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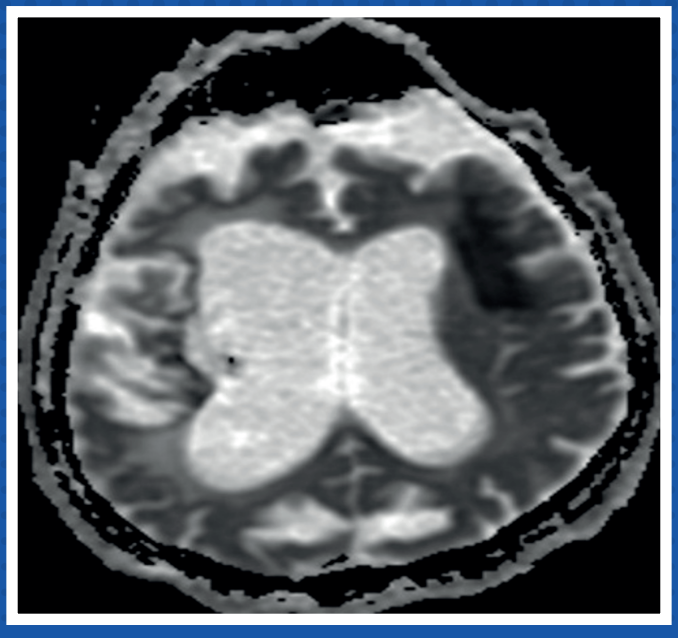

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Editorial

Dear colleagues,

I am glad to announce the publication of Northwestern Medical Journal's last issue in October 2024. We promised to present you an issue with high quality scientific content.

Kılıç and Sarıkaya compared the arthroscopic-assisted mini open and all arthroscopic repair methods in small to large size rotator cuff tears. Coşgun and Kalfaoğlu investigated the comparative evaluation of hepatosteatosis in patients with type 2 diabetes mellitus using non-contrast abdominal CT and laboratory findings. Saraç Atagün and colleagues evaluated the effects of smoking on local and systemic oxidative stress markers in individuals with periodontitis. Köse Çobanoğlu and colleagues examined the anterior pituitary hormone levels in patients with atrial fibrillation. Pala et al. assessed the physiotherapists' sensitivity to palpation pressure. Öz et al. evaluated the risk factors for allergy in gifted and typical children. Demirkol, Afşin and Balcı investigated the effect of lopinavir - ritonavir on mortality in COVID-19 pneumonia. Bal et al. evaluated the auditory middle latency response during the menstrual cycle. Yılmaz Öztorun et al. shed light into retinal nerve fiber layer and choroidal structure in obese children and adolescents. A case report is presented by Bilgili et al. with the title of ''paroxysmal sympathetic hyperactivity syndrome after recurrent stroke''.

We wish as previous ones this issue would be beneficial and satisfying for readers. I would like to thank all writers and reviewers of this issue for their great effort.

Best regards,
Prof. Ahmet Ural, M.D.
Editor-in-chief

NORTHWESTERN MEDICAL JOURNAL

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RESEARCH ARTICLE

Comparison of arthroscopic-assisted mini open and all arthroscopic repair methods in small to large size rotator cuff tears

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ABSTRACT

Aim: This study aimed to compare the functional and clinical results of all arthroscopic (AA) and arthroscopic-assisted mini open (AAMO) rotator cuff tear (RCT) repair methods with a minimum 2 years follow-up.

Methods: In this retrospective study, patients who operated with the AA repair method were included in group 1 and patients who operated with AAMO RCT repair method were included in group 2. Between January 2018 and June 2021. All patients were evaluated with shoulder range of motion (ROM), the Disabilities of the Arm, Shoulder and Hand (DASH), Constant Murley Score (CMS) and visual analog scale (VAS) pain score preoperatively and postoperatively. Postoperative evaluation was made on the 3rd, 6th, 12th, and 24th months. In addition, the length of hospital stay, and surgery time were evaluated.

Results: Eighty patients (48 female, 32 male) were included in group 1, who were treated with the AA technique. Sixty-seven patients (28 male, 39 female) were included in group 2, who were treated with the AAMO technique. The average follow-up time was 29,36 ±3,48 months for group 1, 28,12±2,87 months for group 2. No significant difference was detected between group 1 and group 2 for length of hospital stay and follow-up time ($p>0,05$). At the postoperative 3rd-month follow-up measurements, a statistically significant difference was determined between group 1 and group 2 for abduction, flexion measurements, VAS score, and DASH score ($p=0,03$, $p=0,04$, $p=0,02$, $p=0,01$ respectively). At the 24th month postoperative follow-up, statistically no significant difference was determined between groups 1 and 2 in terms of ROM, VAS, and functional scores.

Conclusion: In the early recovery period, AA repair provides better ROM, DASH, and VAS scores. However, in long-term follow-up, no significant difference was detected in AA and AAMO repair in terms of functional results, ROM, and VAS scores.

Keywords: arthroscopic-assisted mini open repair, arthroscopic repair, rotator cuff tear

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INTRODUCTION

Shoulder pain is one of the common reasons for orthopedic outpatient clinic admissions. And one of the most common causes of shoulder pain is a rotator cuff tear (RCT) (1). One in 5 people in the population and one in 3 people with shoulder pain have RCT (2). RCT repair was first described by Codman (3). There are different RCT repair methods, like all arthroscopic repair (AA), arthroscopic-assisted mini open repair (AAMO), and open repair.

In recent decades, the tendency towards all arthroscopic repair has increased (4-6). AA repairs have some advantages like minimal damage of soft tissue, lower postoperative pain, the possibility of treatment of intra-articular lesions, and smaller incisions (7-9). And AA repair methods complication rate is lower than other methods (10). However, bone-tendon fixation is stronger with open procedures (11).

Levy first described AAMO repair technique (12). The advantages of AAMO repair are lower costs, stronger bone-tendon fixation, shorter operating time, and shorter learning curve (13-15). Good results were achieved with AAMO and AA repair in most studies (4-6).

In many reviews and meta-analyses, no difference was determined between the long-term and medium results of these techniques (6,7). However, some studies report that the functional results of AA repair are better in the early recovery period, there is no significant difference in long-term results (16). There is still debate about the choice of these two techniques in RCT repair. This study aimed to compare the functional and clinical results of AA and AAMO repair methods with a minimum 2-year follow-up. Our hypothesis was that the functional and clinical results of AA repair would be better than AAMO repair.

MATERIALS AND METHODS

Approval for the study was granted by the institutional review board of the authors' affiliated institutions (Project number: E1-23-4422, date: 13/12/2023). All the researchers who participated in the study signed the most recent version of the Helsinki Declaration. All patients signed an informed consent form.

In this retrospective study, between January 2018 and June 2021, medical records from our institution were reviewed and patients who underwent RCT repair were identified. RCTs were classified according to the full-thickness tear size using the classification defined by DeOrio and Cofield. Patients who had small to large RCT and underwent AA or AAMO repair were included in our study. Physical examination, magnetic resonance imaging (MRI), and radiography were used to diagnose RCT.

Inclusion criteria:

- Age between 30 and 75 years
- Small to large RCT on preoperative MRI
- Minimum 2 years follow-up

Exclusion criteria:

- Massive RCT
- Shoulder instability
- Slap lesion
- Pseudoparalysis or pseudoparesis
- Rheumatoid arthritis
- Adhesive capsulitis
- Glenohumeral arthritis
- Glenoid or humeral fracture history
- Osteomyelitis or septic arthritis
- Previous surgery on the affected shoulder
- Cognitive disorders

Patients with missing medical records were excluded from the study. And the surgeon of the case decided which surgical technique to use. Patients who underwent AA repair were included in group 1 and patients who underwent AAMO repair were included in group 2.

All patients were operated in the beach-chair position and under general anesthesia. Standard posterior, anterior and lateral arthroscopy portals were used. Firstly, an arthroscopic examination of the shoulder was performed. Intraarticular pathologies were treated appropriately. Then, subacromial space was entered. Radiofrequency and shaver were used for good visualization. Arthroscopic acromioplasty was

performed with a burr in necessary cases. After arthroscopic debridement and acromioplasty, RCT repair was performed with the AA or the AAMO repair technique. For AAMO, a 4 or 5 cm incision was made starting from the anterior border of the acromion. Afterward, RCT repair was performed with all suture anchors and metal suture anchors.

A shoulder-arm sling with abduction support was used for all patients postoperatively. Pendulum exercises were applied in the first week after surgery. After the first week, passive motion exercises were started. Six weeks after surgery, active range of motion (ROM) exercises were started. And six months after surgery, patients returned to sports activities. All patients were given the same rehabilitation program.

All patients were evaluated with shoulder range of motion (ROM), visual analog scale (VAS) pain score, the Disabilities of the Arm, Shoulder and Hand (DASH) and Constant Murley score (CMS) preoperatively and postoperatively. Postoperative evaluation was performed at 3rd, 6th, 12th, and 24th months. In addition, surgery time and the length of hospital stay were evaluated.

Statistical analysis

Statistical data analyses were performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using the chi-square test. The suitability of continuous variables to normal distribution was examined by calculating skewness and kurtosis values. Continuous variables with normal distribution were compared using the independent samples t-test, and continuous variables with non-normal distribution were compared using the Mann-Whitney U test. Measurements taken before and after the surgery were analyzed using the dependent sample t test. The results were evaluated within 95% confidence intervals, and $P<0.05$ was considered significant.

RESULTS

A hundred and fifty-four patients were included in our study. Two patients were re-operated due to re-rupture. These patients were excluded from the study. Five of the patients' data could not be accessed from the medical record system and they were excluded. Eighty patients (32 male, 48 female) who underwent AA repair were included in group 1. Sixty-seven patients (28 male, 39 female) who underwent AAMO repair were included in group 2. The mean age of the AA group and the AAMO group was 56,39±7,83 and 59,21±8,42 years, respectively. For group 1, 44 right and 36 left shoulders were operated. The operated side was the dominant side for 49 of the group 1. For group 2, 36 right and 31 left shoulders were operated and 38 of them were dominant side. Six patients of group1 and five patients of group 2 were smokers (Table 1).

The average follow-up time was 29,36±3,48 months for the AA group and 28,12±2,87 months for the AAMO group. The mean length of hospital stay was 2,1 days and 2,3 days for the AA group and the AAMO group, respectively. No statistically significant difference was determined between the AA group and the AAMO group for length of hospital stay and follow-up time. (p>0,05) Surgery time was 69,81±18,4 minutes for the AA group and 53,76±14,28 minutes for the AAMO group.

Table 1. Patient characteristics

		Group 1 (n:80)	Group 2 (n:67)	P value
Age (years)		56,39±7,83	59,21±8,42	0,684
Gender	Male	32 (%40)	28 (%41,79)	0,971
	Female	48 (%60)	39 (%58,21)	
Side	Right	44 (%55)	36 (%53,73)	0.952
	Left	36 (%45)	31 (%46,27)	
Dominant side		49 (%61,25)	38 (%56,71)	0.568
Smoker		6 (%7,5)	5 (%7,4)	0,951

Table 2. The mean follow-up time, length of hospital stay and surgery time of the group 1 and group 2			
	Group 1 (n:80)	**Group 2 (n:67)**	**p value**
Follow-up time (months)	29,36±3,48	28,12±2,87	p>0,05
Length of hospital stay (days)	2,1	2,3	p>0,05
Surgery time (minutes)	69,81±18,4	53,76±14,28	p=0,02

Table 3. Preoperative and postoperative shoulder range of motion measurements				
		Group 1	**Group 2**	**p value**
Abduction (degrees)	Preoperative	95±7,47	97±8,65	0,58
	3rd month	130±6,34	112±5,23	**0,03**
	6th month	145±7,22	138±6,83	0,14
	12th month	160±5,32	157±4,71	0,24
	24th month	165±3,41	163±3,28	0,36
Flexion (degrees)	Preoperative	88±8,69	91±7,88	0,62
	3rd month	136±4,33	117±4,56	**0,04**
	6th month	155±6,11	147±5,69	0,28
	12th month	162±4,21	158±5,37	0,84
	24th month	163±2,3	162±3,81	0,45
External rotation (degrees)	Preoperative	39±6,81	41±6,39	0,33
	3rd month	41±5,71	46±4,52	0,25
	6th month	59±4,32	62±5,21	0,61
	12th month	64±5,89	66±3,28	0,30
	24th month	69±3,74	71±2,36	0,41
Internal rotation (degrees)	Preoperative	42±5,56	39±6,23	0,57
	3rd month	51±5,87	54±4,74	0,47
	6th month	64±4,21	63±3,48	0,32
	12th month	71±3,57	68±3,67	0,44
	24th month	74±2,35	71±2,85	0,31

A statistically significant difference was determined between the AA group and the AAMO group. (p=0,02) (Table 2) Biceps tenotomy or tenodesis was performed in patients with biceps tendon pathology.

Preoperative and postoperative shoulder ROM measurements (external and internal rotation, flexion and abduction) were performed. A statistically significant increase was determined between all patients' preoperative and postoperative 24th-month measurements (p<0,05). There was no significant difference between postoperative 24th-month follow-up shoulder ROM of the AA group and the AAMO group. However, in the 3rd month follow-up measurements, a statistically significant difference was observed between the AA group and the AAMO group in abduction and flexion measurements (p=0,03, p=0,04) (Table 3). In group 1, biceps tenotomy was performed in 22 patients, and biceps tenodesis was performed in 4 patients. In group 2, biceps tenotomy was performed in 16 patients and biceps tenodesis was performed in 2 patients. No significant difference was determined between group 1 and group 2 (p>0.05).

Table 4. Preoperative and postoperative VAS and functional scores

		Group 1	Group 2	p value
VAS score	Preoperative	7,2±1,1	7,6±0,9	0,24
	3rd month	3,3±0,6	5,1±0,5	**0,02**
	6th month	2,9±0,8	3,2±0,7	0,61
	12th month	1,6±0,6	1,9±0,5	0,32
	24th month	1,3±0,4	1,3±0,4	0,48
DASH score	Preoperative	56±9,1	54±6,37	0,36
	3rd month	41±6,2	48±4,94	**0,01**
	6th month	38±5,06	39±6,17	0,32
	12th month	33±4,24	32±4,36	0,26
	24th month	29±39	31±3,98	0,29
CMS score	Preoperative	39±3,45	41±2,98	0,67
	3rd month	53±4,56	56±5,39	0,13
	6th month	61±4,82	63±5,68	0,24
	12th month	67±7,28	68±6,74	0,39
	24th month	77±6,37	75±7,49	0,59

VAS: visual analog scale, DASH: the Disabilities of the Arm, Shoulder and Hand, CMS: Constant Murley score.

VAS scores of the AA group and the AAMO group were evaluated. No statistically significant difference was determined between the preoperative and 24th-month follow-up VAS scores of the AA group and the AAMO group (p=0,24, p=0,48). However, for postoperative 3rd month follow-up, there was a statistically significant difference between the VAS score of the AAMO group and the AA group (p=0,02). The VAS score of the AA group was lower. DASH and CMS scores were evaluated for functional outcomes. No statistically significant difference was determined between preoperative and postoperative 24th-month follow-up DASH and CMS scores of the AAMO group and the AA group. Only at postoperative 3rd month follow up, a statistically significant difference was determined between the DASH scores of the AAMO group and the AA group (p=0,01) (Table 4).

DISCUSSION

At the 24th month follow-up, there is no difference between the results of AA and AAMO repair in terms of ROM, DASH, CMS and VAS scores. However, at the 3rd-month follow-up, shoulder abduction and flexion ROM, VAS, and DASH scores are better in the AA group. The length of hospital stay is similar for AA and AAMO techniques. And surgery time is shorter with the AAMO technique.

AA repair is the more frequently preferred RCT repair method today. With the development of arthroscopic techniques and increasing surgical experience, arthroscopic repair is preferred more frequently (17). AAMO repair is an alternative method to AA repair. With the AA method, patients have less pain and better outcomes in early postoperative period (18). Some studies have shown faster rehabilitation, better functional scores, better improvement in VAS score and ROM with the AA method. In the current study, for AA repair, ROM, functional scores and VAS scores are better in early follow-ups.

Many studies have used DASH and CMS to assess functional outcomes (16,18). In our study, while there was no difference in CMS and DASH scores in long term follow-ups, DASH scores were better in the AA repair group in early follow-ups. The better early functional results can be explained by less deltoid muscle damage

and less detachment of muscle fiber from the acromion in the AA repair group (19).

AA repair requires a longer learning curve and higher skill compared to mini open repair. Additionally, the surgery time of AA repair is generally longer. Liu et al. (16) and Cho et al. (20) showed AA repair surgery time was longer than AAMO repair. In our study, the average surgery time for AA repair is longer. Park et al. (21) reported that patients who were treated with AA repair, had fewer scars, shorter hospital stays, less postoperative pain, and earlier rehabilitation. In our study, patients who underwent AA repair had less postoperative pain at 3rd month and scar. However, the length of hospital stay was similar for AA and AAMO repair.

In most of the studies in the literature, no statistically significant difference was determined between the clinical outcomes of AA and AAMO repair. Kang et al. (15) and Köse et al. (22) showed that AA repairs had no superiority over AAMO repair. Zhang et al. (23) showed that no statistically significant difference was determined between the clinical outcomes of the two repair methods. In our study, there was no difference between the clinical outcomes of the two repair methods. However, in his study Zhang et al. (23) also showed that the re-tear rate was higher in AA repairs. In the current study, two of the patients who underwent AA repair developed re-tear.

When the postoperative VAS scores of AA repair and AAMO were compared, in most of the studies, there was no difference after 6 weeks (9). However, Cho et al. (20), showed that postoperative pain was lower on postoperative days 1 and 2. Surgical retraction and split incision of the deltoid may cause postoperative pain in AAMO repair. It can also cause arthrofibrosis. And it may result in decreased muscle strength and difficulty in rehabilitation. In our study, the VAS scores of the patients who underwent AA were lower on the 3rd postoperative month. However, no difference was observed in subsequent controls.

Our study has some limitations. Firstly, the design of the study was retrospective. Secondly, the study groups were not large enough. Thirdly, a standard rehabilitation program was not applied to all patients. Fourthly, some factors, such as single-row or double-row repair, acromioplasty, rehabilitation program, and tear size were not evaluated in our study.

CONCLUSIONS

In the early recovery period, AA repair provides better ROM, DASH, and VAS scores. However, in long-term follow-up, there is no difference between AA and AAMO repair in terms of functional results, ROM, and VAS score.

Ethical approval

This study has been approved by the Ankara Bilkent City Hospital No. 1 Clinical Research Ethics Committee (approval date 13/12/2023, number E1-23-4422). Written informed consent was obtained from the participants.

Author contribution

Concept: EK, BS; Design: EK, BS; Data Collection or Processing: EK; Analysis or Interpretation: EK, BS; Literature Search: EK; Writing: EK. All authors reviewed the results and approved the final version of the article.

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The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLE

Comparative evaluation of hepatosteatosis in patients with type 2 diabetes mellitus using non-contrast abdominal CT and laboratory findings

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Cite as: Coşgun Z, Kalfaoğlu ME. Comparative evaluation of hepatosteatosis in patients with type 2 diabetes mellitus using non-contrast abdominal CT and laboratory findings. Northwestern Med J. 2024;4(4):188-194.

ABSTRACT

Aim: This study aims to underscore the significance of employing multiple parameters from non-contrast abdominal CT scans for the assessment of hepatosteatosis in patients with Type 2 Diabetes Mellitus.

Methods: Non-enhanced Computed Tomography of the diabetic subjects were analyzed. Control subjects were selected from non-diabetic patients who had undergone abdominal tomography within the same period. The craniocaudal length of the liver and liver, spleen, pancreas densities, and epicardial adipose tissue were measured. Additionally, patient demographics and laboratory values were retrospectively obtained.

Results: The craniocaudal length of the liver was significantly greater in the diabetes mellitus group compared to the control group (168.3 ± 17.2 mm vs 152.3 ± 14.8 mm, $p < 0.001$). Hepatosteatosis was observed in 22 individuals with diabetes mellitus, whereas only one participant in the control group had this condition ($p < 0.001$). The diabetes mellitus group exhibited significantly lower median liver density ($p < 0.001$), liver-spleen density ratio ($p = 0.004$), pancreatic head density ($p = 0.001$), and pancreatic body density ($p = 0.013$). Additionally, the average thickness of epicardial adipose tissue was markedly higher in the diabetes mellitus group compared to the control group (8.1 ± 1.9 mm vs 4.9 ± 1.1 mm, $p < 0.001$).

Conclusions: These data indicate an association between hepatosteatosis and increased epicardial adipose tissue thickness, liver and pancreatic densities in individuals with diabetes mellitus. These findings suggest that non-contrast abdominal CT findings such as epicardial adipose tissue thickness and relevant laboratory tests may aid in evaluating metabolic disorders and fat accumulation in diabetic patients.

Keywords: Type 2 diabetes mellitus, hepatosteatosis, liver/spleen ratio, adipose tissue, liver/diagnostic imaging, pericardium/diagnostic imaging, risk factors, spleen/diagnostic imaging

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INTRODUCTION

Diabetes mellitus (DM), with a rapidly escalating prevalence and projections indicating a significant surge in cases by 2030, poses a critical threat to liver health. Characterized by disruptions in metabolism due to insulin abnormalities, DM leads to chronic hyperglycemia and predominantly affects individuals with type-2 DM (90%-95%) (1,2). Previous research has established a clear link between DM and an increased risk of chronic liver conditions and hepatosteatosis (3).

Hepatosteatosis is a prevalent liver disorder characterized by the accumulation of fat within hepatocytes, with estimates suggesting that approximately 25% of the population is affected by this condition (4). Hepatosteatosis is considered a component of metabolic syndrome independent of increased body mass index (5). Additionally, hepatosteatosis has been associated with an increased risk of cardiovascular disease in diabetic patients (6).

In the diagnosis of hepatosteatosis, radiological methods such as magnetic resonance imaging (MRI), ultrasonography, and computed tomography (CT) are utilized. While liver biopsy is considered the gold standard for diagnosis, its invasive nature makes it unsuitable for screening purposes (7). The most commonly used radiological method for diagnosing hepatosteatosis is ultrasonography, which relies on visual comparisons of liver and right kidney echogenicities. Classification is based on increased echogenicity, loss of periportal echogenicity, and loss of diaphragmatic echogenicity, and it is categorized as mild, moderate, or severe (8). MRI is helpful in diagnosing focal hepatosteatosis and distinguishing it from masses. On CT scans, fatty liver appears hypodense, and the liver-to-spleen attenuation ratio is useful in diagnosing hepatosteatosis (9). The measurement of liver density alone may be disadvantageous in differentiating diseases that involve iron or copper deposition. Therefore, in routine clinical practice, the measurement of the liver-to-spleen density ratio is utilized for the diagnosis of hepatosteatosis (10,11).

Epicardial adipose tissue (EAT) is increasingly recognized as a component of metabolic syndrome, particularly in conjunction with hepatosteatosis (12). It is believed that an increase in EAT contributes to an elevated risk of cardiovascular diseases. Furthermore, numerous studies have demonstrated increased EAT in diabetic patients (12,13). Key components of metabolic syndrome, such as insulin resistance and lipid metabolism disorders, may lead to fat accumulation within hepatocytes and in the epicardial region, potentially influencing the development and severity of hepatosteatosis (14,15). Therefore, identifying the presence of hepatosteatosis and noting any associated increase in EAT, especially in diabetic patients, could aid in predicting associated conditions and managing patient care.

In this study, our objective is to comparatively evaluate CT findings of hepatosteatosis in diabetic patients. Additionally, we aim to explore the association between EAT and diabetic subjects.

METHODS

This retrospective study was carried out at the radiology department of Abant İzzet Baysal University İzzet Baysal Training and Research Hospital, following ethical approval (2023/298). After receiving approval from the ethics committee, patients diagnosed with diabetes mellitus who attended our institution between January 1, 2021, and January 31, 2023, were included in the study.

Demographic information including age, gender, height, weight, Hip and Waist Circumference (HC and WC), BMI, Waist to Hip Ratio (WHR), comorbidities, etc., as well as laboratory data such as glucose levels, HbA1C, alanine and aspartate transaminases (ALT and AST), triglyceride, HDL-cholesterol, serum uric acid, etc., were collected. Triglyceride was divided by HDL cholesterol to determine the Triglyceride/HDL ratio (THR), and serum uric acid was divided by HDL cholesterol to determine the UHR.

CT images of patients undergoing follow-up for diabetes mellitus were retrospectively retrieved from the PACS system of our hospital. The study included two groups: patients with diabetes mellitus and those without. The control group consisted of volunteers whose abdominal CT scans were reported as normal. Patients were excluded if they had incomplete or inadequate investigations, suboptimal CT imaging, a history of surgery, or a history of malignancy. Following the application of these exclusion criteria, a total of 85 cases were included in the study.

Every CT scan of the abdomen was performed with a 64-slice scanner (General Electric Revolution EVO, 64x2 slices). The scanning range extended from the base of the lung to the symphysis pubis. Scans were performed during deep inspiration and breath-hold without the use of contrast agents. The CT scanning protocol employed the following parameters: a tube voltage of 120 kVp, a tube current ranging from 70 to 400 mA, a rotation time of 0.5 seconds, a pitch of 1.375, and a slice thickness of 5 mm. Quantification of liver, spleen, and pancreas densities was performed on abdominal CT images by delineating a circular Region of Interest (ROI) with an approximate diameter of 1 cm (Image 1). The density measurements were obtained by averaging the values from three different areas in both the liver and spleen, and arithmetic means were then calculated for both the liver and spleen. In the liver parenchyma, a region of interest (ROI) was selected while excluding blood vessels, bile ducts, and focal liver lesions. Similarly, in the spleen parenchyma, an ROI was chosen excluding blood vessels. Regions affected by artifacts were also excluded. The liver-to-spleen density ratio (LSR) was computed by dividing the mean density of the hepatic ROI by the mean density of the spleen ROI. Hepatosteatosis on CT images was defined by either relative hypoattenuation (where liver attenuation is more than 10 HU lower than spleen attenuation) or absolute low attenuation (where liver attenuation is less than 40 HU). Density measurements for the pancreas were acquired separately for the head and body sections. Additionally, the examination encompassed the assessment of EAT thickness from thoracic sections.

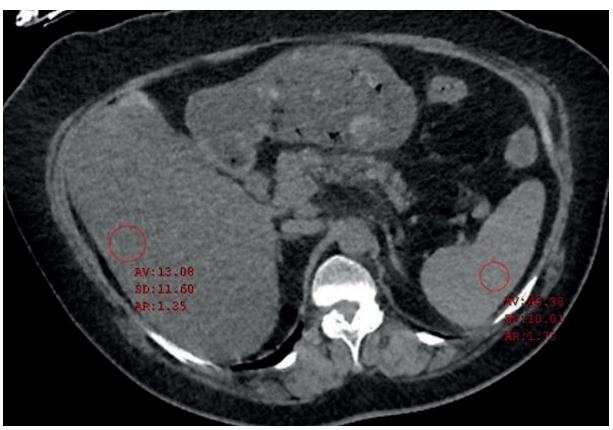

Image 1. Density measurements of liver and spleen in non-contrast abdominal CT examination.

EAT was defined as the adipose tissue located between the surface of the heart and the visceral layer of the pericardium (visceral epicardium). EAT thickness (mm) was measured on the anterior free wall of the right ventricle. Measurements were conducted exclusively at the ventricular base (basal level) due to being derived from the lower thoracic sections of abdominal CT scans. The level at the base of the ventricles was designated as the basal level.

Statistical analyses

SPSS version 18 for Windows was used to conduct the statistical analysis (IBM Corp, Chicago, IL, USA). The study variables' normality was evaluated using the Kolmogorov-Smirnov test. Independent samples t-tests were used to assess variables that fit into a normal distribution. The results are shown as means and standard deviations. The Mann-Whitney U test was used to examine variables that did not have a normal distribution. These variables were expressed as medians (range). The chi-square test was used to compare categorical variables between study groups, and the results were presented as frequencies and percentages. Receiver operating characteristic (ROC) analysis was used to assess the study parameters' specificity and sensitivity in identifying diabetes mellitus. Less than 0.05 was the threshold for statistical significance.

RESULTS

The study population comprised 85 subjects, with 44 in the DM group. Patient characteristics are given in Table 1. Briefly, age and gender distribution were similar. However abdominal obesity indicators were significantly different.

Furthermore, significantly lower values were noted between the DM and control groups for median liver density (p<0.001), liver-spleen density ratio (p=0.004), pancreas head density (p=0.001), and pancreas body density (p=0.013). Refer to Table 2 for a summary of the data from the study and control groups.

Table 1. Demographic characteristics of the study population

		Diabetes Mellitus	Control	p
Gender (n, %)	Women	22 (50%)	21 (51.2%)	0.91
	Men	22 (50%)	20 (48.8%)	0.91
Age (years)		57.9 ± 8.8	55.9 ± 7.6	0.26
BMI (kg/m^2)		32.6 ± 7	29.2 ± 4.9	0.01
WC (cm)		110.7 ± 13	101.6 ± 13	<0.001
WHR (%)		1.09 ± 0.07	0.90 ± 0.08	<0.001

BMI: Body Mass Index, WC: Waist Circumference, WHR: Waist-hip ratio.

Table 2. Data of study and control groups

	Diabetes Mellitus	Control	p
	Median (min-max)		
Glucose (mg/dL)	130.5 (90-320)	98 (80-132)	**<0.001**
HbA1C (%)	6.8 (5.4-19.2)	5.4 (5-6.2)	**<0.001**
AST (U/L)	20.5 (11-53)	20 (7-31)	0.55
ALT (U/L)	19.5 (9-60)	18 (9-44)	**0.07**
HDL Cholesterol (mg/dL)	46.4(20-131)	48.8 (28-156)	0.45
Triglyceride (mg/dL)	141 (49-432)	108 (55-281)	0.09
THR (%)	2.9 (1-21.6)	2.3 (1-9)	0.09
Liver density (HU)	41.5 (12-68)	54 (21-66)	**<0.001**
Spleen density (HU)	46 (28-53)	47 (39-58)	0.07
LSR	0.9 (0.3-1.5)	1.1 (0.5-1.6)	**0.004**
Pancreas head density (HU)	32 (-8-56)	42 (22-53)	**0.001**
Pancreas body density (HU)	34 (-25-54)	38 (25-51)	**0.013**
	Mean ± Std		
Serum Uric Acid (mg/dL)	6.1 ± 1.8	5.3 ± 1.3	**0.023**
UHR (%)	0.14 ± 0.07	0.12 ± 0.06	0.07
Liver length (mm)	168.3 ± 17.2	152.3 ± 14.8	**<0.001**
EAT (mm)	8.1 ± 1.9	4.9 ± 1.1	**<0.001**

AST: Aspartate transaminases, ALT: Alanine transaminases, HDL: High density lipoprotein, THR: Triglyceride/HDL ratio, LSR: Liver/spleen density ratio, UHR: Uric Acid/HDL ratio, EAT: Epicardial adipose tissue, HbA1C: Hemoglobin A1c.

Table 3. Correlation analysis

	Liver density	LSR	EAT	Pancreas head density	Pancreas body density
BMI	r = -0.44	r = -0.31	r = 0.38		
	p < 0.001	p = 0.003	p < 0.001		
Glucose	r = -0.32	r = -0.27	r = 0.34	r = -0.34	r = -0.38
	p = 0.003	p = 0.013	p = 0.001	p = 0.001	p < 0.001
HbA1C	r = -0.24	r = -0.22	r = 0.41	r = -0.24	r = -0.22
	p = 0.02	p = 0.04	p < 0.001	p = 0.026	p = 0.04
WC	r = -0.49	r = -0.33	r = 0.38		
	p < 0.001	p = 0.002	p < 0.001		
WHR	r = -0.44	r = -0.28	r = 0.57		
	p < 0.001	p = 0.003	p < 0.001		

LSR: Liver/spleen density ratio, EAT: Epicardial adipose tissue, BMI: Body Mass Index, WC: Waist Circumference, WHR: Waist-hip ratio, HbA1C: Hemoglobin A1c.

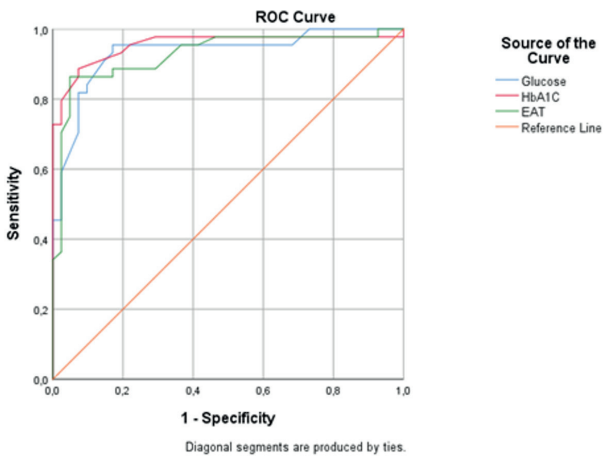

Figure 1. ROC analysis EAT >5.4mm: 89% sensitivity, 83% specificity (AUC: 0.93, p<0.001, 95% CI: 0.87-0.99). Serum glucose >111.5 mg/dL: 93% sensitivity, 83% specificity (AUC: 0.93, p<0.001, 95% CI: 0.87-0.98). Serum HbA1C >5.75%: 93% sensitivity, 81% specificity (AUC: 0.95, p<0.001, 95% CI: 0.90-1).

EAT: Epicardial adipose tissue, HbA1C: Hemoglobin A1c, ROC: Receiver operating characteristic, AUC: Area under the curve.

Correlation analysis revealed significant negative correlations between liver density and BMI, serum glucose levels, serum HbA1C levels, WC, and WHR. Similarly, the LSR exhibited significant negative correlations with BMI, serum glucose levels, serum HbA1C levels, WC, and WHR. Pancreas head density was negatively correlated with serum glucose levels and HbA1C levels, while pancreas body density exhibited negative correlations with serum glucose levels and HbA1C levels. EAT showed significant positive correlations with BMI, serum glucose levels, serum HbA1C levels, WC, and WHR (Table 3).

In ROC analysis, an EAT thickness greater than 5.4 mm demonstrated 89% sensitivity and 83% specificity for detecting diabetes mellitus (DM) (Area under the curve (AUC): 0.93, p < 0.001, 95% CI: 0.87-0.99). Similarly, a serum glucose level exceeding 111.5 mg/dL exhibited 93% sensitivity and 83% specificity for DM detection (AUC: 0.93, p < 0.001, 95% CI: 0.87-0.98). Additionally, a serum HbA1C level above 5.75% showed 93% sensitivity and 81% specificity for detecting DM (AUC: 0.95, p < 0.001, 95% CI: 0.90-1) (see Figure 1).

DISCUSSION

Our study revealed a significant increase in liver sizes among individuals diagnosed with DM, aligning with existing literature and underscoring the prevalent issue of hepatosteatosis within the diabetic population, indicative of notable fat accumulation in the liver (16). This enlargement of the liver in diabetic individuals may serve as a potential indicator of hepatosteatosis, recognized as a component of metabolic syndrome. Moreover, the augmentation in liver sizes correlates with diminished liver functional capacity and heightened susceptibility to progressive liver diseases.

Hence, vigilance in monitoring and assessing liver sizes in diabetic patients holds crucial importance for implementing prospective preventive and therapeutic interventions.

In our study, hepatosteatosis was detected in 22 diabetic patients, whereas only one patient in the control group exhibited this condition. Our findings are consistent with the literature, demonstrating an increased risk of hepatosteatosis in diabetic individuals (17).

In the ROC analysis, we evaluated the diagnostic performance of EAT thickness, serum glucose levels, and serum HbA1C levels in detecting DM. An EAT thickness greater than 5.4 mm demonstrated high sensitivity (89%) and specificity (83%) in identifying DM. Similarly, elevated serum glucose levels (>111.5 mg/dL) and HbA1C levels (>5.75%) showed high sensitivity (93%) and specificity (83% and 81%, respectively) in detecting DM. These findings align with existing literature, emphasizing the interconnectedness between DM, metabolic parameters, and imaging findings. Such observed correlations underscore the potential utility of non-invasive imaging techniques and metabolic markers in the early detection and management of DM and associated complications (18-20).

Our study showed that increased EAT may serve as an indicator of hepatosteatosis. This finding is clinically significant as it suggests that measuring EAT could provide a non-invasive marker to alert physicians to the presence of hepatosteatosis in diabetic patients. The clinical utility of this marker extends further; an increase in EAT has been associated with heightened CV risk, making it a dual-purpose marker that could inform both hepatic and cardiovascular health management. In diabetic patients, particularly those with hepatosteatosis, monitoring EAT could thus facilitate early identification of individuals at greater risk for CV events. This is crucial because recent studies have consistently reported a correlation between elevated EAT and increased CV risk, underscoring the importance of comprehensive risk assessment and proactive management strategies in this population. By incorporating EAT measurement into routine clinical practice, healthcare providers can enhance their ability to detect and mitigate the multifaceted risks associated with diabetes, ultimately improving patient outcomes (21).

The retrospective nature of this study, involving the retrospective collection of data, may introduce limitations in establishing causal relationships. Moreover, the single-center design of the study might restrict the generalizability of the findings and could imply limitations concerning diversity, as it relies on a solitary population sample. The constrained sample size could also pose limitations in terms of statistical power and reliability. Furthermore, having all measurements conducted by a single individual may be less dependable compared to independent verification by another evaluator to ensure consistency in measurements. These limitations could influence the interpretation of the study's results and underscore the necessity for larger-scale, prospective studies.

In conclusion, our findings reveal a significant increase in hepatosteatosis and EAT thickness in individuals diagnosed with DM. Additionally, noteworthy discrepancies in the densities of the liver, pancreas, and other organs were observed. These outcomes underscore the effective utilization of non-contrast abdominal CT scans and pertinent laboratory tests in evaluating metabolic disorders and fat accumulation in diabetic patients. Consequently, early identification and management of heightened hepatosteatosis and EAT thickness in diabetic individuals are imperative for averting metabolic health complications and associated issues. Yet, studies in diabetic subjects that evaluate EAT in subgroups according to the presence of hepatosteatosis are still needed.

Ethical approval

This study has been approved by the Bolu Abant İzzet Baysal University Clinical Researches Ethic Committee (approval date 05/09/2023, number 2023/298). Written informed consent was obtained from the participants.

Author contribution

Concept: ZC, MEK; Design: ZC, MEK; Data Collection or Processing: ZC, MEK; Analysis or Interpretation: ZC; Literature Search: ZC, MEK; Writing: ZC, MEK. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLE

Effects of smoking on local and systemic oxidative stress markers in individuals with periodontitis

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ABSTRACT

Aim: This study aimed to assess the effects of smoking on systemic and local oxidative stress markers in patients with periodontitis.

Methods: A total of 72 patients with periodontitis [38 smokers (S +P+), 34 non-smokers (S-P+)] and 54 periodontally healthy individuals [28 smokers (S+P-), 26 non-smokers (S-P-, control)] were included. After clinical measurements and samplings, the cotinine level, total antioxidant capacity (TAOC), total oxidative status (TOS), and malondialdehyde (MDA) level in the serum and saliva were determined, and the oxidative stress index (OSI) was calculated. Kruskal-Wallis and Mann-Whitney U tests were used for multiple and pairwise comparisons. Correlations were analyzed using Pearson correlation coefficient. $P<0.05$ was considered statistically significant.

Results: Smoking and periodontitis decreased the serum and salivary TAOCs and increased the TOS, MDA level, and OSI. The smokers with periodontitis had the lowest TAOC and the highest TOS, MDA level, and OSI, while the controls had the highest TAOC and the lowest TOS, MDA level, and OSI. The systemic and local effects of smoking seemed more pronounced than those of periodontitis in the oxidative stress study, but no significant difference was identified between the smoking (S+P-) and periodontitis (S-P+) groups. The clinical parameters and oxidative stress markers showed both substantial positive and negative relationships in all groups ($p<0.01$).

Conclusions: It can be concluded that smoking and periodontitis (S+P+) are associated with a decrease in serum and salivary TAOCs and an increase in TOS, MDA levels, and OSI. Smoking has a similar effect as periodontitis on local and systemic oxidative stress, and oxidative stress caused by smoking may be a significant factor in the pathophysiology of periodontitis.

Keywords: Smoking, lipid peroxidation, oxidative stress, periodontitis

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INTRODUCTION

Reactive oxygen species (ROS) are extremely reactive derivatives of oxygen metabolism and can cause tissue destruction through various mechanisms such as DNA damage, lipid peroxidation (LPO), protein damage, oxidation of crucial enzymes, and stimulation of pro-inflammatory cytokine release. The etiology of numerous inflammatory disorders substantially involves ROS, including periodontitis (1,2). In all living organisms, protective antioxidant defense systems have evolved to counteract the damaging effects of ROS (3). In a healthy physiological state, antioxidant defense capability and ROS activity are dynamically balanced. However, oxidative stress may occur, leading to the potential destruction of vital cell components due to diminished antioxidant defense and/or changes in ROS generation or activity (1-4). Although it is not precisely known whether oxidative stress is the cause or result of related diseases, identifying oxidative stress is considered important in clarifying the pathogenic mechanisms of various illnesses (5).

Periodontitis is an inflammatory condition of the supporting tissues of the teeth (6). ROS, LPO products, and antioxidant systems play a crucial role in the pathogenesis of periodontitis (7). According to reports, both oxidative damage and low antioxidant capacity are linked to periodontal disease (8,9). Additionally, local and systemic LPO levels are increased in individuals with periodontitis (9,10).

Smoking is known to be the strongest modifiable risk factor following bacterial plaque accumulation for the incidence and progression of periodontitis (11,12). Smoking can damage periodontal tissues by affecting neutrophil function and cytokine and growth factor production, inhibiting antibody production and fibroblast activity, and decreasing collagen production and vascularity (13).

The high ROS content of cigarettes negatively affects the antioxidant defense mechanism, consequently increasing oxidative stress (11,13). Smoking has also been reported to stimulate the production of ROS from neutrophils (14-16). The presence of the main nicotine metabolite in physiological fluids, cotinine, is a clear sign of current smoking or exposure to cigarette smoke (17). In many studies investigating the relationship between smoking and diseases, cotinine is defined as a chemical determinant of nicotine intake (18).

In the determination of oxidative stress, parameters such as enzymatic and non-enzymatic antioxidant levels, total antioxidant capacity (TAOC), total oxidative status (TOS), LPO product [e.g., malondialdehyde (MDA)] level, and oxidative stress index (OSI) are commonly used (19-21). It has been reported that TAOC decreased while TOS, MDA level, and OSI increased in patients with periodontitis (3,9).

Although smoking has been shown to have detrimental effects on periodontal tissues in numerous studies (12,16), the role played by oxidative stress in this association is still not entirely understood. Accordingly, this study aimed to evaluate the effects of smoking on systemic and local oxidative stress parameters in individuals with periodontitis.

MATERIALS AND METHODS

This study was reviewed and approved by the Ethical Committee of the Karadeniz Technical University Faculty of Medicine (approval number: 2009/44).

Sample size calculation

In the main hypotheses of the study, comparisons between four independent groups were planned. In this study, the sample size was calculated at a 95% confidence level using the G*Power program version 3.1.9.2 (22). The standardized effect size was measured as 0.6386 based on a similar study (CAL: 5.10±0.85 and 4.65±0.52) (23). The minimum sample size for each group was calculated as 20, with a theoretical power of 0.80. Owing to potential mishaps during biochemical analyses, the number of patients was increased by 30% of the calculated sample size, resulting in a minimum sample size of 26 for each group.

Clinical studies

Study groups

The study was conducted in accordance with the Declaration of Helsinki guidelines. A total of 126 individuals were included in this study: 72 patients with periodontitis [38 smokers (S+P+ group), including 17 women and 21 men, mean age: 36.75±8.93 years; 34 non-smokers (S-P+ group), including 16 women and 18 men, mean age: 35.87±8.65 years] and 54 periodontally healthy individuals [28 smokers (S+P- group), including 13 women and 15 men, mean age: 32.17±9.27 years; 26 non-smokers (S-P-/control group), including 12 women and 14 men, mean age: 30.53±8.25 years]. The participants were chosen from those referred to the Karadeniz Technical University Faculty of Dentistry, Department of Periodontology for periodontal issues or routine periodontal checks. The study details were explained to the participants, and written consent was acquired.

In accordance with the standards approved by the 2017 World Workshop, clinical and radiographic evaluations for periodontitis were conducted (24). Patients with stage 3 grade A–C periodontitis were included in the periodontitis groups. Both smoking and non-smoking patients with periodontitis were considered to have poor oral hygiene. There were no prosthetic restorations, and the accumulation of plaque was equivalent to the amount of attachment loss (AL). The control groups (smokers and non-smokers) consisted of periodontally healthy individuals with a PD of ≤3 mm and an AL of ≤1 mm, with adequate dental hygiene, no clinical signs of gingival inflammation, and no prosthetic restorations.

Patients who had no history of any systemic disease, had not received any drug therapy or any antioxidant vitamin therapy in the last 6 months, had not received any periodontal treatment in the last 1 year, were neither pregnant nor lactating, and shared the same dietary preferences and resided in the same geographical area (the Black Sea coastal region of Turkey) were included in the study. Conversely, patients who smoked fewer than 10 cigarettes a day and those who had smoked for less than 2 years were excluded from the study.

Clinical measurements

The PD and CAL (using Williams periodontal probe; 122-006, Hu-Friedy)), gingival index (GI), gingival bleeding index (GBI), and plaque index (PI) were measured in all participants. Radiographs of the entire mouth were taken to assess the extent of periodontal bone loss among the patients. The PD and CAL were assessed at six locations (mesio-buccal, medio-buccal, disto-buccal, mesio-palatal, medio-palatal, and disto-palatal areas) and the GI, GBI, and PI at four locations (mesial, mid-buccal, mid-palatal, and distal areas). The same examiner conducted each clinical and radiographic examination. The participants had a minimum of 20 teeth in total.

Sample collection

Samples were collected in the morning after an overnight fast 2 days after the clinical measurements. The participants were instructed to refrain from eating or drinking in the morning. Before the samples were collected, the participants were evaluated for protocol adherence.

Unstimulated whole saliva samples were collected from the participants. The participants were instructed to rest for 5 min without swallowing their saliva. Pooled saliva at the bottom of the mouth was drained into a collection tube. The saliva was centrifuged at 4,000×g for 10 min at 4°C before analysis. The supernatant fraction was aliquoted into storage vials and then stored in liquid nitrogen until analysis.

Venous blood was collected into plain tubes for serum analysis. Before centrifugation at 1,500×g for 10 min at room temperature, the tubes were maintained at 4°C for an additional 30 min.

Before analysis, the serum samples were aliquoted into cryogenic vials and kept in liquid nitrogen. Each participant served as an analytical unit.

Laboratory studies

TOS assay

The technique created by Erel was used to quantify the serum and salivary TOSs [20]. Hydrogen peroxide (H_2O_2) was used to calibrate the test, and the concentration values were expressed in micromolar H_2O_2 equivalents per liter.

TAOC assay

The serum and salivary TAOCs were measured using commercially available human-specific enzyme-linked immunosorbent assays in accordance with the manufacturer's recommendations (TAOC ELISA Kit, Rel Assay Diagnostics, Gaziantep, Turkey). The Trolox equivalent in millimolar was used to express the findings.

MDA (LPO product) assay

The serum and salivary MDA levels were determined by the high-performance liquid chromatography (HPLC) technique, which was slightly modified from Young and Trimble's method (21). The concentration values were expressed in micromolars.

OSI

The OSI was determined based on the TOS:TAOC ratio. The TAOC expressed in millimolar Trolox equivalents per liter was converted to micromole equivalents per liter. The OSI was calculated using the following formula: OSI=[(TOS in µmol/L)/(TAOC in mmol Trolox equivalent/L)*100].

Cotinine level

The salivary cotinine level was determined using HPLC, as described by Machacek and Jiang (25).

Statistical analyses

The data collected from all participants were imported to the Statistical Package for the Social Sciences (SPSS) for Windows version 16.0 (SPSS Inc., Chicago, IL, USA). Standard descriptive statistics such as means, standard deviations, medians, and frequencies were used to present the characteristics of the sample. The normality of the distribution of the data was examined using the Kolmogorov–Smirnov test. Because the distribution of the data did not meet the requirements for normality and homogeneity of variances, the nonparametric Kruskal–Wallis one-way analysis of variance by ranks and the Mann–Whitney U test were used for the multiple and pairwise comparisons, respectively. The correlations between at least two continuous variables were examined using Pearson's correlation coefficients. $P<0.05$ was considered statistically significant.

RESULTS

Clinical findings

The arithmetic mean values of the clinical parameters are shown in Table 1. All clinical periodontal parameters were significantly higher among the patients with periodontitis than among the periodontally healthy individuals ($p<0.01$). There was no significant difference in the clinical periodontal parameters between the S+P+ and S-P+ groups and between the S+P- and S-P- groups ($p>0.05$).

Laboratory findings (Table 2)

TAOC

The highest and lowest serum and salivary TAOCs were noted in the control and S+P+ groups, respectively (Figure 1).

Table 1. Comparison of clinical parameters in periodontitis groups and periodontally healthy groups

Clinical Parameters	Groups	N	X±SD			Median	χ^2	p
PD (mm)	S+P+	38	3.58	±	0.421*	3.57	103.039	0.001
	S-P+	34	3.52	±	0.607‡	3.42		
	S+P-	28	1.19	±	0.401	1.25		
	S-P-	26	1.2	±	0.395	1.23		
CAL (mm)	S+P+	38	4.17	±	0.739*	4.06	102.91	0.001
	S-P+	34	4.02	±	0.837‡	3.84		
	S+P-	28	1.51	±	0.557	1.55		
	S-P-	26	1.52	±	0.571	1.45		
GI	S+P+	38	1.5	±	0.495*	1.46	107.822	0.001
	S-P+	34	1.79	±	0.325‡	1.75		
	S+P-	28	0.06	±	0.089	0		
	S-P-	26	0.04	±	0.082	0		
GBI (%)	S+P+	38	81.69	±	18.421*	85.87	107.558	0.001
	S-P+	34	87.72	±	11.663‡	88.87		
	S+P-	28	0.03	±	0.06	0		
	S-P-	26	0.02	±	0.048	0		
PI	S+P+	38	2.24	±	0.538*	2.2	108.362	0.001
	S-P+	34	2.06	±	0.436‡	2.02		
	S+P-	28	0.03	±	0.079	0		
	S-P-	26	0.02	±	0.059	0		

Kruskal–Wallis test:

* The S+P+ group is statistically different from the S+P- and ve S-P- groups ($p<0.05$).

‡ The S-P+ group is statistically different from the S+P- and ve S-P- groups ($p<0.05$).

SD: Standart deviation, PD: Pocket Depth, CAL: Clinical Attachment Level, GI: Gingival Index, GBI: Gingival Bleeding Index, PI: Plaque Index

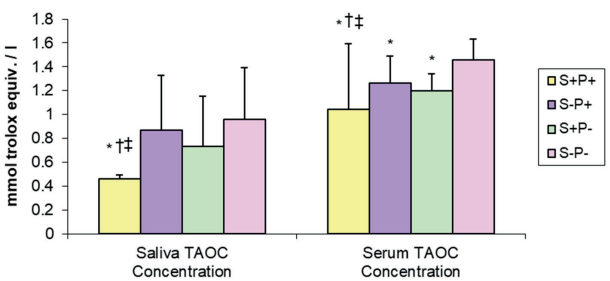

Figure 1. The comparison of the total antioxidant capacity (TAOC) concentrations in serum and saliva between the groups.

* Significant difference as compared with S-P- group ($p<0.05$).
† Significant difference as compared with S-P+ group ($p<0.05$).
‡ Significant difference as compared with S+P- group ($p<0.05$).

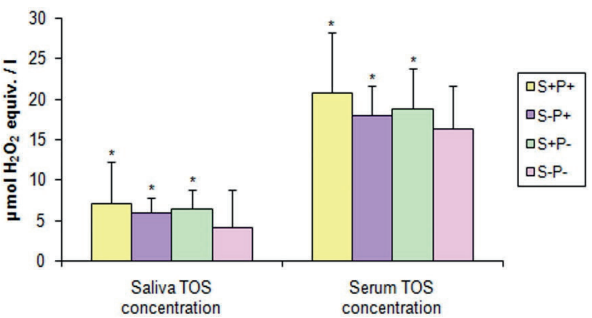

Figure 2. The comparison of the total oxidant status (TOS) concentrations in serum and saliva between the groups.

* Significant difference as compared with S-P- group ($p<0.05$).

Table 2. Comparison of serum and salivary laboratory parameters between periodontitis [smoker (S+P+), non-smoker (S-P+)] and periodontally healthy [smoker (S+P-), non-smoker (S-P-; control)] groups

Laboratory Parameters	Groups	N	X±SD			Median	χ^2	p
Serum TAOC (mmol Trolox Equiv./l)	S+P+	38	1.04	±	0.280*†‡	1.1	47.951	0.000
	S-P+	34	1.26	±	0.232*	1.24		
	S+P-	28	1.20	±	0.143*	1.21		
	S-P-	26	1.46	±	0.174	1.45		
Serum TOS (µmol H_2O_2 Equiv./l)	S+P+	38	20.73	±	7.522*	19.6	8.461	0.037
	S-P+	34	17.96	±	3.71*	18.17		
	S+P-	28	18.87	±	4.92*	19.71		
	S-P-	26	14.38	±	5.219	14.76		
Serum MDA (nmol/ml)	S+P+	38	0.50	±	0.550*	0.27	13.7	0.003
	S-P+	34	0.35	±	0.322	0.21		
	S+P-	28	0.47	±	0.558	0.27		
	S-P-	26	0.20	±	0.13	0.16		
Serum OSI	S+P+	38	2.25	±	1.351*†‡	1.8	32.256	0.000
	S-P+	34	1.47	±	0.492*	1.38		
	S+P-	28	1.59	±	0.421*	1.57		
	S-P-	26	1.04	±	0.385	1.03		
Salivary TAOC (mmol Trolox Equiv./l)	S+P+	38	0.46	±	0.292*†‡	0.39	27.105	0.000
	S-P+	34	0.87	±	0.457	0.86		
	S+P-	28	0.73	±	0.424	0.95		
	S-P-	26	0.96	±	0.433	1.05		
Salivary TOS (µmol H_2O_2 Equiv./l)	S+P+	38	7.14	±	5.137*	6.39	7.951	0.047
	S-P+	34	5.95	±	1.83*	6.14		
	S+P-	28	6.51	±	2.186*	6.39		
	S-P-	26	3.09	±	4.632	0.46		
Salivary MDA (nmol/ml)	S+P+	38	0.10	±	0.035*†‡	0.09	49.582	0.000
	S-P+	34	0.07	±	0.038*	0.06		
	S+P-	28	0.08	±	0.045*	0.07		
	S-P-	26	0.04	±	0.016	0.04		
Salivary OSI	S+P+	38	3.85	±	8.565*	1.72	32.106	0.000
	S-P+	34	1.82	±	3.891*	0.69		
	S+P-	28	2.57	±	4.508*	0.68		
	S-P-	26	0.47	±	0.562	0.23		

Kruskal–Wallis test:

* Statistical difference when compared with S-P- groups ($p<0.05$).

† Statistical difference when compared with S-P+ groups ($p<0.05$).

‡ Statistical difference when compared with S+P- groups ($p<0.05$).

SD: Standart deviation, TAOC: Total Antioxidant Capacity, TOS: Total Oxidant Status, MDA: Malondialdehyde, OSI: Oxidative Stress Index

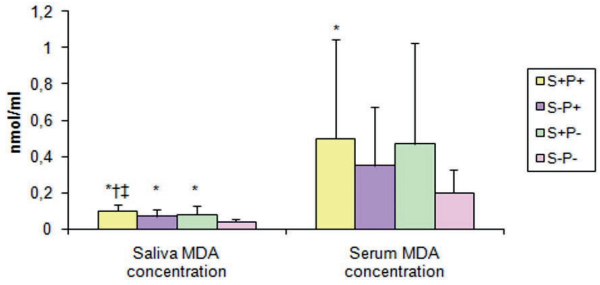

Figure 3. The comparison of the malondialdehyde (MDA) concentrations in serum and saliva between the groups.

* Significant difference as compared with S-P- group (p<0.05).
† Significant difference as compared with S-P+ group (p<0.05).
‡ Significant difference as compared with S+P- group (p<0.05).

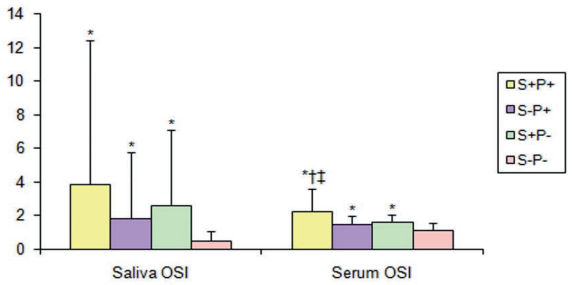

Figure 4. The comparison of the oxidative stress index (OSI) values in serum and saliva between the groups.

* Significant difference as compared with S-P- group (p<0.05).
† Significant difference as compared with S-P+ group (p<0.05).
‡ Significant difference as compared with S+P- group (p<0.05).

TOS

The serum and salivary TOSs were significantly lower in the smoking and/or periodontitis groups than in the control group (p=0.037, p=0.047). The highest and lowest TOSs were observed in the S+P+ and control groups, respectively (Figure 2).

LPO (MDA) level

While the serum MDA level was significantly lower in the S+P+ group than in the control group (p<0.01), no significant difference was found between the other groups (p>0.05). The salivary MDA level was significantly higher in the S+P+ group than in the other groups and the S-P+ and S+P- groups than in the control group (p<0.01). Although the S+P- group had higher serum and salivary MDA levels than the S-P+ group, there was no significant difference between them (p>0.05) (Figure 3). The highest and lowest serum and salivary MDA levels were noted in the S+P+ and control groups, respectively.

OSI

The serum OSI was significantly higher in the S+P+ group than in the other groups and the S-P+ and S+P- groups than in the control group (p<0.01). While the salivary OSI was significantly higher in the smoking and/or periodontitis groups than in the control group (p<0.01), no significant difference was found between the other groups (p>0.05). Further, although the S+P- group had higher serum and salivary OSIs than the S-P+ group, no significant difference was found between them (p>0.05) (Figure 4). The highest and lowest serum and salivary OSIs were observed in the S+P+ and control groups, respectively.

Cotinine level

The salivary cotinine level could only be measured in the S+P+ and S+P- groups. The salivary cotinine level was then significantly higher among the smoking groups than among the non-smoking groups. There was no significant difference in the salivary cotinine level between the S+P+ and S+P- groups (p=0.245) (Table 3).

Table 3. Comparison of saliva cotinine concentrations of (S+P+) and (S+P-) groups

Laboratory Parameters	Groups	N	X±SD			Median	χ^2	p
Saliva Cotinine (µg/l)	S+P+	38	1867.83		1066.54	2177.5	502	0.245
	S+P-	28	1645.53		1294.73	1232		

SD: Standart deviation.

Table 4. Correlations between clinical parameters, serum and saliva TOS, TAOC, MDA and OSI values, and saliva cotinine in all subjects (r, Pearson's correlation coefficient)

	r	p		r	p
PD-serum TAOC	-0.285	0.001	GI-saliva MDA	0.217	0.003
PD-serum OSI	0.246	0.003	GI-saliva cotinine	0.334	0.001
PD-saliva TAOC	-0.183	0.030	GBI-serum TAOC	-0.311	0.000
PD-saliva TOS	0.185	0.029	GBI-serum OSI	0.260	0.002
PD-saliva MDA	0.262	0.002	GBI-saliva TAOC	-0.167	0.049
PD-saliva cotinine	0.371	0.000	GBI-saliva MDA	0.277	0.001
CAL-serum TAOC	-0.256	0.002	GBI-saliva cotinine	0.374	0.000
CAL-serum OSI	0.225	0.007	PI-serum TAOC	-0.299	0.000
CAL-saliva TAOC	-0.177	0.036	PI-serum TOS	0.198	0.019
CAL-saliva MDA	0.250	0.003	PI-serum OSI	0.275	0.001
CAL-saliva cotinine	0.366	0.000	PI-saliva TAOC	-0.206	0.015
GI-serum TAOC	-0.255	0.002	PI-saliva TOS	0.195	0.021
GI-serum OSI	0.193	0.022	PI-saliva MDA	0.273	0.001
GI-saliva TOS	0.190	0.025	PI-saliva cotinine	0.386	0.000

PD: Pocket Depth, CAL: Clinical Attachment Level, GI: Gingival Index, GBI: Gingival Bleeding Index, PI: Plaque Index, TAOC: Total Antioxidant Capacity, TOS: Total Oxidant Status, MDA: Malondialdehyde, OSI: Oxidative Stress Index

Correlations

The correlations between the clinical parameters and oxidative stress parameters are shown in Table 4. Significant positive and negative correlations were detected between the clinical parameters and oxidative stress parameters in all groups.

DISCUSSION

The present study showed that smoking and periodontitis decreased the serum and salivary TAOCs and increased the TOS, MDA level, and OSI. In the literature, various studies have examined the oxidative and antioxidative status among smokers and non-smokers with periodontitis (10,11,13,26-28). To the best of the authors' knowledge, this study is the first to explore the effects of smoking on the TAOC, TOS, and MDA levels both locally and systemically in individuals with periodontitis. Further, the OSI was used to emphasize the relationship between smoking, periodontitis, and oxidative stress.

Herein, the systemic and local TAOCs were significantly reduced among the smokers with periodontitis compared with those among the periodontally healthy smokers and non-smokers and patients with periodontitis. Guentsch et al. (10) found that smokers with periodontitis had a lower TAOC, while Buduneli et al. (11) reported that gingival inflammation and/or smoking did not change the salivary TAOC in individuals with gingivitis. In addition, the serum, plasma, salivary, and gingival crevicular fluid (GCF) TAOCs were significantly lower among individuals with periodontitis than among healthy controls. Baltacıoğlu et al. (3) reported decreased serum and salivary TAOCs in patients with periodontitis. Other studies have revealed that smoking, independent of periodontitis, reduced plasma and serum antioxidant levels (29-32). These previous findings appear to be consistent with the TAOCs noted in the present study.

Currently, it is impractical to detect various oxidant molecules independently, as this approach may not fully reflect the interaction of oxidant molecules with each

other (20). Therefore, assessing the TOS is considered superior to other approaches. In the literature, few studies have evaluated the TOS in individuals with periodontitis (7,31,33). In these studies, the serum, salivary, and GCF TOSs were significantly higher in individuals with periodontitis than in healthy controls, and the TOS increased systemically and locally in individuals with periodontitis. In the present study, the serum and salivary TOSs increased significantly in the smoking and/or periodontitis groups compared with those in the control group, and the highest TOS was noted in the smokers with periodontitis. There was no significant difference between the other groups, except for the control group. These findings indicate that while smoking and/or periodontitis increase oxidative levels, smoking has an additional oxidative effect on periodontitis, although it is not significant.

LPO increases the quantity of end products, especially aldehydes. Therefore, evaluating these products is the current approach for the analysis of oxidative stress. This study also examined the level of MDA, an LPO product, to investigate the effects of smoking and periodontitis on oxidative stress. While the serum MDA level increased among the smokers with periodontitis compared to the controls, there was no significant difference between the other groups, except for the controls. However, the salivary MDA level increased more significantly in the smoking and/or periodontitis groups than did the serum MDA level, and smoking had an additional oxidative effect on periodontitis in terms of the local MDA level. In previous studies examining the serum, salivary, GCF, and gingival MDA levels in individuals with periodontitis, it has been reported that the GCF and salivary MDA levels increase in the presence of periodontitis and smoking, while the systemic MDA level does not change significantly in the presence of periodontitis (9,32-42). These previous findings are similar to the MDA levels observed in the present study.

To the authors' knowledge, only a few studies have focused on the effect of smoking on LPO in patients with periodontitis. Guentsch et al. (10) showed that the MDA levels increased in patients with periodontitis compared to the healthy controls and that the MDA levels were significantly higher in smokers with periodontitis than in periodontally healthy non-smokers. Hendek et al. (43) reported that the GCF level of 4-hydroxynonenal, another LPO product, was significantly high in smokers with periodontitis, but no significant differences were observed in the serum and salivary levels. The present findings are consistent with these previous reports.

The OSI more accurately reflects the degree of oxidative stress. While this index, which is defined as the proportional value between the TOS and TAOC, has been used in various oxidative stress studies in recent years (9,44), it was used in this study to evaluate the relationship between smoking and periodontitis in terms of oxidative injury. In the present study, the serum OSI was significantly higher among the smokers with periodontitis than among the other groups. The salivary OSI was also significantly higher among the smokers with periodontitis, while there were no significant differences between the other groups. These findings show that the systemic and local OSIs are also affected by smoking and periodontitis, in line with the systemic and local TAOCs and TOSs noted herein. While the TAOC is affected by various factors such as nutrition, age, and sex, the TOS is a direct measurement and has certain advantages in predicting oxidative stress. Therefore, the OSI, which is based on the TOS:TAOC ratio, may be more useful in the determination of oxidative stress in individuals with periodontitis.

One of the important limitations of our study is that its cross-sectional design does not allow for an assessment of the causality of the observed relationships. Furthermore, the residual confounding effect of some unmeasured factors (diet, lifestyle, etc.) cannot be completely ruled out.

CONCLUSIONS

In this study, the TAOC, TOS, MDA level, and OSI were investigated in smokers with periodontitis to determine the effects of smoking and periodontitis on oxidative damage. Smoking and/or periodontitis increased the TOS, MDA level, and OSI and decreased the systemic and local TAOCs. These findings indicate that smoking has a similar effect on oxidative stress parameters as periodontitis. However, the much higher amount of oxidative stress seen in both smokers and individuals

with periodontitis may represent an important contribution to understanding the pathophysiology of smoking-related periodontal destruction. The present data could be supported by future studies, emphasizing the importance of efforts that aim to stop smoking in periodontal treatment strategies.

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Ethical approval

This study has been approved by the Ethical Committee of the Karadeniz Technical University Faculty of Medicine (approval date 11/06/2009, number 2009/44). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: ÖSA; Concept: ÖSA, EB; Design: EB, AA, ÖSA; Data Collection or Processing: ÖSA, AA, FBY; Analysis or Interpretation: ÖSA, EB; Literature Search: ÖSA, EB, PY, MAK, GA; Writing: ÖSA, EB. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLE

Evaluation of anterior pituitary hormone levels in patients with atrial fibrillation

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ABSTRACT

Aim: The risk of ischemic stroke is increased 5-fold in patients with atrial fibrillation (the most common reason for cardiac arrhythmia). The aim is to investigate whether insufficiency in anterior pituitary hormones develops in patients diagnosed with atrial fibrillation and no history of cerebrovascular accident.

Method: A group of 65 patients with chronic /paroxysmal atrial fibrillation without a history of cerebrovascular accident and a group of 65 healthy controls without arrhythmia were included in this study. Atrial fibrillation was diagnosed by electrocardiography or 24-hour rhythm holter. Demographic data, biochemical tests, echocardiography findings were compared between the groups. P<0.05 was considered statistically significant.

Results: There was no statistical difference in gender and age distribution between groups (p<0.05). (Patient group: Mean age 68 ± 7 years (16 (24.6%) male and 49 (75.4%) female) / Control group: Mean age 67 ± 6 years (18 (27.7%) male and 47 (72.3%) female). Serum insulin-like growth factor-1, adrenocorticotropic hormone and cortisol levels were significantly lower in the patient group compared to the control group (p=0.048, p=0.005, p=0.023). There was no significant difference in serum thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, and prolactin levels between groups. Left atrial diameter and left ventricular end-diastolic diameter were higher in the patient group (p<0.0001). The left ventricular ejection fraction value was lower in the patient group (p<0.0001).

Conclusion: It was thought that the reason for the low level of insulin-like growth factor-1 in the setting of normal liver and kidney functions and simultaneous cortisol and adrenocorticotropic hormone deficiency, in patients with atrial fibrillation with no history of cerebrovascular accident might be due to silent cerebral ischemia leading to pituitary dysfunction.

Keywords: Anterior pituitary hormones, atrial fibrillation, embolism

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, occurring in 1-2% of the general population (1). Atrial fibrillation is associated with more than a 2-fold increment in the odds for silent cerebral infarctions and a 5-fold increase in the risk of ischemic stroke and is responsible for one-fifth of all strokes (2,3). The main risk factors that lead to the development of atrial fibrillation are age, hypertension, heart failure, rheumatic heart disease, hypertrophic cardiomyopathy, mitral valve prolapse and thyrotoxicosis. Epidemiological and clinical studies have shown that AF is an independent risk factor for stroke (3). Apart from major thromboembolism, cerebral infarcts due to microembolism have been described in AF patients (4,5).

The pituitary gland is a well-blooded organ and very sensitive to ischemia. Anterior pituitary gland insufficiency, 'hypopituitarism', is a clinical syndrome that develops as a result of the insufficiency of one or more hormones produced in this gland. In this study, we aimed to investigate whether insufficiency in anterior pituitary hormones develops in patients with AF who did not have an obvious clinical finding of stroke.

MATERIALS AND METHODS

This is an IRB (Institutional Review Board) approved single-institution study (B.10.4.İSM.4.06.68.49/2012). Patients between the ages of 50 and 85 who applied to the internal medicine outpatient clinic were included in the study. The patient group was composed of patients with a diagnosis of chronic AF or who have a paroxysmal AF attack shown in previous electrocardiography (ECG) or 24-hour rhythm Holter tests. Patients who did not have AF or any other rhythm problem were included in the control group. Patients with cerebrovascular disease, malignancies, acromegaly, chronic liver disease, chronic kidney disease, and patients using glucocorticoids, oral contraceptives (OCS), estrogens and androgens were excluded from the study. All females in both groups were in the postmenopausal period.

Biochemical tests of all patients included lipid profile, liver and kidney function tests, complete blood count, serum insulin, C-peptide, free triiodothyroxine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), brain natriuretic peptide (BNP), adrenocorticotropic hormone (ACTH), cortisol, total testosterone (TT), follicle-stimulating hormone (FSH), Luteinizing hormone (LH), sex hormone binding globulin (SHBG), Insulin-like growth factor-1 (IGF-1), prolactin (PRL), estradiol (E2), HbA1c, D-dimer were measured. In principle, in diagnosing central hormone deficiencies (secondary or tertiary deficiencies), both basal pituitary and target gland hormone levels should be measured. The target hormone for ACTH is basal cortisol and for GH, IGF-1. However, stimulation tests are required for the definitive assessment of ACTH and GH insufficiency. Stimulation tests are not performed in AF patients because they are contraindicated. GH measurement was not available, so serum IGF-1 levels were measured. Patients with chronic liver and kidney diseases, which may affect serum IGF-1 levels, were excluded from the study. Peripheral venous blood samples were taken from the patients after 10-12 hours overnight fast. These blood samples were centrifuged at 3000 rpm for 4 minutes in a refrigerated centrifuge without waiting and stored at -80°C. To avoid undesirable variations, samples were run with the same batch on the same day. Echocardiography (ECHO) measurements were performed on the patients using the Vivid 3 cardiac ultrasound device (GE Vingmed Ultrasound, Horten, Norway) and a 2.5 - 3.5-MHz probe.

In statistical analysis, normal distribution analysis was tested with the Kolmogorov-Smirnov test. For normally distributed data, differences between groups were compared with the Student t-test, and for non-normally distributed data, differences between groups were compared with the Mann-Whitney U test. Categorical variables were compared with the Chi-square test. Correlation analyses were performed with the Pearson correlation test for normally distributed data, and with the Spearman correlation test for non-normally distributed data. The results were evaluated within the 95% confidence interval, and $p<0.05$ was accepted for statistical significance.

RESULTS

Of the 130 patients participating in the study, 34 were men and 96 were women. The atrial fibrillation group consisted of 65 patients and the control group consisted of 65 patients. Gender, age, and BMI (body mass index) were found to be similar in both groups.

In the patient group, 31 (47.7%) of the patients were using warfarin, 26 (40%) were using acetylsalicylic acid (ASA), and 3 (4.6%) were using clopidogrel. In the control group, there were no patients using warfarin, 5 (7.7%) were using ASA and 1 (1.5%) was using clopidogrel. The characteristics of the patient and control groups are shown in Table 1.

Table 1. The characteristics of the patient and control groups

	Patient Group		**Control Group**		**P**
Age (year)	68 ± 7		67 ± 6		>0.05
	Female	Male	Female	Male	>0.05
	49 (%75.4)	16 (%24.6)	47 (%72.3)	18 (%27.7)	
HbA1c (%)	6.28 ± 0.88		6.25 ± 0.64		>0.05
BMI (kg/m^2)	26 (18-38)		26.5 (18.2-36.5)		>0.05
Waist Circumference (cm)	88.15 ± 7.13		86.95 ± 6.13		>0.05

*Data were expressed as mean ± standard deviation, median (interquartile range), or n (%).

P value was calculated using the T test, Mann–Whitney U test, and chi-square test.

BMI: Body mass index.

Table 2. The comparison of hormone levels of the patient and control group

Parameter (normal range)	**Patient Group**	**Control Group**	**P**
Insulin (1.9-25 µIU/mL)	13.7 ± 14.1	11.4 ± 6.3	>0.05
C-peptide (1.1-3.2 ng/mL)	4.5 ± 3.1	2.9 ± 1.36	<**0.0001**
Free T3 (2.5-5 pg/mL)	2.6 ± 0.6	2.8 ± 0.41	**0.039**
Free T4 (0.9-1.7 ng/dL)	1.17 ± 0.37	1.14 ± 0.42	>0.05
TSH (0.4-4 µIU/L)	1.94 ± 2.16	2.42 ± 2.38	>0.05
BNP (0-125 pg/mL)	1600.7 ± 1565.7	125 ± 80.3	<**0.0001**
ACTH (9-25 pg/mL)	16.6 ± 12.7	22.88 ± 15.9	**0.005**
Cortisol (5-20 µg/dL)	11.4 ± 5.1	13.4 ± 5.6	**0.023**
TT (300-1000 ng/mL)	0.9 ± 1.4	1.44 ± 1.97	>0.05
FSH (30-118 mIU/mL)	49 ± 30.3	52.8 ± 41.5	>0.05
LH (12-55 mIU/mL)	20.1 ± 13.2	20.9 ± 15.5	>0.05
SHBG (10-57 nmol/L)	59.7 ± 28.3	34.4 ± 15.8	<**0.0001**
IGF-1 (10-1000 ng/mL)	88.8 ± 36.1	109.6 ± 55.9	**0.048**
PRL (< 25 ng/mL)	9.41 ± 5.90	7.5 ± 3.9	>0.05
E2 (0-30 pg/mL)	22.8 ± 19.1	29.8 ± 24.8	>0.05

Data were expressed as mean ± standard deviation.

P value was calculated by T test or Mann–Whitney U test.

C-peptide, FT3: Free triiodothyroxine, FT4: Free thyroxine, TSH: Thyroid stimulating hormone, BNP: Brain Natriuretic Peptide, ACTH: adrenocorticotropic hormone, cortisol, TT: Total testosterone, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, SHBG: Sex hormone binding globulin, IGF-1: Insulin-like growth factor-1, PRL: Prolactin, E2: Estradiol.

Hormone levels of the patient and control groups are shown in Table 2. There was no significant difference in the comparison of serum TSH, insulin, FSH, LH, PRL, E2, TT levels between groups. Serum C-peptide, BNP, SHBG levels were significantly higher in the patient group than in the control group (p<0.0001). Serum FT3, ACTH, cortisol and IGF-1 levels were lower in the patient group than in the control group (p<0.05). There was also a significant positive correlation between serum BNP and C-peptide levels (r=0.288, p:0.003) and SHBG levels (r=0.305, p:0.002).

ECHO findings of the patient and control groups were evaluated. The left atrial diameter (LAD) and left ventricular end-diastolic diameter (LVEDD) of the two groups were higher in the patient group (p<0.0001). The left ventricular ejection fraction (LVEF) value was lower in the patient group (p<0.0001). There was a strong positive correlation between LAD and BNP levels (r=0.666, p<0.0001) and SHBG levels (r=0.406, p<0.0001).

Biochemical and hematological findings of both groups are shown in Table 3. There was no significant difference between the two groups in serum fasting blood glucose, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), low-density lipoprotein (LDL), triglyceride, total cholesterol, hemoglobin, hematocrit, erythrocyte sedimentation rate (ESR) values (Table 3). Serum total protein, albumin and high-density lipoprotein cholesterol (HDL) levels were found to be significantly lower in the AF group compared to the control group (p<0.05) (Table 3). Serum urate, lactate dehydrogenase (LDH), D-dimer levels were found to be higher in the AF group than in the control group, and the difference was statistically significant (p <0.05) (Table 3).

Table 3. The comparison of biochemical and complete blood count tests of the patient and control group

Parameter (normal range)	Patient Group	Control Group	P
FBG (100-125 mg/dL)	117.3 ± 37.9	105.2 ± 17.8	>0.05
Urea (10-20 mg/dL)	36.1 ± 19.37	30.5 ± 8.2	>0.05
Serum creatinine (0.50-1.30 mg/dL)	0.89 ± 0.2	0.8 ± 0.1	>0.05
AST (15-50 IU/L)	23.3 ± 10.1	20.6 ± 6.8	>0.05
ALT (10-40 IU/L)	23.4 ± 17.6	19.4 ± 8.3	>0.05
LDH (140-280 IU/L)	261 ± 109.4	180 ± 33.2	**<0.0001**
Total Protein (6.4-8.3 g/dL)	7.09 ± 0.54	7.3 ± 0.6	**0.007**
Albumin (3.5-5.5 g/dL)	3.95 ± 0.37	4.1 ± 0.4	**0.001**
HDL (35-55 mg/dL)	43 ± 10.2	47.4 ± 9.2	**0.028**
LDL (30-130 mg/dL)	116.9 ± 39.1	109.9 ± 30.3	>0.05
Triglyceride (0-149 mg/dL)	132.6 ± 66.5	153.4 ± 88.7	>0.05
Total cholesterol (0-200 mg/dL)	187 ± 47.6	198.4 ± 38.1	>0.05
Urate (2.6-6 mg/dL)	5.4 (3.2-5.9)	3.4 (2.2-4.8)	**0.007**
Hemoglobin (13-17.5 g/dL)	13.2 ± 1.7	13.7 ± 1.1	>0.05
Hematocrit (40-51 %)	39.3 ± 5	39.6 ± 3.2	>0.05
ESR (0-20 mm/h)	25 (3-80)	23 (6-75)	>0.05
D-dimer (< 250 ng/ml)	417 ± 344.4	256.2 ± 125.9	**0.013**

Data were expressed as mean ± standard deviation, median (interquartile range).

P value was calculated by T test or Mann–Whitney U test.

FBG: Fasting blood glucose, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein, LDH: Lactate dehydrogenase, ESR: Erythrocyte Sedimentation Rate.

DISCUSSION

Atrial fibrillation is an arrhythmia that is becoming increasingly common, with its frequency doubling every decade, causing significant morbidity and mortality, and is responsible for one-fifth of all ischemic strokes (3,6). Apart from major thromboembolism, cerebral infarcts due to microembolism have been described in AF patients (4,5). As is known, the pituitary gland is an organ with a high blood supply and is very sensitive to ischemia. Susceptibility of cells to ischemia, in order from most to least: somatotrophs, gonadotrophs, corticotrophs, thyrotrophs and lactotrophs. Busch et al. (7) reveal a quantitatively lower IGF-1 levels and IGF-1/IGFBP-3 ratios in individuals with AF than individuals without AF in a large population-based study. Duron et al. (8) reported similar results as low IGF-I and IGFBP-3 serum levels were independently associated with AF in an elderly population. However, the exact underlying mechanisms of a decreased level of IGF-1 and the presence of AF could not be elucidated by the authors (7,8). In our study, serum IGF-1 level in AF patients was significantly lower than in the control group. There was no liver dysfunction in our patients and no statistical difference in the liver function tests between the groups. Therefore, it was thought that the low IGF-1 may be due to pituitary origin rather than liver dysfunction.

Larsson et al. (9) encouraged AF monitoring in patients with Cushing syndrome due to hypercortisolemia as a potential risk of AF. Nevertheless, there has been no published study on the cause of low levels of cortisol and ACTH in patients with AF so far. In our study, ACTH and cortisol levels were low in the patient group. Because the secretion pulses are uncertain and have a short half-life, significant changes occur in the ACTH level during the day, so random ACTH measurements are not recommended. Similarly, cortisol exhibits a diurnal rhythm, with levels being highest in the early morning hours and lowest in the late afternoon and evening. The gold standard is insulin tolerance test (ITT) to detect growth hormone (GH) deficiency and ACTH reserve, however, ITT is contraindicated in AF patients due to a high risk of cardiovascular or cerebrovascular events. For this reason, ITT could not be performed on our patients yet, hormone levels were studied in the morning serum samples in order to minimize diurnal impact.

Some previous studies have shown that there is a hypercoagulant environment and cerebral microembolism occurs in patients with atrial fibrillation (10-12). Nevertheless, since there is no study on pituitary microembolism in patients with AF in the literature, we could not compare our findings with another study. In a prospective study by Boehncke et al. (13), in the follow-up of patients after ischemic stroke, variable degrees of pituitary dysfunction were detected in 82% of the patients. It was shown that GH insufficiency (79.5%) and secondary adrenal insufficiency (14.6%) developed predominantly. Secondary gonadal failure was detected in 4.3% of the patients. Additionally, pituitary dysfunction was found to be independent of post-stroke time, stroke type, and gender (13). As a result of this study, it was shown that pituitary ischemia and associated pituitary dysfunction may develop as a complication of ischemic stroke, and therefore pituitary function tests were recommended to be performed in patients with stroke (13). Similarly, in our study, mainly IGF-1, ACTH and cortisol levels were lower in the patient group, and this might be the result of growth hormone and ACTH deficiency due to pituitary microvascular ischemia.

Most of the testosterone and estrogen in the bloodstream are bound to SHBG, a very small part of the total sex hormone concentration (1% - 5%) is free, and biological activity is created by the free fractions. Therefore, SHBG levels may directly alter sex hormone bioavailability. Three recent large-scale population-based studies have shown that male sex hormones may be modulators of cardiac endocrine functions (14-16). These studies showed that circulating BNP and N-terminal proBNP levels were inversely proportional to free and total testosterone in both genders. There was a positive relationship between SHBG, BNP and N-terminal proBNP levels in adolescents and adults of both genders. No significant relationship was detected with estrogen. According to these results, it has been suggested that androgens suppress N-terminal proBNP and this situation can be explained by the changes in free testosterone levels due to sex hormone-related differences in natriuretic peptides (14-16). In our study, there was no significant difference in age and

BMI between both groups and SHBG levels were significantly higher in patients with AF compared to the control group and were correlated with increased BNP levels. High SHBG levels suggest that circulating free androgen levels in patients with AF may be lower than in the control group. BNP and C-peptide levels were also significantly higher in the group of patients with AF in our study. It has been declared that a high plasma BNP and C-peptide levels might be the risk factor for atrial fibrillation (17,18).

There was no significant difference in FT4 and TSH levels between the patient and control groups, and the FT3 level was lower in the patient group than in the control group. However, it was not detected within the limits of hypothyroidism. It was thought that this clinical picture, called 'euthyroid patient syndrome', developed as a result of the mechanisms proposed in its pathogenesis such as insufficiency of peripheral metabolism in extrathyroidal tissues and inhibition the 'type 1 deiodinase' enzyme that converts T4 to T3 in the periphery by inflammatory cytokines released during the emergence of chronic systemic diseases (19).

There are some limitations of this study. Given the cross-sectional nature of the study, we were not able to reveal the exact cause-effect relationship of lower levels of pituitary hormones in AF patients compared to the control group. The sample size was relatively small, however, in both groups, the number of individuals, mean age and gender ratios were similar. Additionally, as mentioned above, some dynamic tests could not be performed to detect hormone deficiency in patients with AF due to contraindications. Despite these limitations, this study is the first in the literature in order to draw attention to the fact that silent microembolism in AF patients may lead to pituitary ischemia.

CONCLUSION

These findings support that silent cerebral ischemia may lead to pituitary dysfunction in patients with AF and no history of cerebrovascular accident. The pathogenesis of the relationship between cerebral ischemia and pituitary dysfunction is still unclear. Individuals with hypopituitarism have a higher risk of morbidity and mortality than healthy individuals. Even if no obvious stroke occurs, pituitary dysfunction should be investigated in suspected cases in patients with AF.

Ethical approval

This study has been approved by the Keçiören Training and Research Hospital Clinical Research Ethics Committee (approval date 11/04/2012, number B.10.4.İSM.4.06.68.49/2012). Written informed consent was obtained from the participants.

Author contribution

Concept: DTE; Design: BY; Data Collection or Processing: RKC; Analysis or Interpretation: RKC, BY; Literature Search: RKC, EB; Writing: RKC. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLE

Assessment of physiotherapists' sensitivity to palpation pressure

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ABSTRACT

Aim: This study was planned to investigate the pressure sensitivity applied by physiotherapists during palpation and the effect of their experience on palpation sensitivity.

Methods: 62 physiotherapists with an age of 31.06 ± 5.29 years and a working experience of 6.88 ± 4.76 years were included in the study. The physiotherapists were divided into two groups: those working in the field of manual therapy and those not working. The participants were asked to apply pressure on an electronic scale with four different weights (500 gr, 1000 gr, 2000 gr, and 4000 gr, respectively). The display screen of the scale on which the measurement was made was blinded to the physiotherapists. After the first measurements, a short training was given and the same measurements were repeated randomly.

Results: In the first evaluation made before the training, it was found that there was a statistical difference between the two groups in the application of 500 grams of pressure ($p=0.003$). However, no significant difference was found between the two groups in the measurements made after the training ($p>0.05$). It was observed that the level of professional experience did not significantly affect pressure sensitivity ($p>0.05$).

Conclusion: This study demonstrates that manual therapy physiotherapists had increased palpation sensitivity when using smaller weights. It is therefore advised that physiotherapists undergo training to enhance their palpation sensitivity, as this is an effective diagnostic and therapeutic technique.

Keywords: Physiotherapists, palpation pressure, manual therapy, training, sensitivity

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INTRODUCTION

One of the best diagnostic and treatment tools for physiotherapists working in musculoskeletal rehabilitation is the hands (1). Manual physiotherapy techniques applied by hand in the treatment of musculoskeletal problems are muscle energy techniques, myofascial release techniques, joint mobilization, and manipulation techniques. Although there are different concepts, the umbrella term used for approaches that include these techniques is manual therapy (2). The amount of pressure applied during palpation is very important for effective manual therapy. Palpation skills are critical both in the accurate diagnosis and treatment of somatic dysfunction (3,4). The pressure applied during palpation should be low enough not to cause complaints in the patient and sufficient to produce therapeutic effects (5). Palpation skills can be improved with intensive practice and training (6,7).

The success of joint mobilization, muscle relaxation, and trigger point release techniques depends on the physiotherapist's accuracy in assessing tissue resistance (8). Physiotherapists must be able to accurately assess the elasticity of the tissue they are interested in and pathological changes in the tone of this tissue using palpation skills (3,9). It has been shown that effective and accurate palpation helps in making a diagnosis and as a result, the quality of the therapeutic intervention increases (8). Myburgh et al. (10) stated that appropriate pressure and application skills are influenced by many factors such as the therapist's expertise, experience and training. Iwata et al. (11) and Snodgrass et al. (12) emphasized that continuous feedback and practice are essential to ensure accuracy in palpation pressure in training programs to improve palpation skills. Aasa et al. (13) and Mora-Relucio et al. (14) also showed in their study that physiotherapists with manual therapy experience had different palpation skills compared to those without. They also emphasized the importance of specialization in the field.

The use of proven palpation skills as a therapeutic and diagnostic tool is essential in the management of musculoskeletal disorders (15). Ineffective palpation leads to misdiagnosis of dysfunction, which highlights the importance for physiotherapists to acquire high proficiency in palpation skills (16). Jaeger (17) stated that the pressure between 2-4 kilograms is effective in relaxing trigger points and that the pressure in this range has good therapeutic effects. It has been emphasized in many previous studies that finding an appropriate pressure in trigger point treatment is important in terms of treatment efficacy. The same researchers stated that continuous pressure between 2-4 kg not only relaxes the trigger point but also reduces pain. Wytrazek et al. (18) and Fischer (19) have reported that approximately 3 kilograms of pressure produced effective improvement in the treatment of myofascial pain problems in the musculoskeletal system.

Although it is accepted that correct palpation is important, there is limited research examining the amount of pressure applied by physiotherapists in clinical practice and evaluating whether the pressure applied in the clinic is adequate. The lack of detailed access to data obtained from studies poses an obstacle to the development of standard training protocols and assessment tools. Additionally, due to the lack of a standard in techniques used during pressure application among physiotherapists with different levels of experience and expertise, more comprehensive research is needed in this area (20). The aim of our study was to measure physiotherapists' sensitivity to pressure during palpation, and in addition to this, to assess their ability to apply pressure levels consistently and accurately in controllable situations. Another aim of our study was to determine the pressure application skills and sensitivities of physiotherapists with different experience and expertise levels.

MATERIALS AND METHOD

Participants

The relevant study was given ethical approval by the Bolu Abant İzzet Baysal University Ethics Committee on 22.11.2022 (Decision No: 2022/305) and written consent was obtained from all participants in the study.

The power analysis of the sample size was performed using GPower 3.1 program. This situation is consistent with the report submitted to the ethics committee.

Kamp et al. (21) published in 2019, it was concluded that it was appropriate to include at least 25 physiotherapists in each group with 80% power and 5% margin of error. Our study results meet the power value calculated by including a total of 62 therapists in the study by including the number of missing errors. A total of 62 physiotherapists actively practicing physiotherapy participated in the study. Participants were divided into two groups according to their specialization: manual therapy group (n=31) and non-manual techniques (neurodevelopmental therapy) group (n=31) (Table 1). Further statistical stratification was applied according to years of professional experience and participants were divided into 3 groups. These groups can be expressed as 0-5 years (24 participants), 6-10 years (23 participants), 11-20 years (n=15) (Table 2). Therapists with neurologic conditions such as carpal tunnel syndrome, cervical myelopathy, pronator teres syndrome, which may have a negative impact on palpation skills were excluded.

Equipment and procedure

In the study, an electronic scale with a sensitivity of ±1 gram was used to measure the pressure applied by physiotherapists with their hands. Each participant was asked to apply 500 grams, 1000 grams, 2000 grams, and 4000 grams of pressure 3 times respectively. The values obtained from the measurements were recorded and the arithmetic averages of these measurements were calculated. During the measurements, the screen of the scale was positioned so that it could be seen by the evaluator but not by the physiotherapist applying the pressure. After completing the first set of measurements, participants were allowed to practice independently with the electronic balance for up to 5 minutes to familiarize themselves with the equipment and improve their technique. After this practice period, the display of the balance was turned off as mentioned before and the measurements were repeated. In the final measurements (as a repetition of the initial application), the participants were asked to apply 500 grams, 1000 grams, 2000 grams, and 4000 grams of pressure in a random order 3 times each.

Table 1. Demographic Data Table by Therapeutic Method

	Non-Manual Therapy	Manual therapy	Total	P value
N	31	31	62	
Age	32.10 ± 5.52	30.03 ± 4.93	31.06 ± 5.29	0.125
Height	174.39 ± 9.10	169.13 ± 8.11	171.76 ± 8.95	**0.019**
Weight	78.32 ± 17.35	67.00 ± 13.67	72.66 ± 16.51	**0.006**
Total years of experience	8.19 ± 5.30	5.57 ± 3.81	6.88 ± 4.76	**0.030**
Active professional years	7.68 ± 5.26	5.03 ± 3.94	6.35 ± 4.80	**0.029**
Active weekly working day	5.39 ± 0.60	5.35 ± 0.80	5.37 ± 0.70	0.825

Table 2. Demographic Data Table by Years of Experience

	0-5	6-10	11-20	Total
N	24	23	15	62
Age	26.46 ± 3.09	31.57 ± 2.56	37.67 ± 3.56	31.06 ± 5.29
Height	171.50 ± 7.96	171.57 ± 9.13	172.47 ± 10.65	171.76 ± 8.95
Weight	68.42 ± 12.44	72.13 ± 15.13	80.27 ± 21.90	72.66 ± 16.51
Total years of experience	2.53 ± 1.26	7.00 ± 1.38	13.67 ± 3.39	6.88 ± 4.76
Active professional years	1.95 ± 1.24	6.43 ± 1.16	13.27 ± 3.37	6.35 ± 4.80
Active weekly working day	5.46 ± 0.59	5.35 ± 0.83	5.27 ± 0.68	5.37 ± 0.70

Data analysis

Data were analyzed with the licensed SPSS-25 program (IBM Corporation, Armonk, NY, USA). Histograms and Kolmogorov-Smirnov Test were used to assess the normality of the data distribution. Depending on the normality of the data, an independent sample T test or Mann-Whitney U test was used to compare the mean pressure application between groups. ANOVA test was used to examine the relationship between "years of experience" and "pressure application accuracy".

Validity and reliability

The validity of the palpation pressures applied by the therapists (internal consistency) was assessed by comparing the consistency of measurements across trials. Studies have shown that effective deactivation of trigger points can usually be achieved with continuous pressure of about 2 to 4 kilograms (17-19). Therefore, the ability to apply these pressures correctly is crucial for therapeutic efficacy. The reliability of the measurements was assessed by calculating intraclass correlation coefficients for repeated trials.

RESULTS

Independent sample T-test was used to analyze the pressure application between physiotherapists with manual therapy expertise and physiotherapists from another specialty (Table 3). The primary measurements yielded the following results: 500 grams (p=0.003), 1000 grams (p=0.898), 2000 grams (p=0.134) and 4000 grams (p=0.333). After a short training, the results of the statistical analysis were measured at

Table 3. Pressure Sensitivity Table by Years of Experience

		0-5	6-10	11-20	Total	P value
		n=24	n=23	n=15	n=62	
Pre-Study	500 gr	862.92 ± 1001.23	858.04 ± 902.24	954.64 ± 1572.17	883.30 ± 1113.78	p = 0.961
	1000 gr	1981.00 ± 2382.69	1573.80 ± 1663.34	990.69 ± 1218.96	1590.35 ± 1904.73	p = 0.291
	2000 gr	2090.14 ± 2296.60	2055.04 ± 2302.76	1130.69 ± 1303.45	1844.99 ± 2111.12	p = 0.327
	4000 gr	2269.89 ± 1706.79	2414.28 ± 1848.86	1700.62 ± 1523.87	2185.73 ± 1715.96	p = 0.442
After Study	500 gr	483.75 ± 660.70	529.55 ± 520.33	376.96 ± 295.56	474.90 ± 534.61	p = 0.694
	1000 gr	628.51 ± 782.92	740.13 ± 791.13	355.62 ± 333.40	603.90 ± 710.46	p = 0.262
	2000 gr	688.29 ± 491.84	694.58 ± 697.64	660.29 ± 390.60	683.85 ± 549.49	p = 0.982
	4000 gr	1083.28 ± 996.59	1102.58 ± 1121.01	1078.20 ± 738.60	1089.21 ± 976.23	p = 0.997

Table 4. Pressure Sensitivity Table by Therapeutic Method

		Non-Manual Therapy	Manual therapy	Total	P value
		n=31	n=31	n=62	
Pre-Study	500 gr	1208.51 ± 1399.38	558.10 ± 587.82	883.30 ± 1113.78	p = 0.003
	1000 gr	1747.10 ± 1853.33	1433.60 ± 1972.64	1590.35 ± 1904.73	p = 0.898
	2000 gr	2123.17 ± 2314.62	1566.82 ± 1882.76	1844.99 ± 2111.12	p = 0.134
	4000 gr	2448.96 ± 1836.54	1922.49 ± 1571.98	2185.73 ± 1715.96	p = 0.333
After Study	500 gr	542.43 ± 655.22	407.38 ± 377.36	474.90 ± 534.61	p = 0.082
	1000 gr	513.91 ± 678.08	693.88 ± 741.49	603.90 ± 710.46	p = 0.424
	2000 gr	649.97 ± 404.20	717.73 ± 669.48	683.85 ± 549.49	p = 0.231
	4000 gr	1090.71 ± 800.21	1087.71 ± 1139.07	1089.21 ± 976.23	p = 0.315

500 grams (p=0.082), 1000 grams (p=0.424), 2000 grams (p=0.231) and 4000 grams (p=0.315). These findings showed that there was a significant difference between the group with and without manual therapy expertise only in the 500 gram analysis before the training session (Table 4).

According to the ANOVA test results, it was reported that there was no significant difference between the different levels of experience (0-5, 6-10 and 11-20 years). P-values were achieved for 500 grams (p=0.961), 1000 grams (p=0.291), 2000 grams (p=0.327) and 4000 grams (p=0.442). These findings showed that the experience level of a physiotherapist did not statistically affect the accuracy of pressure application. After a short training, the results of the statistical analysis changed. P-values were achieved for 500 grams (p=0.694), 1000 grams (p=0.262), 2000 grams (p=0.982) and 4000 grams (p=0.997).

DISCUSSION

The findings of this study indicate that there could be some differences in palpation pressure sensitivity among physiotherapists specialized in different fields, irrespective of their experience level. Despite the common assumption that increased experience and specialization in manual therapy will lead to greater success in the application of prescribed pressures, the data of this study suggest that these factors alone are insufficient for optimal palpation competence. These findings are in line with the views of Lavazza et al. (7) and Keating et al. (22) who found that consistent pressure application is influenced by a number of factors, including the therapist's expertise, experience and quality of training.

The results of our study revealed a significant change in pressure application sensitivity before and after the therapist's self-study. This difference is particularly evident in the significant difference (p=0.003) in the application of 500 grams of pressure at baseline between the therapy groups with and without manual therapy expertise, indicating the importance of specialized training interventions. The non-significant results obtained after training show that skill gaps can be filled effectively through appropriate training, consistent with the findings of Lavazza et al. (23), who emphasized the importance of targeted training programs and feedback added to these training programs in the development of palpation skills.

The lack of significant differences in the ability to apply palpation pressure between different levels of experience (0-5, 6-10 and 11-20 years) suggests that secondary factors such as training in palpation or manual therapy may play more critical roles. This situation is supported by the statement by Myburgh et al. (10) that "palpation sensitivity is necessary for the effectiveness of manual therapy". Significant improvements in pressure accuracy after a short training demonstrates the potential for rapid skill development through targeted interventions, regardless of previous experience levels.

This study provides insights into differences in palpation skills between physiotherapists with and without manual therapy experience and highlights the importance of palpation skills training (24,25). Our results suggest that the implementation of standardized training protocols can improve overall palpation accuracy by reducing variations in the literature. Effective palpation skills are critical for accurate diagnosis and treatment, and stand out as a fundamental parameter in manual therapy practice, as they significantly affect patient outcomes and comfort (11,26). Another contribution of the study to the literature is to contribute to ongoing studies on the need for standardized diagnosis and treatment protocols in physical therapy. Differences in palpation methods observed among physiotherapists with different levels of competence highlight the need for further academic research and the development of standard guidelines (20). This study provided findings that could contribute to the development of palpation skills and provided valuable information for future research and training programs aimed at improving treatment effectiveness.

In line with these findings, future studies should investigate the long-term effects of comprehensive training interventions on palpation skills. Additionally, examining the effect of standardized training protocols on different regions and practice standards may increase the generalizability of our results.

One of the strengths of this study is that it provided a comprehensive view of palpation skills by selecting participants with different levels of expertise and experience. Additionally, the use of an electronic scale for precise and objective pressure measurements increases the reliability of the findings. Furthermore, this study effectively demonstrated the potential for skill development through training by assessing pressure accuracy before and after a short training session. However, our study has some limitations. Focusing on physiotherapists in Turkey may limit the generalizability of the results as training and practice standards in other regions may differ. The short training period may not reflect the long-term effects of more comprehensive training programs on palpation skills. Furthermore, categorizing participants according to their self-reported experience may introduce bias as subjective assessments of skills and experience may differ.

CONCLUSION

This study highlights the importance of targeted training in improving palpation pressure accuracy among physiotherapists. While experience and expertise are valuable, they alone may not provide sufficient accuracy in palpation pressure. Consistent pressure skills can be significantly improved through specific training programs. Future research should examine the long-term effects of comprehensive training interventions and the establishment of standard protocols to further improve palpation skills. Precise palpation pressure is critical for effective diagnosis and treatment in manual therapy. Quality data from these initial steps will significantly contribute to overall treatment success by improving patient outcomes and comfort.

Ethical approval

This study has been approved by the Bolu Abant İzzet Baysal University Ethics Committee (approval date 22/11/2022, number 2022/305). Written informed consent was obtained from the participants.

Author contribution

Designed and coordinated the study idea: ÖOP; Concept: ÖOP, NY; Design: MFU; Data Collection or Processing: ÖOP, NY, BB, MAA; Analysis or Interpretation: ÖOP; Literature Search: NY, BB, MAA; Writing: ÖOP, NY, BB, MAA, MFU. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLE

Giftedness and allergy: A comparative study of the risk factors in gifted and typical children

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ABSTRACT

Aim: To compare the various parameters associated with giftedness and allergy in gifted children within their group and with typical children of average intelligence.

Methods: The case-control questionnaire study was conducted in Adıyaman, Türkiye, in April-May 2023. The study included 75 gifted and 190 typical children aged 6-14. The face-to-face survey consisted of 37 questions, 16 of which were added to the 21 questions of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3.

Results: The prevalence of recurrent ear infections in gifted children (33.3%) was found to be significantly higher than in typical students (20.5%) (P= 0.028). The rate of asthma in gifted students with recurrent ear infections (40%) was found to be significantly higher than the rate in gifted students without recurrent ear infections (16%) (P=0.022). The rate of allergic rhinitis in gifted students with food allergies (38.5%) was found to be significantly higher than the rate of those without food allergies (11.3%) (P=0.029). The high food selectivity (21.3%) of gifted students was found to be significantly higher than that of typical students (8.4%) (P=0.002). Among the gifted students, 50% of those who were very selective about food had asthma (P=0.014), and 37.5% had allergic rhinitis (P=0.029).

Conclusions: The study has shown the association between giftedness and various allergic conditions, suggesting that certain factors like recurrent otitis and food selectivity behavior may contribute to the higher prevalence of these conditions in gifted children.

Keywords: Gifted, talented, allergy, asthma, allergic rhinitis

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INTRODUCTION

There is no consensus among the terms "gifted", "talented", "highly talented", "gifted and talented", and "special talented" when defining individuals with higher intelligence and talent than the average population. These terms can be used interchangeably depending on the time, country, and geographic region (1).

Although there are various approaches, children who score two standard deviations above the mean on Intelligence Quotient (IQ) tests can be considered gifted (2). When a threshold value of IQ ≥ 130 is used, approximately 2.14% of the population falls into the gifted category. It is also possible to view giftedness as an above-average cognitive ability that interacts with other individual and environmental variables rather than relying solely on IQ. In such cases, a threshold value of IQ ≥ 120 is used, and the gifted population ranges from 5-8% (2,3). However, the definition of giftedness may differ from country to country (4). Gifted children exhibit superior cognitive abilities in maths, arts, and languages compared to moderately gifted peers and show marked differences in the physical, mental, and emotional domains (5).

Two-thirds of gifted children reported having various types of allergies (6). In a study conducted by Karpinski et al. (7), a comparison between gifted individuals and the average population revealed higher rates of asthma (15.4%, 7.4%), food allergy (9.6%, 3.7%), environmental allergy (33.2%, 10.6%), autism spectrum disorder (ASD) (1.2%, 1.0%), autoimmune disease (14.7%, 8.0%), depression (26.8%, 9.5%), and anxiety (20.0%, 10.9%). They attributed these findings to a psychoneuroimmunological mechanism, suggesting that gifted individuals experience physical and mental overexcitability. Their heightened awareness keeps them in a constant state of vigilance, leading to persistent activation of the sympathetic nervous system, which can negatively impact the immune system. Consequently, this heightened immune response may contribute to the development of autoimmune diseases and allergies (7).

Science and Arts Centers (SAC) in Türkiye are educational institutions affiliated with the Ministry of National Education. They cater to gifted students in pre-school, primary, secondary, and high school, offering specialized education in areas such as painting, music, or general mental abilities based on their selection through examinations. These institutions provide group education to children on weekdays and weekends, ensuring their formal education in traditional institutions is maintained (8).

This study aimed to compare allergic disorders, including asthma, allergic rhinitis, eczema, and food allergy, in gifted children at primary and secondary school age in Adıyaman, a southeastern province of Turkey, with typical children of average intelligence.

Additionally, the study was designed to compare various individual and environmental parameters associated with giftedness and allergy and socio-demographic characteristics with typical children of average intelligence. Moreover, the study aimed to compare these parameters, specifically among gifted students.

MATERIALS AND METHODS

Study design and population

This case-control questionnaire study was conducted in Adıyaman between April and May 2023. The case group consisted of gifted primary and secondary school students who studied at SAC alongside their traditional educational institutions. On the other hand, the control group included typical primary and secondary school students with average intelligence who attended solely traditional educational institutions. The study participants were children between the ages of 6 and 14. Those with any acute illness, individuals taking medication, individuals with epilepsy, Down syndrome, kidney failure, and similar chronic conditions were excluded from the study.

Data collection tools

ISAAC, an international study, introduced a three-phase questionnaire in 1995 by Asher et al. (9) to assess the prevalence and severity of asthma, rhinitis, and eczema in children. Phase 1 utilizes baseline questionnaires to evaluate the prevalence and severity of asthma and allergic diseases in specific populations.

Phase 2 investigates potential causal factors based on the findings from Phase 1. Phase 3 replicates Phase 1 to monitor prevalence trends. Phase 3 involves a questionnaire consisting of 8 questions for asthma, six for rhinitis, and seven for eczema (9). The Turkish translation of the ISAAC questionnaire was conducted by Oneş et al. (10) in 1997 to determine the prevalence of asthma in Istanbul.

In the present study, an additional 16 questions were incorporated into the existing 21 questions from ISAAC Phase 3. These additional questions included ten related to socio-demographic characteristics, four related to allergies, and two related to giftedness. The complete questionnaire consisted of 37 questions, and it was administered through face-to-face interviews. In the case group, 75 out of 100 children (75%) agreed to participate in the study, while in the control group, 190 out of 200 children (95%) volunteered to participate.

Ethics statement

The study was approved by multiple authorities. Specifically, the approval was obtained from the Adıyaman Provincial Health Directorate with the decision number E-13389845-051.08-206611150, dated January 9, 2023. Additionally, the Adıyaman Provincial Directorate of National Education granted approval with the decision number E-36700636-605.01-68004132, dated January 10, 2023. The study also received approval from the Adıyaman University Non-Interventional Research Ethics Committee with decision number 2023/1-3, dated January 24, 2023.

Since all participants in the study were under the age of 18, written consent was obtained from their families, indicating their agreement to participate. Moreover, all procedures were conducted following the principles outlined in the Declaration of Helsinki and by relevant local laws and regulations.

Statistical analysis

The analysis was conducted using the SPSS software package (SPSS Inc., Chicago, IL), version 22. Descriptive statistics were used to present categorical data as n and % values and continuous data as mean ± standard deviation (Mean ± SD) values. Chi-square analysis (Pearson Chi-square) was employed to compare categorical variables between groups. The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables, and the Mann-Whitney U test was utilized to compare paired groups. The statistical significance level for the analysis was set at $p<0.05$.

RESULTS

A total of 265 children participated in the study, 75 in the case group and 190 in the control group. In the case group, 56% were girls and 44% were boys, whereas, in the control group, 51.1% were girls and 48.9% were boys. There was no significant difference in gender between the two groups (p=0.468).

The mean age of the participants was 11.7 ± 2.2 years in the case group and 11.9 ± 1.6 years in the control group. There was no significant difference in age between the groups (p=0.271).

The number of siblings was significantly lower in the case group than in the control group (p<0.001). The income level of individuals in the case group was significantly higher than those in the control group (p=0.014). The rate of snoring, especially during respiratory tract infections, was significantly higher in the case group (32%) compared to the control group (16.8%) (p=0.025). The prevalence of recurrent ear infections was significantly higher in the case group (33.3%) than in the control group (20.5%) (p=0.028).

Regarding food selectivity, 22.7% of the individuals in the case group were not selective, 56% were selective, and 21.3% were highly selective. In the control group, 40% were not selective, 51.6% were selective, and 8.4% were highly selective. There was a significant difference in selectivity between the groups (p=0.002). The prevalence of food allergy in the case group (17.3%) was significantly higher than that in the control group (8.4%) (p=0.036). No significant differences were found between the groups in terms of other parameters (p>0.05) (Table 1, Table 2).

The prevalence of wheezing/whistling in the chest in the case group (32%) was significantly higher than the rate in the control group (18.4%) (p=0.017).

Table 1. Comparison of sociodemographic characteristics of the groups				
		Case (n=75)	**Control (n=190)**	**p**
Age, Mean ± SD		11.7±2.2	11.9±1.6	0.271 **
Maternal age, Mean ± SD		39.9±4.1	39.7±4.8	0.633 **
Father age, Mean ± SD		43.1±4.8	43.8±5.2	0.349 **
Total family income, Mean ± SD		53786.7±158125.1	27233.2±27279.3	**0.014 ** **
Number of siblings, Mean ± SD		1.9±.7	2.8±1.2	**<0.001 ** **
Gender	Female	42 (56%)	97 (51.1%)	0.468*
	Male	33 (44%)	93 (48.9%)	
School	Primary school	20 (26.7%)	61 (32.1%)	0.387 *
	Middle school	55 (73.3%)	129 (67.9%)	
Mother education status	Middle school and below	8 (10.7%)	34 (17.9%)	0,147 *
	High school and above	67 (89.3%)	156 (82.1%)	
Father education status	Middle school and below	4 (5.3%)	25 (13.2%)	0,066 *
	High school and above	71 (94.7%)	165 (86.8%)	

* Chi-square analysis, ** Mann Whitney U test was applied.

Table 2. Comparison of various characteristics of groups				
		Case (n=75)	**Control (n=190)**	**p**
Living place	Rural	2 (2.7%)	13 (6.8%)	0.246*
	Urban	73 (97.3%)	177 (93.2%)	
Tobacco smoke at home	Yes	22 (29.3%)	76 (40.0%)	0.105*
	No	53 (70.7%)	114 (60.0%)	
Presence of pets at home	Yes	14 (18.7%)	31 (16.3%)	0.646 *
	No	61 (81.3%)	159 (83.7%)	
Night snoring	Never	50 (66.7%)	153 (80.5%)	**0.025 ***
	Always	1 (1.3%)	5 (2.6%)	
	Only in the presence of respiratory infection	24 (32%)	32 (16.8%)	
Recurrent ear infection	Yes	25 (33.3%)	39 (20.5%)	**0.028 ***
	No	50 (66.7%)	151 (79.5%)	
Food selectivity behavior	I never select any food	17 (22.7%)	76 (40.0%)	**0.002 ***
	I am selective	42 (56%)	98 (51.6%)	
	I am very selective	16 (21.3%)	16 (8.4%)	
Food allergy	Yes	13 (17.3%)	16 (8.4%)	**0.036 ***
	No	62 (82.7)	174 (91.6%)	
Handedness	Right	68 (90.7%)	174 (91.6%)	0.812 *
	Left	7 (9.3%)	16 (8.4%)	

* Chi-square analysis, ** Mann Whitney U test was applied.

Similarly, the prevalence of wheezing/whistling in the chest during the past 12 months in the case group (26.7%) was significantly higher than the rate in the control group (10%) (p=0.001). The prevalence of physician-diagnosed asthma in the case group (24%) was significantly higher than the rate in the control group (13.2%) (p=0.031). Additionally, the prevalence of wheezing/whistling in the chest during the past 12 months in the case group (20%) was found to be significantly higher than the rate in the control group (10%) during the same period (p=0.028) (Table 3).

The prevalence of sneezing or a runny or blocked nose in the case group in the absence of cold/flu was significantly higher (60%) compared to the control group (41.6%) (p=0.007). Similarly, the prevalence of sneezing, or a runny or blocked nose in the absence of cold/flu in the last 12 months was significantly higher in the case group (36%) than the rate in the control group (23.2%) (p=0.033). The rate of accompanying itchy-watery eyes with these symptoms in the last 12 months was significantly higher in the case group (21.3%) than in the control group (11.6%) (p=0.041). Additionally, the rate of physician-diagnosed allergic

Table 3. Comparison of asthma questions according to groups

		Case	Control	p*
		Number (%)	Number (%)	
Have you ever had wheezing or whistling in the chest at any time in the past?	Yes	24 (32%)	35 (18.4%)	**0.017**
	No	51 (68.0%)	155 (81.6%)	
Have you had wheezing or whistling in the chest in the last 12 months?	Yes	20 (26.7%)	19 (10.0%)	**0.001**
	None	55 (73.3%)	171 (90.0%)	
How many attacks of wheezing/whistling have you had in the last 12 months?	None	2 (10.0%)	4 (21.1%)	0.083
	1-3	8 (40.0%)	12 (63.2%)	
	4-12	5 (25.0%)	3 (15.8%)	
	>12	5 (25.0%)	0	
In the last 12 months, how often, on average, has your sleep been disturbed due to wheezing?	Never	5 (25.0%)	7 (36.8%)	0.243
	Less than one night per week	8 (40.0%)	10 (52.6%)	
	One or more nights per week	7 (35.0%)	2 (10.5%)	
In the last 12 months, has wheezing ever been severe enough to limit your speech to only one or two words at a time between breaths?	Yes	11 (55.0%)	7 (36.8%)	0.256
	No	9 (45.0%)	12 (63.2%)	
Have you ever had physician-diagnosed asthma?	Yes	18 (24.0%)	25 (13.2%)	**0.031**
	No	57 (76.0%)	165 (86.8%)	
In the last 12 months, has your chest sounded wheezy during or after exercise?	Yes	15 (20.0%)	19 (10.0%)	**0.028**
	No	60 (80.0%)	171 (90.0)	
In the last 12 months, have you had a dry cough at night, apart from a cough associated with a cold or a chest infection?	Yes	37 (49.3%)	72 (37.9%)	0.088
	No	38 (50.7%)	118 (62.1%)	

* Chi-square analysis was applied.

rhinitis was significantly higher in the case group (16%) than in the control group (6.3%) (p=0.013) (Table 4).

The rate of physician-diagnosed eczema in the case group was 18.7%, while it was 13.2% in the control group, and no significant difference was found between the two groups (p=0.254) (Table 5).

Among gifted students, the prevalence of allergic rhinitis in rural areas (100%) was significantly higher than the rate of allergic rhinitis in urban areas (13.7%) (p=0.024). The prevalence of asthma in students who were exposed to tobacco smoke at home (40.9%) was significantly higher than the rate of asthma (17%) in students who were not exposed to tobacco smoke at

Table 4. Comparison of allergic rhinitis questions according to groups

		Case	Control	p *
		Number (%)	Number (%)	
Have you ever had a problem with sneezing, or a runny, or a blocked nose when you did not have a cold or the flu?	Yes	45 (60.0%	79 (41.6%)	**0.007**
	No	30 (40.0%)	111 (58.4%)	
In the past 12 months, have you had a problem with sneezing, or a runny, or a blocked nose when you did not have a cold or the flu?	Yes	27 (36.0%)	44 (23.2%)	**0.033**
	No	48 (64.0%)	146 (76.8%)	
In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?	Yes	16 (21.3%)	22 (11.6%)	**0.041**
	No	59 (78.7%)	168 (88.4%)	
In which of the past 12 months did this nose problem occur?	January	14 (51.9%)	22 (50.00%)	0.880
	February	13 (48.1%)	21 (47.7%)	0.973
	March	11 (40.7%)	20 (45.5%)	0.697
	April	9 (33.3%)	10 (22.7%)	0.327
	May	4 (14.8%)	6 (13.6%)	1.000
	June	3 (11.1%)	4 (9.1%)	1.000
	July	2 (7.4%)	2 (4.5%)	0.632
	August	1 (3.7%)	1 (2.3%)	1.000
	September	2 (7.4%)	3 (6.8%)	1.000
	October	3 (11.1%)	4 (9.1%)	1.000
	November	5 (18.5%)	7 (15.9%)	0.757
	December	8 (29.6%)	13 (29.5%)	1.000
In the past 12 months, how much did this nose problem interfere with your Daily activities?	Not at all	4 (14.8%)	7 (15.9%)	0.215
	A little	9 (33.3%)	24 (54.5%)	
	A moderate amount	10 (37.0%)	11 (25.0%)	
	A lot	4 (14.8%)	2 (4.5%)	
Have you ever had hay fever?	Yes	12 (16.0%)	12 (6.3%)	**0.013**
	No	63 (84.0%)	178 (93.7%)	

* Chi-square analysis was applied.

Table 5. Comparison of eczema questions according to groups

		Case	Control	p *
		Number (%)	Number (%)	
Have you ever had an itchy rash coming and going for at least six months?	Yes	7(9.3%)	7 (3.7%)	0.074
	No	68 (90.7%)	183 (96.3%)	
Have you had this itchy rash at any time in the last 12 months?	Yes	3 (42.9%)	2 (28.6%)	1.000
	No	4 (57.1%)	5 (71.4%)	
Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?	Yes	3 (42.9%)	2 (28.6%)	1.000
	No	4 (57.1%)	5 (71.4%)	
At what age did this itchy rash first occur?	Under two years	3 (42.9%)	2(28.6%)	1.000
	Age 2-4	2 (28.6%)	3 (42.9%)	
	Age 5 or more	2 (28.6%)	2 (28.6%)	
Has this rash cleared completely at any time during the last 12 months?	Yes	4 (57.1%)	2 (28.6%)	0.592
	No	3 (42.9%)	5 (71.4%)	
In the last 12 months, how often, on average, have you been kept awake at night by this itchy rash?	Never	66 (88.0%)	153 (80.5%)	0.240
	Less than one night per week	7 (9.3%)	33 (17.4%)	
	One or more nights per week	2 (2.7%)	4 (2.1%)	
Have you ever had physician-diagnosed eczema?	Yes	14 (18.7%)	25 (13.2%)	0.254
	No	61 (81.3%)	165 (86.8%)	

* Chi-square analysis was applied.

home (p=0.027). The prevalence of asthma in students with recurrent ear infections (40%) was significantly higher than the rate of asthma (16%) in students without recurrent ear infections (p=0.022). There was a significant difference in asthma among students based on their level of food selectivity, with 5.9% of non-selective students, 21.4% of selective students, and 50% of very selective students having asthma (p=0.014). Similarly, there was a significant difference in the occurrence of allergic rhinitis among students based on their level of food selectivity, with 5.9% of non-selective students, 11.9% of selective students, and 37.5% of very selective students having allergic rhinitis (p=0.029). The prevalence of food allergy did not show a significant difference among different levels of food selectivity, with 11.8% of non-selective students, 10.7% of selective students, and 9.4% of very selective students having food allergies (p=0.922). The prevalence of allergic rhinitis in students with food allergies (38.5%) was significantly higher than that in students without food allergies (11.3%) (p=0.029) (Table 6).

Table 6. Comparison of the presence of asthma, allergic rhinitis, and eczema according to various parameters in gifted students

		Presence of asthma		Presence of allergic rhinitis		Presence of eczema	
		Number (%)	p *	Number (%)	p *	Number (%)	p *
Gender	Female	10 (23.8%)	0.965	7 (16.7%)	0.859	6 (14.3%)	0.272
	Male	8 (24.2%)		5 (15.2%)		8 (24.2%)	
Living place	Rural area	2 (100%)	0.055	2 (100%)	**0.024**	1 (50%)	0.341
	Urban area	16 (21.9%)		10 (13.7%)		13 (17.8%)	
School	Primary school	6 (30%)	0.544	5 (25%)	0.284	4 (20%)	0.858
	Middle school	12 (21.8%)		7 (12.7%)		10 (18.2%)	
Tobacco smoke at home	Yes	9 (40.9%)	**0.027**	5 (22.7%)	0.318	2 (9.1%)	0.210
	No	9 (17%)		7 (13.2%)		12 (22.6%)	
Pets at home	Yes	4 (28.6%)	0.731	4 (28.6%)	0.220	2 (14.3%)	0.641
	No	14 (23.0%)		8 (13.1%)		12 (19.7%)	
Night snoring	Never	12 (24.0%)	0.848	6 (12%)	0.316	9 (18%)	0.805
	Always	0		0		0	
	Only in the presence of respiratory tract infection	6 (25%)		6 (25%)		5 (20.8%)	
Recurren ear infection	Yes	10 (40%)	**0.022**	7 (28%)	0.091	2 (8%)	0.122
	No	8 (16%)		5 (10%)		12 (24%)	
Food selectivity behavior	I never select any food	1 (5.9%)	**0.014**	1 (5.9%)	**0.028**	1 (5.9%)	0.292
	I am selective	9 (21.4%)		5 (11.9%)		10 (23.8%)	
	I am very selective	8 (50%)		6 (37.5%)		3 (18.8%)	
Food allergy	Yes	6 (46.2%)	0.069	5 (38.5%)	**0.029**	3 (23.1%)	0.699
	No	12 (19.4%)		7 (11.3%)		11 (17.7%)	

* Chi-square analysis was applied.

DISCUSSION

Numerous studies have indicated that the socioeconomic background, as well as the social, emotional, and cognitive status of individuals, have a positive effect on intelligence (11). In a study conducted in 2023, Bıçakçı (12) reported that the prevalence of giftedness is higher among individuals with higher economic incomes, those residing in urban areas, and those with highly educated parents. The current study found that the income level of families with gifted children was significantly higher than that of families with average children (p=0.014). However, no significant association was observed between giftedness and the education level of parents or the rural/urban residence of the children.

In the current study, gifted children were found to have a significantly lower number of siblings compared to typical children (p<0.001). However, it is worth noting that Coşkun's (13) study conducted in 2018 reported no significant association between the number of siblings and giftedness. Additionally, David and Landau[14] noted a decline in the number of siblings in gifted families between 1983 and 2003.

In the present study, no significant difference in handedness was found between gifted students and typical students. This finding aligns with the results of Papadatou-Pastou and Tomprou's (15) meta-analysis, which also concluded that there was no difference in handedness between gifted and typical individuals. However, it is important to note that Piro et al. (16) reported a higher rate of left-handedness among gifted students in their study.

In the present study, the rate of snoring in gifted students (32%) when they had a respiratory tract infection was found to be significantly higher than the rate of typical students (16.8%) (p=0.025). Nosetti et al. (17) reported that 35% of children with primary snoring have allergic rhinitis and that snoring increases when a respiratory tract infection occurs.

In addition, the rate of recurrent ear infections was found to be significantly higher in gifted children (33.3%) than in typical students (20.5%) in the present study (p=0.028). Previous studies have shown that many factors, such as genetics, environment, and allergies, including allergic rhinitis and asthma, play a role in snoring and recurrent ear infections (18,19).

In the present study, 22.7% of the gifted students were not selective in food, 56% were selective, and 21.3% were very selective. Among typical students, 40% were not selective in food, 51.6% were selective, and 8.4% were very selective. There was a significant difference in selectivity between the groups (p=0.002). Similar to our findings, Daniels and Piechowski (20) stated that food selectivity was high in gifted children. Neihart (21) also stated that gifted children prefer foods with specific textures.

Similar to the present study, Parker et al. (22) reported that the prevalence of allergy in gifted students was nearly twice that of typical students (32.4%, 18.2%), and the prevalence of asthma was more than twice as high (2.8%, 1.3%). Karpinski et al. (7) also found higher rates of asthma (15.4%, 7.4%), food allergy (9.6%, 3.7%), and environmental allergy (33.2%, 10.6%) in gifted individuals compared to the average population. Shichtman[23] stated that some studies have found a high prevalence of allergies in gifted individuals due to their high sensitivity, with allergy-related conditions such as dermatitis, allergic rhinitis, and asthma being more common. However, Fries et al. (24) reported that while the prevalence of certain diseases such as chronic fatigue syndrome, autism spectrum disorders, depression, anxiety, and irritable bowel syndrome was higher in gifted individuals compared to the average population, there was no difference in terms of asthma and allergies.

In the present study, there was no difference in the incidence of asthma and eczema based on the place of residence. However, the rate of allergic rhinitis (100%) in gifted students living in rural areas was found to be significantly higher than in those living in urban areas (13.7%) (p=0.024). In a systematic review and meta-analysis conducted by Song et al. (25), no difference in allergic rhinitis was found in children aged 0-18 years between those living in urban and rural areas. However, asthma was reported to be more prevalent in urban areas. On the other hand, Moitra et al. (26) stated that many allergic diseases, including allergic rhinitis, are more common in urban areas due to air pollution, gas, dust, and fumes.

In the present study, the prevalence of asthma was found to be significantly higher among gifted students who were exposed to tobacco smoke at home (40.9%) than among those who were not exposed to smoke at home (17%) (p=0.027). Despite the claim of no difference, many studies (27,28) argue that exposure to environmental tobacco smoke, primarily in the home, increases the prevalence of various allergic diseases, including asthma. He et al. (29) reported that exposure to tobacco smoke increases the risk of asthma by 24%.

In the present study, the prevalence of asthma was found to be significantly higher among gifted students with recurrent ear infections (40%) than among those without recurrent ear infections (16%) (p=0.022). Consistent with the present study, previous research indicates that otitis media, allergic rhinitis, and asthma are often associated with eustachian tube dysfunction, and children with recurrent otitis media are at a higher risk of developing asthma (30,31). Kim et al. (32) in their study, found a higher prevalence of asthma in the group with chronic otitis media when compared to the control group (17.5% vs. 14.3%, $p < 0.001$).

In the present study, the prevalence of asthma was 5.9% among gifted students who did not select food, 21.4% among those who were selective, and 50% among those who were very selective, with a significant difference observed between these groups (p=0.014). Similarly, allergic rhinitis was observed in 5.9% of those who did not select foods at all, 11.9% of those who were selective, and 37.5% of those who were very selective, with a significant difference between these groups (p=0.029). These findings suggest a strong association between food selectivity behavior and allergic disorders, specifically asthma and allergic rhinitis, in gifted students. Interestingly, the present study did not find a relationship between food selectivity behavior and food allergy.

In the present study, no significant difference was observed in the rates of asthma and eczema among gifted students with food allergies. However, the rate of allergic rhinitis was found to be significantly higher in individuals with food allergies (38.5%) compared to those without food allergies (11.3%) (p=0.029). These findings align with the observations of Pénard-Morand et al. (33) who reported a positive association between food allergy, asthma, and allergic rhinitis. Nutten (34) also highlighted that atopic dermatitis and food allergy often coexist and that the presence of atopic dermatitis and food allergy in early childhood increases the risk of developing allergic rhinitis and asthma later in life. Furthermore, Tan and Corren (35) emphasized that asthma, allergic rhinitis, food allergy, and atopic dermatitis share common mechanisms involving the triggering of specific IgE in the nose, lungs, gastrointestinal tract, and skin. Taken together, these findings support the notion of interconnectedness among these allergic conditions.

Factors that cause air pollution such as dust increase the risk of allergic reactions and related allergic diseases due to themselves and the chemical, biological, and mineralogic components they carry (36). The occurrence of two earthquakes in Adıyaman on February 6, 2023, destroying numerous buildings, led to the release of dust and smoke from debris. The subsequent air pollution from the debris removal and demolition of severely damaged buildings and new construction sites replacing the destroyed buildings may have contributed to increased allergic reactions among the children in the study or potentially led to the misdiagnosis of dust-related disorders as allergic diseases. It should be noted that only two out of the 75 gifted students in the study (2.67%) lived in rural areas, and both had asthma and also allergic rhinitis. This limited representation of the rural areas in the study may have reduced the statistical power to compare the differences between urban and rural areas. Many studies have reported that there are exacerbations of many allergic diseases, such as asthma, during the spring season in the northern hemisphere, including Türkiye (37). Another limitation of the study is that it was conducted in the spring, rather than in the winter after the earthquakes, when allergic symptoms and diseases are typically heightened.

The study revealed higher rates of food allergy, recurrent ear infections, food selectivity, physician-diagnosed allergic rhinitis, self-reported allergic rhinitis, and asthma among gifted children. Moreover, the study showed that gifted children with recurrent ear infections have a higher prevalence of asthma, those with food allergies have a higher prevalence of allergic rhinitis, and those with food selectivity, regardless of food allergy, have higher rates of asthma and allergic rhinitis. These findings highlight the association between giftedness and various allergic conditions, suggesting that certain factors like recurrent otitis and food selectivity behavior may contribute to the higher prevalence of these conditions in gifted children.

Ethical approval

This study has been approved by the Adıyaman University Non-Interventional Research Ethics Committee (approval date 24/01/2023, number 2023/1-3). Written informed consent was obtained from the participants.

Author contribution

Concept: EÖ, OK; Design: MT, FEK; Data Collection or Processing: OK, HA; Analysis or Interpretation: OK, FB; Literature Search: EÖ, HT; Writing: EÖ, OK, OK. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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NORTHWESTERN MEDICAL JOURNAL

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RESEARCH ARTICLE

The effect of lopinavir - ritonavir on mortality in COVID-19 pneumonia

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ABSTRACT

Aim: COVID-19 is a lethal disease for which there is still no specific treatment. The study aims to retrospectively investigate the effect of adding lopinavir/ritonavir to the treatment of patients using favipiravir (in the ward or intensive care unit) on mortality.

Methods: This study was conducted in 181 Rt-PCR(+) adult patients with severe and critical COVID-19. Demographic and laboratory data, antiviral agents used in treatment (with or without lopinavir-ritonavir), presence of intubation, and clinical outcome were recorded. The patients were categorized into Group 1 (not receiving lopinavir-ritonavir), Group 2 (administered lopinavir-ritonavir in ward), and Group 3 (administered lopinavir-ritonavir in the intensive care unit).

Results: The lowest mortality rate was found with Group 2 (21.4%) while this rate was 77.9% for Group 3 and 42.3% for Group 1 ($p<0.001$). There was no significant difference in length of hospital stay among groups ($p>0.05$). While 35.2% (25 patients) of Group 1 needed intubation, this rate was 21.4% (9 patients) in Group 2 ($p<0.001$).

Conclusions: This study demonstrated that lopinavir / ritonavir treatment reduced mortality and the need for intubation when initiated before the critical pneumonia phase. Lopinavir/ritonavir may be useful in the treatment of COVID-19, especially as part of the combination regimen.

Keywords: COVID-19, Lopinavir / ritonavir, pneumonia

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INTRODUCTION

The fatality rate of COVID-19 cases is 3.4% worldwide, which is higher than that of seasonal flu (1). There is no specific treatment for this lethal disease, and pharmacological agents are urgently needed. Lopinavir is an inhibitor of human immunodeficiency virus (HIV) type 1 aspartate protease and was approved for severe acute respiratory syndrome (SARS) infection in 2003. Ritonavir is combined with lopinavir to increase plasma half-life by inhibiting cytochrome P450 (2). In vitro studies have shown that lopinavir/ritonavir is effective against SARS-CoV-2 at acceptable concentrations (3).

In light of this information, this study was conducted to retrospectively examine the efficacy of adding lopinavir-ritonavir as an antiviral agent would prove in reducing mortality with the treatment of favipiravir continued for 10 days in the cases where pneumonia showed a progressive trend and inflammation markers continued to increase.

METHODS

Study design and participants

This study is a single-center, retrospective study, and it was conducted on patients hospitalized in the ward and intensive care unit at Izzet Baysal State Hospital (Bolu, Turkey). 181 Rt-PCR (+) adult patients with severe and critical COVID-19 pneumonia in line with WHO Interim guidance (3) were included as participants in the study.

Patients under 18 years of age, pregnant, and postpartum were not included in the study. The demographic and laboratory data of the patients, antiviral medications used, presence of intubation, and treatment results were recorded retrospectively. Favipiravir (2x1600 mg/day loading, 2x 600 mg/day maintenance) was given routinely to all patients, and lopinavir-ritonavir was added to some of the patients who developed severe or critical pneumonia despite using Favipiravir treatment. The patients were categorized as Group 1 (not receiving lopinavir-ritonavir), Group 2 (administered lopinavir-ritonavir in the ward), and Group 3 (administered lopinavir-ritonavir in the intensive care unit). Informed consent was obtained from the patients, and ethics committee approval was granted from the hospital (Date: 05.01.2021 / No: 2020/325).

Data collection

Laboratory data of the patients (complete blood count, biochemical parameters, coagulation parameters, procalcitonin) antiviral drug treatments (with and without lopinavir-ritonavir), length of hospital stay, and presence of intubation were recorded.

Outcomes

The primary outcome is mortality from hospital treatment. The secondary outcome is the length of stay in the hospital.

Statistical analysis

The data obtained in the study was analyzed in the SPSS 20 software. The normality of distribution was tested based on the coefficients of skewness and kurtosis with the ± 2 intervals in addition to the Kolmogorov-Smirnov test (4). One-way ANOVA test was used in comparing the arithmetic means of the groups with normal distribution. For the difference between groups, the Scheffe test was used if the variances were homogeneous; on the other hand, the Games-Howell test was used if the variances were not homogeneous. The Kruskal-Wallis test was used in comparing the medians of the groups that did not show normal distribution. Bonferroni correction was made to determine the difference when the difference between groups was significant. The relationship between categorical variables was examined by Chi-Square analysis. $p<0.05$ was determined as the level of statistical significance.

RESULTS

The mean age of the patients was 67.46 ± 14.09 years, and the mean age in Group 1 and Group 3 was significantly higher than that of Group 2 ($p<0.05$) (Table 1). Troponin values of Group 1 and 3 were found to be significantly higher than group 2 ($p<0.05$), but

no significant difference was found between Group 1 and 3 (p>0.05). Procalcitonin values of Group 3 were significantly higher than those in Group 2 (p<0.05). There was no significant difference between the other groups (p>0.05) (Table 2).

Table 1. Relationship of groups with gender, intubation and mortality

	Group 1 (n=71, 39.2%)	Group 2 (n=42, 23.2%)	Group 3 (n=68, 37.6%)	All patients (n=181)	x^2 value	p-value
Gender					2.496	0.287
Female	18 (25.4%)	16 (38.1%)	24 (35.3%)	58 (32.0%)		
Male	53 (74.6%)	26 (61.9%)	44 (64.7%)	123 (68.0%)		
Intubation					86.398	0.000*,1
Yes	25 (35.2%)	9 (21.4%)	68 (100%)	102 (56.4%)		
No	46 (64.8%)	33 (78.6%)	0 (0.0%)	79 (43.6%)		
Mortality					36.614	0.000*,1
Cured	41 (57.7%)	33 (78.6%)	15 (22.1%)	89 (49.2%)		
Exitus	30 (42.3%)	9 (21. %4)	53 (77.9%)	92 (50.8%)		

* p<0.05 statistically significant, [1] Chi-Square test

Table 2. Mean ± SD values of laboratory values

	Group 1 (n=71, 39.2%)	Group 2 (n=42, 23.2%)	Group 3 (n=68, 37.6%)	All patients (n=181)	p-value
$\bar{x}$ ± SS					
Age	68.62±12.22[a]	58.38±14.97[b]	71.85±12.97[c]	67.46±14.09	**0.000*,1 a>b (0.000) c>b (0.000)**
CRP (mg/L)	99.38±39.64	89.26±44.78	92.82±48.85	94.5±44.42	0.466
Ferritin (ug/L)	540.46±428.17	391.30±329.59	496.69±404.79	489.28±400.33	0.158
Median (Q1-Q3)					
Length of stay	12 (7-22)	9 (6-15)	9 (5-13.5)	10 (6-18)	0.060
D-Dimer (mg/L)	0.42 (0.21-1.13)	0.43 (0.16-0.75)	0.48 (0.27-1.13)	0.44 (0.22-1)	0.532
Troponin (ng/L)	13.7 (7.1-35.8)[a]	7.35 (4.9-15)[b]	19.5 (10-40.2)[c]	12.55 (6.6-30.08)	**0.000*,2 a>b (0.008) c>b (0.000)**
Lymphocyte (K/uL)	0.7 (0.4-1)	0.8 (0.5-1.4)	0.8 (0.5-1.15)	0.7 (0.5-1.1)	0.122
Lymphocyte % (K/uL)	9.9 (5.3-18.1)	10.7 (7-15.9)	9.8 (4.4-14.3)	10 (5.3-16.2)	0.193
LDH (U/L)	440 (332-610)	477 (384-585)	451 (321-586)	467.5 (335.5-591.25)	0.547
Procalcitonin (ng/mL)	0.14 (0.05-0.62)[a]	0.115 (0.045-0.32)[b]	0.31 (0.1-0.99)[c]	0.17 (0.06-0.68)	**0.007*,2 c>b (0.011)**
Thrombocyte (K/uL)	193 (139-262)	216 (173-285)	199.5 (144-255.5)	207 (149-263.5)	0.189

* p<0.05 Statistically significant, [1] One-Way ANOVA, [2] KWH:Krukal-Wallis H test

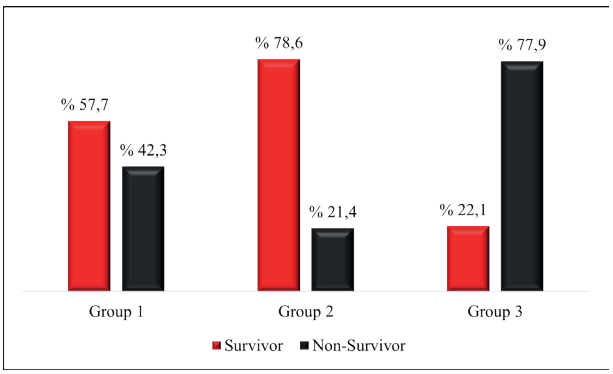

Figure 1. Mortality rates in treatment groups.

The mortality rate in Group 3 (53 patients, 77.9%) and Group 1 (30 patients, 42.3%) is significantly higher than in Group 2 (9 patients, 21.4%) (p <0.05) (Figure 1). While the need for intubation was 35.2% in group 1, this rate was found to be 21.4% in Group 2 during the clinical observation (p<0.05). Lopinavir/ritonavir was added to the treatment of Group 3 while the patients in this group were already intubated. There was no significant difference in length of hospital stay between groups (p>0.05).

DISCUSSION

In COVID-19, antivirals (lopinavir-ritonavir, remdesivir, interferons, chloroquine, and hydroxychloroquine), anti-inflammatory agents (glucocorticoids, tocilizumab), immunotherapy (convalescent plasma) and adjuvant treatments (herbal medicine, hormones, mesenchymal stem cells) are emphasized (5).

Favipiravir is a nucleotide analogue and RNA polymerase inhibitor, and it is included in the standard treatment in the COVID-19 Guide of the Ministry of Health in our country (6). While the patients included in the study were using favipiravir (2x1600 mg/day loading, 2x600 mg/day maintenance), they were hospitalized in the service or intensive care unit due to the progress of severe or critical COVID-19 pneumonia. While Favipiravir treatment of all patients was completed within 10 days, Lopinavir 200 mg/ritonavir 50 mg (2x400/100 mg, oral) was added to the treatment of one group of patients. The patients were categorized into Group 1 (not receiving lopinavir-ritonavir), Group 2 (administered lopinavir-ritonavir in the ward), and Group 3 (administered lopinavir-ritonavir in the intensive care unit).

The mean age of the patients was 67.46 ± 14.09 years, and the mean age in group 1 and group 3 was significantly higher than in group 2 (p<0.05). The Centers for Disease Control (CDC) indicate that age is a risk factor for severe diseases and complications (7).

Troponin values of Group 1 and 3 were found to be significantly higher than group 2 (p<0.05), but no significant difference was found between Group 1 and 3 (p>0.05). Guo et al. (8) found troponin increase in 27.3% of the patients hospitalized with the diagnosis of COVID-19 and reported increased hospital mortality in those patients as compared to the patients with normal troponin values. (59.6 % and % 8,9, p<0.001).

Procalcitonin values were significantly higher in Group 3 than in Group 2 (p<0.05). There was no significant difference between the among groups (p>0.05). In the meta-analysis study by Lippi et al. (9), it was reported that the risk of serious SARS-CoV-2 infection increased approximately 5-fold with increasing procalcitonin values. Procalcitonin levels could be an indicator of the severe course of COVID-19 (10).

The mortality rate in Group 3 (53 patients, 77.9%) and Group 1 (30 patients, 42.3%) was significantly higher than Group 2 (9 patients, 21.4%) (p<0.05). There was no significant difference between the three groups in terms of length of hospital stay (p>0.05). This result shows that adding lopinavir/ritonavir to the treatment does not increase the cost of hospitalization. While 35.2% (25 patients) of the participants in Group 1 needed intubation, this rate was 21.4% (9 patients) in Group 2 during clinical observation (p<0.05). Lopinavir/ritonavir was added to the treatment of the patients in group 3 while they were already under intubation. Mortality after intubation is generally quite high in COVID-19. One cohort study reported 32 mortalities out of 33 intubated patients (97%) (11), while another cohort study reported 30 mortalities out of 37 patients (81%) (12).

In a randomized controlled study, no significant relationship was found between lopinavir-ritonavir treatment and mortality or clinical improvement in COVID-19 as compared to standard support therapy. However, in the group receiving lopinavir-ritonavir, the need for non-invasive or invasive mechanical ventilation for serious complications (including acute kidney injury and secondary infections) and respiratory failure was reported to be less than in the group receiving no treatment (13).

Some studies also report that lopinavir–ritonavir treatment does not have any positive effects (13) and that this treatment does not cure clinical outcomes in patients hospitalized with the diagnosis of COVID-19 (14).

In the study comparing favipiravir and lopinavir/ritonavir treatment, viral clearance time was shorter and radiological improvement was higher in the favipiravir group (15). However, there are no studies on favipiravir and lopinavir/ritonavir combination. It has been reported to be beneficial in only 3 disease case series (16). However, combinations with other agents have been studied. For example, when lopinavir/ritonavir, hydroxychloroquine and interferon-b-1b were given to 5 severe cases of COVID-19 pneumonia, all patients recovered, and no significant side effects were observed (17).

CONCLUSIONS

These clinical studies are generally conducted on small numbers of cases and are not placebo-controlled, therefore additional studies are needed. The study showed that when lopinavir/ritonavir treatment is initiated in the ward prior to the onset of critical pneumonia stage, it reduces mortality and the need for intubation. In conclusion, lopinavir / ritonavir may be useful in the treatment of COVID-19, especially as part of the combination regimen.

Ethical approval

This study has been approved by the Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee (approval date 05.01.2021, number 2020/325). Written informed consent was obtained from the participants.

Author contribution

Concept: MED, EA, MB; Design: MED, EA, MB; Data Collection or Processing: MED, EA, MB; Analysis or Interpretation: MED, EA, MB; Literature Search: MED, EA; Writing: MED, EA, MB. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLE

Evaluation of auditory middle latency response during the menstrual cycle

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ABSTRACT

Aim: The hormone levels during the menstrual cycle, directly and indirectly, affect the hearing system. In our study, it was aimed to examine the effects of changing hormone levels during the menstrual cycle on auditory middle latency responses in healthy individuals with different stimuli types and the psychosomatic effects of premenstrual complaints on auditory performance.

Methods: In the study, 20 healthy women aged 18-35 years, with regular menstrual cycles and no auditory or vestibular complaints were evaluated for auditory middle latency responses with click and level-specific (LS) CE-Chirp® stimuli during the menstruation period of the follicular phase (1-5 day, menstrual phase), the ovulation phase (14-17 day) and the luteal phase (21-28 day). To evaluate the effect of premenstrual complaints on auditory performance, the participants were asked 5 questions.

Results: In the auditory middle latency assessment with click stimuli, a statistically larger Na-Pa amplitude was obtained in the menstruation phase compared to the ovulation phase in both ears. In the auditory middle latency evaluation with LS CE-Chirp® stimulus, statistically shortened Nb latencies were obtained in the right ear in the menstruation phase compared to the ovulation phase.

Conclusion: Although the clear effect of changing gonadal hormone levels on auditory evoked middle latency responses could not be determined, the findings show that neural transmission increases in the menstrual phase when the estrogen level is low. Click stimulus is more sensitive to hormonal changes, and the use of click stimulus has been recommended in the later side of lesion studies. In our study, no psychosomatic effect of complaints in the premenstrual period on auditory performance was observed.

Keywords: auditory middle latency response, menstrual cycle

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INTRODUCTION

Auditory evoked middle latency responses (AMLR) are electrical potentials of the thalamocortical area measured by electrodes placed on the scalp at 10-50 ms after auditory stimulation (1). AMLR consists of Po, Pa, Pb, Pc positive and Na, Nb, Nc negative peaks (2). It is utilized in clinics to estimate behavioral hearing thresholds, localize brain lesions (thalamocortical area), diagnose auditory processing problems, and evaluate cochlear implant candidates. AMLR is also used to evaluate auditory system development with the Pb wave, which is a biomarker of auditory system maturation (3). Many factors affect AMLR, including hormonal changes (4).

Menstrual cycle refers to the 28-day periods that begin in the menarche and continue until menopause in women. These 28-day periods consist of follicular, ovulation, and luteal phases; many hormonal changes are observed during these phases. During the menstrual cycle, the main changes occur in the production of the female ovarian hormones estrogen and progesterone (5). Changing hormone levels during the menstrual cycle have been proven in studies to have direct and indirect effects on the cochlea and central auditory system (6). The presence of estrogen receptors in inner and outer hair cells, spiral ganglion, stria vascularis, and brain explains this situation (7). The precise effect of estrogen and progesterone on the auditory system is unknown. However, estrogen causes changes in cochlear blood flow and affects the auditory system and central nervous system by increasing the production of neurotransmitters such as glutamate, dopamine, and GABA (8,9). Furthermore, there is evidence that estrogen influences brain volume (10). According to another research, premenstrual symptoms that begin 7-10 days before menstruation, as well as the link between estrogen and the limbic system, cause changes in auditory function (11).

Although the effects of changing estrogen and progesterone levels on the auditory system during the menstrual cycle in the literature have been mostly examined at the brain stem and cortical levels, there are limited studies examining AMLR (12,13). Considering that gonadal hormone receptors are localized in different parts of the auditory system, it is predicted that different effects may occur in different parts of the central auditory system. Due to the limited number of studies examining the effects of changing hormone levels on AMLR during the menstrual cycle, our study aimed to investigate the effect on the thalamocortical level in different phases of the menstrual cycle in healthy individuals, to compare the sensitivity of different stimuli types to hormonal changes, and to examine the psychosomatic effect of premenstrual complaints on auditory performance (12,13).

MATERIALS AND METHODS

The clinical trial was conducted at Bezmialem Vakif University, Audiology Clinic. Permission was obtained from the Non-Interventional Ethics Committee of Bezmialem Vakif University to conduct the study (Ethics Committee No: 2022/15). It was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Twenty healthy women between 18-35 years of age with menstrual bleeding at 21/35-day intervals were included in the study (14). The study's inclusion criteria are as follows: normal otoscopic evaluation findings, presence of bilateral Type-A tympanogram and ipsilateral and contralateral acoustic reflexes at 500-1000-2000-4000 Hz in immitancemetric evaluation, pure tone hearing thresholds of 15 dB HL or less at octave frequencies between 250-8000 Hz and being right-handed. Subjects with neurological, psychiatric, metabolic disease, dizziness, or using oral contraceptives were excluded from the study.

The acoustic immittance measurement was performed with the GSI Tymp Star Pro (Grason-Stadler, Minnesota, USA) clinical tympanometer device. Acoustic immittance tests included 226 Hz tympanometry, and thresholds for ipsilateral and contralateral acoustic reflexes at 500Hz, 1000Hz, 2000Hz, and 4000Hz.

The Madsen Astera 2 (GN Otometrics, Denmark) or the AC40 (Interacoustics, Eden Prairie, MN) clinical audiometry was used for audiometric evaluation. Pure tone audiometry was performed at frequencies of 250, 500, 1,000, 2,000, 4,000, 6,000, and 8,000 Hz via TDH39 supra-aural headphones. Bone conduction was tested at 500, 1,000, 2,000, and 4,000 Hz via a B71 bone conductor.

AMLR

An Interacoustics Eclipse EP25 (Middelfart, Denmark) was used for AMLR. AMLR was performed three times with click and LS CE-Chirp® stimuli during the menstrual period:1st the follicular phase when estrogen levels were low (1-5 days, menstrual phase), 2nd the ovulation phase when estrogen levels were high (14-17 days), and 3rd the luteal phase when progesterone hormone was dominant (21-28 days) (5). ER-3A insert earphones were placed in the outer ear canal of the participants to transmit the sounds. Click and LS CE-Chirp® were presented to the patient at 70 dB nHL, at the rate of 6.1, in alternating polarity. Absolute latencies of Na, Pa, Nb, Pb waves, Na-Pa interwave latencies, and amplitudes of wave Na-Pa were determined.

5 questions prepared by the researchers, including complaints in the premenstrual period

To assess the psychosomatic influence of premenstrual period complaints on the auditory system, participants were led to 5 questions created by the researchers, in which their premenstrual period complaints were appraised (Table 1). Participants gave yes/no answers to the first 4 questions. They rated the last question on a scale of 0 to 5.

Data analysis

Descriptive statistics of the parameters were calculated using IBM SPSS Statistics 22.0 program. The sample size was set at a minimum of 20 to provide 80% power at the 95% confidence level. Statistical significance was set at $p<0.05$. The distribution of the data was analyzed by using the Shapiro-Wilk test. The analysis of normally distributed data was done with the T- test, and the analysis of the non-normally distributed data was done with the Mann- Whitney U test.

RESULTS

In the study, AMLR was evaluated with click and LS CE-Chirp® stimuli in different phases of the menstrual cycle. Absolute latencies of Na, Pa, Nb, Pb waves, Na-Pa interwave latencies, and amplitudes of wave Na-Pa were evaluated.

The Na, Pa, Nb, Pb absolute latencies and Na-Pa interwave latencies values obtained in the right and left ears in the AMLR evaluation performed with a click stimulus in different phases are given in Table 2. In the evaluation of AMLR with a click stimulus, no significant difference between the phases was obtained in the Na, Pa, Nb, Pb wave absolute latencies and Na-Pa interwave latencies values in the right and left ears.

In Figure 1, there is an AMLR wave obtained with a click stimulus in different phases. The blue wave indicates the menstrual phase, the light gray wave indicates the ovulation phase and the orange wave indicates the luteal phase.

Table 1. 5 questions prepared by the researchers, including complaints in the premenstrual period

Are you easily irritated during your premenstrual period? (Yes/No)
Does your appetite grow during your premenstrual period? (Yes/No)
Do you have difficulty focus on in the premenstrual period? (Yes/No)
Does your desire to eat chocolate foods increase during the premenstrual period? (Yes/No)
How much does your mood change in the premenstrual period affect your life? (Score 1 to 5)

Table 2. Na, Pa, Nb, Pb wave absolute latencies and Na-Pa interwave latencies in the right and left ears in different phases in the auditory middle latency evaluation with click stimulus

Parameter And Evaluated Ear (Mean±SD)		Menstrual Phase	Ovulation Phase	Luteal Phase	p value
Na Latency (ms)	Right	15,01 ± 2,76	15,85 ± 1,97	15,71 ± 2,68	0,127
	Left	15,06 ± 2,81	15,7 ± 2,5	15 ± 2,63	0,081
Pa Latency (ms)	Right	26,28 ± 4,24	28,1 ± 5,34	26,53 ± 4,72	0,178
	Left	27,08 ± 6,46	27,58 ± 3,24	26,10 ± 4,44	0,622
Nb Latency (ms)	Right	41,26 ± 4,49	42,5 ± 7,63	40,88 ± 5,7	0,311
	Left	41,98 ± 6,77	42,74 ± 6,25	42,95 ± 6,20	0,595
Pb Latency (ms)	Right	56,36 ± 6,27	57,6 ± 6,83	55,18 ± 12,96	0,698
	Left	57,29 ± 6,61	56,65 ± 6,36	58,6 ± 7,42	0,168
Na-Pa Latency (ms)	Right	11,26 ± 3,07	12,55 ± 5,01	10,81 ± 3,81	0,786
	Left	12,01 ± 4,38	11,38 ± 3,86	11,1 ± 3,04	0,183

The Na, Pa, Nb, Pb absolute latencies and Na-Pa interwave latencies values obtained in the right and left ears in the AMLR evaluation performed with an LS CE-Chirp® stimulus in different phases are given in Table 3. Statistically shortened Nb latencies in the right ear were obtained in the menstrual phase compared to the ovulation phase in the auditory middle latency measurement recorded with LS CE-Chirp® stimuli in different phases (p=0,011) (Table 3).

The Na-Pa amplitude values obtained in the right and left ears in the AMLR evaluation performed with a click and LS CE-Chirp® stimulus in different phases are given in Figure 2. In the evaluation of AMLR with click stimulus, statistically larger Na-Pa amplitude was obtained in both ears in the menstrual phase compared to the ovulation phase (right ear p= 0,011) (left ear p= 0,002) (Figure 2).

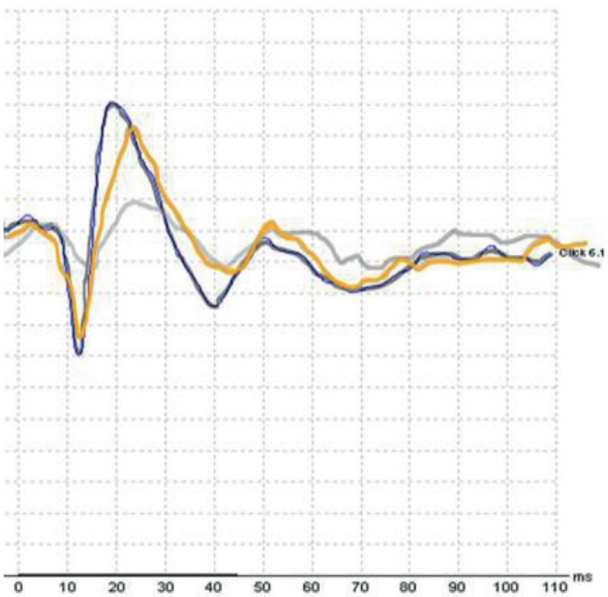

Figure 1. AMLR waves obtained with click stimulus in different phases (The blue wave; menstrual phase, the light gray wave; ovulation phase, and the orange wave; luteal phase).

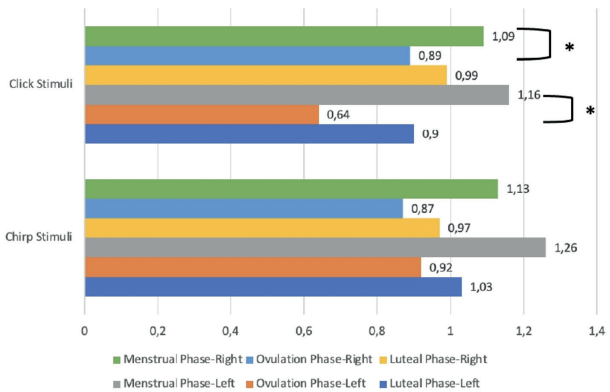

Figure 2. Na-Pa amplitude value in the right and left ears in different phases in the auditory middle latency evaluation with click and LS CE-Chirp® stimulus

*Indicates values are significant at the 0.05 level.

Table 3. Na, Pa, Nb, Pb wave absolute latencies and Na-Pa interwave latencies in the right and left ears in different phases in the auditory middle latency evaluation with LS CE-Chirp® stimulus

Parameter And Evaluated Ear (Mean±SD)		Menstrual Phase	Ovulation Phase	Luteal Phase	p value
Na Latency (ms)	Right	15,06 ± 2,31	16,3 ± 2,1	15,55 ± 2,03	0,302
	Left	15,73 ± 4,1	15,36 ± 2,85	15,25 ± 2,92	0,779
Pa Latency (ms)	Right	26,38 ± 3,54	27,61 ± 3,84	27,48 ± 3,93	0,271
	Left	26,58 ± 5	27,89 ± 3,91	27,46 ± 4,9	0,529
Nb Latency (ms)	Right	**39,78*** ± 5,98	41,46 ± 9,02	42,29 ± 7,08	**0,011***
	Left	41,75 ± 7,71	42,83 ± 6,98	42,53 ± 8,37	0,815
Pb Latency (ms)	Right	57,18 ± 8,53	58,58 ± 7,61	57,83 ± 9,26	0,619
	Left	56,13 ± 8,32	59,88 ± 9,06	57,71 ± 7,71	0,784
Na-Pa Latency (ms)	Right	11,55 ± 2,51	11,31 ± 3,53	11,91 ± 3,92	0,861
	Left	11,54 ± 3,57	12,53 ± 3,38	12,2 ± 3,72	0,618

Table 4. Answers to questions directed to participants

Questions	Yes	No
Are you easily irritated during your premenstrual period?	80%	20%
Does your appetite grow during your premenstrual period?	85%	15%
Do you have difficulty focus on in the premenstrual period?	65%	35%
Does your desire to eat chocolate foods increase during the premenstrual period?	85%	15%
How much does your mood change in the premenstrual period affect your life?	Minimum score: 2 Maximum score: 5 Mean score:3,35	

The answers to the questions directed to the participants are given in Table 4.

DISCUSSION

The study was conducted to evaluate the effects of hormonal changes during the menstrual cycle on AMLR in healthy individuals, to compare the sensitivity of stimulus types to intrinsic factors, and to examine the psychosomatic effects of premenstrual complaints on auditory performance. The AMLR test with a click and LS CE-Chirp® stimuli was performed on the participants in the menstrual phase, ovulation phase, and luteal phase. In the AMLR test performed with a click stimulus, a larger Na-Pa amplitude was obtained in both ears in the menstrual phase compared to the ovulation phase. This is explained by the decrease in estrogen levels in the menstrual phase causing an increase in neural transmission (15). In addition, Prabhu et al. (16) examined the impact of changing hormone levels in the menstrual cycle on the frequency following response (FFR). In the study, larger amplitudes and shorter latencies were obtained in the menstrual phase, and these results supported that the decrease in estrogen level, similar to our study, increases neural transmission.

In the evaluation of AMLR with LS CE-Chirp® stimulus, Nb latency was shortened in the menstrual phase compared to the ovulation phase in the right ear. We think that the shortened Nb latency obtained in the right ear during the menstrual phase may be related to the increase in the right ear advantage due to a decrease in estrogen level. In the literature, there were studies in which the auditory brainstem latency and middle and late latency are shortened during the menstrual phase (4,17). This is explained by the fact

that there is a decrease in the production of GABA, an inhibitory neurotransmitter, as a result of a decrease in estrogen levels in the menstrual phase, and an increase in neural transmission (17).

While some studies in the literature suggest that estrogen reduces neuronal transmission, other studies suggest the exact reverse (12,13). Khaliq et al. (12) examined the AMLR responses after estrogen replacement therapy in 32 postmenopausal women, statistically shortened Po, Na, and Pa latencies were obtained after estrogen replacement in the participants. Kilicdag et al. (18) also found that estrogen therapy reduces aging in postmenopausal women. In the literature, it has been observed that there is a shortening of auditory brainstem responses, improvement in dichotic listening, understanding in noise, and working memory performance in the ovulation phase when the estrogen level is high (11,19,20). This is explained by the fact that increased estrogen levels increase dopamine and glutamate production and contribute to auditory processing (20,21). Also, Tucker et al. (22) examined AMLR according to gender and found prolonged wave latencies in males and larger amplitudes in females. This condition has been associated with high estrogen levels in women.

Atcherson et al. (23) compared chirp, click, and tone burst stimuli in AMLR. Although they thought that the peak-peak amplitude values would be large in the chirp stimulus, they did not find a difference between the stimuli. In our study, the sensitivity of click and LS CE-Chirp® stimuli to hormonal changes was examined. The increase in bilateral Na-Pa amplitude obtained during the menstrual phase in the AMLR evaluation with click stimulus suggested that click stimulus is more sensitive to intrinsic factors and may be preferred in the subsequent site of lesion studies. Studies have also found that AMLR responses may influence depending on right-left handedness and that Pb latency is prolonged in left-handed individuals (24-26). This difference has been reported to be related to anatomical and functional differences in left-handed individuals (26). Considering the studies in the literature, left-handed individuals were not included in our study.

Most of the participants in the 5 questions prepared by the researchers; stated that they are prone to irritability in the premenstrual period, their appetite is increased, their desire to eat chocolate increases and they experience distraction. With the scores given, the participants showed that mood changes in the premenstrual period significantly affected their lives. Carneiro et al. (11) found that complaints such as anxiety, mood change, and irritability in the premenstrual period affect the results of the dichotic test and that the right ear advantage decreases in the luteal phase, which includes the premenstrual period. Considering that AMLR is affected by the attention state of individuals, it is thought that AMLR responses due to distraction complaints occurring in the premenstrual period may be affected and mood changes in this period may cause a psychosomatic effect on the auditory system (27). However, in our study, no significant difference was observed in wave latencies in the luteal phase, which includes the premenstrual period.

CONCLUSION

There are many studies in the literature showing that changing hormone levels during the menstrual cycle affect the auditory system. Although the clear effect of changing gonadal hormone levels on AMLR could not be determined in our study, the findings show that neural transmission increases in the menstrual phase when the estrogen level is low.

In our study, evaluation was performed with click and LS CE-Chirp® stimuli. An increase in bilateral Na-Pa amplitude was observed in the menstrual phase compared to the ovulation phase in the evaluation with click stimuli. This demonstrated the sensitivity of click stimulus to intrinsic factors and suggested that click stimulus may be preferred in the future site of lesion studies.

Additionally, we suggest that menstrual phases should be considered, especially in studies involving female participants. Although studies have shown that premenstrual period complaints have a psychosomatic effect on auditory performance, our study did not show any effect on AMLR due to premenstrual complaints.

We think that future studies using electrophysiological testing in which individuals may actively participate might produce different outcomes.

Ethical approval

This study has been approved by the Non-Interventional Ethics Committee of Bezmialem Vakif University (approval date 10/02/2022, number 2022/15). Written informed consent was obtained from the participants.

Author contribution

Concept: NB; Design: NB; Data Collection or Processing: AA, ÖGT, İNS, MBB; Analysis or Interpretation: MBB; Literature Search: NTE, NB; Writing: NB, NTE. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLE

Evaluation of retinal nerve fiber layer and choroidal structure in obese children and adolescents

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ABSTRACT

Aim: Obesity-related vascular damage and endothelial dysfunction have deleterious effects on the ocular vasculature. It was aimed to examine optical coherence tomography (OCT) parameters in obese and overweight children and to define their relationship with metabolic markers in this study.

Methods: The patient group consisted of 26 obese, 24 overweight patients aged between 8 and 18 years. The control group consisted of 25 healthy children with normal body mass index (BMI). This was a cross-sectional observational study. Serum glucose, lipid parameters, and homeostasis model assessment of insulin resistance (HOMA-IR) were investigated. Measurement of choroidal thickness was performed with Cirrus HD-OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA). Retinal nerve fiber layer (RNFL) thickness was determined by an automatic computer algorithm without the need for user measurement.

Results: There were no differences in subfoveal, nasal, temporal choroidal thickness, and RNFL between obese, overweight, and control groups ($p>0.05$). A positive (linear) moderate relationship was found between RNFL and the HOMA-IR of 26 patients in the obese group ($r=0.389$) ($p=0.049$). A positively weak correlation was found between height and RNFL in obese patient group ($r=0.264$, $p=0.028$).

Conclusion: In the study, RNFL thickness increased as HOMA-IR level increased in obese children and adolescents. RNFL decreased as the height increased in obese children and adolescents. We believe that more comprehensive data about the effect of obesity on RNFL and choroidal thickness will be obtained with prospective studies in which the obese patient group with insulin resistance is taken separately and disease durations are defined, and long-term patient follow-up is performed.

Keywords: Choroidal thickness, insulin resistance, obese children, retinal nerve fiber layer

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INTRODUCTION

Childhood obesity is an increasingly common health problem in developed and developing countries, regardless of age, gender, and ethnicity (1). In the occurrence of hypertension, diabetes mellitus, dyslipidemia, and progressive cardiovascular diseases, obesity is crucial (2). Obesity-related vascular damage and endothelial dysfunction have deleterious effects on the ocular vasculature and ocular blood flow (3). The choroid provides metabolites to the retinal pigment epithelium. Choroid has an essential impact on evaluating the ocular vascular structure (4).

Optical coherence tomography (OCT) was first used by Huang et al. (5). It is a basic non-invasive test for macular and optic nerve diseases. OCT takes images of the retina using a laser beam. It is also suitable for children as it is a non-contact, transpupillary, and painless imaging method (6). SD-OCT has allowed choroidal thickness measurement and detection of choroidal changes nowadays (7).

The number of studies investigating OCT parameters in obese and overweight children is limited in the literature and the results contradicts with each other. We aimed to investigate OCT parameters in obese and overweight children and to determine the relationships with metabolic markers.

MATERIAL AND METHODS

In our cross-sectional observational study, 26 obese and 24 overweight patients aged between 8 and 18 years who were brought to the pediatrics clinic of the hospital between July 2022 and December 2022 were included. 25 healthy children with normal weight were included in the healthy group. Informed consent was obtained from the parents of the children before the eye examination. The patients and the control groups were selected by randomization. The study was carried out with the permission of the Ethical Committee of University Hospital. (Date: 26.05.2022, Decision Number: 2022-61, report number:2022-71). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The weight of the patients was measured with electronic scales. Their height was measured standing with the Harpenden Stadiometer. The BMI formula was obtained by dividing the weight measurement by the height's square. A BMI between 18.5-24.99 was defined as normal weight, between 25-29.99 overweight, 30 and above were defined as obese. Triceps thickness and waist circumference were measured using a non-stretchable paper tape. After fasting for 10 hours, blood samples were taken from patients. Serum glucose and lipid parameters have been investigated. The homeostasis model assessment of insulin resistance (HOMA-IR) was detected as fasting insulin × fasting glucose / 405 to learn about insulin resistance (8). The patients were referred to ophthalmology for choroidal and optic nerve evaluations.

Inclusion criteria included having full visual acuity (according to the Snellen chart) and no eye pathology other than refractive error. The right eyes of the children were included in the study. Of the volunteers, participants with hypertension, diabetes mellitus, cardiac anomaly, those who were pregnant or breastfeeding, those who had undergone ocular surgery, those who had myopia greater than 3D, hypermetropia, and astigmatism greater than 1D weren't included in either of the groups in the study. A complete ophthalmoscopic evaluation of visual acuity, intraocular pressure measurement, light reflexes, eye movements, and anterior and posterior segment examination has been made.

Measurement of choroidal thickness with optical coherence tomography and RNFL analysis

Upon the instillation of 5% tropicamide, Cirrus HD-OCT was used for the measurement. Measurements with signal quality below 6 in both choroidal thickness and RNFL analysis were excluded.

In the reading of the choroid, the enhanced depth imaging system (EDI) mode of the device was used. The first measurement site was made subfoveal. Then, measurements were made from 6 points in the temporal and nasal directions from the subfoveal region, 3 temporal and 3 nasals, at 500 micron intervals and up to 1500 microns. Temporal and nasal choroidal thicknesses were calculated by taking the average of 3 choroidal thicknesses. Since the measurements were done manually, they were repeated by two different individuals. The mean choroidal thickness was found by taking an average of 7 measurements. Automatic computer mechanism defined retinal nerve fiber layer thickness (RNFL).

Categorical variables were presented as numbers. Continuous variables were presented as mean ± SD (min-max, median, Q1-Q3 when available). For the comparison of categorical expressions, the Chi-square test was applied. Continuous variables were tested for normal distribution using the Shapiro-Wilk test. Post hoc p analysis was performed after the study (Table 1). In the matched groups, Mann Whitney U test was performed. Kruskal Wallis analysis was performed that did not show normal distribution. Post hoc Bonferroni analysis was used to determine the source of the difference between the groups. To define the relation between continuous variables, the correlation test of Spearman's rho was made. A p-value less than 0.05 ($p<0.05$) was considered statistically significant. Analysis was performed using statistical package SPSS version 23.0 (IBM Corp., Armonk, NY, USA) for Windows.

RESULTS

26 obese patients, 24 overweight patients, and 25 healthy control patients were included in the research. 34 of them were boys and 41 of them were girls. Children's average age was 168 months in the obese patient group, and it was higher than the overweight and healthy children ($p=0.016$). When the differences between the groups were examined; the weight, BMI, and triceps thickness values were found higher in obese patients than others ($p<0.01$). The levels of HOMA-IR were 5.25 (4.22-6.18) in the obese patient group, 3.75 (2.59-5.15) in the overweight group and 3.3 (2.15-4.9) in the healthy control group. It was higher in obese children than in overweight and healthy children ($p=0.003$). Cholesterol and triglyceride levels were compared between the groups but there was no statistically significant correlation between groups in terms of cholesterol and triglyceride ($p>0.05$). Data for clinical, anthropometric measurements and other biochemical analyses are shown in Table 1.

There were no differences in subfoveal, nasal, temporal, or mean choroidal thickness between obese, overweight, and healthy subjects (respectively $p=0.451$, 0.677, 0.175, 0.472). No statistical significance was found on RNFL thickness. Intraocular pressure was measured in the obese patient group, overweight and healthy children. Intraocular pressure was lower in obese children 10 (10-12) mmHg than overweight children 12 (10-12.75) mmHg but the difference was not statistically significant ($p>0.05$). Median values of choroidal thickness, RNFL, and intraocular pressure are shown in Table 2.

The correlation between variables and RNFL in the obese patient group is made by Spearman correlation analysis and is shown in Table 3. A moderate positively (linear) relationship has been detected between the right eye RNFL thickness and the HOMA-IR value of 26 patients in the obese group ($r=0.389$) ($p=0.049$). A negatively weak correlation was detected between the height measurement and the right eye RNFL thicknesses in the obese patient group ($r=-0.26$, $p=0.028$). It was not detected any relation between weight, triceps thickness, waist circumference, BMI which were other anthropometric measurements and RNFL thicknesses ($p>0.05$). There was no significant correlation between both glucose and cholesterol levels and RNFL levels ($p>0.05$).

The patients were diagnosed with obesity when they came to the outpatient clinic for examination and were then sent for an eye examination. Therefore, it is not known how long these patients have been obese. These patients are not followed for a certain period of time due to obesity.

Table 1. Comparison of body mass measurements and biochemical analysis

	Obese (a)	**Overweight (b)**	**Contro l(c)**		
	Med (Q1-Q3)	**Med (Q1-Q3)**	**Med (Q1-Q3)**	**p‡**	**Post Hoc p**
Age (month)	168 (131.5-180)	125.5 (111.25-175)	121 (114.5-156)	**0.016***	a-b; p=0.027
Height (cm)	163 (156.88-165.78)	149.05 (140.5-162)	151 (143-155.9)	**0.001****	a-b; p=0.034 a-c; p=0.003
Weight (kg)	86.25 (72.75-94.43)	60.95 (55.05-68.15)	51 (45.45-57.2)	**0.000****	a-b; p=0.000 a-c; p=0.000 b-c; p=0.006
BMI (kg/m^2)	32.75 (30.37-33.8)	27 (26.07-27.9)	23 (21.45-23.9)	**0.000****	a-b; p=0.000 a-c; p=0.000 b-c; p=0.006
Systolic tension (mmHg)	120 (110-126.25)	105 (100-120)	110 (95-120)	**0.011***	a-c; p=0.009
Diastolic tension (mmHg)	80 (70-80)	70 (60-80)	70 (60-70)	**0.026***	a-c; p=0.024
Triceps thickness (mm)	33 (31.88-34.25)	31 (28.25-32)	27 (25-27.25)	**0.000****	a-b; p=0.008 a-c; p=0.000 b-c; p=0.000
Waist circumference (cm)	104 (99.75-108.38)	91.5 (89-96.75)	80 (72-85)	**0.000****	a-b; p=0.000 a-c; p=0.000 b-c; p=0.000
Glucose (g/dl)	92 (88-98)	82 (84-96)	82 (80-91)	**0.046**	
Total cholesterol (mg/dl)	143 (134-170.5)	157 (138.5-183.75)	157 (140.5-176.5)	0.494	
HDL cholesterol (mg/dl)	47 (35.75-53.25)	50 (42.25-59.75)	50 (45-56.5)	0.352	
LDL cholesterol (mg/dl)	81 (72.75-94.25)	83.5 (74.25-105.5)	89 (77-103.5)	0.300	
Triglyceride (mg/dl)	114 (89.25-156.75)	100.5 (84.5-159)	102 (79.5-126.5)	0.283	
HOMA-IR	5.25 (4.22-6.18)	3.75 (2.59-5.15)	3.3 (2.15-4.9)	**0.003****	a-b; p=0.019 a-c; p=0.008

* p<0.05, ** p<0.001; †: Chi-square, ‡: Kruskal Wallis, Post Hoc Bonferroni, BMI: body mass index, HOMA-IR: The homeostasis model assessment of insulin resistance.

Table 2. The measurements of choroidal thickness, RNFL, intraocular pressure in obese and overwheight and control groups

Variable	Obese (n=26)	Overweight (n=24)	Control (n=25)	p‡
	Med (Q1-Q3)	Med (Q1-Q3)	Med (Q1-Q3)	
Subfoveal choroidal thickness (µm)	302.5 (266-348.5)	329 (257.5-355)	313 (280-371.5)	0.451
Nasal choroidal thickness (µm)	273 (216-301)	281 (229-330)	260 (235.5-314)	0.677
Temporal choroidal thickness (µm)	272 (257.5-310)	298.5 (245.8-328.8)	300 (274-354)	0.175
Average choroidal thickness (µm)	285 (245.75-314.5)	306 (254.8-335.5)	300 (262.3-342)	0.472
RNFL (µm)	92.5 (85.75-95.25)	91 (83.25-96.25)	95 (84-97)	0.733
Intraocular pressure (mmHg)	10 (10-12)	12 (10-12.75)	10 (10-14)	0.313

* p<0.05, ‡: Kruskal Wallis, RNFL: retinal nerve fiber layer.

Table 3. Correlation between RNFL and variables in obese patient group

	RNFL	
	r	p
Age	-0.319	0.112
Height	-0,26*	**0.028**
Weight	0.001	0.998
BMI	0.278	0.169
Sistolic tension	-0.136	0.507
Diastolic tension	-0.165	0.420
Triceps thickness	0.076	0.711
Waist circumference	0.250	0.219
Glucose	0.031	0.880
HOMA-IR	0.389*	**0.049**
HDL cholesterol	-0.249	0.219
LDL cholesterol	-0.070	0.734
Triglyserid	-0.046	0.822

* p<0.05, Spearman's rho RNFL:retinal nerve fiber layer, BMI: body mass index, HOMA-IR: The homeostasis model assessment of insulin resistance.

DISCUSSION AND CONCLUSION

When comparing obese patients, overweight and healthy control groups, triceps thickness, height, weight, waist circumference, and BMI measurements were significantly higher in obese patients. HOMA-IR and RNFL thickness are significantly positively correlated in obese children. Height measurement and RNFL thicknesses are significantly negatively correlated. Subfoveal, nasal, temporal and mean choroidal thicknesses, and RNFL levels did not differ significantly between obese, overweight, and healthy children.

For the retina to be functional, an anatomically standard choroidal structure is crucial. Various systemic pathologies may affect the choroid (9). It is probable to observe alterations in the choroid with the developments in optical coherence tomography technologies (7).

Erşan et al. (10) detected that subfoveal choroidal thickness was thinner in obese children. In the study of Topcu-Yilmaz et al. (4), they found that subfoveal choroidal thicknesses of obese patients who had insulin resistance were significantly thinner than in healthy children in those with foveal 1000 µm and 1500 µm temporal locations. However, Bulus et al. (3) reported that subfoveal choroidal thickness was detected to become higher in obese children and adolescents. Celik et al. (11) reported that choroidal thickness in the subfoveal region was increased in obese patients. There were also differences in terms of choroidal thickness in obese children between the studies. We did not detect significant differences in obese children compared to healthy children with normal BMI relating to temporal, subfoveal, and mean choroidal thicknesses. However, the mean BMI of the patients in our study was lower than that of other studies. Since obese patients with hypercholesterolemia were not included as a different subgroup, it may affect the outcome as an additional risk factor. The mechanism of metabolic changes in obesity is quite complex. While a vasoconstriction

state may occur due to the hyperdynamic cardiac state and sympathetic discharge occurring in obesity, an increase in vascular permeability and thickening of the choroid can be expected due to increased inflammatory markers in obesity (12). As a common result of these mixed mechanisms, no effect on the choroid may have occurred.

Evaluation of RNFL has a significant importance in optic nerve damage's identification in hypertension, inflammatory diseases owing to avoid definite visual field disorders (13). In the study by Özen et al. (14) of 38 obese and 40 healthy children, there was a reduction in RNFL thickness in obese patients. On the other hand, they realized that this reduction did not make a statistically significant difference compared to healthy children. Baran et al. (15) observed that there were significant thinning of RNFL thicknesses in obese children. It was thought that it may cause an increased risk of developing glaucoma at a younger age, especially in children with central obesity. Pacheco-Cervera et al. (16) reported a significant decrease in RNFL thickness in the morbidly obese patient group (BMI-SDS >4). In the study of Hazar et al. (17), groups of children with obesity and obesity-related hypertension were included and in obesity related hypertension group RNFL was significantly thinner, but inferior RNFL thickness wasn't significantly thinner in the obesity group. There were conflicting results among studies in the literature regarding the effect of obesity on RNFL thickness in children. Optic atrophy and thinning of the RNFL have been reported over time (18). We found that the RNFL thicknesses in obese children were thinner than in healthy children, but the thinning was not statistically significant. The differences between the studies in the literature and our research is that the follow-up period of the patients with obesity were not long, and the body mass indexes were obtained much higher in other studies. Furthermore, this difference in our study may be due to the lack of clear information about how long the patients in the studies have had obesity and the studies were not planned according to the duration of the disease.

In a study examining RNFL thickness in healthy children; no correlation was found between height, weight, gender and RNFL (19). Khawaja et al. (20) reported that a negative correlation between BMI and RNFL in male-female adults without gender predominance. Negatively moderate correlation was detected among height measurement and RNFL in our study. It was observed that RNFL thickness decreased as the height increased in obese pediatric patients. However, no significant correlation was found between BMI and RNFL. Among the anthropometric measurements, only the relationship between height measurement and RNFL differed from the studies in the literature. Tall children were probably older. The age and axial length distribution could have caused this result in this group.

HOMA-IR value and the RNFL thickness positively significantly correlated with each other. We observed that metabolic disorders due to obesity affected the RNFL. The reason for RNFL changes in obesity was not clear. Studies examining the relationship between HOMA-IR and RNFL are very limited in the literature. In studies of Özen et al. (14) and Karti et al. (21), they detected a negative correlation between HOMA-IR and RNFL. There was a positive correlation between HOMA-IR and RNFL in our study. It can be thought that high HOMA-IR values may cause inflammation in the RNFL in the acute period and therefore an increase in RNFL and thinning secondary to atrophy may be observed in cases that become chronic.

Inflammation caused by insulin resistance may cause an increase in thickness in the RNFL with the effect of vascular permeability and edema in the acute period, and thinning by causing atrophy in the chronic period. For this reason, the duration of obesity of patients and how long they suffer from insulin resistance gain importance. It is clear that there is a need to compare the data of obese groups determined according to disease duration.

Study Limitations: The low number of patients included in the study is one of the limitations of this study. The other limitation is that it is not known how long the patients with insulin resistance among obese and overweight patients have insulin resistance.

In our study, we found that RNFL thickness increased as the HOMA-IR level increased, and RNFL decreased as the height increased in obese children and adolescents. It was not detected any difference in RNFL thickness and choroidal thickness among obese children with the healthy control group. We believe that more comprehensive data on the influence of obesity on RNFL and choroid thickness will be obtained with prospective studies that separate obese patient group with insulin resistance, define disease duration and follow patients over time.

Ethical approval

This study has been approved by the Ethical Committee of Ömer Halisdemir University Hospital (approval date 26/05/2022, number 2022-61). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: GYB; Concept: ZYÖ; Design: KRZ, GYB; Data Collection or Processing: ZYÖ, GYB; Analysis or Interpretation: KRZ, ZYÖ; Literature Search: ZYÖ; Writing: ZYÖ. All authors reviewed the results and approved the final version of the article.

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The authors declare that there is no conflict of interest.

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CASE REPORT

Paroxysmal sympathetic hyperactivity syndrome after recurrent stroke: A case report

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ABSTRACT

Paroxysmal sympathetic hyperactivity (PSH) is a state of autonomic dysfunction characterized by symptoms such as tachypnea, tachycardia, hypertension, hyperthermia, sweating, and dystonia. It can occur after traumatic brain injury, hypoxic-ischemic encephalopathy, and diseases such as stroke. Hypoxia, extensive axonal damage, and young age are believed to predispose to the development of PSH. These patients may be diagnosed with pulmonary embolism, septicemia, or epileptic seizures. Delays in diagnosis prolong hospital stay. Here, we present an 81-year-old man who developed PSH after a recurrent stroke and our management.

Keywords: Paroxysmal sympathetic hyperactivity, Ischemic stroke, Autonomic dysfunction

INTRODUCTION

Paroxysmal sympathetic hyperactivity (PSH) is an autonomic dysfunction characterized by tachypnea, tachycardia, hypertension, hyperthermia, sweating, and motor features such as dystonia (1). PSH may occur after brain damage such as traumatic brain injury (79%), hypoxic-ischemic encephalopathy (10%), and stroke (2,3). Hypoxia, extensive axonal damage, and young age are believed to predispose to the development of PSH (2). The exact pathophysiology of PSH is unknown (3). According to previous studies, PSH has not been associated with increased mortality or poor prognosis (3). Diagnosis can be delayed due to its rarity and confusion with some other diseases. This delay results in patients receiving incorrect treatments and prolongs their hospital stay. Here we present an elderly patient who developed PSH after a recurrent ischemic stroke.

CASE REPORT

An 81-year-old male patient presented to the emergency department with complaints of speech disorder the day before. He had a history of Parkinson's disease and epilepsy.

He had been bedridden due to a stroke 19 years ago. He was regularly using acetylsalicylic acid 100 milligrams once a day and phenytoin 100 milligrams (mg) 3 times

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a day. According to the neurological examination, the patient's consciousness was inclined to sleep. The cranial nerve examination was normal. He had newly developed motor aphasia and right sequela hemiparesis. Diffusion magnetic resonance imaging revealed limited diffusion consistent with an ischemic infarction in the left insular cortex (Figure 1). The patient was admitted to the neurology service with the diagnosis of acute ischemic infarction. Antithrombotic therapy was started. During the follow-up of the patient, saccadic eye movements and construction in the whole body appeared. He also exhibited high blood pressure, tachycardia, tachypnea, and flushing. Diazepam was administered to the patient considering epileptic seizure. Then, levetiracetam was added to his treatment. The patient responded to the treatment. Meanwhile, no abnormality was observed in the EEG taken twice.

In the follow-up radiological examinations, no pathological finding that could be related to the clinical findings was found.

After being transferred to the intensive care unit, the patient was intubated, and a barbiturate (pentobarbital) infusion was administered for 72 hours.

During the follow-up, the sympathetic episodes recurred after 72 hours. Benzodiazepine (midazolam) infusion was given followed by dexmedetomidine. When the treatment was discontinued, the attacks recurred. We considered PSH because there was no response to epilepsy treatment, typical epileptic attacks were not observed, and accompanying sympathetic discharge findings were present. We diagnosed PSH 7 days after ICU admission.

The PSH test, proposed by Baguley et al. (1), was used for the diagnosis, and the PSH index score was 15 points in our patient (Table 1). We considered a possible diagnosis of PSH according to these criteria.

The patient was managed using beta-blockers propranolol (80 mg daily), trazodone (100 mg daily), and gabapentin (1800 mg daily); so, the frequency and

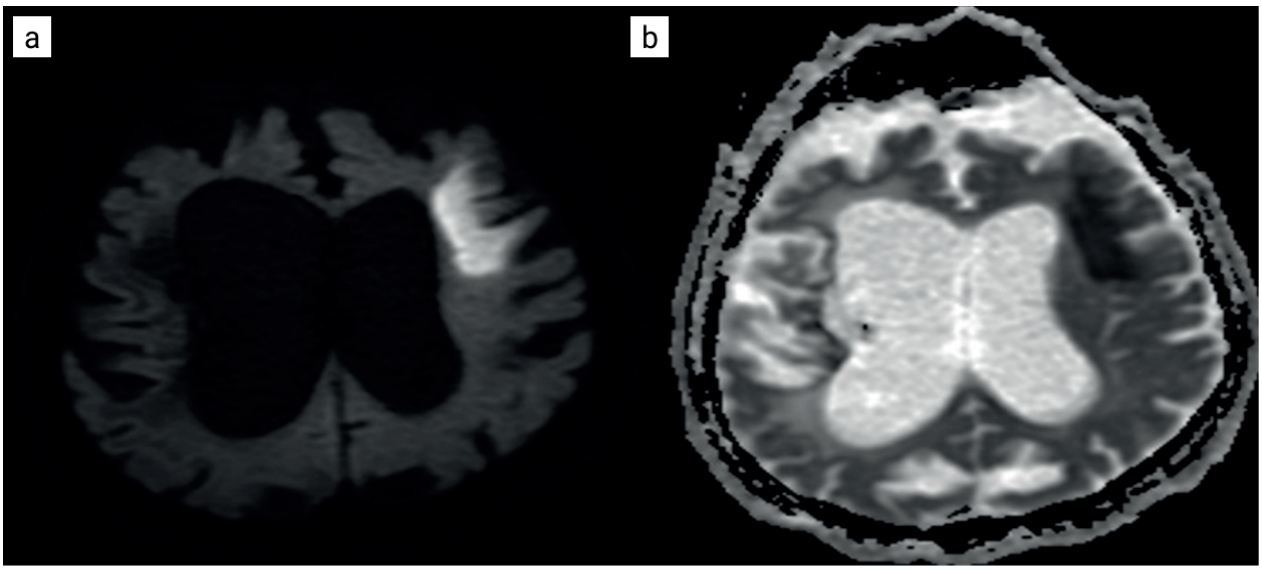

Figure 1. The DWI scan shows a left-sided hyperintensity in the frontal lobe (a), which can be appreciated as a hypointensity on the ADC trace map (b).

Table 1. The patient's baguley score measured during paroxysmal sympathetic hyperactivity

	0	1	2	3	Score
Heart rate (BPM)	<100	100 to 119	120 to 139	≥140	3
Respiratory rate (breaths/minute)	<18	18 to 23	24 to 29	≥30	3
Systolic blood pressure (mmHg)	<140	140 to 159	160 to 179	≥180	2
Temperature (°C)	<37	37 to 37.9	38 to 38.9	≥39	1
Sweating	Nil (none)	Mild (moist skin)	Moderate (beads of sweat)	Severe (profuse generalized sweating)	1
Posturing during episodes	Nil (none)	Mild (increased tone but not requiring treatment)	Moderate (increased tone requiring treatment)	Severe (very increased tone refractory to treatment)	0
				CFS subtotal =	10
Likelihood Tool (DLT)					
Score as "1" if present					**Score**
Clinical features occur simultaneously					
Episodes are paroxysmal in nature					1
Over-reactivity to normally nonpainful stimuli					
Features persist ≥3 consecutive days					1
Features persist ≥2 weeks post-brain injury					
Features persist despite treatment of differential diagnoses					1
Medication administered to decrease sympathetic features					1
≥2 episodes daily					1
Absence of parasympathetic features during episodes					
Absence of other presumed cause of features					
Antecedent acquired brain injury					
				DLT subtotal =	5
				Combined total (CFS + DLT) =	15

severity of attacks decreased. Episodes completely disappeared after a while. The patient later died due to metabolic disorders and respiratory failure.

DISCUSSION

Paroxysmal sympathetic hyperactivity (PSH) is an autonomic dysfunction characterized by tachypnea, tachycardia, hypertension, hyperthermia, sweating, and motor features such as dystonia. PSH is more commonly observed in young patients (2).

Paroxysmal sympathetic hyperactivity may occur after brain damage such as traumatic brain injury (79%), hypoxic-ischemic encephalopathy (10%), and stroke (3).

The incidence of PSH is particularly high in patients with axonal damage and deep brain damage (4).

Hydrocephalus (2.6%), brain tumors, central nervous system infections, and hypoglycemia are rare causes of PSH (3). Previous studies have shown that PSH does not raise morbidity or worse clinical outcomes (3).

Septicemia, epilepsy, pulmonary embolism, and some serious diseases may have symptoms similar to PSH. In the presence of these diseases, PSH may not be considered in the foreground.

Such as, while hyperthermia primarily suggests septicemia, pulmonary embolism is suspected if hyperthermia accompanies tachypnea. Dystonic posture may suggest an epileptic seizure diagnosis (5). Our patient was elderly and had many comorbid conditions. We thought the epileptic seizure was due to the patient's posture. We considered PSH because of its resistance to antiepileptics and accompanying autonomic findings.

The exact pathophysiology of PSH is unknown. Different theories have been put forward. The first is the disconnection theory, which is explained by the damage to the connection between the sympathetic nerves, centered in the hypothalamus and brainstem, and the higher cerebral cortex (3,6).

Another theory postulates an imbalance between excitation and inhibition, causing mismatched dendritic arborization and stimulation of spinal cord circuits (7).

Additionally, the insula may play a role in the hyperactivity of the sympathetic nervous system (8).

Bilateral insula, supramarginal gyrus, and amygdala are associated with the sympathetic nervous system (9). Our patient had an insular infarction. Sympathetic nerve hyperexcitation leads to PSH by increasing catecholamine release.

Studies have shown that sympathetic hyperactivity in PSH causes an increase in catecholamine release, with elevated levels of adrenocorticotropin, epinephrine, norepinephrine, and dopamine during attacks (10).

The goal of treatments is to reduce excessive sympathetic nerve activity. There is no definitive protocol for PSH treatment management. The treatment aims to distinguish which symptoms are urgent and the need for priority (11). Many combinations of drugs acting through different pathways can be used in treatment. Since the pathology of the disease is not clear, symptom control comes to the fore in treatment (12,13). It has been reported that opioids (morphine and fentanyl), intravenous anesthetics (propofol), neuromodulators (gabapentin, bromocriptine, baclofen, benzodiazepines (diazepam, midazolam, Lorazepam and clonazepam), alfa-2 agonists (clonidine, dexmedetomidine), peripherally acting muscle relaxants (dantrolene) and beta-adrenergic blockers (propranolol, labetalol, metoprolol) can be used (7). The ideal treatment is to use short-acting drugs, choose the appropriate regimen and avoid uncontrolled drugs.

In addition, it is recommended to treat hyperthermia with antipyretics, agitation with sedatives, and hypertension with antihypertensive agents (12,13). In our patient, epilepsy and cardiac-pulmonary symptoms were primarily considered. On the other hand, autonomic findings at follow-up and inadequate response to primary treatment led us to the diagnosis of PSH. The disease could then be brought under control with treatments performed on this axis.

CONCLUSIONS

Paroxysmal sympathetic hyperactivity is rare in patients with stroke. Typical symptoms can occur in many other diseases, so it is possible to experience delays in diagnosis. The treatment is possible with drugs affecting different mechanisms. Early diagnosis of PSH can shorten the hospital stay and prevent wrong treatments. In this case report, we wanted to draw attention to this rare disease and raise awareness.

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Ethical approval

Written informed consent was obtained from the participants.

Author contribution

Concept: FB, SY; Design: FB, ŞAT; Data Collection or Processing: FB, SE; Analysis or Interpretation: SY; Literature Search: FB, ŞAT, SE; Writing: FB, SE, ŞAT. All authors reviewed the results and approved the final version of the article.

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