entire scale and its subdimensions. For instance, the highest score possible is 220, and accordingly, 50% of this score is 110 points. Therefore, scores of 111 and above are indicative of PMS. The Cronbach's alpha was 0.75 for the scale (12), and this value was found to be 0.96 for this study.

Personal Indecisiveness Scale (PIS)

The PIS scale developed by Bacanlı (2005) consists of 18 items to measure how people make decisions and how indecisive they are. The scale has two subdimensions: Exploratory Indecisiveness and Impetuous Indecisiveness. Exploratory Indecisiveness contains items such as "I make my decisions and give up quickly," while Impetuous Indecisiveness has items such as the following: "I have difficulties when I need to make urgent decisions." The possible scores on this 5-point Likert-type scale range from 18 to 90. The scores for the Exploratory Indecisiveness subdimension range between 10 and 50, and the scores for the Impetuous Indecisiveness subdimension vary between eight and 40. A higher score means a higher level of indecisiveness, while a lower score indicates that decision-making skills are adequate. Cronbach's alpha of this scale was 0.90 (14), which was found to be 0.94 for this study.

Problem Solving Inventory (PSI)

This inventory was developed by Heppner and Petersen in 1982 and adapted into Turkish by Şahin, Şahin, and Heppner in 1993. The PSI is an instrument that assesses what people think about problem solving and relevant approaches. It has six subdimensions based on approaches: an avoidant approach, a self-confident approach, a thinking approach, a planned approach, an impetuous approach, and an evaluator approach. With 32 items assessed within this 6-point Likert-type scale, the lowest possible score is 32, while the highest is 192. A higher score on the entire inventory indicates that the individual perceives themselves as inadequate in terms of problem-solving skills. Cronbach's alpha of this inventory was 0.88 (15), which was found to be 0.71 in this study.

Statistical Analysis

The data were assessed using the Statistical Package for the Social Sciences version 25.0 for Windows (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to measure the goodness of fit, and the data were found to show normal distribution. To compare the quantitative variables between the students who did and did not have PMS, an independent t-test and a chi-squared test were utilized to compare the categorical data. The variables affecting the severity of PMS symptoms were determined using backward stepwise logistic regression analysis. To determine the impact of each independent variable (menarche age, personal indecisiveness, and problem-solving skills) on the dependent variable (PMS), variables at $P < .05$ were included within the logistic regression analysis. The significance level was accepted as 0.05.

Results

A total of 1,157 female students participated in the study. Their mean PMSS score was 127.65±35.50, and 70.4% (n=817) had PMS, while 29.6% (n=343) did not have the condition. The PMS symptoms reported by the students included the following: fatigue (71.9%), irritability (69.5%), depressive feelings (69.1%), pain (67.9%), changed appetite (65.9%), changed sleep (64.0%), swelling (63.6%), depressive thoughts (54.6%), and anxiety (46.9%) (Figure 1).

Baseline Characteristics of Female Students

The comparison of the distribution of characteristics of students according to the presence of PMS is presented in Table 1. It was determined that there was no significant difference between the groups of students who had PMS and those who did not in terms of age, place of residence, department, body mass index, duration of menstrual flow, and post-menstruation duration (P>0.05). However, the difference in terms of menarche age between the groups of students who did and did not have PMS was found to be statistically significant (P<0.05) (Table 1).

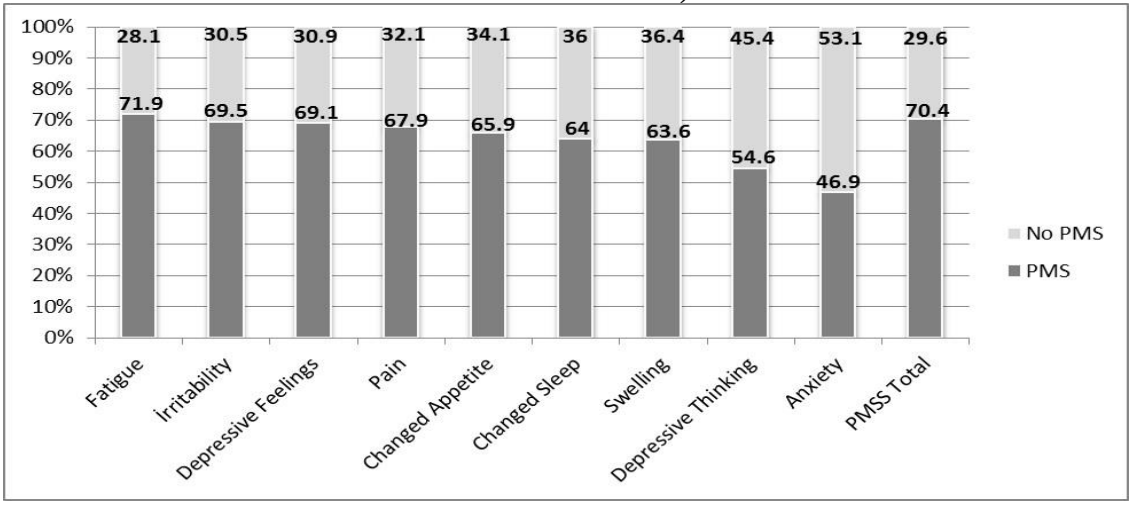

Figure 1. Prevelance of PMS symptoms in students

Bivariate analysis with PMSS

Table 2 presents the relationship between PMS, personal indecisiveness, problem solving, and the relevant subdimensions. A positive and significant relationship was found between the PMSS scores, PIS total scores, and exploratory and impetuous approach scores (r=.519, r=.490, and r=.484, respectively; p<0.05 for all). A positive and significant relationship was also found between the PMSS scores, PSI total scores, and the avoidant, self-confident, thinking, and planned approach scores (r=.103, r=.114, r=.107, r=.195, and r=.135, respectively; P<0.05 for all). In contrast, a negative and significant relationship was found between the PMSS scores and the impetuous approach scores (r=-.155; P<0.05) (Table 2).

Table 3 presents comparison of PIS and PSI average scores of students according to the presence of PMS. Students with PMS had higher total indecisiveness scale scores and higher mean subscale scores compared to those who did not have PMS; a statistically significant difference was also found between the groups (p<0.001). Students with PMS had higher total PSI scores and higher mean self-confident, thinking, planned, and avoidant approach subscale scores compared to those who did not have PMS; a statistically significant difference was also found between the groups (p<0.001). Students who did not have PMS had a higher mean impetuous approach subscale score in terms of problem solving compared to those with PMS; a statistically significant difference was also found between the groups (p<0.001) (Table 3).

The Logistic Regression Model of PMS Symptoms

The bivariate analyses revealed that there was a significant relationship between PMS and menarche age, PIS score, PSI score, and the subdimension scores. The results of the logistic regression analysis within the model established with the factors noted above are presented in Table 4. According to the results, students whose menarche age was 12 years and under (OR: .828), and who exhibited the indecisive approach (OR: 1.062), were impetuous while making decisions (OR: 1.063), and were exploratory while making decisions (OR: 1.055) were determined to be at an increased risk for developing PMS. In addition, students' inadequate self-perception (OR: .952), avoidance (OR: 1.084), lack of self-confidence (OR: 1.066), and acting without thinking in problem solving (OR: 1.091) were determined to be important risk factors for PMS (Table 4).

Table 1. Comparison of the distribution of characteristics of students according to the presence of PMS

Characteristics	No PMS (n=343)		PMS (n=814)		Total (n=1157)		Test and *P* value
	n	%	n	%	n	%	
Age, y							
17-20	159	29.5	380	70.5	539	46.6	χ^2=3.162
21-22	120	27.6	314	72.4	434	37.5	*P*=0.206
≥ 23	64	34.8	120	65.2	184	15.9	
Place of residence							
Home	142	31.2	313	68.8	455	39.3	χ^2=0.879
Dormitory	201	28.6	501	71.4	702	60.7	*P*=0.349
Department							
Life Science	60	28.0	154	72.0	214	18.5	χ^2=1.867
Social Sciences	148	28.4	374	71.6	522	45.1	*P*=0.393
Health Sciences	135	32.1	286	67.9	421	36.4	
Body mass index [a]							
Weak (≤18.5)	53	31.5	115	68.5	168	14.5	χ^2=0.532
Normal (18.6 - 24.9)	252	29.5	625	70.5	887	76.7	*P*=0.766
Overweight (≥25)	38	27.5	74	72.5	102	8.8	
Age of menarche, y							
≤ 12	62	22.5	214	77.5	276	23.9	χ^2=8.964
> 12	281	31.9	600	68.1	881	76.1	*P*=0.003
Duration of menstrual flow, d							
3-6	233	31.1	516	68.9	749	64.7	χ^2=2.178
7-11	110	27.0	298	73.0	408	35.3	*P*=0.140
Post-menstruation duration							
Currently mens	70	27.2	187	72.8	257	22.2	
Within 1 week after mens	79	30.2	133	69.8	262	22.6	χ^2=2.310
Within 2 week after mens	98	32.7	202	67.3	300	26.0	*P*=0.511
Within 3 week after mens	96	28.4	56	71.6	338	29.2	

a Calculated as weight in kilograms divided by height in meters squared.

Table 2. The relationship between PMS, personal indecisiveness, problem solving, and the relevant subdimensions (n=1157)

	Mean	SD	PIS Total	Exploratory	Impetuous	PSI Total	Avoidant	Self-confident	Thinking	Planned	Impetuous	Evaluator
Depressive feelings	21.03	6.87	.415**	.401**	.375**	.060*	.031	.079**	.148**	.132**	-.122**	-.023
Anxiety	17.30	6.59	.481**	.442**	.463**	.099**	.177**	.078**	.131**	.101**	-.140**	.032
Fatigue	18.87	5.85	.405**	.386**	.374**	.073*	.088**	.073*	.154**	.101**	-.116**	-.027
Irritability	15.42	5.41	.421**	.394**	.397**	.072*	.078**	.080**	.152**	.107**	-.134**	.005
Depressive thoughts	18.77	6.90	.542**	.500**	.520**	.101**	.141**	.083**	.146**	.135**	-.144**	.035
Pain	9.02	3.07	.327**	.313**	.299**	.091**	.014	.125**	.198**	.111**	-.093**	-.050
Changed appetite	9.17	3.47	.209**	.212**	.177**	.047	.025	.062*	.130**	.049	-.074*	-.027
Changed sleep	8.87	3.43	.381**	.356**	.359**	.112**	.127**	.105**	.158**	.064*	-.073*	-.020
Swelling	9.15	3.77	.257**	.253**	.227**	.065*	.046	.089**	.184**	.104**	-.146**	-.013
PMSS total	127.65	35.50	.519**	.490**	.484**	.103**	.114**	.107**	.195**	.135**	-.155**	-.006

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
SD: Standard Deviation; PIS: Personal Indecisiveness Scale; PSI: Problem Solving Inventory; PMSS: Premenstrual Syndrome Scale

Table 3. Comparison of PIS and PSI average scores of students according to the presence of PMS

Scales	No PMS (n=343) Mean ± SD	PMS (n=814) Mean ± SD	Test and *P* value	
PIS Total	41.00±13.90	56.75±18.42	t= -15.907	*P*<0.001
Exploratory	23.90±8.44	32.85±10.77	t= -15.103	*P*<0.001
Impetuous	17.09±6.72	23.90±8.97	t= -14.165	*P*<0.001
PSI Total	100.38±16.65	103.99±14.40	t= -3.498	*P*<0.001
Avoidant	10.84±5.08	12.23±4.97	t= -4.326	*P*<0.001
Self-confident	19.68±5.66	20.72±5.19	t= -2.923	*P*<0.001
Thinking	15.53±5.76	17.19±5.30	t= -4.738	*P*<0.001
Planned	12.05±3.94	12.85±3.54	t= -3.372	*P*<0.001
Impetuous	33.08±7.90	31.79±6.97	t= 2.624	*P*<0.001
Evaluator	9.17±3.77	9.17±3.57	t= -0.032	*P*=0.975

SD: Standard Deviation; PIS: Personal Indecisiveness Scale; PSI: Problem Solving Inventory; PMS: Premenstrual Syndrome

Table 4. Logistic regression analysis performed to examine the effect of students' menarche age, personal indecisiveness, problem solving, and sub-dimensions on PMS (n=1157)

	B	SE	df	*P*	OR	95% CI	
						Lower	Upper
Age of menarche [a], y							
≤ 12	(Reference)						
> 12	-0.188	.057	1	0.001	.828	.741	.926
PIS Total [b]	0.060	.011	1	<0.001	1.062	1.039	1.086
PIS Exploratory [b]	0.061	.011	1	<0.001	1.063	1.039	1.087
PIS Impetuous [b]	0.054	.015	1	<0.001	1.055	1.025	1.086
PSI Total [b]	-0.049	.023	1	0.035	.952	.909	.997
PSI Avoidant [b]	0.081	.029	1	0.006	1.084	1.024	1.148
PSI Self-confident [b]	0.061	.032	1	0.047	1.066	1.001	1.133
PSI Thinking [b]	0.087	.027	1	0.001	1.091	1.034	1.151
PSI Planned [b]	0.040	.043	1	0.359	1.041	.956	1.133
PSI Impetuous [b]	0.031	.025	1	0.218	1.031	.982	1.083

[a] Categorical data were used.
[b] Numerical data were used.
PIS: Personal Indecisiveness Scale; PSI: Problem Solving Inventory; PMS: Premenstrual Syndrome
B: Regression Coefficient; SE: Standard Error; OR: Odds Ratio; CI: Confidence Interval.

Discussion

In this study conducted with university students in Turkey, the prevalence of PMS was determined to be high at 70.3%. This finding is consistent with the results of previous studies in our country reporting a prevalence of PMS between 5% and 72% (16-18). The prevalence of PMS among women of the same age group was reported by Tanrıverdi et al. to be 67.5% (19), by Yaşar et al. to be 70.2% (20), and by Pınar et al. to be 72.1% (21), which is also consistent with the results of the present study. Studies conducted outside Turkey have reported the PMS prevalence to be between 6% and 85% among adolescents (22-25). The PMS prevalence among adolescents living outside Turkey was reported to be 60.3% by Silva et al. (26) and 84.3% by Houston et al. (27). The broad range of PMS prevalence within the literature may be due to the different age groups of the women forming the samples and from the absence of a global method for defining PMS.

This study found the most common symptoms in the premenstrual period of the students to be fatigue, irritability, depressive feelings, pain, changed appetite, and changed sleep, in order of prevalence. Other studies have also reported complaints such as fatigue, depression, and irritability during PMS (28-30). It is widely known that these complaints can significantly negative affect students' self-confidence, social and family relationships, and academic success (31-33).

In this study, the PMS prevalence was found to be higher in students whose first menarche age was 12 and below. The literature emphasizes that the relationship between menarche age and PMS is not clear (22, 33). In addition to the existence of studies reporting that a younger age of first menarche increases the risk of PMS (33), there are also studies that do not support this relationship (33). Nevertheless, it has been established that one of the most important causes of PMS is hormonal factors (33-34). Thus, a probable reason for the association between early menarche and PMS has been attributed to the similarity of hormonal patterns in early maturing and adult women (35).

This study found that students were more indecisive and impetuous in addition to being not exploratory while making a decision during PMS compared to those not who did not have PMS. This result may indicate that PMS negatively affects decision making. Studies conducted in various fields have found that individuals who were indecisive were in more adverse circumstances in terms of variables affecting their psychological health, and were therefore more likely to have problems with self-respect, self-confidence, shyness, creativity, perfection, control, and personal and social engagement (36, 37). Moreover, indecisiveness, distrust, shyness, dependency, and dissatisfaction with oneself have been found to be related (38). Some researchers have also indicated that there is a significant relationship between considering oneself as negative and indecisiveness (36, 38). While the existing literature does not include any studies examining the relationship between PMS and indecisiveness, the results of this study support the relationship between these variables.

This study also found a significant relationship between PMS and problem solving in students through a bivariate analysis. According to the results of the regression analysis with the variables affecting PMS, students with PMS had higher self-perception while problem solving, were more avoidant in problem solving, were less confident in problem solving, and were more likely to act without thinking in problem solving than students without PMS.

PMS symptoms are various and affect women not only physically but also psychologically, which can cause some limitations in daily life. Buddhabunyakan et al. found that PMS causes a lack of concentration, a lack of motivation, and lower personal or collaborative job performance in students (39). Similarly, in the study conducted by Sharma et al., it was found that students with PMS had a higher rate of school absenteeism and more concentration problems, and 25% of those who were employed had to leave their jobs due to the problems brought about by PMS (40). All these problems may negatively affect the problem-solving approaches of the students with PMS.

Limitations of the Study

This study has certain limitations. First, the cross-sectional form of this study prevents any results from being determined in terms of causality. Prospective cohort studies are more reliable in terms of determining PMS and its risk factors. Second, the study was conducted at a single university; therefore, the results may not be generalizable to all young women. Third, the data were collected through the self-report method. Future studies may therefore be conducted through alternative methods, such as interviews, employed in a more detailed and complete manner.

Conclusion

The results of this study indicate that PMS was a significant risk factor in terms of indecisiveness and

problem-solving inadequacy. Health care professionals who provide health education and health-promoting services have important roles in preventing and reducing the negative effects of PMS. Healthcare professionals should be aware of not only the physiological effects of PMS but also its effects on daily life. Thus, it is important for healthcare professionals to understand the relationship between the menstrual cycle, menstrual disorders, and their effects on daily life. A good understanding of the relationship between these variables will provide young women with more valuable information about their own situations.

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Systematic Birth Preparation Programs Positively Influence the Childbirth Fear: A cross-sectional study.

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Abstract

Objective: The primary target of birth preparation program is guiding women to realistic expectations for the birth experience. The aim of the present study is to evaluate the influence of a systematic multidisciplinary birth preparation program on delivery expectation, childbirth fear, mode of delivery and neonatal outcomes.
Methods: 159 nulliparous pregnant women in their 3rd trimester were enrolled in this cross-sectional cohort study between January 2018 and March 2020. Women who participated to the systematic birth preparation program were grouped as Group A (n = 80) and those who refused to participate were considered Group B (n = 79). Fear of childbirth was scanned by Wijma Delivery Expectancy Questionnaire Version-A; socio-demographic and obstetric features were assessed through a self-developed survey by face-to-face interview. The mode of delivery, labor induction needs, cesarean indications, birth weights, APGAR scores, newborns hospitalization requirements if any were noted.
Results: The Wijma-A mean score was 44.60 ± 19.63 in those who attended the systematic birth preparation program and 72.05 ± 24.82 in those who did not ($p<0.001$). Childbirth fear was significantly lower in attended group when pregnant women were evaluated according to the four different level childbirth fear categories ($p<0.001$). The birth weights were significantly higher in attended group ($p=0.017$). There was no significant difference between the two groups in terms of mode of delivery, APGAR scores, neonatal hospitalization and labor induction requirements ($p>0.05$).
Conclusion: The present study shows that systematic and multidisciplinary birth preparation program may positively influence the childbirth fear and increase the birth weights of neonates.
Key words: Systematic birth preparation program, pregnancy, vaginal delivery, childbirth fear, Wijma-A delivery expectancy questionnaire.

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Introduction

Pregnancy is the extra-ordinary important and excited period in reproductive aged women's life. In this period, the psychological as well as physical well-being is necessary to minimize perinatal morbidity and mortality. Uncomplicated delivery with proper antenatal follow-up is the main goal. Although vaginal route of delivery is a natural process, most of the women have fear of childbirth during pregnancy (1). Childbirth fear increases the delivery durations, women's request for cesarean sections, leads to use more labor induction agents and accordingly increasing the elective or urgent cesarean sections rates and perinatal morbidity (2). Furthermore, increasing rates of perinatal morbidity may lead mothers to postpartum depression and lack of lactation (3).

The causes of childbirth fear are classified as biological situations, psychological situations and lack of social support (1). Some studies indicates that nulliparous women have higher levels of childbirth fear than multiparous women (4). Some studies show that educational level positively influences the childbirth fear, but there are also some studies which did not state any relationship (5, 6).

Systematic and multidisciplinary birth preparation programs are offered to ensure that the pregnancy process continues physically and psychologically healthy, to guide women to realistic expectations for the birth experience, to prevent unsatisfactory situations as postpartum depression, sexual dysfunction, to increase the success of postpartum breastfeeding, and maintaining a healthy birth experience and puerperium (7). Pregnant women can practice the necessary physical activities to prevent lumbopelvic pain and facilitate delivery process (8). Techniques for pain reduction and tips for women's autonomy are taught for to minimize the maternal request for a cesarean section. Adequate knowledge about the second stage of the labor may help to reduce fear; pain relief techniques and breath exercises may encourage a fearless vaginal route delivery (9).

This study was design to evaluate the effectiveness of systematic birth preparation program on delivery expectancy and childbirth fear. Secondly, we investigated the relation of systematic birth preparation program with the mode of delivery and neonatal outcomes.

Methods

Systematic Birth Preparation Program

Giresun University Maternal and Children Disease's Education and Training Hospital is a tertiary center and is the first center in black sea part of Turkey that is qualified as "Mother-friendly Hospital" by the Ministry of Health. It has been providing a systematic birth preparation program to 2nd and 3rd trimester pregnant women named "Pregnant School" since January 2017. Between 18 and 22 gestational weeks, pregnant women are informed about the program in the outpatient clinics and those who wish to participate are enrolled. Each education group consists of 8 participants and 4 education session once in a week for 1 month. The contents of the sessions, each of which lasted 3 hours, are given in Table 1. The signs and stages of labor, breathing exercises, pain relief techniques are given to reduce the childbirth fear and to encourage the vaginal delivery. Hydrotherapy, reflexology, yoga and pilates are examples of pain relief techniques which are taught to the participants to control birth pain. Educations are carried out with Power Point presentations and flip-chart. Childbirth models, exercise balls, gymnastic mats and lactation pumps are present to apply. An obstetrician and gynecologist, a nutritionist, a psychologist, a lactation consultant, and a nurse constitute the educational staff. The partners are also attending to the 4th session of the program and a certificate is given to the women at the end. Meanwhile, both groups are following routine antenatal care with physicians.

Participants

This is a cross-sectional cohort study of 159 healthy nulliparous pregnant women admitted to Giresun University Maternal and Children Disease's Education and Training Hospital for antenatal follow up between January 2018 and March 2020. Initially 171 healthy nulliparous women were included; 12 patients (5 patients from Group A and 7 patients from group B) did not give birth in the same hospital and excluded from the study. The study was approved by the Giresun University, Ethical Committee for Human Research (Institutional Review Board: 09.11.2020/09).

Table 1. The systematic birth preparation program sessions.

Session 1		**Session 2**		**Session 3**		**Session 4**	
Lecture	Trainer	Lecture	Trainer	Lecture	Trainer	Lecture	Trainer
The anatomy and function of the reproductive organs	Obstetrician & Gynecologist	Antenatal exercises and yoga	Nurse	The signs and stages of labor	Obstetrician & Gynecologist	Postpartum contraception methods	Obstetrician & Gynecologist
The growth of fetus	Obstetrician & Gynecologist	Perineal massage for vaginal route delivery	Nurse	Breath exercises	Nurse	Antenatal and postpartum sexual life	Nurse
General knowledge about antenatal period	Obstetrician & Gynecologist	Diet during pregnancy	Nutritionist	Pain relief techniques	Psychologist	Breastfeeding and neonatal care	Lactation consultant

Low-risk nulliparous pregnant women with healthy singleton pregnancies in their third trimester (between 28- 40th gestational weeks), between the ages of 18-40, without psychiatric disorder and admitted to the antenatal care from the first trimester of their pregnancy were included to the study. Exclusion criteria were high-risk pregnancies like preeclampsia, multiple pregnancies or fetus with congenital anomalies, previous birth experience, adolescent pregnancies, maternal psychiatric disorders, substance abuse, single mothers, planned Ceserean births, history of sexual transmitted disease and participation to different birth preparation programs such as hypnobirthing or mindfulness. Also, women who quited the program before completing were excluded from the study.

Group A is study group which consists of 80 nulliparous patients who fully completed the systematic birth preparation program and Group B is control group which includes 79 nulliparous patients who never attend to the program. They were asked to complete the self-developed survey and the validated Wijma A Birth Expectancy Questionnaire- version A (W-DEQ-A) in their 3rd trimester (28-40 weeks of gestation).

Self-developed survey and Wijma Birth Expectancy Questionnaire Version-A (W-DEQ-A)

Baseline socio-demographic and obstetric features included maternal age (yrs), gestational age at the time of survey, educational level, maternal systemic diseases such as presence of diabetes, obesity or cardiac problems prior to pregnancy, paternal emotional support, whether there is a planned pregnancy and if they had different education options other than systematic birth preparation program were filled through a short self-developed survey with face-to face interview. Gestational age was calculated according to the last menstrual period, or the first trimester crown-rump length of the fetus was used for the ones which do not correlate with the last menstrual period date.

The participants were asked to fill the validated W-DEQ-A (10). It was prepared for screening feelings and thoughts of pregnant women about their labor, and it is useful to outline how they imagine their labor will be. There are 33 items in this Likert-type scale, whose translation has reliability and validity studies and measures pre-natal anxiety and fear (11). Each statement is scored between 0 and 5, totally has six degrees. The scale's minimum score is 0 and the maximum score is 165. As the score increases, anxiety and childbirth fear is rising. During the analysis of the data, the scores were grouped into four categories, a score <37 shows low level of fear, a score between 38-65 shows moderate level of fear,

a score between 66-84 shows severe level of fear and a score above 85 shows very severe level of fear.

After the completion of the pregnancy, type of the delivery, if there is requirement for labor induction, cesarean indication if any, birth weight, neonatal APGAR scores, neonatal hospitalization or intensive care need and its indication were noted. The fetal distress indication was based on Dellinger et al. (12), prolonged labor was defined according to Cohen et al. (13) and the cephalopelvic disproportion criteria was evaluated according to Maharaj (14). All vaginal deliveries were carried out in two different rooms under equal conditions by midwives who received the same in-service training in the last year. Epidural analgesia was not applied, and episiotomy was routinely performed in primiparous patients.

The primary outcomes were the comparison of W-DEQ-A mean scores between group A and group B. Secondary outcomes were the relation of the birth education program with the mode of delivery and the neonatal outcomes.

Statistical Analysis

Statistical analyses were performed by using SPSS Statistics version 24.0 (IBM Corporation, Armonk, New York, USA). Number (n), frequency (%) for discrete data and mean ± standard deviation (X ± SD) for continuous data were used. Kolmogorov Smirnov Test, histogram, skewness and kurtosis values were used to evaluate whether the data conformed to the normal distribution. As the data showed normal distribution, Chi-square Test and Independent Sample t Test was used among parametric tests. The p value <0.05 was considered statistically significant.

Results

A total of 159 nulliparous pregnant women without a history of psychiatric illness were included. 80 pregnant women who completed the program (Group A) and 79 pregnant women who never attended to the program (Group B) participated to the study. In the demographic analysis, the mean maternal age, week of gestation in which the questionnaire applied, maternal education level, presence of co-morbid systemic maternal disease, emotional support from the male partner were statistically similar in both groups (Table 2).

It was stated that 57 % of 79 nulliparous pregnant women in group B who did not participate to the birth preparation program did not receive any alternative education, whereas 22.8 % received information from the internet, 11.4 % were informed by a healthcare professional and 8.9 % applied to pregnancy education books (Table 2).

Wijma Birth Expectancy Questionnaire- Version A mean score was 44.60 ± 19.63 in group A and 72.05 ± 24.82 in group B, it was determined that the anxiety of birth expectancy was significantly lower in patients who participated in the systematic and multidisciplinary birth preparation program (p <0.001) (Table 3). Distribution of pregnant women according to childbirth fear categories were statistically significantly different when two groups compared (p=0.000) (Table 3).

When the mode of delivery was compared as spontaneous vaginal delivery or cesarean section, there was no statistically significant difference between the groups (p =0.805). When the birth weight of newborns was compared, it was found that the average was 3432.69 ± 421.16 in Group A and 3276.46 ±392.09 in Group B which was statistically significant (p=0.017). There were no significant difference between the two groups in terms of APGAR scores, neonatal hospitalization and labor induction requirements (p>0.05) (Table 4).

Discussion

In the present study, the findings showed a significantly lower childbirth fear and higher birth weight in the systematic birth preparation attended group. However, the other factors such as the mode of delivery, APGAR scores, neonatal hospitalization and labor induction requirements did not change with attending the systematic birth preparation class.

Akca et al. reported that the systematic birth preparation program promotes better communication between patients and healthcare professional and increases postpartum women's satisfaction with the childbirth (7). Their study differs from our study as it was performed after the birth to analyze the birth experience. Furthermore, there are some studies that present mindfulness as an alternative program for the antepartum and postpartum period (15). Sacristan-Martin et al. applied the Mindfulness-based Childbirth and Parenting Program and they evaluated the progress of women in four different time zones as before program, after program, at three months and six months after childbirth mainly for perinatal depression (15). They found that an effective childbirth education program may be helpful to prevent perinatal depression. The present study evaluated the childbirth fear with the validated scale developed by a psychologist (10, 11). Our results showed that an easy to implement and low cost program is effective to decrease the childbirth fear and maternal anxiety.

Table 2. Socio-demographic features of pregnant women

	Attended to SBPP**		Non-attended to SBPP		Analyze t/ χ^2	*p*
Age (Min-Max)	26.70 ± 3.71 (20-39)		26.61 ±5.04 (19-41)		1.417 *	0.158
Gestational age	36.74 ± 2.53 (27-40)		36.16 ±2.56 (27-40)		0.132 *	0.895
Education	**n**	**%**	**N**	**%**		
Primary school	5	6.2	3	3.8		
Middle school	9	11.3	17	21.5		
High school	24	30.0	23	29.1	7.031	0.134
University	38	47.5	36	45.6		
Graduate	4	5.0	-	-		
Chronic systemic disorders						
Yes	13	16.2	7	8.9	1.974	0.160
No	67	83.8	72	91.1		
Partner support						
Yes	78	97.5	75	94.9	0.719	0.396
No	2	2.5	4	5.1		
Other education methods						
SBPP**	80	100.0	-	-		
Healthcare professional			9	11.4		
Books			7	8.8	159.000	0.000
Internet			18	22.8		
Untrained			45	57.0		

***:** Independent Sample t Test
**: Systematic Birth Preparation Program

Table 3. Distribution of Pregnant Women According to mean value of the Wijma Birth Expectancy Questionnaire- Version A Total Score and Fear of Childbirth Categories

	Attended to SBPP** (n:80)		Non-attended to SBPP (n:79)		t	*P*
Wijma Total Score (Min-Max)	44.60 ± 19.63 (6-93)		72.05 ±24.82 (22-128)		-7.739	0.000
Childbirth Fear Score Categories	**Attended to SBPP** (n:80)**		**Non-attended to SBPP (n:79)**		χ^2	*P*
	n	**%**	**n**	**%**		
≤ 37: Mild	29	36.3	5	6.3		
	39	48.8	30	38.0		
38-65: Moderate	10	12.5	22	27.8		
	2	2.5	22	27.8	39.277	0.000
66-84: Severe						
≥ 85: Very severe						

**: Systematic Birth Preparation Program

Table 4. The relation of systematic birth preparation program with the mode of delivery and neonatal outcomes

	Attended to SBPP**		Non-attended to SBPP		Analyze t/ χ^2	*P*
Birth weight (gr) (Min-Max)	3432.69 ± 421.16 (2500- 4430)		3276.46 ± 392.09 (2500-4250)		2.420 *	**0.017**
APGAR-1' (Min-Max)	7.96±0.56 (5-9)		7.94±0.46 (5-9)		0.316 *	0.752
APGAR-2' (Min-Max)	8.89±0.55 (5-10)		8.87±0.40 (7-10)		0.184 *	0.855
Mode of Delivery	**N**	**%**	**N**	**%**		
Vaginal	37	46.3	35	44.3	0.061	0.805
Cesarean section	43	53.8	44	55.7		
Cesarean indications						
Prolonged labor	8	10	11	13	15.280	0.084
Fetal distress	8	10	9	11.4		
Fetal macrosomia	8	10	2	2.5		
CPD	6	7.5	6	7.6		
Malpresentation	1	1.3	6	7.6		
Other indications	12	15	10	12,7		
Neonatal Hospitalization						
Yes	13	16.3	22	27.8	3.115	0.078
No	67	83.8	57	72.2		
Hospitalization indications						
Jaundice	6	7.5	12	15.2	3.115	0.078
RDS	0	0	2	2.5		
TTN	3	3.8	5	6.3		
MAS	1	1.3	1	1.3		
Other indications	3	3.8	2	2.5		
Labor induction						
Yes	15	18.8	21	26.6	1.392	0.238
No	65	81.2	58	73.4		

*: Independent Sample t Test

**: Systematic Birth Preparation Program

CPD: Cephalopelvic disproportion, APGAR: Activity, Pulse, Grimace, Appearance, Respiration, RDS: Respiratuar distress syndrome, TTN: Transient tachypnea of the newborn, MAS: Meconium aspiration syndrome.

The pregnancy period is influenced by childbirth fear and not thinking to tolerate labor pain is the important factor why women desire elective cesarean section and results with an increase in perinatal morbidity and mortality (16). Although cesarean section can be absolutely necessary to save the mother's and newborn's life in emergent conditions, this type of delivery is associated with increased perinatal and neonatal morbidity and mortality (17, 18). In order to minimize maternal request for cesarean section, Ozdemir et al. studied the effect of birth preparation program to vaginal delivery fear and quality of life (9). They found that vaginal deliveries were higher in women who requested the elective cesarean section before the program and participated in the program afterwards. However, the significant difference between two groups in vaginal and cesarean deliveries could not be confirmed in the current study.

In a randomized controlled trial with 1410 participants, midwife's psycho-education intervention positively influenced childbirth fear and improved vaginal birth rates (19). However, their sample included women who had previously experienced birth, carrying multiple gestations and having psychiatric health disorders. The strengths of our study are to compare the childbirth fear in nulliparous women who do not have any previous experience and to exclude the criteria such as psychiatric disorders, preterm delivery or multiple

pregnancies. In literature, there are some studies about the correlation between childbirth fear and sociodemographic features as age, gestational week, parity, education level (20). In this study, the demographic features are not significantly different between study and control groups which make the results more realistic. Ketema et al. performed a meta-analysis about the relationship of mother's relevant education and obstetric complications and showed the usefulness of the program in daily practice (21).

The limited aspect is that the social and cultural factors that play an important role in the antenatal period should be considered in more detail in future studies. This study was carried on in a single center, but due to the different perspectives in different regions, women's view about vaginal delivery and childbirth fear may differ. Multicenter studies may be helpful to compare the effectiveness of systematic birth preparation class in different regions. Small number of participants is another limitation. Furthermore, the partner's social support can be evaluated in detail.

Conclusion

The systematic and multidisciplinary birth pre paration programs maintain realistic prenatal expectations for delivery and childbirth and seem to eliminate the birth anxiety.

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Serotonin Transporter Gene Polymorphism in Patients with Schizophrenic Disorders

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Abstract

Objective: Studies performed to solve the genetic basis of schizophrenia have focused on the role of serotonin in the etiology of schizophrenia and the function of serotonin transporter gene. This study aimed to investigate whether there was a relationship between schizophrenia and polymorphism of the Variable Number of Tandem Repeats (VTNR) and 5-HTT Gene-Linked Polymorphic Region (5-HTTLPR) variants in the transcriptional control region of the serotonin transporter gene or not.

Method: A total of 55 schizophrenia patients who were diagnosed according to the diagnostic criteria of DSM-IV-TR and 32 healthy volunteers (the control group) were included in the study. DNAs were extracted from the bloods collected from the patient and control groups with the salting-out method. Alleles of the serotonin transporter gene polymorphism were determined with the polymerase chain reaction (PCR) method.

Results: Based on the serotonin transporter gene intron 2 VNTR polymorphism, the distribution of 12/12, 12/10, 10/10, and 12/9 genotypes was 47.3%, 47.3%, 3.6%, and 1.8% in the patients and 46.9%, 46.9% and 6.3% respectively in the control group. There was no 12/9 genotype in the control group. The distribution of L/L, L/S and S/S genotypes according to the 5-HTTLPR polymorphism was 30.9%, 41.8% and 27.3% in the patients and 28.1%, 50.0% and 21.9% respectively in the control group.

Conclusion: Although the allele and genotype distributions of the serotonin transporter gene polymorphism relatively differed between the patient and control groups this difference was not statistically significant.

Key Words: Schizophrenia, serotonin transporter gene, VNTR, HTTLPR, polymorphism

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Introduction

Schizophrenia is one of the psychiatric disorders which cause several emotional, thought, and behavioral disorders and in which significant changes occur in the structure, physiology and chemistry of the brain and its etiology is not exactly known (1,2).

The annual prevalence of the disease which is generally seen in the early ages is 1% and the lifetime prevalence of it is accepted as 1.5% (3,4).

Several factors play a role in the etiology of schizophrenia and the relationship of many social, biological, genetic, endocrine, neurochemical, and neurophysiological changes with this disease have been investigated (4,5). While the evidence clearly reveals that both environmental and genetic factors (polygenic-multifactorial) play a role in the disease the researchers have focused on the gene studies in order to understand the biological bases of the disease (6,7). It has been reported that genetic degradations can disrupt the chemical balance of the brain and thereby causing schizophrenia and schizophrenia-like disorders (8). With the introduction of new antipsychotics, studies on the neurotransmitter system have focused on the role of serotonin (5,9).

Serotonin plays a regulatory role in the early development of central nervous system and cell proliferation, migration, and differentiation. It has been reported that serotonin contributes to the perception, attention, mood, sexual function, appetite, motor behavior, sleep, memory disorders, aggression, and somatic functions in schizophrenia (5,10).

Serotonin transporter protein plays a significant role in the homeostasis of serotonin in brain and reuptake of it from synaptic space to presynaptic space. The serotonin transporter gene (STG) synthesizing this protein is mapped to the chromosome 17q11.1-q12 by the Solute Carrier Family 6 Member 4 (SLC6A4) gene code and it has two basic polymorphic regions. One of these polymorphisms is the Variable Number of Tandem Repeats (VNTR) based on the repeat of a 15-18 bp-region in the second intron of the gene (STG.in.2). The other is the 44 bp insertion/deletion polymorphism constituted by 20-22 bp tandem repeats in the promoter region (5-HTT gene-linked polymorphic region: 5-HTTLPR) (6,11).

The relationship of the serotonin transporter gene polymorphisms including VNTR and 5-HTTLPR with several diseases has been investigated and it has been reported that the results in the studies investigating the relationship with schizophrenia are contradictory. While it has been reported in some studies that there is an association between the serotonin transporter gene polymorphism and the disease (10,12,13) some studies assert that there is no association (14-16).

As significant results were obtained in some populations in the polymorphism studies on the serotonin transporter gene in the patients with schizophrenia this study aimed to determine whether there was a relationship between schizophrenia and the polymorphism of VNTR and 5-HTTLPR variants in the transcriptional control region of the serotonin transporter gene in the schizophrenia patients living in Sivas region in Turkey and whether the patients with the polymorphism of these gene were susceptible to the disease or not.

Methods

This study was performed in the Department of Psychiatry of Cumhuriyet University Faculty of Medicine, the Research Center of Cumhuriyet University Faculty of Medicine and the Department of Medical Biology and Genetics of Mersin University Faculty of Medicine. The study was approved by the Ethics Committee of Cumhuriyet University Faculty of Medicine (B.30.1.CUM.O.1H.00.00/04). The patient group consisted of 55 individuals between the ages of 18-72 who were diagnosed with schizophrenia according to the diagnostic criteria of the Diagnostic and Statistical Manuel of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (17) in the Department of Psychiatry of Cumhuriyet University Faculty of Medicine. The control group consisted of 32 healthy individuals between the ages of 18-77 who had no mental disorders in their medical history or psychiatric examination and who were similar to the patient group in terms of age and gender. All the patients completed the Sociodemographic information form. The Sociodemographic information form included questions about the patients' age, gender, educational status, marital status, occupation, whether there was consanguinity between their parents, the degree of affinity if there was consanguinity, whether the family members had a psychiatric disorder or not, and whether the family members had congenital anomaly or not. The patients with head trauma history, oral contraceptive use history and congenital anomaly history were excluded from the study.

The blood collected as 7-8 ml from the patient and control individuals was put into 15 ml centrifuge tubes including 1 ml of EDTA (2%). They were stored in the fridge at -20^{o}C until the isolation process. DNA isolation was obtained with the salting-out method. The method is based on the lysis of all the disrupted structures other than DNA, its

precipitation with a saline solution and isolation of the genomic DNA in the liquid part above through the concentration with ethyl alcohol. Then, the gene regions of both polymorphisms are amplified with the polymerase chain reaction (PCR) method and statistically assessed after being electrophoresed. This article was produced from the specialization in medicine thesis.

Statistical analysis

The relationship between the schizophrenia and the serotonin transporter gene intron 2 (STG.in.2) VNTR and 5-HTTLPR polymorphisms in terms of genotypes and alleles was assessed using the SPSS (Statistical Package for Social Sciences, version 10.0) software program with chi-square analysis. Whether the genotype frequencies of both polymorphisms were in the Hardy-Weinberg equilibrium or not was determined with the Chi-square test.

Results

In this study, the serotonin transporter gene VNTR polymorphism in the intron 2 and insertion/deletion polymorphism (5-HTTLPR) in the transcriptional control region among the DNAs belonging to 55 schizophrenia patients (the patient group) and 32 healthy individuals (the control group) were investigated with the PCR method. The polymorphisms in this gene were genotyped and their gene frequencies were calculated.

Mean age of the individuals was 35.67±13.25 in the patient group and 34.75±11.33 in the control group. The difference between the groups in terms of age was not statistically significant (t=0.32; p>0.05). Mean age of the individuals was 35.67±13.25 in the patient group and 34.75±11.33 in the control group. The difference between the groups in terms of age was not statistically significant (t=0.32; p>0.05). While 32 (58.2%) out of 55 individuals in the patient group were male, 23 (41.8%) were female and 12 (37.5%) out of 32 individuals in the control group were male, 20 (62.5%) were female. The difference between the groups in terms of gender was not statistically significant (χ^2=3.46; p>0.05). A significant difference was found between the individuals in both groups in terms of their family history of schizophrenia (p<0.05). Of the individuals in the patient group, 16 (29.1%) had family history. No one in the control group had family history. The risk of having a schizophrenic disorder was 0.71 times higher in the individuals with a psychiatric disorder in their family history compared with those without any psychiatric disorder in their family history (Odds=0.71, CI 95% 0.59; 0.84) and this rate was statistically significant (Table 1).

Table 1. Distribution of the Family History of Schizophrenia in the Patient and Control Groups

	Family History of Schizophrenia					
	Yes		No		Total	
Groups	n	%	n	%	n	%
Patient	16	29.1	39	70.9	55	100.0
Control	0	0	32	100.0	32	100.0
Total	16	18.4	71	81.6	87	100.0

(χ^2=11.40, P=0.001)

When the serotonin transporter gene VNTR polymorphism was compared with the marker in the imaging system the samples of 360 bp fragment were assessed as 10 allele and the samples of 390 bp fragment as 12 allele. The genotyping was recorded as 10/10 when there was a single band in 360 bp fragment, 12/12 when there was a single band in 390 bp fragment and 10/12 when there were two bands (Figure 1).

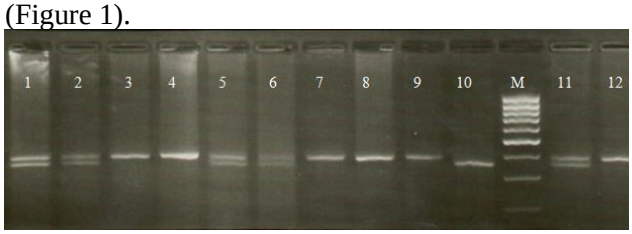

Figure 1. The end result of electrophoresis of SERT VNTR polymorphism alleles. The bands belonging to the samples numbered 3, 4, 7, 8, 9, and 12 show that the individuals have only 12 allele and 12/12 genotype; the bands belonging to the samples numbered 1, 2, 5, 6, and 11 show that the individuals have both 12 and 10 alleles and 12/10 genotype; the band belonging to the sample numbered 10 shows that the individuals have 10 allele and 10/10 genotype; and M shows the marker

As a result of the assays, the number of 12 alleles was 79 (71.8%), the number of 10 alleles was 30 (27.3%) and the number of 9 alleles was 1 (0.9%) in terms of the serotonin transporter gene VNTR polymorphism in the group consisting of schizophrenic patients. In the control group, the number of 12 alleles was 45 (70.3%) and the number of 10 alleles was 19 (29.7%) (Table 2). The association of the allele frequencies of this polymorphism with the groups was assessed with Chi-square analysis and no significant change was observed in the allele frequency (p=0.712).

Table 2. Allele frequencies of the serotonin transporter gene VNTR polymorphism

	Alleles							
	12		10		9		Total	
Groups	n	%	n	%	n	%	n	%
Patient	79	71.8	30	27.3	1	0.9	110	100.0
Control	45	70.3	19	29.7	0	0	64	100.0
Total	124	71.3	49	28.2	1	0.6	174	100.0

When this polymorphism was assessed in terms of genotypes 26 individuals (47.3%) in the patient group had 12/12 genotype, 26 (47.3%) had 12/10 genotype, 2 (3.6%) had 10/10 genotype, and 1 (1.8%) had 12/9 genotype. In the control group, 15 individuals (46.9%) had 12/12 genotype, 15 (46.9%) had 12/10 genotype and 2 (6.3%) had 10/10 genotype. There was no 12/9 genotype in the control group (Table 3). The risk (Odds) of being different for the serotonin transporter gene VNTR polymorphism was 1.13 times higher in the patient group than the control group, but this rate was not statistically significant (CI 95% 0.49; 2.63) and the individuals with 12 allele had 1.07 times higher risk compared with those with 10 allele, but this risk was not statistically significant (95% 0.54; 2.12, p=0.832).

Table 3. Genotype frequencies of the serotonin transporter gene VNTR polymorphism

	Genotypes									
	12/12		12/10		10/10		12/9		Total	
Groups	n	%	n	%	n	%	n	%	n	%
Patient	26	47.3	26	47.3	2	3.6	1	1.8	55	100.0
Control	15	46.9	15	46.9	2	6.3	0	0	32	100.0
Total	41	47.1	41	47.1	4	4.6	1	1.1	87	100.0

(χ^2=0.88, P=0.829)

In the serotonin transporter gene 5-HTTLPR polymorphism, the samples of 528 bp fragment were assessed as L allele and the samples of 484 bp fragment as S allele. The genotyping was recorded as S/S when there was a single band at 484 bp fragment, as L/L when there was a single band at 528 bp fragment and as L/S when two bands were observed at both 528 bp and 484 bp fragments (Figure 2).

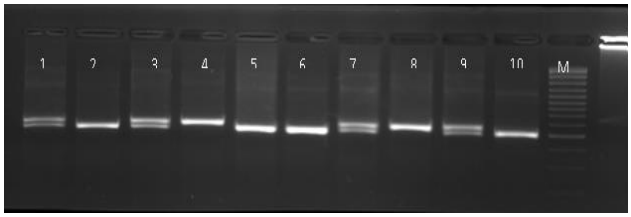

Figure 2. The end result image of electrophoresis of SERT 5-HTTLPR polymorphism alleles. The samples numbered 4 and 8 show only L allele (L/L genotype) and the samples numbered 2, 5, 6, and 10 show S allele (S/S genotype). The samples numbered 1, 3, 7, and 9 show that the individuals have both L and S alleles (L/S genotype) and M shows the marker

As a result of the assays, 57 L alleles (51.8%) and 53 S alleles (48.2%) in terms of 5-HTTLPR polymorphism were found in the patient group. There were 34 L alleles (53.1%) and 30 S alleles (46.9%) in the control group (Table 4). No statistically significant association was found between the prevalence of L and S alleles of the serotonin transporter gene 5-HTTLPR polymorphisms and the disease (p=0.868).

Table 4. Allele frequencies of serotonin transporter gene 5-HTTLPR polymorphism

	Alleles					
	L		S		Total	
Groups	n	%	n	%	n	%
Patient	57	51.8	53	48.2	110	100.0
Control	34	53.1	30	46.9	64	100.0
Total	91	52.3	83	47.7	174	100.0

(χ^2=0.03, P=0.868)

According to the serotonin transporter gene 5-HTTLPR polymorphism, 17 individuals (30.9%) in the patient group had L/L genotype, 23 (41.8%) had L/S genotype and 15 (27.3%) had S/S genotype. In the control group, 9 individuals (28.1%) had L/L genotype, 16 (50.0%) had L/S genotype and 7 (21.9%) had S/S genotype (Table 5). The risk (Odds) of being different for 5-HTTLPR polymorphism was 0.083 times higher in the patient group than in the control group, but this rate was not statistically significant (CI 95% 0.48; 1.78, p=0.745). Although the individuals with L allele had 0.94 times higher risk compared with those with S allele this risk was not statistically significant (CI 95% 0.51; 1.75, p=0.868).

Table 5. Genotype frequencies of serotonin transporter gene 5-HTTLPR polymorphism

	Genotypes							
	L/L		L/S		S/S		Total	
Groups	n	%	n	%	n	%	n	%
Patient	17	30.9	23	41.8	15	27.3	55	100.0
Control	9	28.1	16	50.0	7	21.9	32	100.0
Total	26	29.9	39	44.8	22	25.3	87	100.0

(χ^2=0.58, P=0.745)

The serotonin transporter gene intron 2 VNTR and 5-HTTLPR polymorphisms of both patient and control groups were in the Hardy-Weinberg equilibrium in terms of their genotypes. This caused no difference in the genotype distribution of the serotonin transporter gene polymorphisms among the patients with schizophrenia.

Discussion

In this study, the relationship between schizophrenia and the serotonin transporter gene intron 2 (STG.in.2) VNTR and 5-HTTLPR polymorphisms was investigated. According to the polymorphisms of this gene, no difference was found between the two groups in terms of allele and genotype distribution in the DNAs obtained from the individuals in the patient and control groups for that purpose.

Family studies have been performed to understand whether the genetic factors contribute to the etiology of schizophrenia or not. The mean risk of having schizophrenia was significantly higher in the first-degree relatives of the schizophrenia patients than in

the other groups (18,19). In our study, when the individuals in both groups were compared in terms of family history no family history was found in the control group while 29.1% of the individuals in the patient group had a family history. The difference between the groups in terms of family history was statistically significant ($p<0.05$), which is similar to the findings in other studies.

When the serotonin transporter gene VNTR polymorphism was assessed in terms of the allele frequencies at the end of the assays the schizophrenia group had 12 allele at a rate of 71.8%, 10 allele at a rate of 27.3% and 9 allele at a rate of 0.9%. The control group had 12 allele at a rate of 70.3% and 10 allele at a rate of 29.7%. No significant change was observed between the groups in terms of allele frequencies of this polymorphism ($p=0.712$). According to the assessment of the serotonin transporter gene VNTR polymorphism in terms of genotypes, 47.3% of the individuals in the patient group had 12/12 genotype, 47.3% had 12/10 genotype, 3.6% had 10/10 genotype, and 1.8% had 12/9 genotype. Of the individuals in the control group, 46.9% had 12/12 genotype, 46.9% had 12/10 genotype and 6.3% had 10/10 genotype. No 12/9 genotype was found in the control group. The risk of being different for serotonin transporter gene VNTR polymorphism was not statistically significant in the patient individuals compared with the individuals in the control group (CI 95% 0.49; 2.63) and the individuals with 12 allele had 1.07 times higher risk compared with those with 10 allele, but this risk was not statistically significant (95% 0.54; 2.12, $p=0.832$).

The serotonin transporter gene VNTR polymorphism has been investigated in different populations among the patients with schizophrenia. According to a study performed in Germany, STG.in.2 VNTR polymorphisms had a weak effect on the expression of serotonin transporter gene (20). No significant association was reported between serotonin 2A receptor (5-HT2A) and serotonin transporter gene VNTR polymorphism in patients with schizophrenia in Spain (15). The contribution of SLC6A4 variations to the suicide attempt in Scandinavian schizophrenic individuals was investigated and no association was found with schizophrenia (21). The association between serotonin transporter gene VNTR polymorphism and schizophrenia susceptibility and clinical subtypes of the disease was investigated in the studies performed in Turkey and no significant result was found (14,22). In our study, no significant difference was found between the genotype and allele frequencies of both the schizophrenia group and control group. In addition, the allele and genotype frequencies of the groups were assessed, but the groups were not assessed in terms of the subtypes of schizophrenia. No significant association was reported between schizophrenia and VNTR polymorphisms, which is like the findings of the studies in literature.

In a study performed on the white population in Taiwan, it was concluded that STG in.2.12 was prevalent and could play a role in the etiology of schizophrenia, which is different from the results of our study (10). It was concluded in a study in Berlin that schizoparanoid patients exhibited homozygosis for STG.in.2.12 allele more frequently than the other types of schizophrenia and control groups and that STG in.2.9 allele had a risk for the residual subtype of schizophrenia. Another result of the same study was that no association was found between the polymorphism and response to the treatment in the measurements performed with positive and negative marker scale (12). In our study, no assessment was performed in terms of schizophrenia subtypes and treatment and no significant association with STG.in.2.12 and STG.in.2.9 was found, which is different from the findings in these studies.

When the allele distribution of serotonin transporter gene 5-HTTLPR polymorphism was assessed as a result of the assays it was observed that 51.8% of the schizophrenia group exhibited L allele distribution and 48.2% exhibited S allele distribution. Of the control group, 53.1% exhibited L allele distribution and 46.9% exhibited S allele distribution. No statistically significant association between the prevalence of L and S alleles of the serotonin transporter gene 5-HTTLPR polymorphisms and the disease was found ($p=0.868$). According to the genotype distributions of the serotonin transporter gene 5-HTTLPR polymorphism, 30.9% of the individuals in the schizophrenia group were found as L/L, 41.8% as L/S and 27.3% as S/S. The genotype distribution in the control group was found as LL in 28.1%, L/S in 50.0% and S/S in 21.9%. The risk of being different for 5-HTTLPR polymorphism was not statistically significant in the patient individuals compared with the individuals in the control group (CI 95% 0.48; 1.78, $p=0.745$) and the individuals with S allele had 0.94 times higher risk compared with those with L allele, but this risk was not statistically significant (CI 95% 0.51; 1.75, $p=0.868$).

The serotonin transporter gene 5-HTTLPR polymorphism has been investigated in different populations among the patients with schizophrenia. It was revealed that 5-HTTLPR polymorphism had no significant contribution to the schizophrenia

susceptibility in Korean population and was not associated with clinical variables except for family history in at least the Korean population (23). The association between the serotonin transporter promoter and intron 2 polymorphisms and allelic variants and gene expression was investigated in Germany and it was concluded that 5-HTTLPR polymorphisms had a weak effect on the expression of serotonin transporter gene (20). No significant association between serotonin 2A receptor (5-HT2A) and serotonin transporter gene 5-HTTLPR polymorphism was reported in Spain (15). The serotonin transporter gene 5-HTTLPR polymorphism in the Russian population was associated with affective psychoses, but not associated with schizophrenia (24). In Croatian population, no difference was reported in the 5-HTTLPR genotype frequencies between the schizophrenic patients and healthy controls (16). Studies in Turkey have concluded that there is no significant difference between the patient and control groups in terms of the genotype distribution of serotonin transporter gene 5-HTTLPR variant (14,22). Our results were like those results in literate and no significant association was found between the psychopathology of schizophrenia and serotonin transporter gene 5-HTTLPR polymorphism. It was reported in Costa Rica that 5-HTTLPR polymorphism caused a significant increase in the risk for depressive syndromes seen in schizophrenia and had no association with the suicidal behavior (25). In the Southern India, it was stated that SLC6A4 had a strong role in a specific behavioral endophenotype and schizophrenia and significant allelic and genotypic associations with 5-HTTLPR and STG.in.2 polymorphisms were reported (13). In our study, no significant association was found between schizophrenia and 5-HTTLPR, which is different from the findings in the studies above, and the symptoms of the disease were not assessed.

This information suggests that the serotonin transporter gene plays no major role in the schizophrenia susceptibility. It confirms the idea that the activity of this gene can interact with the rate of transcription and cause changes that can clinically be assessed. Maybe, the polymorphic features of the serotonin transporter gene can be playing a role in the etiology of schizophrenia by interacting with the environmental factors.

Conclusion

When the results of our study are generally assessed we can observe that the serotonin transporter gene polymorphisms were not associated with schizophrenia. One of the reasons of this result can be that the study was performed on a limited number of sampling groups and another one can be that clinical subtypes of schizophrenia were not assessed.

Comprehensive studies including the various risk factors, environmental factors, and gene polymorphisms of the other neurotransmitters to determine the etiology of schizophrenia can contribute to obtaining new methods and promising results in the treatment of the disease.

Ethics Committee Approval: The study was approved by the Ethics Committee of Cumhuriyet University Faculty of Medicine (B.30.1.CUM.O.1H.00.00/04).

Peer-review: Externally peer-reviewed.

Author Contributions:

Concept, Design, Literature search, Data Collection and Processing, Analysis or Interpretation, Writing – FC, OD

Conflict of Interest: The authors have no interests to declare

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Analysis of Plasma Orexin Levels in Pedıatrıc Migraine Patients: A Prospectıve Controlled Clinical Study

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Abstract

Objective: Migraine is the most common primary headache disorder in children. However, its pathogenetic mechanisms are not fully understood. Researchers focused on Orexin A (a neuropeptide with anti-nociceptive effects) and Orexin B (a neuropeptide with pro-nociceptive effects), but the literature is scarce in terms of studies investigating the plasma levels of these neuropeptides in pediatric migraine patients. We aimed to compare the plasma levels of orexins between pediatric migraine patients and healthy controls

Methods: Children aged between 5 and 18 who were under diagnostic evaluation for and diagnosed with migraine in Ondokuz Mayıs University, Department of Pediatric Neurology between December 2018 and December 2019, constituted the target population. All study group patients (Group 1) were diagnosed with migraine according to IHS 2004 criteria. The control group (Group 2) consisted of healthy children. Data including age, gender, and presence or absence of aura were recorded. Two blood samples were taken from the patients in Group 1. The first sample was withdrawn during a non-attack period, and the second sample was withdrawn during the initial migraine attack. Only one blood sampling was done in the control group. Plasma Orexin A and Orexin B levels were analyzed by radioimmunoassay and compared between Group 1 and Group 2 during non-attack and attack periods. Also, intra-group comparative analyses were performed. Non-parametric tests were used for statistical analysis.

Results: This study included 98 patients, 52 children with migraine (Group 1), and 46 healthy children (Group 2). Mean patient age was 12,5±3,1 year in Group 1 and 12,3±3,4 years in Group 2. There was no difference between patient groups in terms of gender (p=0,103) and age (p=0,734). Plasma Orexin A levels of the migraine patients were higher than control group participants during the non-attack period, while Orexin B levels of the migraine patients were higher than migraine patients during the attack period. The mean plasma Orexin A level was significantly higher during the non-attack period than the attack period (p=0,002). The mean plasma Orexin B level was significantly higher during the attack than in the non-attack period (p=0,002). The presence of aura did not impact plasma orexin levels during both attack and non-attack periods.

Conclusions: The plasma level of Orexin A is elevated in migraine patients, probably as a response to nociceptive signals, and migraine attack is associated with elevated plasma Orexin B levels. Targeting the orexinergic system seems like a reasonable approach to improving the treatment of migraine disease.

Key words: migraine, arexin, pediatric, headache, treatment, children

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Introduction

The International Headache Society (IHS) defines migraine as recurrent, unilateral, pulsating headache of moderate or severe intensity which lasts for 4 to 72 hours (1,2). It is estimated that migraine affects 3-10% of children (3-5). Migraine is the most common primary headache disorder in children and adolescents, and approximately 18% of cases encountered in pediatric emergency rooms are migraine-related (6,7).

Tajti et al. reported that the trigeminovascular system (TVS), which includes trigeminal ganglion, meningeal vasculature, thalamus, and somatosensory cortex, took an important role in the pathogenesis of migraine (8). They also denoted that activation of TVS and neurogenic dural vasodilatation could be involved in the pathogenesis of migraine, and orexins were the neuropeptides involved in the central and peripheral sensitization of the trigeminal system. It is known that orexins are responsible for the regulation of autonomic functions and the sleep-wake cycle (8). Since migraine is related to autonomic dysfunction and sleep disorders such as insomnia; these authors noted that further clinical trials were needed to identify better the role of orexins in the pathogenesis of migraine (8).

Despite the questions regarding the essential role of orexins (i.e., orexin A and orexin B) in migraine pathogenesis, the literature is scarce regarding clinical studies analyzing the levels of these neuropeptides in migraine patients (8-10) A few numbers of clinical trials conducted with adult patients gave contradictory results and –to the best of our knowledge- there have been no published reports assessing the levels of these neuropeptides in pediatric migraine patients (8-10).

This study aimed to investigate the plasma levels of orexin A (OrxA) and orexin B (OrxB) in pediatric migraine patients, expecting our findings to contribute to the ongoing research regarding the pathogenesis of pediatric migraine.

Methods

This prospective study was approved by the ethical review committee of Ondokuz Mayıs University (OMU) Hospital (2018/174). Pediatric patients under diagnostic evaluation for and subsequently diagnosed with migraine in OMU Children's Hospital, Department of Pediatric Neurology, between December 2018 and December 2019 constituted this study's target population. All study group patients were under diagnostic management with the preliminary diagnosis of migraine and had a migraine attack during this diagnostic evaluation period before initiating a prophylactic migraine treatment. All these patients were later diagnosed with migraine as per IHS 2004 criteria.1 For the control group, participants were selected among children who presented to Healthy Children's Outpatient Clinic of the same hospital during the same time frame.

Patients whose parents approved their participation were assigned to this study. All parents gave their written consent before the participation of their children in this study. Patients who were younger than five or older than 18 patients diagnosed with a migraine disease before the study period and prescribed prophylactic treatment were omitted. Patients who have another type of chronic headache syndrome or any other endocrinologic, cardiovascular, or neurologic disease that can cause autonomic dysfunction were also excluded. The control group consisted of completely healthy children aged between 5 and 18 without a family history of migraine. All authors had full access to all study patient data during the study period.

All study group (Group 1) and control group (Group 2) participants underwent a thorough neurological examination. All study participants' demographic data and migraine-related data, including age, gender, presence, or absence of aura, were recorded. Two fasting blood samples were withdrawn from the patients in Group 1. The first blood sample was withdrawn during the initial outpatient encounter while the patient was in a non-attack period and under diagnostic management with the preliminary migraine diagnosis. The second blood sample was withdrawn during the first migraine attack of these patients after their first presentation to the pediatric neurology outpatient clinic and before initiation of prophylactic treatment. Both blood samples were taken from antecubital veins in the presence of ethylenediaminetetraacetic acid (EDTA; 1 mg/ml), and each one was 3-4 milliliters in volume. These samples were immediately centrifuged at 3000 g for 10 minutes, and the plasma was kept in Eppendorf tubes and stored at -80 ˚C until orexin level analysis. Plasma orexin levels were analyzed by radioimmunoassay (Peninsula Lab, San Carlos, CA, US) method following extraction using cartridges (Waters Associates, Milford, MA, US). The OrxA and OrxB kits were able to measure orexin levels as low as 10 pg/ml. Intra-assay coefficients of variation were 5% and 5.3% for OrxA and OrxB, respectively.

Only one blood sampling was done in the control group using the same approach, and plasma orexin levels were analyzed using the same method.

Plasma OrxA and OrxB levels were compared between Group 1 (migraine patients) and Group 2 (healthy controls) during non-attack and attack periods in Group 1. Also, intra-group comparative analyses were performed in Group 1 to compare plasma OrxA and OrxB levels during non-attack and attack periods and investigate the potential impact of aura on these levels.

Statistical analysis

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) 16.0 software. The results were given as means and standard deviations. Non-parametric tests, including the Mann-Whitney U test, Fisher's exact test, chi-square test, and Kruskal-Wallis test, were used to compare the groups. The p value was considered significant when it was lower than 0,05.

Results

The entire study cohort included 98 participants; 52 children diagnosed with migraine (Group 1) and 46 healthy controls (Group 2). There were 30 girls and 22 boys in Group 1, while there were 18 girls and 28 boys in Group 2. Mean patient age was 12,5±3,1 year in Group 1 and 12,3±3,4 years in Group 2. There was no difference between the two groups in terms of gender distribution (p=0,103) and age (p=0,734). Plasma OrxA and OrxB levels of the patients in Group 1 during non-attack and attack periods and control group participants are displayed in Table 1.

The mean plasma OrxA level of the patients in Group 1 analyzed during the attack period was 639,4±334,1 [26,0-1106,4] pg/ml. Comparison of this level with the mean plasma OrxA level of Group 2 (503,6±322 pg/ml) [19,4-990,3] revealed a statistically significant difference (p=0,014). The mean plasma OrxB level of the patients in Group 1 analyzed during the attack period was (1,7±1,5) [1,1-12] pg/ml). Comparison of this result with the mean plasma OrxB level of Group 2 (1,3±0,3 pg/ml) [1,1-3,3] revealed statistical significance (p=0,005). Thus, these comparative analyses elucidated that plasma OrxA levels of the migraine patients were higher than the levels of control group participants during the non-attack period, while plasma OrxB levels of the migraine patients were higher than the levels of migraine patients during the attack.

Comparison of the plasma OrxA and plasma OrxB levels of the migraine patients (Group 1) during non-attack and attack periods showed that the mean plasma OrxA level was significantly higher during the non-attack period compared with the attack period (p=0,002) (Table 2). On the other hand, the plasma OrxB level was significantly higher during the attack than in the non-attack period (p=0,002).

Among the 52 patients in Group 1, 36 (69,2%) were diagnosed with migraine without aura, while 16 (30,8%) had migraine with aura. The comparison of the mean plasma OrxA and OrxB levels of the patients in Group 1 as per presence or absence of aura revealed no difference between these two subgroups during both attack and non-attack periods (Tables 3 and 4).

Table 1. Plasma OrxA and OrxB levels of the pediatric migraine patients during non-attack and attack periods compared with the levels of healthy controls

	Control group (n=46)	**Study group (n=52) Non-attack period**		**Study group (n=52) Attack period**	
	(mean±SD) [range]	(mean±SD) [range]	p values	(mean±SD) [range]	p values
OrxA levels	503,6±322 [19,4–990,3]	639,4±334,1 [26,0–1106,4]	**p=0,014**	476,4±242,2 [24,4–780,1]	p=0,381
OrxB levels	1,3±0,3 [1,1–3,3]	1,3±0,2 [1,1–2,3]	p=0,287	1,7±1,5 [1,1–12,0]	**p=0,005**

Table 2. Plasma OrxA and OrxB levels of the pediatric migraine patients during non-attack and attack periods compared with the levels of healthy controls

	Study group (n=52) (Non-attack period)	**Study group (n=52) (Attack period)**	
	(mean±SD)	**(mean±SD)**	**p values**
Orexin A levels	639,4±334,1	476,4±242,2	**p=0,002**
Orexin B levels	1,3±0,2	1,7±1,5	**p=0,002**

Table 3. Comparison of the attack period plasma OrxA and OrxB levels between pediatric migraine patients without and with aura

	Migraine without aura (n=36)	**Migraine with aura (n=16)**	
	(mean±SD)	**(mean±SD)**	**p values**
Plasma OrxA levels	463,8±254,1	504,9±217	0,781
Plasma OrxB levels	1,8±1,8	1,5 ± 0,3	0,422

Table 4. Comparison of the non-attack period plasma OrxA and OrxB levels between pediatric migraine patients without and with aura

	Migraine without aura (n=36)	**Migraine with aura (n=16)**	
	(mean±SD)	**(mean±SD)**	**p values**
Plasma OrxA levels	629,4 ± 330,8	661,9 ± 351,2	0,481
Plasma OrxB levels	1,3 ± 0,2	1,4 ± 0,2	0,077

Discussion

The orxA (also called hypocretin 1) and orxB (also called hypocretin 2) are both neuropeptides synthesized by the neurons located at the lateral hypothalamic area and dorsomedial hypothalamic nucleus (9). The orexinergic neurons in these locations project into areas such as periaqueductal gray (PAG), nucleus raphe magnus (NRM), and locus ceruleus (LS), which are considered as migraine generators. These areas are rich in terms of orexin receptors: The OX1R (i.e., HCRTR1) is selectively expressed in LC while OX2R (i.e., HCRTR2) is selectively expressed in NRM (11). Holland et al reported that orexins could reduce neurogenic dural vasodilatation and inhibit TVS via activation of OX1R (i.e., anti-nociceptive effects) (12). They could cause neurogenic dural vasodilatation and stimulate TVS via activation of OX2R (i.e., pro-nociceptive effects). It is widely accepted that activation of OX1R leads to analgesic effects via attenuated A- and C-fiber responses to dural stimulation, while activation of OX2R leads to pro-nociceptive effects due to exaggerated A- and C- fiber response to dural stimulation (13,14). These findings indicate that activation of OX1R reduces the risk of having a migraine attack, while activation of OX2R increases this risk. Of note, Rainero et al. stated that OX1R had 50-fold more affinity to OrxA than OrxB, while OX2R had similar affinities for both receptors (15).

Conventional migraine medications target the trigeminovascular system; however, Akerman et al. stated that the hypothalamus should be the target for new-generation migraine treatments (16). Hoffmann et al. worked on an experimental animal model and demonstrated that targeting the hypothalamic orexinergic system by a dual orexin receptor antagonist (DORA) DORA-12 could be a potential prophylactic treatment method for migraine (17). In this study, DORA-12 attenuated the neurogenic dural vasodilatation and TVS activation. As such, Cady et al. found in an experimental animal study that dual antagonism of OX1R and OX2R by DORA-12 inhibited trigeminal neural activation (18). It is important to note that DORAs are currently used in treating insomnia, and DORA-12 is the precursor of suvorexant.

Contrary to these findings, Chabi et al., who analyzed the efficacy of filorexant –another DORA- in the prophylactic treatment of adult migraine in a randomized, double-blind, placebo-controlled study setting, concluded that this medication was not effective in preventing migraine attacks (19). They gave 10 mg filorexant daily at night-time to their patients with migraine. This dosage selection was based on the fact that the same dose was used to treat insomnia (18-20). It is known that migraine and sleep disorders are closely related to each other (20). Chabi et al. denoted that most of their migraine patients did not have an accompanying sleep disorder (19). They stated that DORAs might be effective in migraine patients who had a concurrent sleep disorder.

In our study, we did not assess our patients in terms of sleep disorders. This fact can be considered as a weakness of our study. On the other hand, it should be noted that our study did not aim to analyze the efficacy of medications in the treatment or prevention of migraine attacks in children. Instead, we investigated the plasma levels of OrxA and OrxB to contribute to the research regarding the role of these neuropeptides in the pathogenesis of pediatric migraine. It is widely accepted that introduction of triptans led to remarkable progress in the acute pharmacologic treatment of migraine (21). However, despite the progress regarding acute treatment

options, there have been no significant improvements recently in preventive treatment protocols (22).

Ravid et al. reported that orxA inhibited neurogenic dural vasodilatation by reducing the release of calcitonin gene-related peptide (CGRP) from the trigeminal nerve endings (23). It is known that CGRP is a potent vasodilator that is highly effective on dural circulation (24). Moreover, stimulation of the trigeminal ganglion is known to induce secretion of CGRP into the cranial circulation during the initial period of a migraine attack (25). Therefore, current migraine research is focusing on CGRP and orexins for enriching the treatment options.

Sarchielli et al. also investigated the role of OrxA in the pathogenesis of migraine (9). These authors compared the baseline (i.e., non-attack) cerebrospinal fluid (CSF) OrxA levels of 27 adult migraine patients with healthy controls and found that the levels were significantly higher in the former group. They concluded that the increase in the OrxA levels might be due to a hypothalamic response to the stress induced by chronic headaches.

Caproni et al. analyzed the baseline plasma OrxA and OrxB levels in 39 adult patients who were on prophylactic migraine treatment with amitriptyline (10). They reported that plasma OrxA and OrxB levels decreased significantly in the 3rd month of this treatment. These authors stated that their findings were contradictory to the results reported by Sarchielli et al., and they ascribed this difference to the fact that they measured the levels of the orexins in serum while Sarchielli et al. worked on CSF samples (9,10). The analyses of Caproni et al. revealed that pretreatment serum OrxA and OrxB levels of the adult patients with migraine were significantly lower than the levels of healthy controls (10). They concluded that the orexinergic pathway could be defective in patients with migraine.

Since Caproni et al. reported that serum OrxA and OrxB levels of adult migraine patients were significantly lower than those of healthy controls, their findings contradict ours (10). However, it should be considered that our study was conducted with recently diagnosed pediatric migraine patients, while Caproni et al. worked on adult patients (10). We hypothesize that the orexinergic neurons' responsiveness to the ‘nociceptive milieu’, which can lead to reactive elevation of OrxA levels, might decline by time due to changes in receptor affinities of orexinergic neurons.

As per our knowledge, our study is the first to assess plasma orexin levels in pediatric migraine patients and compare the findings of the attack period with those of the non-attack period. Our results indicated that plasma OrxA levels of pediatric migraine patients analyzed during the non-attack period were significantly higher than those of healthy controls. This finding is in accordance with the anti-nociceptive effects of OrxA. On the other hand, plasma OrxB levels of the patients measured during the attack period were significantly higher than healthy controls. This result is in line with the pro-nociceptive effects of OrxB. We also found that plasma OrxA levels were significantly higher during the attack period than the non-attack period. The plasma OrxB levels analyzed during the attack period were significantly higher than plasma OrxB levels measured during the non-attack period. Despite the difference in the analyzed samples, our findings are in line with the results reported by Sarchielli et al., who reported that baseline CSF OrxA levels of migraine patients were higher than those of healthy subjects (9). We postulate that the level of OrxA, which is a neuropeptide with anti-nociceptive effects, is elevated in migraine patients due to nociceptive signals (i.e., reactive elevation) and that migraine attack is associated with elevated OrxB levels. It is known that OrxB is pro-nociceptive, and its dominance may pave the way for a migraine attack. As per our findings, plasma OrxA and OrxB levels did not differ significantly with the presence or absence of aura in pediatric migraine patients. Although these data imply that plasma orexin levels are not directly related to aural symptoms, it is essential to note that the ‘potential role of orexins in the pathogenesis of migraine aura’ was not the primary focus of this study. On the other hand, our results indicated that the potential relationship between plasma orexin levels and migraine attacks was independent of aura's presence or absence.

Conclusion

Although it is known that orexins are involved in the pathogenesis of migraine, there are only a few clinical studies analyzing their levels in migraine patients. Our study is the first to analyze the plasma orexin levels in pediatric migraine patients to the best of our knowledge. Our analysis showed that plasma OrxA levels were higher in pediatric migraine patients than healthy controls during the non-attack period, while plasma OrxB levels were higher than healthy controls during attack periods. As per our findings, plasma orexin levels were not directly related to the presence or absence of aura in pediatric migraine patients. We conclude that research focusing on targeting the orexinergic system for improving the preventive treatment of migraine

should be supported. Our findings indicate that this approach looks promising for the well-being of pediatric migraine patients.

Ethics Committee Approval: This prospective study was approved by the ethical review committee of Ondokuz Mayıs University (OMU) Hospital (2018/174)
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Author Contributions:
Concept H. I, O. F. A; ***Design*** H.A; ***Literature search,*** H. A, ***Data Collection and Processing*** H. I, O.F.A, H.A, E.C.C; ***Analysis or Interpretation,*** H. I, O.F.A, H.A, E.C.C; ***Writing*** H. I, O.F.A, H.A, E.C.C
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Skin Traction Tecnique for Closure of Large and Complex Skin Defects in Special Cases

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Abstract

Objective: During the period of COVID-19 pandemic, the reconstructive surgeons don't want to take risks of complex and long operations, and to struggle with long recovery time after surgery as well as with associated donor-site morbidity. Therefore, they prefer much more simple techniques. The objective of this study is to evidence that skin traction technique is a simple, short term, useful, and good option for closing open wound complex defect which needs the reconstruction with large flap.

Methods: Skin traction techniques were applied to ten patients who had large complex defects in our clinic between March 2020 and March 2021. Patient's data including demographic characteristic, comorbidities, causes of defects, anatomic localization of defects, size of defect, time of closure defect, time interval of tightening suture, number of tightening sutures, time of staying in hospital, general complication was recorded.

Results: The study included 8 males and 2 females. The average age of patients was 42.8 years ranging from 22 to 60. The size of defects ranged between 8x5 cm and 18x10 cm with an average of 11.7x7.2 cm. The average duration of follow-up was 6 months. After 3 months, we evaluated subjectively quality of skin thickness, mobility, and colour. Skin was thinner and less mobile in the areas that were reconstructed with graft when compared with skin traction territories where the colour of skin was also normal in the cases with skin defect which was repaired by primarily closure after skin traction. All patients were satisfied with results. Complications such as skin necrosis at the traction site and hematoma were not observed. Superficial wound infection was seen in one patient, and it was resolved with antibiotherapy.

Conclusions: We suggest using the traction suture technique for complex defects as an easy, cheap, and short-time procedure to reconstruct large and complex skin defects especially in recipient vessel problems, cases suffered from flap failure, patients with comorbidities and special conditions (for example, during the COVID-19 pandemic).

Key words: Adenoma, Surgery, Trans-sphenoidal, Pituitary.

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Introduction

Many surgical methods have been applied for the closure of large skin defects such as primer skin graft, vacuum assisted closure, tissue stretching and expansion, local flaps, and free flaps. These methods are preferred according to criteria as follows: 1. exposed of nerve, vessel, bone, and tendon, 2. presence of deperiosted bone, 3. localization and size of the defect, 4. the degree of nerve and vascular injury, and 5. detailed history of patient as age and associated vascular comorbidity (1).

Reconstructive ladder goes through simple to complex. However, this diagram may be reversed for complex large defect when no suitable recipient vessels and no options of reliable local flaps are found and already all free flaps options are exhausted (1, 2). During the period of COVID-19 pandemic, the reconstructive surgeons don't want to take risks of complex and long operations, and to struggle with long recovery time after surgery as well as with associated donor-site morbidity. Therefore, they can prefer much more simple techniques as medical dressing with different drug, VAC (vacuum assisted closure) therapy, and skin traction.

Optimal amplitude mechanic force, tension and waveform may provide skin elongation due to skin's viscoelastic properties. Primary closure may be provided by the viscoelastic properties of the skin. The skin's mechanic properties such as mechanical creep and stress relaxation were described more than 40 years ago (1, 2). As a result, if skin is stretched with a constant force as a result, skin will expand during it is kept under tension, the phenomenon is called as mechanical creep. If the skin is stretched to a constant distance, it will expand. The reduction of force or tension on the skin over time after it has expanded is called stress relaxation. Tissue traction can be used for closure complex defect by utilizing skin's mechanic properties (3, 4).

The aim of this study is to evidence that skin traction technique is simple, short term, useful, and good option for closing open wound complex defect which needs the reconstruction with large flap.

Methods

Skin traction techniques were applied to ten patients who had large complex defects in our clinic between March 2020 and March 2021. The essential approval was obtained from Alaaddin Keykubat University Training and Research Hospital to use the hospital database. The study protocol was approved by the ethics committee of Faculty of Medicine, Alanya Alaaddin Keykubat University. Patient's data including dermographic characteristic, comorbidite, causes of defects, anatomic localization of defects, size of defect, time of closure defect, time interval of tightening suture, number of tightening suture, time of staying in hospital, general complication were recorded.

Surgical Technique

Serial debridments were performed till the nonviable tissue was discarded in all patients. Skin traction sessions were initiated with using simple skin sutures across the wound edges with 2.0 prolen which had cutting needle while patients were under sedation or local anasthesia. First suture loop was placed at 1,5 cm away from wound edges on the healthy skin. Minimal three and maximum ten traction sutures were needed for each of defects. The skin traction was applied untill the skin was blanched and appeared too tight. All wounds were cleaned, and their dressings were changed daily. When skin relaxation was achieved, traction suture was renewed. However, renewing time was different in all patients due to their skin mechanical properties. In the follow-up period, the skin edges and distal extremity were evaluated by clinical observation—capillary refilling, skin color, peripheric artery pulsation, and sensation—

Results

The study included 8 males and 2 females. The average age of patients was 42.8 years ranging from 22 to 60. The etiological causes of defects were traffic accident in four patients, gunshot injury in two patients, job-related injury in one patient, diabatic foot in one patient, whereas one of them has congenital foot deformity. When the location of defects was evaluated, the defects were located in the lower extremity in nine cases and in the upper extremity in one case. The size of defects ranged between 8x5 cm and 18x10 cm with an average of 11.7x7.2 cm (Table 1).

Patient	Age (year)	Gender	Localization of defects	Size of defect (cm)
1	22	M	L-LE Anterolateral tibia	12x10
2	41	F	R-UE Forearm	12X8
3	58	M	L-LE Calcaneus	8X5
4	25	F	L-LE Plantar surface	9x5
5	60	M	R-LE Medial tibia	11x10
6	34	M	L-LE Anteriolateral tibia	12x10
7	50	M	L-LE Foot lateral surface	10x4
8	35	M	R-LE Anterior tibia	9x5
9	55	M	L-LE Knee medial surface	10x5
10	48	M	L-LE Anterolateral tibia	18x10

Debridement's and skin traction procedures of all the patients were generally performed by ambulatory surgery under local anesthesia. Also, vacuum assisted therapy and traction sutures were used simultaneously in one patient. Skin traction provided enough time for evolving granulation tissue and decreasing defect sizes in five patients and then these defects were grafted. Skin tractions were enabled us to close five of these defect primarily.

The average duration of follow-up was 6 months. After 3 months, we evaluated subjectively quality of skin thickness, mobility, and colour. Skin was thinner and less mobile in the areas that were reconstructed with graft when compared with skin traction territories where the colour of skin was also normal in the cases with skin defect which was repaired by primarily closure after skin traction. All patients were satisfied with results.

Complications such as skin necrosis at the traction site and hematoma were not observed. Superficial wound infection was seen in one patient, and it was resolved with antibiotherapy.

Case Reports

Case 1

A 22-years-old man underwent gunshot injury, and 12x10 cm soft tissue defect was on the anterolateral tibia with exposed tibia bone and tendons. The wound was prepared for closure of defect by debridement. Six traction sutures were placed with 2.0 prolen and then sutures were tightened within three days. Defect could be repaired with primary closure expect only a limited area in which splint thickness graft was used. The wound was healed after a month (Figure 1).

Figure 1. Photographs of case 1st (A: View of defect before debridement, B: View of exposed tendons and tibia bone after debridement, C: View of repaired defect by skin traction and skin graft after 2 months postoperatively)

Case 2

A 58-year-old man who was referred with the 8x5 cm diabetic ulcer on the left heel with exposed calcaneus bone. After debridement, four traction sutures were used, and sutures were tightened within six days when defect was closed. The defect was closed by using simple interrupted sutures. The wound was healed after twenty-one days (Figure 2).

Figure 2. Photographs of case 2nd (A: View of defect of heel preoperatively, B/C: Application of skin traction, D: View of repaired defect by skin traction after 6 months postoperatively)

Case 3

A 25-year-old female patient who had congenital foot deformity: There was a 6x5 cm pressure sore on the plantar surface of the foot, in which the plantar fascia was exposed due to the changes in areas which were the load-bearing and imposed to pressure. Plantar forefoot defect was closed by medial plantar Fascio cutaneous island flap. Unfortunately, after total flap necrosis skin defect with an area of 9x5 cm was observed. Therefore, other reconstruction options were not remaining. Five traction sutures were used and tightened sequentially every 7 days. The defect was closed by using simple interrupted sutures. The wound was healed after forty-five days (Figure 3).

Figure 3: Photographs of case 3rd (A: View of defect before debridement, B/C/D/E: Application of skin traction, F: View of repaired defect by skin traction in the early postoperative period)

Discussion

Soft tissue defects can be repaired by various reconstruction methods. Complex defects of upper or lower extremity which are with exposed tendon, vascular structure, and nerve are difficult for reconstruction (1). This kind of large defect needs free flaps because of restricted options of local flap, no suitable pedicle, and the needs for flaps with different textures. Yet, this method requires long operation times, experienced surgeon, suitable recipient vessel with donor area morbidity (1). Especially if there is not a good recipient vessel, sometimes it leads to amputation. Also, after flap failure, the surgeon has no other option when limb salvage is still feasible (1,5).

VAC device should not be used for covering over extensive bone or an extensive fracture line. Therefore, the indication of VAC device is restricted. VAC device is a valuable adjunctive therapy method. Medical dressing is a long-term treatment which has an important disadvantage because of infection (2).

During the COVID-19 pandemic, some easier surgery methods with a short operation time and an ease of postoperative care, and without donor site morbidity are more suitable instead of more aggressive procedures. In accordingly, skin traction is a preferred option (6).

The mechanical properties of human skin and visco-elastic parameter were described by Gibson in 1977. The viscoelastic property of mechanical creep and stress relaxion were adverted in various studies (7). Mechanic stimuli such as shear force, tension, compression, and hydrostatic pressure convert to electrical signal by mechanosensory and mechanic stretching modulates growth direction (3, 4, 8). Mechanical creep means that if skin is stretched with constant, optimal amplitude force, it will grow and extend. Extensible connective tissue contains fibrous collagen network and elastin within extracellular matrix. Also stress relaxation mean if the skin is stretched to constant distance, skin will extend and then the tension of skin will reduce (9, 10). Consequently, skin is elongated by this viscoelastic property, and thus skin allows to use primary closure of wound.

Multiple techniques subsist to close wound and fasciotomy or perform scar revision by dermatotraction such as Schoelace tecnique, Marburger skin approximation (11), skin traction wire (12), clips and needles method (9), skin tape application, skin streching device, and presuturing (13). The major disadvantage in these techniques is need additional surgical instruments; as an example, a silastic vessel loop is needed for schoelace technique. In our technique, any of specific surgical instruments is not used except sutures. Skin traction technique is cheaper and easier than the other techniques.

Another advantage of our technique is that the quality of skin was always found to be satisfactory. Stretching site was preserved of sensation and colour. Five of defects could be closed primary and three of defects were closed with STSG. However, this method allows a significant decrease in applied graft area. Stretching site is more successful in terms of skin sensation and colour than graft area.

The stretching force as a limiting factor for using this technique has not been exaggerated because of skin viability. Safe stretching indicator was defined as skin pallor and pain. Another limiting factor is the difficulty of using irregular traumatic wound.

Conclusion

The suggested method can be applied with cheap and available materials in everywhere and everybody, depending on viscoelastic properties and ability of expandability of skin. We suggest to use the traction suture technique for complex defects as an easy, cheap, and short-time procedure to reconstruct large and complex skin defects especially in recipient vessel problems, cases suffered from flap failure, patients with comorbidities and special conditions (for example, during the COVID-19 pandemic).

Ethics Committee Approval: This study was conducted with the approval of the ethics committee of Alaaddin Keykubat University Training and Research Hospital, Clinical Research Ethics Committee. (Ethics Committee date and Decision no: 23/06/2021 -11/07)
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Predictor Role of Systemic Inflammation in Ovarian Cancer

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Abstract

Objective: The study aims to investigate the diagnostic value of hemogram derived systemic inflammation parameters in ovarian cancer.

Methods: Totally, the study group consisted of 60 patients with suspected ovarian masses who underwent surgery between February 1th, 2020, and May 1th, 2021, in Ordu University Training and Research Hospital. The patients included in the study were divided into two groups according to postoperative histopathological diagnosis, benign group (consisting of 39 patients) and malign group (consisting of 21 patients). The analysis of the receiver operating characteristic (ROC) curve was used to discover the optimal cut-off values of the hemogram derived blood parameters to predict ovarian cancer.

Results: In the cancer group; 85% of the patients were diagnosed with epithelial ovarian cancer and 62% at late stage. As compares with benign ovarian mass group, the ovarian cancer group had higher neutrophil counts (6.67+3.17 vs 4.64+1.94) (p=0.006), but lower lymphocyte counts (1.60+0.68 vs 2.22+0.64) (p=0.003). The high NLR values (cut-off 2.557) predict ovarian cancer with 71.4% sensitivity and 69.2% specificity (AUC 0.817, p=0.000, CI=0.712-0.922). The high dNLR values (cut- off 1.881) also predict cancer with similar sensitivity and specificity as NLR (AUC 0.814, p=0.000, CI 0.708-0.921). Significant cut-off values for the other hemogram derived parameters were 0.26, 0.0165, 159.66 and 770.611 for MLR, NPR, PLR and SII, respectively. Additionally, the high values of CA 125 (cut-off 34.45) and CA 15-3 (cut-off 16.4) was founded to be related with ovarian cancer.

Conclusions: This paper revealed that high inflammatory parameters such as NLR and dNLR in patients with ovarian masses are mainly associated with ovarian cancer. In the study, it was emphasized that simple and easily accessible hemogram parameters should be used in addition to tumor biomarkers such as CA 125, CA 15-3, which are routinely used in predicting ovarian cancers. We think that more valuable results will be achieved with comprehensive studies designed prospectively.

Key words: Neutrophil-to-lymphocyte ratio, derived neutrophil-to-lymphocyte ratio, systemic inflammation, ovarian cancer.

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Introduction

Ovarian cancer is a fairly common malignancy among women. Although, its frequency varies between countries, it ranks third after cervical cancer and uterine corpus cancer. Additionally, ovarian cancer is the most common cause of gynecological cancer-related deaths due to its high incidence and high mortality rate (1). The fact that ovarian cancer is generally asymptomatic at an early stage, and the limited number of sensitive and specific diagnostic markers cause more than two-thirds of the patients to be diagnosed at an advanced stage. Although treatments such as staging or debulking surgery and chemotherapy continue to evolve over the years, the five-year survival rate remains under 30%, due to early metastasis and late diagnosis (2).

Although tumor biomarkers such as CA125 (cancer antigen 125), CA15-3 (cancer antigen 15-3), CA19-9 (cancer antigen 19-9), CEA (carcino embryonic antigen) and AFP (alfa feto protein), which have been used for many years, are in the first place in diagnosis, many other markers have been investigated for early diagnosis of ovarian cancer and to predict prognosis. But which marker should be used is still a matter of debate. Therefore, finding effective markers and using them together with conventional tumor biomarkers is very important in the diagnosis and treatment of ovarian cancer, which is a serious public health problem (3).

Emerging evidence revealed that up to 20% of the cancers were caused by chronic inflammation, and systemic inflammatory response played a key role in the initiation, invasion, progression and distant metastasis of malignancies. Numerous markers of inflammatory-immune response have been proposed as potential prognostic factors for cancer. Among these inflammation markers hemogram derived ratios such as NLR and dNLR are routinely tested and widely used in clinical practice (4-6).

A newly identified marker, dNLR, calculated using the formula for neutrophil count/non-neutrophil white blood cell count, has been widely investigated to predict prognosis in many types of cancer, including breast, urological, digestive cancers and malignant melanoma (4,5,7,8). However, the diagnostic value of these inflammatory parameters in gynecological (especially ovarian) cancers remains unclear. In the current study, we aimed to reveal the clinical importance of inflammatory parameters in ovarian cancer and to investigate the success in predicting malignancy in ovarian masses.

Methods

This retrospective, single-center study was conducted between February 1st, 2020, and May 1th, 2021, in Ordu University Training and Research Hospital. The study was approved by the ethics committee of Ordu University Medical Faculty.

We retrospectively analyzed 96 patients with suspected ovarian mass who underwent surgery. Non-confirmed PCR negative cases, even if they were symptomatic or with a history of contact, were excluded from the study. Pregnancy, age < 18 years, acute inflammation, blood disease and smokers were excluded from cohort. 11 covid-19 suspected/positive, 18 smokers, 4 tubo-ovarian abscess/pelvic infections, 2 blood diseases, 1 pregnant patient were excluded from the study. As a result, a cohort was formed with 60 patients who met the study criteria.

Patients with ovarian masses included in the study were divided into two groups according to their postoperative histopathological diagnosis. Thence, there was benign group (consisting of 39 patients) and malign group (consisting of 21 patients).

As a routine protocol, hemogram and tumor biomarkers (Ca 125, Ca 15-3, Ca 19-9, CEA, AFP) tests were applied to each patient for preoperative evaluation. Blood samples were taken from all patients upon admission before any treatment began. Primary objective of the study is whether hematological parameters and some inflammatory indices derived from hematological parameters may be used in ovarian cancer patients pre-operatively as simple screening.

Hematologic indices, hematologic ratios and tumor biomarkers were presented in Table 1. These hematological indices were calculated as NLR, which is the ratio between the count of neutrophils (×109cells/L) and the count of lymphocytes (×109 cells/L), dNLR is neutrophils/(white blood cells-neutrophils), PLR is the ratio between the count of platelets (×1011 cells/L) and the count of lymphocytes (×109 cells/L) and the SII is defined as the counts of neutrophils (×109 cells/L) multiplied by the counts of platelets (×1011 cells/L) and divided by the count of lymphocytes (×109 cells/L), NPR is the ratio between the count of neutrophils (×109 cells/L) and the count of platelets (×1011 cells/L).

Statistical analysis

For analyzing the results of the study, IBM SPSS version 20 (SPSS Inc., Chicago, IL, USA) program was used. Analyzes were carried out in a 95% (p=0.05) confidence interval. Because the study period is short and so study population is limited and

retrospective design of the study, sample size is not calculated. Descriptive statistical methods and comparative statistics had been used in the study. Descriptive data derived from the study were presented as mean ± standard deviation. The normality distribution of numerical variables was studied with the Kolmogorov-Smirnov and the Shapiro-Wilks tests. The independent samples t-test was used for numerical variables with normal distribution and Mann-Whitney U test was used for those which not distributed normally. The analysis of the receiver operating characteristic (ROC) curve was used to discover the optimal cut-off values of the hemogram derived blood parameters to predict ovarian cancer. AUC was interpreted as excellent if 0.9-AUC-1, good if 0.8-AUC-0.9, moderate if 0.7-AUC-0.8, poor if 0.6-AUC-0.7, and failed if 0.5-AUC-0.6.

Results

Totally, sixty women who were operated for an ovarian mass were included in the retrospective, cohort study. Twenty-one had pathologically confirmed ovarian cancer and thirty-nine were diagnosed benign ovarian cysts.

The demographic and clinical characteristics are presented in Table 1. The age range of patients was 18-80 years. Although the mean age was lower in the benign group (42.03+13.6), no statistically significant difference was observed with the mean age of the malignant group (49.1+13.6) (p=0.661). Additionally, there was no significant difference in body mass indexes between the groups (23.6+4.4 vs 22.7+3.4) (p=0.342).

In the cancer group, eighteen women (85.75) had epithelial ovarian cancer, while three patients had a non-epithelial tumor subtype. FIGO (International Federation of Gynecology and Obstetrics) staging was performed in cases with ovarian cancer. FIGO stages were as follows; 1- six patients, 2- two patients, 3- eleven patients, 4- 2 patients. Approximately 62% of patients had advanced (stage 3-4) ovarian cancer.

The hematologic and tumor biomarkers of the study group are presented in Table 2. As compares with benign ovarian mass group, the ovarian cancer group had significantly higher neutrophil counts (6.67+3.17 vs 4.64+1.94) (p=0.006), but lower lymphocyte counts (1.60+0.68 vs 2.22+0.64) (p=0.003). Accordingly, we found that many hemogram derived parameters, especially NLR (neutrophil-to-lymphocyte ratio) and dNLR (derived neutrophil-to-lymphocyte ratio), increased due to systemic inflammation in the ovarian cancer group. In addition, we found statistically significantly higher tumor biomarkers CA 125 and CA 15-3 in the ovarian cancer group. On the other hand, no significant difference between the groups in terms of CA 19-9, CEA and AFP values was detected.

ROC curves were made to compare the diagnostic utility of tumor biomarkers (CA 125, CA 15-3, CA 19-9, CEA, AFP) and hemogram derived ratios (NLR, dNLR, MLR, PLR, NPR, SII) in diagnosing ovarian cancer. ROC graphics and Area Under the Curve (AUC) values are presented in Figure 1 and Table 3.

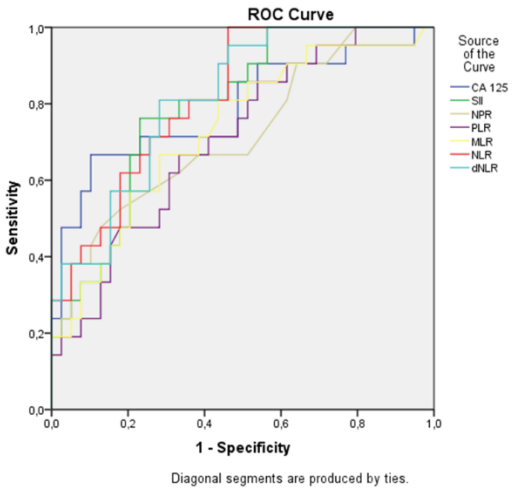

Figure 1. ROC graphics

We found that the high NLR and dNLR had an impact in ovarian cancer. The high NLR values (cut-off 2.557) predict ovarian cancer with 71.4% sensitivity and 69.2% specificity (AUC 0.817, p=0.000, CI=0.712-0.922). The high dNLR values (cut- off 1.881) also predict cancer with similar sensitivity and specificity as NLR (AUC 0.814, p=0.000, CI 0.708-0.921). Significant cut-off values for the other hemogram derived parameters were 0.26, 0.0165, 159.66 and 770.611 for MLR, NPR, PLR and SII, respectively. Additionally, the high values of CA 125 (cut-off 34.45) and CA 15-3 (cut-off 16.4) was founded to be related with ovarian cancer.

Table 1. The demographic and clinical characteristics of the study group

Characteristics	Ovarian cancer (n=21)	Benign ovarian masses (n=39)	P value
Age	49.10±13.68	42.03±13.03	0.661
BMI	23.6±4.4	22.7±3.4	0.342
Tumor subtype			
Epithelial	18		
Non-epithelial	3		
FIGO stage			
I	6		
II	2		
III	11		
IV	2		

Abbreviations: BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics

Table 2. Hematologic and tumor biomarkers of the study group **

Biomarker	Ovarian cancer (n=21)	Benign ovarian masses (n=39)	P value
WBC	9.08±3.26	7.62±2.41	0.140
HB	11.95±1.67	11.96±1.55	0.843
NEU	6.77±3.17	4.64±1.94	0.006*
LYM	1.60±0.68	2.22±0.64	0.003*
MONO	0.54±0.21	0.53±0.16	0.798
EOS	0.11±0.09	0.20±0.26	0.158
BASO	0.034±0.022	0.031±0.020	0.721
MCV	85.22±6.82	84.14±7.40	0.369
MCH	27.32±2.66	27.12±3.02	0.969
MCHC	32.02±1.06	32.17±1.53	0.090
PCT	0.28±0.04	0.30±0.08	0.309
PDW	11.10±2.24	10.67±1.94	0.721
RDW	44.78±7.90	41.69±9.62	0.117
PLT	287.47±55.97	310.48±84.82	0.120
NLR	5.81±6.22	2.19±1.06	0.000*
dNLR	3.75±3.58	1.58±0.64	0.000*
MLR	0.37±0.18	0.25±0.10	0.003*
PLR	226.44±159.35	148.18±52.58	0.008*
NPR	0.024±0.015	0.015±0.006	0.005*
MPVPR	0.035±0.009	0.034±0.012	0.281
LYM*PLT	474.02±283.50	705.34±303.79	0.003*
RDWPR	0.16±0.04	0.014±0.05	0.072
SII	1646.38±1728.93	710.90±503.99	0.000*
CA 125	295.06±408.20	37.11±66.12	0.000*
CA 15-3	41.43±40.68	12.68±6.09	0.000*
CA 19-9	971.89±4359.99	15.21±27.35	0.138
CEA	8.45±21.3	1.80±2.05	0.055
AFP	11.42±44.36	1.84±1.21	0.710

Abbreviations: WBC, white blood cell; HB, hemoglobin; NEU, neutrophil; LYM, lymphocyte; MONO, monocyte; EOS, eosinophil; BASO, basophil; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PCT, platecrit; PDW, platelet distribution width; RDW, red cell distribution width; PLT, platelet; NLR, neutrophil-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NPR, neutrophil-to-platelet ratio; MPVPR, mean platelet volume-to-platelet ratio; LYM*PLT, lymphocyte*platelet; RDWPR, red cell distribution width-to-platelet ratio; SII, systemic immune inflammation index; CA 125, cancer antigen 125; Ca 15-3, cancer antigen 15-3; CA 19-9, cancer antigen 19-9; CEA, carcino embryonic antigen; AFP, alfa feto protein

*statically significant

**values are given as mean ± standard deviation

Table 3: Area Under the Curve (AUC) values

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval		Cut off value	Sensitivity	Spesificity
				Lower Bound	Upper Bound			
Hemogram derived ratios								
NLR	.817	.054	.000*	.712	.922	2.557	71.2	69.2
dNLR	.814	.054	.000*	.708	.921	1.881	71.4	71.8
MLR	.732	.068	.003*	.598	.866	0.26	66.7	61.5
NPR	.720	.070	.005*	.582	.858	0.016	66	62
PLR	.709	.068	.008*	.576	.842	159.6	61.9	69.2
SII	.794	.057	.000*	.681	.906	770.6	76.2	76.9
Tumor biomarkers								
CA 125	.789	.067	.000*	.657	.921	37.4	71.4	74.4
CA 15-3	.817	.064	.000*	.693	.942	17.4	76.2	74.4

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

*Statically significant

Discussion

The systemic inflammatory response plays a significant role in tumor development and progression. Although the genetic predisposition in the development of cancer cannot be denied, many studies have shown that inflammation caused DNA damage and excessive production of cytokines (including IL-2, IL-6, TNF-alfa and VEGF) triggered the initiation and progression of cancer. In addition, it has been determined that inflammation inhibits the apoptosis of DNA damaged cells and increases angiogenesis that helps growth of tumor tissue (9-11).

Although some studies were conflicting, recent evidence showed that systemic inflammatory response markers such as NLR, dNLR, MLR, NPR, PLR and SII were associated with prognosis of various cancer. In a meta-analysis of 6585 patients published in 2019 investigating urological cancers, high dNLR values were associated with decreased cancer-specific survival in renal cell carcinoma, prostate cancer, and urothelial cancers (8). In a study investigating the clinical outcome of patients diagnosed with metastatic gallbladder cancer, it was shown that dNLR and CEA values predict a better prognosis when used together (12).

In a meta-analysis report investigating poor prognosis in 10599 breast cancer patients, high dNLR value was found to be associated with poorer overall and recurrence-free survival (7). In another breast cancer study, NLR, dNLR, PLR values were found to be associated with both disease-specific and disease-free survival. Especially in patients with breast cancer with high PLR values, more lymph node metastases were detected (6). Furthermore, the relationship between dNLR and cancer survival has been demonstrated in many cancers such as malignant melanoma and digestive cancers (4,5).

In the literature, studies investigating hematological parameters and gynecological cancers are insufficient. In a study investigating cervical cancer prognosis, NLR, dNLR, and PLR were associated with lymph node metastasis, recurrence-free and overall survival (13). In a meta-analysis of data from 3390 patients diagnosed with endometrial cancer, high pretreatment NLR and PLR values were founded to be associated with poor prognosis (14). In two studies examining lymph node metastasis in endometrial cancer, it was shown that hemogram parameters predict lymph node metastasis (15,16). In three other endometrial cancer studies, hemogram parameters showing systemic inflammation were shown to be associated with cancer stage, overall survival, and lymphovascular-myometrial-cervical invasion (17-19).

In studies on ovarian cancer, it has been shown that high NLR and dNLR values worsen the prognosis and can be used together with tumor biomarkers such as CA 125 to predict ovarian cancer (20-22).

In our study, the hemogram derived parameters (NLR, dNLR, MLR, NPR, PLR, LYM*PLT and SII) revealing systemic inflammation in the ovarian cancer group was significantly higher. Although tumor biomarkers (especially CA 125) are in widespread use, their low sensitivity and specificity has always been a problem. In the current study we also found that CA 125 and CA 15-3 predicted ovarian cancer with an average sensitivity and specificity of 70-76%. Therefore, we think that the use of NLR and dNLR ratio and tumor biomarkers together will be more useful in predicting ovarian cancer.

The limitations of the study were the retrospective design and small cohort of the study. In the future, there is a need for studies with larger patient numbers in which the subtypes of benign ovarian masses are also examined in detail. Being a single center study and evaluation of the patients by the same team overall period are other advantages of the study. On the other hand, examining many hemogram and hemogram derived parameters together with tumor biomarkers is the main factor that strengthens our study.

Conclusion

Today, the importance of systemic inflammation in cancer development is frequently studied. In support of this, we found the hemogram derived parameters (NLR, dNLR, MLR, NPR, PLR, LYM*PLT and SII) in the ovarian cancer group was significantly higher than in the benign ovarian mass.

In the study, it was emphasized that simple and easily accessible hemogram parameters should be used in addition to tumor biomarkers such as CA 125, CA 15-3, which are routinely used in predicting ovarian cancers. We think that more valuable results will be achieved with comprehensive studies designed prospectively.

Ethics Committee Approval: This study was conducted with the approval of the ethics committee of Ordu University Faculty of Medicine, Non-Invasive Clinical Research Ethics Committee. (Ethics Committee date and Decision no: 12.08.2021 2021/186)
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Family Physicians' Work Load, Personal Protection and Isolation Behaviors in the COVID-19 Pandemic

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Abstract

Objective: COVID-19 pandemic, which has been affecting the world for months, has affected health workers both in terms of working conditions and personal lifestyle. The aim of this study is to identify the changing workload of family physicians actively working in our country and to determine the factors affecting social protection behaviors.

Methods: Between March 2020 and April 2020, a survey of 20 questions was conducted for family physicians via google forms.

Results: Data of 392 Physicians, 52.8% (n = 207) female and 47.2% (n = 185) male, were included in the study. While 33.4% (n = 131) stated that they lived in the same house but in a different room with their families, 48.2% (n = 189) stated that they applied social distance by staying at least one meter away from their families. If physicians had children, they applied social isolation significantly more ($p<0.001$). Having relatives with a chronic illness at home also resulted in a significant increase in social isolation ($p<0.001$). Family physicians stated that they spend an average of 1.8 (Min1-Max 3) hours per day for the purpose of guiding patients both at home and for other needs.

Conclusions: Primary care medicine has adapted to the situation by taking protective measures quickly in this pandemic, which has shaken the World. Family Physicians, whose most important task is preventive health service, performed their tasks in the follow-up and implementation of quarantine and home monitoring, even though they were sometimes away from their families.

Key words: Pandemic, Family physician, COVID-19, Personal protection, Social isolation

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Introduction

We are in a period where the importance of words and concepts has experienced more confusion than ever before. In the next process, pandemic, self-protection, public health, global threat now seems to be the concepts that humanity will deal with for a long time. Along with the global threat, guidelines have been prepared by the health ministries and institutions of all countries to create the healthiest algorithm for the pandemic (1). While people are recommended to stay at home for self-protection in this period, it is stated that healthcare workers who must serve by taking all kinds of risks are at risk both physically and psychologically (2). It is reported that healthcare professionals have difficulty in striking a balance between not infecting their family with the virus and their obligation to serve patients in the pandemic (3).

Due to the fact that the vast majority of healthcare workers at the Zhongnan hospital in Wuhan were infected with the virüs, it was suggested healthcare professionals must use personal protective equipment (PPE) to protect themselves (4). Faced with a burden that pushes the hospital conditions in this extraordinary pandemic, health systems started to use the way to follow infected patients with good general condition and contact cases at home. In the guide prepared in England, the family physicians working in primary care are provided with algorithms that help to diagnose the disease quickly. In the same guideline, family physicians were advised to assess patients online or by telephone, and to observe patients who are monitored in home isolation (5).

Remote patient management in primary care has been used as a method with important gains for many years (6). In our country, Family physicians working within the scope of biopsychosocial approach to their patients also serve their patients remotely when necessary.

According to the results of the studies conducted in the pandemic, the presence of chronic disease, the association of diseases that suppress the immune system are the conditions that affect mortality the most (7,8). In this pandemic, it is an important service that family physicians provide remote counseling to patients with chronic diseases. In addition to overseeing patient health in pandemics, patient control over the phone has a major contribution to public health (9).

The purpose of this study is to discuss the contribution of family physicians working in pandemic to preventive healthcare by evaluating the changing patient profile and working habits in the new period. Another aim of the study is to identify personal protective measures depending on the patient load, and social isolation behaviors with their family.

Methods

Study design

The study was planned descriptively in cross-section.After creating the hypothesis of the study, the Ethics committee application files were sent online to the relevant institutions and obtained for study permission. Data collection tools were shaped during the permission waiting process. A 20-question survey was created by researchers and was delivered to physicians through various communication networks. The survey questions used in the study were prepared based on the articles published in the early stages of the pandemic. In the survey created, the physicians were asked about age, gender, the city they work in, the use of personal protective equipment, social isolation behavior, the number of covid positive and covid contact patients, and the daily working time spent on the telephone.

Participants

Working active in primary care was determined as a criterion for inclusion in the study. The survey created for the study was sent to approximately 1100 family physicians working in different patient burdens. The physcians were given time to fill in the survey, considering the workload. The responses of family physicians who filled the survey sent were included in the study.

Study period

It took approximately 2 months between the dates of March 2020 and May 2020 to plan the study, obtain the permission of the ethics committee and collect the data. Permission was obtained from the Ministry of Health and Duzce University Ethics Committee for the study. (Approval No: 2020/78)

Statistical analysis

Statistical analysis for the study was made in SPSS 22.0 for Windows package program. Descriptive statistics are expressed as mean ± standard deviation for numerical variables, number, and percentage for categorical variables. Kolmogorov Smirnov test was used to investigate the suitability of the data for normal distribution. In comparison of the data, Pearson Chi-square was used depending on the expected value rule for categorical variables and Independent Sample Test was used for numerical variables. For statistical significance, $p < 0.05$ value was accepted as a criterion.

Results

For the study, the survey was sent to 1100 family physicians working in different cities. The response rate was %35.6 (n=392) for the study. 52.8% (n = 207) female and 47.2% (n = 185) male physician, who completed the survey sent to our study, with an average age of 40.24, were included. While 53.8% (n = 211) of the physicians participating in our study were working in small, populated provinces, 46.2% (n = 181) working in cities with large populations. While 66.8% (n = 262) physicians were in the city center, 23.0% (n = 90) were in the district and 10.2% (n = 40) were in the village. 11.2% (n = 44) of the physicians had a chronic disease; 4.3% (n = 17) were hypertension, 3.1% (n = 12) were diabetes, 2.3% (n = 9) were asthmatic, 1.5% (n = 6) were using immunosuppressive agents. 8.6 % (n = 34) of the physicians stated that they lived in a place separate from their home while working in the pandemic. While 33.4% (n = 131) stated that they lived in the same house but in a different room with their family, 48.2% (n = 189) stated that they applied social distance by staying at least one meter away from their family. 9.7% (n = 38) of physicians stated that they do not practice any social distance between their families.

89.3% (n = 350) of physicians used masks while working, 55.6% (n = 218) gloves, 35.2% (n = 138) protective glasses, 26.0% (n = 102) visor, 14.5% (n = 57) of them stated that they used protective overalls (Table 1).

The average number of covid positive patients followed by the pandemic since the beginning of the pandemic was 9.6 (Min 2- Max 40), the average number of covid contact patients was 37.38 (Min 2-Max 140), the average number of seasonal influenza patients was 5.64 (Min. 0-Max 20). In addition, 4.07 (Min 0- Max 20) patients stated that they provided prescriptions, reports and remote guidance services for various chronic conditions as well as for chronic disease. Family physicians stated that they spend an average of 1.8 (Min1-Max 3) hours per day for the purpose of guiding patients both at home and for other needs (Table 2).

There was no difference in terms of protective equipment type used according to the age and gender of the physicians. If physicians had children, they applied social isolation significantly more ($p<0.001$). Having relatives with a chronic illness at home also resulted in a significant increase in social isolation ($p<0.001$). There was no significant difference according to the use of protective equipment between family physicians working in cities where more crowded cities and more covid positive cases were seen and working in cities where fewer cases were seen (Table 3).

Table 1. Dynamics and Prevention Behaviors of Physicians in the Pandemic Process

	Descriptive Results	**Frequencies**
Age	40.24±8.85	
Gender	Male	185
	Female	207
Number of Physicians according to the city population	High-population city	181
	Low population city	211
Chronic disease of physicians	Yes	44
	No	348
Chronic disease type	Hypertension	17
	Diabetes	12
	Asthma	9
	Immune suppressive disease	6
Social izolation	Separate house	34
	Same house 1 meter social distance	189
	Same house in a separate room	131
	No isolation	38
PPE	Mask	350
	Gloves	218
	Goggles	138
	Visors	102
	Protective overalls	57

Table 2. Patient Profile of Family Physicians During the Pandemic.

	Mean	Min- Max
Covid positive patient (Follow-up at home)	9.6	2 - 40
Covid contact patient (Follow-up at home)	37.38	2 - 140
Patient in need of remote service	4.07	0-20
Time spent on telephone service (hours)	1.80	1-3

Table 3. Physician's age, gender, covid positive and contact number of patient follow-ups, protective equipment and social isolation practice

		P
Age	Mask	0.006*
	Goggles	0.882*
	Gloves	0.850*
	Visors	0.333*
	Protective overalls	0.030*
Gender	Mask	0.411†
	Goggles	0.978†
	Gloves	0.320†
	Visors	0.469†
	Protective overalls	0.752†
The presence of children at home	Social isolation	0.001†
Living with a relative with chronic disease at home	Social isolation	< 0.001†
High number of covid cases	Social isolation	0.142†
High number of covid cases	PPE	0.512†

*: Independent samples test , †: Chi-Square test

Discussion

In the study, it was observed that family physicians took into account the use of PPE. While the most used PPE is determined as a mask, physicians generally was preferring to use more than one PPE. It is also emphasized in other studies that family physicians, who are the first point of contact with the patient, adopt to use protective materials to protect themselves in viral pandemics (10,11). Talking about the risk of contamination in various study units, Chersich and colleagues say that healthcare professionals in primary care may have difficulties in maintaining social distance, where there is a heavy patient burden (12). Family physicians who are at risk in contact with cases that have not been diagnosed yet usually feel uneasy (13). Until an effective vaccine and drug against the new type of corona virus is found the best known safeguard measure is social distance and hygiene rules. In this context, it is emphasized that family physicians following infants and pregnant patients should pay attention to the rules of prevention (14).

According to the results of the study, family physicians spend a part of their daily work by telephone for guidance and patient follow-up. Just before the pandemic has not become widespread throughout the country, The Ministry of Health has published an implementation guide for the follow-up of covid positive patients and their relatives (15). According to this guide, the covid positive patients and their relatives of which no hospitalization is required with good general condition, will be kept and followed-up in their homes for 14 days. In order to prevent the spread of pandemics, a decision was made to prevent patients over 65 years old and chronic diseases from leaving the home. While the social

needs of elderly and chronic patients who could not go out were met by local administrations, their health needs were met by primary care health workers (16). In this period, the most important function of family physicians was to monitor the patients 'and their relatives' symptoms and health status by calling their patients every day to prevent the spread of pandemics. In addition to covid positive and covid contact patient follow-up, they stated that they performed remote triage and evaluation for their patients who were at risk of coming out and coming to the healthcare institution. Triage by phone for cancer patients, who are in the patient group, elimination of some simple complaints remotely, and the preparation of reports and prescriptions, when necessary, are the proposed advantages during this pandemic period (17).

Before the COVID-19 pandemic, Telemedicine was used and recommended as an application with many promising advantages (18). Having a tool that patients can consult with their physicians in real time is even more important in this pandemic. It is predicted that telemedicine applications that will help reduce transmission during the pandemic period will be used increasingly (19). Providing the use of telemedicine, which is said to change the traditional medical approach, in a more organized and safe way in future pandemics is one of the most trending topics of today (20). For family physicians who support their patients with chronic diseases by remote health care, it is recommended to create regulatory guides for the applications to be performed while meeting their needs especially during the pandemic period (21). The social isolation applied among the relatives of the physicians participating in the study is also striking. Physicians who have children at home or have a chronic disease show more behavior to isolate themselves from their relatives. In the H1N1 pandemic in 2010, it was reported that health care workers who have the same concerns experience intense anxiety about both their own health and the health of their families (22) In the study some physicians also stated that they preferred to stay in a different place by separating the house with their relatives when they worked in the pandemic.

The Second Xiangya Hospital and Mental Health Institute, which provides isolated resting areas for healthcare professionals to reduce their psychological effects and fears about this issue, considers social isolation behaviors from their relatives, as natural and somewhat relaxing (23). It is emphasized that primary care services, which has a key contribution in the spread of the pandemic as the first meeting point with the patient, although it has limited test possibilities, will continue to alleviate the tertiary health burden (24). Family Physicians, the primary duty of which is preventive health care, has performed the most important tasks in this pandemic, which threatens the health of people, in following up and implementing quarantine and home monitoring procedures.

Limitations

The study had some limitations. Most importantly, since it is a cross-sectional study, the results cannot be generalized to the whole country and family physicians. Another limitation is that the patient data stated by the doctors were not checked from the database. The number of patients followed by doctors is based on their individual statements.

Conclusion

The results of the study showed that family physicians spent a significant part of their daily work during the pandemic period with home covid patients and patients with covid contact for remote monitoring. In this context, it is a very important support in pandemic control that they contribute to the studies of filiation, which is the most important step in preventing pandemic spread. In addition, it has been determined that they provide remote guidance and counseling by dealing with patients with chronic diseases or immunocompromised patients who are inconvenient to leave the house. Primary care physicians, who are the most trusted healthcare professionals of patients who are afraid to go to health institutions in order not to meet the new type of corona virus, will also play a key role in the pandemic waves that may occur.

Ethics Committee Approval: This study was conducted with the approval of the ethics committee of Duzce University Faculty of Medicine, Non-Invasive Clinical Research Ethics Committee. (Ethics Committee date and Decision no: (date: 11.05.2020/no:2020/78)
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CASE REPORT **DOI:** 10.19127/mbsjohs.936171

A Case of Recurrent Granulomatous Disease

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Abstract
Chronic granulomatous disease (CGD) is an extremely rare genetically heterogeneous disorder characterized by serious life-threatening infections. CGD is caused by a defect of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system. The disease is characterized by increased inflammation and granuloma formation secondary to recurrent infections. CGD typically involves the lungs, liver, and lymph nodes. Most patients with CGD are diagnosed in childhood. In this case report, we aimed to present a patient with recurrent granulomatous diseases who could not be diagnosed despite reaching adulthood. A nineteen-year-old male patient who was previously diagnosed with granulomatous inflammation and lymphadenopathy and had consanguineous parents was examined for persistent fever and cough and diagnosed with chronic granulomatous disease. This case is presented to show that in countries where consanguineous marriage is common, this genetic disorder can also be diagnosed in adulthood.
Key words: Fever, Genetic Disorders, Granuloma, Lymphadenopathy, Pneumonia

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Introduction

Chronic granulomatous disease (CGD) is a genetic disorder characterized by recurrent, life-threatening bacterial and fungal infections, and granuloma formation. Phagocytic cells are programmed to show rapid response to cells invaded by microorganisms. With the innate immune response system, called phagocytosis, reactive oxygen intermediates are produced due to proteolytic destruction of phagosomes (1). Monocytes and neutrophils use oxygen as phagocytic cells by physical and chemical reactions, leading to respiratory burst. In this burst, NADPH (nicotinamide adenine dinucleotide phosphate) oxidase protein pathway is used (2). The NADPH oxidase complex is activated by phagocytosis and electrons are transferred from NADPH to oxygen to kill intracellular bacteria and fungi by forming lytic enzymes such as superoxide radicals and hydrogen peroxide. Due to genetic defects of NADPH oxidase, phagocytes cannot destroy these pathogens (3). These genetic defects arise from mutations that result in loss or functionally inactivation of one of the subunits of the NADPH oxidase complex (gp91phox, p47phox, p22phox, p67phox, p40phox) (4).

Although CGD is usually inherited as an X chromosome-linked trait, there are also forms inherited through autosomal recessive mode. Therefore, the disease can be seen in both sexes. The frequency of CGD in the USA is about 1 in 200,000 live births. The disease primarily affects men since most mutations are X-linked. However, in societies where consanguineous marriage is common, autosomal recessive forms of the disease are more common than X-linked forms, with a higher overall incidence rate (5). Patients diagnosed with CGD may present with growth retardation, abnormal wound healing, diarrhea, and infected dermatitis. Patients may have hepatomegaly, splenomegaly, and lymphadenitis on physical examination. Patients with CGD can present at any age from infancy to adulthood, but the majority of patients present before 5 years of age (5).

Laboratory findings may include anemia, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, hypoalbuminemia, and hypergammaglobulinemia (6). The diagnosis is made by neutrophil function test and genotyping (3).

In this case report, we present a patient suffering from recurrent granulomatous lymphadenopathies from childhood to adulthood who was diagnosed with chronic granulomatous disease.

Case

A nineteen-year-old male patient who was dealing with farming presented to our clinic with cough, fever, and loss of appetite. The patient's history revealed that he had undergone submandibular lymph node excision fifteen years ago and received antituberculosis treatment for ten months after his pathology result was reported as caseating granulomatous inflammation. Because his chest imaging showed mediastinal lymphadenopathies and tree-in-bud pattern in the lower lobe of the right lung when examined for similar complaints six years ago, he received antituberculosis treatment again. His family history revealed that his parents had consanguineous marriage. The patient's general condition was poor, he was cachectic, his body temperature was 38ºC, heart rate was 98/min, respiratory rate was 24/min, blood pressure was 140/90 mmHg, and crackles were auscultated on respiratory examination. The laboratory test results were as follows: Hgb, 12 g/dL; WBC, 10.9 thousand/uL; neutrophil, 8.29 thousand/uL; CRP, 27 mg/dL; ESR, 76 mm/hour; albumin, 2.5 g/dL; total protein, within normal range. According to his test results, he had anemia, hypoalbuminemia with elevated CRP and ESR. The patient's chest imaging showed irregular coarse septal thickening in both lungs, alveolar ground-glass opacities, and mediastinal lymphadenopathy (Figure 1).

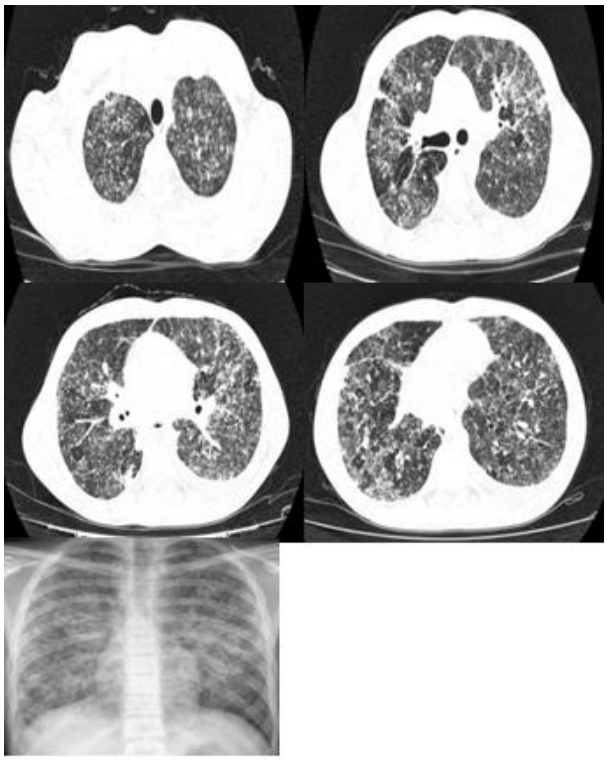

Figure1. Admission chest radiography and chest computed tomography

The patient underwent bronchoscopy. Two biopsy samples were taken distal to the anterior segment of the right upper lobe as well as a lavage sample from the right upper lobe for tuberculosis culture, acid-alcohol resistant bacilli (AARB), mycobacterium PCR, and non-specific culture. The bronchial lavage was negative for mycobacterium PCR, AARB with no growth in the nonspecific culture. No specific pathology was observed in the distal biopsy samples. The patient was consulted with thoracic surgery and wedge resection was recommended. The wedge resection pathology result was reported as suppurative necrotizing granulomatous inflammation. Thereupon, the patient was initiated on antituberculosis treatment. Since the patient achieved no clinical or radiological improvement during the follow-ups, methylprednisolone 40 mg/day was added to his current treatment. It was decided to examine the patient with partially regressed complaints after methylprednisolone treatment for hereditary immunodeficiency syndromes because of the history of consanguineous parents. The patient who was found to have no oxidative burst in the dihydrorhodamine (DHR) test was diagnosed with chronic granulomatous disease, and mutation analysis was ordered. The antituberculosis treatment was discontinued, and he was initiated on voriconazole and continued to receive methylprednisolone. His clinical complaints declined in the follow-ups, intravenous voriconazole was completed to 14 days, and the patient was discharged with oral 3 mg kg voriconazole and oral steroid therapy.

The post-discharge 1-month follow-up chest radiograph of the patient with no active complaint showed significantly regressed infiltrations (Figure 2).

Figure 2. Post-discharge 1-month follow-up chest radiograph

Discussion

Chronic granulomatous disease is a disorder with phenotypic and genotypic variations typically characterized by recurrent fungal and/or bacterial infections from infancy. Some patients might present with symptoms in late childhood or even adulthood (4).

The diagnostic tests are based on the assessment of oxidative burst by measuring superoxide production. These tests include direct measurement of superoxide production, ferricytochrome C reduction test, anti-HIV (by chemiluminescence method), nitroblue tetrazolium reduction test (NBT), and dihydrorhodamine-123 (DHR) oxidation method (3). Today, the DHR-123 method is preferred because it helps the differentiation of X-linked and autosomal forms and is sensitive even to a small number of cells. The DHR-123 method is particularly helpful in diagnosing patients with X-linked CGD early and optimizing treatments such as medication, bone marrow transplant and gene therapy (7).

Despite prophylactic treatments, patients might have recurrent infections. For example, a study of three hundred and sixty-eight CGD patients reported the most prevalent infections as pneumonia, suppurative lymphadenitis, cutaneous and subcutaneous abscess, liver abscess, osteomyelitis, and sepsis (5).

Pneumonia is the most common type of infection in CGD and typically causative pathogens are Staphylococcus aureus, Aspergillus species, Burkholderia cepacia and enteric gram-negative bacteria. Aspergillus and other fungal infections of the lung also present difficult challenges as they typically require long-term treatment (3-6 months). Cutaneous abscesses and lymphadenitis represent the next most common types of infection in CGD and are typically caused by S. aureus, followed by various gram-negative organisms, including B. cepacia complex and Serratia marcescens. Hepatic abscesses are also quite common in CGD and are typically caused by S. aureus. Likewise, perirectal abscesses are common and, once formed, can persist for years despite aggressive antimicrobial therapy and rigorous local care. Osteomyelitis is another important infection in CGD and is caused by hematogenous spread of microorganisms (S. aureus, Salmonella spp., S. marcescens). Other common microbial agents are Escherichia coli spp., Listeria spp., Klebsiella spp., Nocardia and Candida spp. (8)

In a study evaluating the incidence of severe infections in patients followed up by a single-center, Aspergillus species (2.6 cases per 100 patient-year), S. Aureus (1.44 cases per 100 patient-year),

Burkholderia (Pseudomonas) cepacia complex (1.06 cases per 100 patient-years), Serratia marcescens (0.98 cases per 100 patient-years), Nocardia species (0.81 cases per 100 patient-years) could be isolated as causal pathogens of infections (9).

While infections caused by bacterial factors manifest themselves with symptoms such as fever and leukocytosis, fungal infections can be asymptomatic and can be noted during routine screenings or in an advanced stage (10). Infections caused by fungal factors are less common than bacterial infections but have a more fatal course. Novel antifungal agents such as lifelong itraconazole prophylaxis, voriconazole and posaconazole have reduced the frequency of infection and the risk of death. Lung infection can develop by inhalation of fungal pathogens, especially aspergillus species (5).

Especially individuals dealing with farming can develop mulch pneumonitis due to Aspergillus species with the inhalation of organic substances such as piles of hay and dead leaves. This entity is a hypersensitivity reaction characterized by a sudden shortness of breath, fever, and radiological pulmonary infiltrates due to inhalation of organic substances and fungi. In such cases, steroid therapy should be given in addition to antifungal treatment, and even if the infection is controlled, steroid therapy should be continued for a long time (11).

Besides infections, non-infectious complications such as inflammation and granuloma formation and autoimmune diseases may also develop in CGD (12). Non-caseating granulomas form especially in the brain, lung, liver, gastrointestinal and genitourinary tracts. In many granulomas, the causal pathogen is not identified and rapid response is achieved to steroid therapy (13).

In chronic granulomatous disease, trimethoprim-sulfamethoxazole (TMP-SMX) is given prophylactically in two divided doses of 5 mg/kg/day, while dicloxacillin, oral cephalosporin, or fluoroquinolone is preferred as an alternative for allergic patients (14). TMP-SMX prophylaxis should be applied for life. In the case of acute infection, treatment should be initiated in the form of oral ciprofloxacin and intravenous meropenem empirically until the causal pathogen is identified. In addition, TMP-SMX initiated at a prophylaxis dose should be doubled, and voriconazole should be added to the treatment in the presence of pneumonia (15).

With the use of TMP-SMX treatment for routine prophylaxis, the incidence of bacterial infections, especially staphylococci, has decreased. While the incidence of pneumonia due to mycobacterial infections has been reported as 6% in the United States, this rate has been reported to be higher in countries where tuberculosis is endemic (16).

Although antimicrobial drugs and immunomodulatory agents are primarily utilized to prevent or treat developing infections, hematopoietic stem cell transplantation is the only definitive cure for CGD (17). Allogeneic stem cell transplantation has been increasingly used in recent years with enhanced preparative treatment, 'graft-versus-host' disease prophylaxis, high-resolution matching of tissue groups, and the adjustment of pre-transplant and post-transplant therapies, and has become an appropriate and successful treatment method for CGD patients with infectious and inflammatory complications.

Our patient was suspected of having the diagnosis of CGD because of persistent fever despite antibiotic and antituberculosis treatment, the presence of mediastinal lymphadenopathy and pulmonary parenchymal infiltrates, and the consanguineous marriage of the parents. The fact that our patient benefited from steroid therapy in addition to antifungal treatment, was dealing with farming, and especially had contact with the barn suggests that the lung findings are consistent with the "mulch pneumonitis" clinic due to Aspergillus. Our patient who had granulomatous lung diseases caused by an unidentified pathogenic agent, especially since childhood, and who did not benefit from treatments was examined for immunodeficiency syndromes and was diagnosed with CGD as the dihydrorhodamine (DHR) test revealed the absence of oxidative burst.

Conclusion

It should be kept in mind that albeit rarely, CGD can also be diagnosed in adulthood in countries where genetic conditions are common due to the high prevalence of consanguineous marriages such as our country. Patients with recurrent infectious/non-infectious granulomatous lesions should be evaluated for CGD.

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Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **August 2021; 7(2):301-303**

CASE REPORT **DOI:** 10.19127/mbsjohs.892718

Attention to Pain in the Lower Extremities: Chondroblastoma

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Abstract
Lower extremity pain is frequent in children, and it is usually caused by growth pain. Besides this, a variety of situations including infections, inflammation, trauma and also malignancies can result in swelling, pain, or restriction of movement in the knee during childhood period. When we faced with knee swelling especially in a boy, it is absolutely necessary to take a detailed history of the patient and careful physical examination must be done. Here, a 15-year-old case is presented with complaints of pain and swelling in the knee region. This case received accurate diagnosis and treatment through radiologic and pathologic cooperation after clinical examination.
Key words: Chondroblastoma, lower extremity, pain.

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Introduction

Musculo-skeletal system complaints are very common in the development period, especially in children (1). The incidence varies from 4-30% (2). Pain complaints may be divided in two as those in the joints and outside the joints (widespread pain) (1). Differential diagnosis for musculo-skeletal system pain is broad; however, generally it is observed with mechanical causes more than inflammatory causes. However, topics that should not be missed include trauma or malignancy. For this reason, detailed clinical assessment, and radiological assessment in necessary situations, are important.

Here, we report a case who presented with pain and swelling in his knee and later diagnosed with chondroblastoma, to draw attention tumoral diseases in the differential diagnosis of lower extremity pain especially in boys.

Case

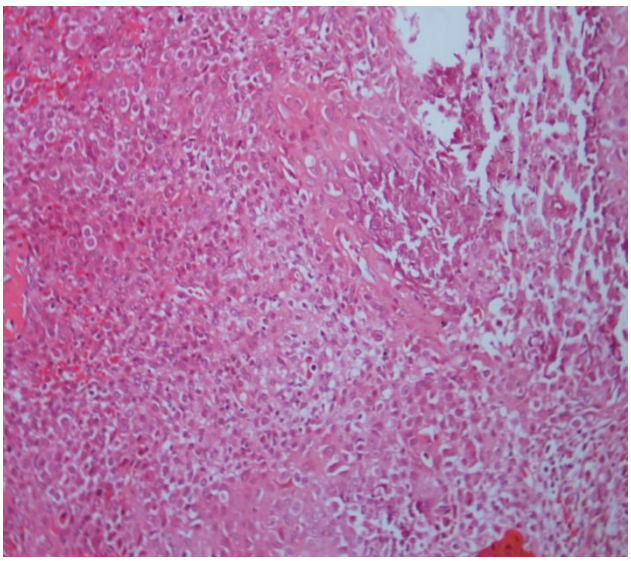
A 15-year-old male patient attended hospital with complaint of pain in the knee. Examination noted pain and additional swelling distal of the right femur. Movement limitation was present. As a result of assessment, routine biochemical tests were requested in addition to magnetic resonance (MR) imaging. MR results provided preliminary diagnosis of osteomyelitis or malignancy or chondroblastoma and biopsy was recommended. Biopsy was sent to the pathology department for diagnostic assessment.

Histopathological assessment observed cellularity adjacent to fibro-collagenized tissue and areas rich in terms of matrix. Cellular areas observed chondroblasts as round or polygonal cells with oval or circular nuclei and well-defined eosinophilic cytoplasm, in addition to calcification with chicken-wire appearance and many osteoclastic-type giant cells. Additionally, osteoid and chondroid areas were occasionally observed. Necrosis and mitosis were not observed.

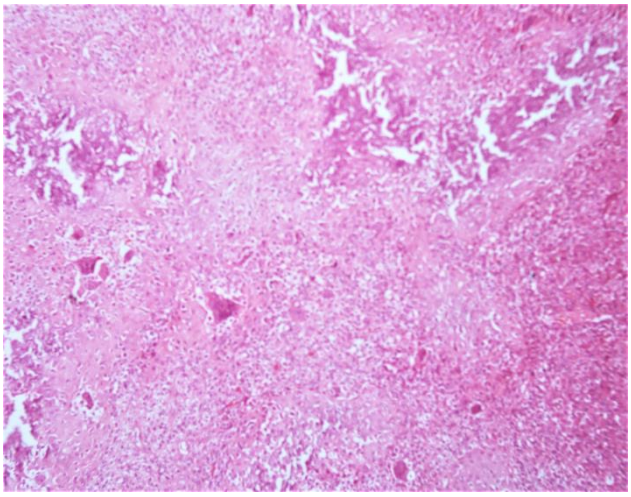
The results of histopathologic assessment reported the case as chondroblastoma.

Discussion

Muscle and joint complaints are frequently encountered in children during growth and development, especially, when considered separately from the geriatric period. When general complaints are examined, pain, swelling, and movement limitation in addition to fever and redness in inflammatory situations are notable. For this reason, detailed assessment is necessary. Radiological imaging and histopathological assessment complement each other, especially in cases with swelling observed.



Picture 1. Large mononuclear cells with oval nucleus buried within immature chondroid material (h&ex200)



Picture 2. Calcification with chicken wire appearance and many osteoclastic-type giant cells (h&ex200)

In this case, biochemical tests did not observe data in relation to inflammation. Radiological assessment recommended differential diagnosis for osteomyelitis, chondroblastoma and malignancy primarily. Chronic inflammation findings involving plasma cells or fibrosis as in osteomyelitis were not observed. In terms of malignancy, osteosarcoma comes to mind initially when the knee region is mentioned. From this aspect, microscopic assessment did not observe osteoid construction or atypical osteocytes.

In the case, microscopic cellularity was notable. Additionally, chondroblasts in the form of polygonal cells with round or oval nuclei and giant cells with

osteoclastic-type calcification were observed. The important microscopic image for chondroblastoma especially of a chicken-wire matrix appearance around chondroblasts was observed.

Chondroblastoma is a rarely-observed primary bone tumor comprising less than 1% of bone tumors. Generally, these patients are males in the adolescent period with open growth plates. They may be painful and frequently cause joint effusion. Additionally, they limit joint movement (3). In this case, some of these findings were observed to a mild degree. It is more frequent in males, with mean age of incidence from 10 to 25 years. Sometimes it may be encountered at older ages (4). This case was 15 years old, in the frequently observed group. Chondroblastoma may be confused with aneurysmal bone cyst, fibrosarcoma or metastatic situations (5).

Here again, clinical, radiological, and pathologic assessment are important for differential diagnosis. Chondroblastoma generally have epiphyseal localization. In 2% and 82% of cases they have a tendency to localize in the tubular long bones. The most common is proximal tibia localization, but they may be encountered in different localizations (6). One of the rare localizations in the literature was a case with acromion localization presented by Arikan et al. (7). Ozkurt et al. reported a case with talus localization (8). In our reported case, localization was in the distal region of the femur, which aroused clinical and radiological suspicion in terms of inflammatory situations and malignancy.

Metastasis is generally don't expected in chondroblastoma cases. Additionally, rare metastasis may occur as invasion of soft tissue around the bone and aggressive behavior like malignant transformation (9,10). For chondroblastoma treatment, surgery is at the forefront, with techniques like cryosurgery and phenol administration mentioned in the literature to reduce the chance of recurrence (8). Chemotherapy has no place in terms of treatment and radiotherapy is reported to be controversial (8). This case was operated on and is still in follow-up. This case was operated on and is still being followed up.

Conclusion

In conclusion, attention should definitely be paid to complaints about the musculoskeletal system at any age. Findings obtained after clinical examination are valuable. In required situations, clinical, radiological, and pathologic assessment results will further increase this value.

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Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **August 2021; 7(2):304-307**

CASE REPORT **DOI:** 10.19127/mbsjohs.925756

A different etiology of pneumothorax: Truck tire explosion!

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Abstract
A Pneumothorax (PNX) is the accumulation of air in the pleural space. PNX, which occurs due to the blast effect of an intense explosion, is a rare and important cause in etiology, as it is generally seen as spontaneous PNX. Blast injuries have become more common in the last century causing by terrorist attack events like bomb explosions and home-related or industrial accidents. While repairing or servicing a large tire, the explosion of the tire may result in high mortality and morbidity. In this case report, we present a 37-year-old male truck driver with barotraumatic PNX and rib fractures that developed due to a truck tire explosion.
Key words: Blast injuries, pneumothorax, tire, trauma

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Introduction

A Pneumothorax (PNX) is the accumulation of air in the pleural space. PNX occurs when air accumulates between the visceral and parietal pleura inside the thorax. This increased air pressure makes the lung collapsed (1,2). Generally, PNX occurs spontaneously in people with risk factors such as tall, body mass index under 19 and male gender. However, a traumatic PNX can be the result of penetrating or blunt trauma (3). The PNX prevalence in cases of blunt trauma is 15-49% (4). Blast injuries have become more common in the last century causing by terrorist attack events like bomb explosions and home-related or industrial accidents (5,6). The blast injuries of large tires similar to the explosion of landmines have not included chemical or thermal damages (7). While repairing or servicing a large tire, the explosion of the tire may result in high mortality and morbidity. Usually, the patients are young mechanics or drivers (8,9). The main problematic issue is to prevent the people from this kind of blast trauma.

Case Report

A 37-year-old male patient was admitted to our hospital emergency department (ED) because of blast trauma. The cause of blast injury is that the patient hits the tire with a hammer to check the pressure. As a result of this action, the tire was exploded, and the patient took the blast effect of the explosion directly to his chest. The patient's symptoms were dyspnea and pain in the chest. He has many petechial lesions on the skin of the anterior chest wall and a decrement in breathing sound at the left hemithorax. Thorax computed tomography (TCT) showed hemopneumothorax and seven rib fractures (two of them are separated) at the left hemithorax (Fig. 1a). There were also contusions at the apex of the right lung. In the presence of these findings, the patient underwent tube thoracostomy at the ED (Fig. 1b). The transthoracic echocardiogram examination of the patient revealed no pathology for cardiac problems due to barotrauma. The tube thoracostomy of the patient, who had no air leak and PNX on the third day of hospitalization, was ended (Fig. 1c). The patient's treatment was completed and discharged.

Figure 1a. The TCT scan of patient before tube thoracostomy.

Figure 1b. The chest x-ray of patient after tube thoracostomy.

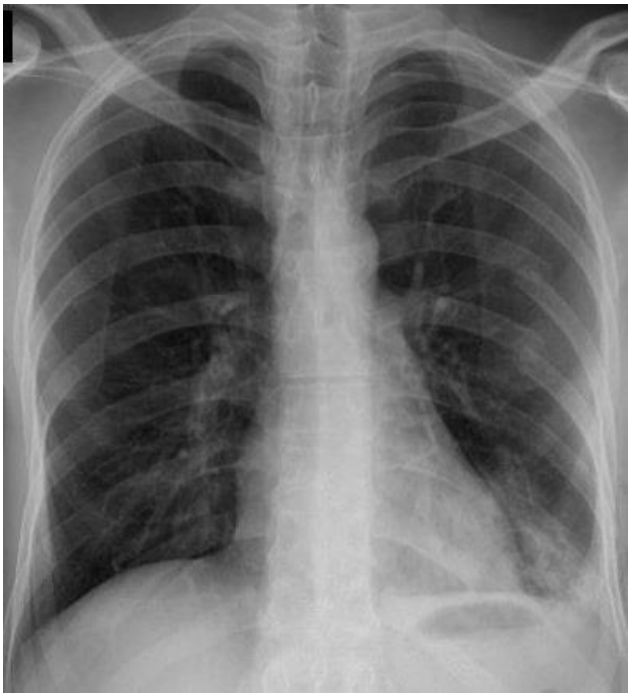

Figure 1c. The final chest x-ray of patient after treatment.

Discussion

Barotrauma-related PNX is less common than other PNX types like spontaneous or iatrogenic PNX. However, a traumatic PNX can be the result of blunt (bomb explosion, car accident, falling from high in construction areas) or penetrating trauma (gunshots and knife attacks) (3). The ratio of PNX prevalence in cases of blunt trauma is 15-59% (4). In another study, PNX has detected twenty-five (11.8%) of 212 patients with blunt trauma (10) In this case, an interesting and rare cause of barotrauma-related PNX was seen in the ED.

Barotrauma defines the damage that the airline and the alveoli are exposed to. The primary effect of injury is becoming the shock waves. The shock wave shows the most critical effect in the lungs (compare with the other air-containing organs such as nasal sinuses and eardrum) (11,12). That kind of injuries results in PNX, hemothorax, pulmonary contusion and rib fractures (6). In this study, the patient had hemopneumothorax and seven rib fractures at the left hemithorax and contusions at the apex of right lung as seen in the literature.

Blast injuries have become more common in the last century causing terrorist attack events like bomb explosions, and home-related or industrial accidents (5,6). The blast injuries of large tires similar to explosion of landmines but have not include chemical or thermal damages (7). While repairing or servicing a large tire, the explosion of the tire may result in high mortality and morbidity. Usually, the patients are young mechanics or drivers (8,9). Chest traumas are 33% of the cases hospitalized because of trauma (13). In the first four decades of lifetime, chest trauma composes 25% deaths because of trauma and the mechanism of the defect is blunt in 70% of these trauma cases (14,15). In this study, the patient was a 37-year-old male truck driver and compatible with the literature. An explosion of the truck tire injured him while he was repairing it.

Prevention must be the doctors' ultimate target. This aim is the most cost-effective way to reduce the harmful effect of an injury (16). Professional tire servicing or repairing a truck tire with proper equipment are the most significant preventive measures (17). Like in the other literature studies, the patient was not using any protective pieces of equipment during work and got injured because of it.

Conclusion

Consequently, the large tire blasts constituted the high energy traumas and might cause serious injuries, leading to high morbidity or mortality rates. Especially in our country, increasing the consciousness of this critical problem is essential. Preventive mechanisms must be developed both with the education system and with the law, and they should be used in everyday life routine.

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Author Contributions:
Concept, Design, Literature search, Data Collection and Processing, Analysis or Interpretation, Writing – B.H
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Financial Disclosure: The author declared that this study hasn't received no financial support.

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