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Research Article

Case Report

Follicular dendritic cell sarcoma of the spleen: A case report

Follicular dendritic cell sarcoma of the spleen

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A cross-sectional study determining the relationship between eating and drinking skills and functional independence levels of patients with cerebral palsy

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Ethics Committee Approval
Ethics Committee approval was taken from the Ethics Committee of Health Sciences University Kocaeli Derince Training and Research Hospital (date: February 13, 2020; number: 2020-2). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: In cerebral palsy (CP), drinking/eating disorders are considered common. To evaluate these disorders, a very detailed and lengthy evaluation is required. Few tools are available to identify children who need to be evaluated. This study determined whether the functional independence level of children with CP is sufficient to predict their drinking/eating skills and to determine the relationship between this functional level and these skills.

Methods: A total of 105 children with CP aged 4–8 years participated in a cross-sectional study in our outpatient clinic. Functional classification was assigned using the Gross Motor Function Classification System and Manuel Ability Classification System (GMFCS and MACS, respectively). For a functional assessment of daily life, the Pediatric Evaluation of Disability Inventory (PEDI) was performed by asking a relative of the child. The Eating and Drinking Abilities Classification System (EDACS) level was added to the study after asking the caregivers of the patients for eating/drinking evaluations.

Results: According to the current results, we found a negative correlation between EDACS and PEDI scores. As the EDACS grade increased, the PEDI subscale and total scores decreased in a statistically significant manner ($P < 0.001$), while the GMFCS and MACS scale increased statistically ($P < 0.001$). As the PEDI subscale and total scores increased, the levels of GMFCS and MACS decreased in a statistically significantly ($P < 0.001$).

Conclusions: The performances of children with CP in terms of activities of daily living are closely related to their performance in eating/drinking activities. If children are independent in their mobility, social functions, and daily self-care, they are also more independent in terms of eating/drinking.

Keywords: Cerebral palsy, Eating and Drinking Abilities Classification System, Gross Motor Function Classification System, Manuel Ability Classification System, Pediatric Evaluation of Disability Inventory

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Introduction

Cerebral palsy (CP) is defined as some non-progressive, permanent but unchanged movement or posture and motor function disorders due to lesions or abnormalities of the immature/developing brain [1,2]. The resulting activity restrictions impact both gross and fine motor movements, drinking and eating, and speech and communication [3–5]. A simple functional capacity grading system has been used by clinicians and researchers over the past two decades [3]. The development of functional scales, such as the Gross Motor Function Classification and Manuel Ability Classification Systems (GMFCS and MACS, respectively) for CP has revolutionized the way we define gross motor and manual abilities in these patients [6,7]. Daily living instrumental activities constitute the broader activities necessary for independent living, including social tasks and community mobility. For rapid diagnosis and treatment, children with disabilities are examined over their daily activities using three areas: (1) mobility, (2) self-care and (3) social function [8]. The Pediatric Evaluation of Disability Inventory (PEDI) examines the tasks that children can perform in their daily lives [9].

Nutritional difficulties are an important component of the pathogenesis of malnutrition in children with CP and can cause an increase in the risk of growth retardation. One of the main measures of health in children is physical growth. Malnutrition causes a decrease in brain function and respiratory muscle strength, immune function impairment, growth retardation, impaired blood circulation, and poor wound healing [10–12]. People with CP have difficulties in closing their lips when swallowing, which contributes to escape of the food bolus and malnutrition and prevents assessment of effective food intake [10,11]. Prevention, diagnosis, and early treatment of nutritional problems in children with CP have been considered, and their importance in preventing acute and chronic negative consequences has been investigated. The assessment methods for investigating the detailed feeding/swallowing and nutrition for all children with CP are too lengthy and complex to be routinely completed. Early detection of feeding/swallowing problems or malnutrition in children using a valid screening tool can be beneficial for comprehensive evaluation and treatment [13]. The Eating and Drinking Abilities Classification System (EDACS) was recently developed to categorize eating and drinking abilities in CP patients and is similar to other functional classification systems [14,15]. EDACS describes all drinking/eating abilities of children and young people with CP from 3 to 5 years of age at different levels using the basic features of efficiency and safety in nutrition. EDACS focuses on a person's normal drinking, chewing, biting, and swallowing performance in addition to coordination of these activities with breathing. Details of food and liquid tissues that can be managed without choking or aspiration have been described at different ability levels [16].

When the literature is reviewed, no comprehensive study examining the relationship between eating/drinking, daily living functions, and participation in these activities in children with CP can be found. This study investigated the association between the levels of activities of daily living of children with CP, the level of participation in these activities, and the EDACS classification levels that classify their performance in eating/drinking activities. In this respect, our study will contribute to the literature concerning this topic.

Materials and methods

Before the study, ethics committee approval was obtained from Health Sciences University Kocaeli Derince Training and Research Hospital (2020-2). Power analysis was done before the study. At least 93 children with CP were included in the study to test the statistical significance of a correlation of at least 0.30 between their abilities in daily living activities and their eating and drinking skills classification system (EDACS) scores at the 85% power and 5% error level. One hundred five children with CP between the ages of 4 and 8 who were admitted to our outpatient clinic between February and March 2020 with GMFCS grades 1–5 and MACS grades 1–5 were included in the study. Written consent for participation in the study was obtained from the person caring for the patient before the study. Demographic data of the patients were recorded. History taking and neurological examinations of the patients were performed by experienced physiatrists. Functional classification was based on both GMFCS and MACS results. For functional assessment of daily life, PEDI was performed by asking the patient's caregiver. For the evaluation of eating and drinking function, EDACS level was also recorded by asking the patient's caregiver.

Measurement

Gross Motor Function Classification System (GMFCS)

GMFCS is a standardized classification system developed by Palisano et al. [17, 18] in 1997 and expanded in 2007 for classifying the gross motor functions of children with CP. It is a standardized method that classifies gross motor function at five levels, especially motor function differences in terms of sitting and walking in children with CP [17, 19, 20]. The groups were determined as <2, 2–4, 4–6, 6–12, and 12–18 years old [18].

Manuel Ability Classification System (MACS)

MACS was developed by Eliasson et al. [21]. MACS specifies details related to hand function in daily activities of children with CP. MACS defines five levels. The determination of levels is according to the child's capability to hold objects by herself/himself and the need for help and adaptation in performing daily life's manual activities. The MACS assessment also highlights the differences between the two close levels to facilitate matching the desired level with the patient [21]. The MACS was designed to be used in children aged 4–18 and as a mini MACS in children between 1 and 4 years [9]. It is valid in Turkish (ICC: 0.89-0.96) and has been proven to be reliable (Spearman's rho: 0.91–0.98) [22].

Pediatric Evaluation of Disability Inventory (PEDI)

PEDI is a comprehensive clinical evaluation scale developed and used in 1992 by Haley et al. [8] to determine children's functional performance and capability from six months to 7.5 years old. It is a scale used to find the presence of functional deficits or delays in the clinic and its area and degree(if any). Erkin et al. [23] conducted a Turkish validity (Cronbach alpha >0.98 and intraclass correlation coefficient

[ICC] > 0.96) and reliability (Spearman rho > 0.86) study with 573 healthy children aged between six months and 7.5 years. PEDI is one of the most appropriate functional scales for all children with physical disability and/or both physical and cognitive impairment. PEDI consists of three main scales: (1) modifications, (2) caregiver assistance, and (3) functional skills. Each of these scales consists of 197 items addressing social function, mobility, and self-care to evaluate a child's daily activities in terms of both ability and performance. PEDI has two main sub-sections: (1) functional skills and (2) caregiver assistance [8, 24, 25].

Eating and Drinking Abilities Classification System (EDACS)

EDACS was created to classify CP children's eating and drinking functions and determine whether they can perform safe and effective eating and drinking abilities [14]. A Turkish translation and cultural adaptation study was done by Kerem Günel et al. [26]. This system has five different levels that categorize a patient's abilities ranging from level 1, which is independent eating and drinking, to level 5, which indicates maximum challenges to eating and drinking. This system is divided into three levels that categorize a patient's need for nutritional assistance: (1) fully dependent, (2) assistance required, or (3) independent [27].

Statistical analysis

IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA) was used for data analyses. The Kolmogorov–Smirnov test determined the normal distributions of metric discrete variables. A Levene test was used to examine the assumption of homogeneity of variances. Descriptive statistics were expressed as median (25^{th}–75^{th}) percentile or number of cases and % of total cases where appropriate. Degrees of association between examined scales (namely, EDACS, PEDI, GMFCS and MACS) were evaluated by Spearman's ranked-order correlation analysis. Whether the differences among EDACS stages in terms of PEDI, GMFCS, and MACS scores were statistically significant or not was evaluated by Kruskal–Wallis test. In order to determine the stage difference, a Dunn–Bonferroni multiple comparison test was used after obtaining a statistically significant P-value based on the Kruskal–Wallis test. A *P*-value < 0.05 was considered statistically significant.

Results

Descriptive statistics regarding the demographic and clinical characteristics of the cases are given in Table 1. Table 2 contains descriptive statistics for all scales used in the study.

According to the current results, as EDACS levels increased, the PEDI subscale and total scores decreased in a statistically significant manner, while the levels of the GMFCS and MACS scales increased significantly ($P < 0.001$). As the PEDI subscale and total scores increased, the levels of GMFCS and MACS decreased in a statistically significant manner ($P < 0.001$). Also, as the GMFCS level increased, the MACS level increased significantly ($P < 0.001$) as shown in Table 3.

Table 1: Demographical and clinical characteristics of cases and caregivers

	n = 105
Age (years)	5 (4–7)
Gender	
Girls	46 (43.8%)
Boys	59 (56.2%)
Diagnosis	
Diplegic	45 (42.9%)
Total	50 (47.6%)
Hemiplegic	8 (7.5%)
Dyskinetic	1 (1.0%)
Ataxic	1 (1.0%)
Orthesis	
Safo	72 (68.6%)
Ankle afo	3 (2.9%)
Dafo	2 (1.9%)
Caregiver	
Mother	97 (92.4%)
Father	6 (5.7%)
Other	2 (1.9%)
Caregiver's age (years)	34.5 (30–39)
No. of children	2 (2–3)
Caregiver's education	
Primary school	26 (24.8%)
Secondary school	65 (61.9%)
University	14 (13.3%)

The metric discrete variables are shown as median (25^{th}–75^{th}) percentiles; otherwise the number of cases and percentages were used for categorical data.

Table 2: Descriptive statistics for examined questionnaires

	n = 105
EDACS	2 (1–3)
1	47 (44.8%)
2	30 (28.5%)
3	13 (12.4%)
4	15 (14.3%)
PEDI	
Self-care	27 (17–44.5)
Mobility	24 (10–44.5)
Social	30 (17.5–49)
Overall	85 (50–131.5)
GMFCS	3 (2–4)
1	15 (14.3%)
2	31 (29.5%)
3	19 (18.1%)
4	20 (19.0%)
5	20 (19.0%)
MACS	2 (2–3)
1	14 (13.3%)
2	45 (42.9%)
3	25 (23.8%)
4	12 (11.4%)
5	9 (8.6%)

Descriptive statistics were expressed as median (25^{th}–75^{th}) percentiles or number of cases and %, where appropriate. EDACS: The Eating and Drinking Abilities Classification System, PEDI: The Pediatric Evaluation of Disability Inventory, GMFCS: Gross Motor Function, MACS: Manuel Ability Classification System.

Table 3: The results of correlation analyses among examined questionnaires

	Self-care	Mobility	Social	Overall	GMFCS	MACS
EDACS						
r	−0.518	−0.450	−0.426	−0.499	0.545	0.660
P-value †	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PEDI Self-care						
r		0.802	0.841	0.952	−0.679	−0.732
P-value †		<0.001	<0.001	<0.001	<0.001	<0.001
PEDI Mobility						
r			0.666	0.893	−0.754	−0.620
P-value †			<0.001	<0.001	<0.001	<0.001
PEDI Social						
r				0.904	−0.571	−0.595
P-value †				<0.001	<0.001	<0.001
PEDI Overall						
r					−0.731	−0.704
P-value †					<0.001	<0.001
GMFCS						
r						0.659
P-value †						<0.001

r: Coefficient of correlation, † Spearman's ranked-order correlation analysis. EDACS: The Eating and Drinking Abilities Classification System, PEDI: The Pediatric Evaluation of Disability Inventory, GMFCS: Gross Motor Function, MACS: Manuel Ability Classification System.

Table 4 contains the PEDI subscale and total scores of the cases according to their EDACS levels and comparisons made regarding whether a change in terms of GMFCS and MACS occurred. A statistically significant change in PEDI self-care subscale scores according to EDACS level ($P < 0.001$) and the situation causing this difference was found; the self-care scores of the patients with EDACS 3 and 4 were lower than those with EDACS 1 ($P = 0.005$ and $P < 0.001$, respectively). In addition, patients with EDACS 4 had statistically significantly

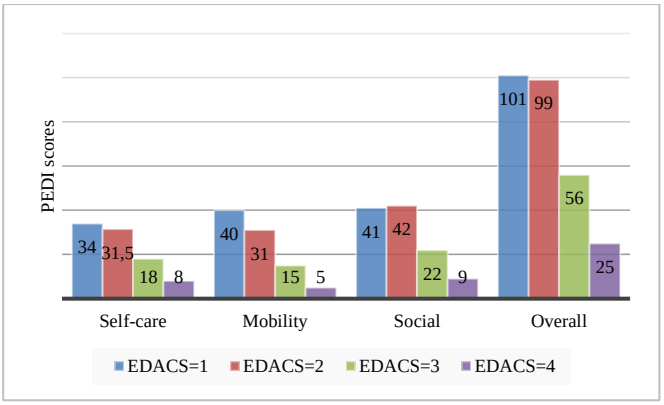
lower self-care scores than subjects with EDACS 2 ($P < 0.001$) as shown in Figure 1.

Table 4: The comparisons among EDACS grade in terms of other examined questionnaires

	EDACS	Descriptive statistics	*P*-value †
PEDI Self-care	1	34.0 (25.0–49.0)	<0.001 [a,b,c]
	2	31.5 (20.3–45.3)	
	3	18.0 (12.0–23.0)	
	4	8.0 (4.0–12.0)	
PEDI Mobility	1	40.0 (16.0–51.0)	<0.001 [a,b,c]
	2	31.0 (12.8–44.3)	
	3	15.0 (8.0–27.0)	
	4	5.0 (1.0–10.0)	
PEDI Social	1	41.0 (23.0–52.0)	<0.001 [a,b,c,d]
	2	42.0 (25.0–52.5)	
	3	22.0 (16.0–27.0)	
	4	9.0 (7.0–20.0)	
PEDI Overall	1	101.0 (78.0–153.0)	<0.001 [a,b,c,d]
	2	99.0 (79.0–145.0)	
	3	56.0 (36.5–69.0)	
	4	25.0 (13.0–45.0)	
GMFCS	1	2.0 (2.0–3.0)	<0.001 [a,b,c]
	2	2.0 (2.0–4.0)	
	3	4.0 (3.0–4.5)	
	4	5.0 (5.0–5.0)	
MACS	1	2.0 (1.0–2.0)	<0.001 [a,b,c,d]
	2	2.0 (2.0–3.0)	
	3	3.0 (3.0–4.0)	
	4	5.0 (4.0–5.0)	

Descriptive statistics were expressed as median (25^{th}–75^{th}) percentiles, † Kruskal–Wallis test, a: EDACS 1 versus 3 ($P < 0.05$), b: EDACS 1 versus 4 ($P < 0.001$), c: EDACS 2 versus 4 ($P < 0.01$), d: EDACS 2 *versus* 3 ($P < 0.05$). EDACS: The Eating and Drinking Abilities Classification System, PEDI: The Pediatric Evaluation of Disability Inventory, GMFCS: Gross Motor Function, MACS: Manuel Ability Classification System.

Figure 1: PEDI mobility subscale scores according to EDACS levels



PEDI: The Pediatric Evaluation of Disability Inventory, EDACS: The Eating and Drinking Abilities Classification System

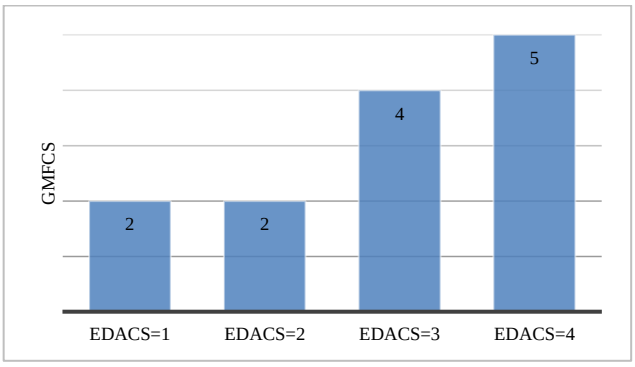
A statistically significant change in PEDI mobility subscale scores according to EDACS level ($P < 0.001$) was found, and this difference most likely occurred because the mobility scores of the patients with EDACS 3 and 4 were lower than those with EDACS 1 ($P = 0.030$ and $P < 0.001$, respectively). In addition, the mobility scores of the patients with EDACS 4 were significantly lower than those with EDACS 2 ($P = 0.003$) as shown in Figure 1.

A statistically significant change in PEDI social subscale scores according to EDACS level ($P < 0.001$) was found because the social subscale scores of patients with EDACS 3 and 4 were lower than those with EDACS 1 ($P = 0.027$ and $P < 0.001$, respectively). In addition, the social subscale scores of the patients with EDACS 3 and 4 were significantly lower than those with EDACS 2 ($P = 0.022$ and $P < 0.001$, respectively) as shown in see Figure 1.

A statistically significant change in PEDI total scale scores according to EDACS level ($P < 0.001$) was noted because the total scale scores of the patients with EDACS 3 and 4 were lower than those with EDACS 1 ($P = 0.007$ and $P < 0.001$, respectively). Also, according to the cases with EDACS 2, the total scores of the cases with EDACS 3 and 4 were statistically significantly lower ($P = 0.049$ and $P < 0.001$, respectively) as shown in Figure 1.

A statistically significant change in GMFCS scores according to EDACS level was found ($P < 0.001$) because the GMFCS scores of patients with EDACS 3 and 4 were higher than those with EDACS 1 ($P = 0.020$ and $P < 0.001$, respectively). In addition, the GMFCS scores of patients with EDACS 4 were statistically significantly higher than those with EDACS 2 ($P < 0.001$) as shown in Figure 2.

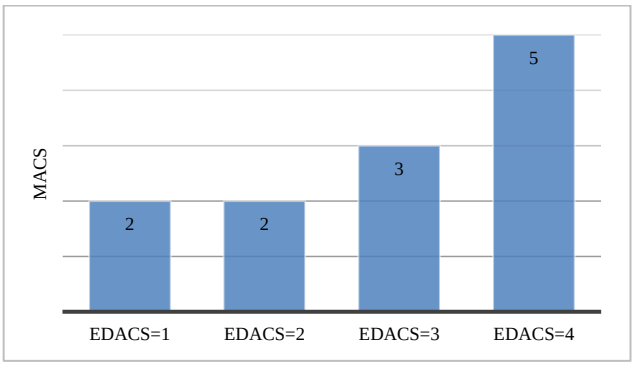
Figure 2: GMFCS scores according to EDACS levels



GMFCS: Gross Motor Function, EDACS: The Eating and Drinking Abilities Classification System

A statistically significant change in MACS scores according to the EDACS grade ($P < 0.001$) was noted because the MACS scores of the EDACS 3 and 4 patients were higher than those with EDACS 1 ($P < 0.001$ and $P < 0.001$, respectively). In addition, the MACS scores of patients with EDACS 3 and 4 were statistically significantly higher than those with EDACS 2 ($P = 0.014$ and $P < 0.001$, respectively) as shown in Figure 3.

Figure 3: MACS scores according to EDACS levels



MACS: Manuel Ability Classification System, EDACS: The Eating and Drinking Abilities Classification System

Discussion

It is estimated that some degree of difficulty eating or drinking is seen in 27% to 90% of people with CP [3]. This study found a statistically significant relationship between the CP children's performances in eating and drinking activities and their performances in terms of daily living activities. Namely, according to EDACS classification, children in Stage 1 (children who can eat in a safe and effective manner) had higher PEDI total scores. A more child who was more independent in terms of eating and drinking functions was found to have more successful performances in terms of social functions, mobility, and daily self-care. A study conducted by Goh et al. Reported a strong relationship between EDACS and three areas of PEDI [28].

When we examined the subgroups of PEDI, a positive correlation was found between EDACS classification and PEDI

self-care scores, indicating that the more successful the child is in self-care, the more successful she/he can be in terms of eating and drinking functions. Learning to be independent in children with CP can be difficult due to developmental delays and physical impairments [29]. Since poor performance in self-care also affects eating and drinking performances, children with self-care problems will experience nutritional disorders and growth and development retardation.

According to EDACS, we found a decrease in eating/drinking functions in children with reduced motor skills. It has been observed that both motor and eating/drinking skills are correlated. In this case, in cases in which the motor skills of children with CP are low, we should definitely not ignore their eating/drinking functions and nutritional status. In previous studies, it has been shown that gross motor function limitations and eating/drinking performances are closely related for children with cerebral palsy [30–33]. In our study, we found that GMFCS and EDACS levels have a close relationship to dysphagia and gross motor function. Children with GMFCS levels IV to V have a significantly higher risk for dysphagia than children with GMFCS level I [28]. Selley et al. [33] stated that children with low gross motor function have nutritional problems and have a long feeding period during the day need to change their nutrient content and consistency and that specially designed seating and auxiliary devices should be used during feeding. Due to these problems, it was observed that the level of participation and variety of activities of the child and his/her family in indoor and outdoor environments is low. In a study by Benfer et al. [34] examining oropharyngeal dysphagia in children < 3 years old with CP, it was found that dysphagia severity was highly correlated with the GMFCS level. However, Benfer emphasized that dysphagia can be seen in children with CP who have a mild GMFCS level, and all children with CP must be examined regarding dysphagia regardless of the GMFCS level. In our study, in agreement with previous studies, the GMFCS levels of children with low EDACS levels were also low. Although no studies addressing the correlation between PEDI mobility and EDACS are available, many literature studies showing the relationship between PEDI mobility and GMFCS levels have been published [35, 36]. In our study, children with CP with insufficient mobility functions functioned as a worse level than both GMFCS and EDACS classification system indicated.

In the literature, no comprehensive studies have examined the relationship between eating/drinking function and activity participation in children with CP. In our study, the EDACS classification level was poor in those who were insufficient in the PEDI social area section. The EDACS 1 level child had a higher performance in the social field, while the performance of a child with EDACS 5 was less. In fact, children with severe motor impairment are more affected cognitively. The participation of children who have weak cognitive and motor skills is also low in the social area. In addition, EDACS levels will also deteriorate as these children have excessive dysfunction in the muscles around the mouth, salivation dysfunction, and chewing problems. In our study, we found a correlation between PEDI total score and other GMFCS and MACS levels. In a previous study, children with MACS and GMFCS levels I or II scored higher than children with MACS and GMFCS levels III–IV in self-care and mobility areas based on the PEDI, and significant differences between all classification levels were found. Stepwise multiple regression analysis showed that the strongest predictor of self-care skills (66%) and mobility skills (76%) were MACS and GMFCS, respectively. A strong correlation was found between age and mobility among children classified as GMFCS level I, between children classified as MACS level I or II, and between age and self-care abilities [37].

Previous studies have shown that those with good hand function are also good at self-care activities [35, 38]. Therefore, children whose EDACS level is worsening will also have a bad MACS level. In several cross-sectional studies, MACS has been associated with self-care in children with CP. These longitudinal studies provide information about the rate of self-care development in children with CP based on the manual skill classification level [38, 39]. Self-care is based on a complicated interaction of factors such as manual skills, skeletal integrity, muscle function, sensory integration, somatosensory functions, vision, visual motor skills, motivation to explore the environment, cognition, and cultural influences [40].

The limitation of our study is that the inter-rater reliability of the Turkish version of EDACS was not determined. Further studies should be conducted concerning this issue.

Conclusion

Our study showed that the inadequacy in daily living activities also causes eating and drinking disorders. We recommend that EDACS be used by clinicians in order to easily determine the eating/drinking functional levels of children with CP and to provide information about interventions to prevent nutritional deficiencies. Functional eating/drinking skills of children with CP are closely related to the levels of motor function, daily living skills, and social functions.

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The evaluation of ultrasonographic hip measurement differences among physicians according to the Graf method in newborns

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Ethics Committee Approval
This study was carried out after obtaining the approval of the Clinical Research Ethics Committee of Malatya Turgut Özal University, with the protocol number 2021/56 dated August 20, 2021.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Hip ultrasonography (USG) is the most important diagnostic method in developmental hip dysplasia in newborns. However, a disadvantage of the ultrasonography method is that there can be measurement differences among doctors measuring the same hip. We aimed to investigate the causes and solutions of this situation. We further strived to measure the hip ultrasonography performed by different physicians using the Graf method and comparing the obtained values.

Methods: Hip USGs of newborns admitted to Malatya Turgut Ozal University Faculty of Medicine Hospital between Jan. 8, 2020 and Jan. 5,.2021 were measured and classified using the Graf method. The study type is consistent with retrospective cohort studies. Newborns aged 0-22 weeks without any additional pathology were included in the study. A radiologist and two orthopedists measured and interpreted the images separately in accordance with the Graf method. The first hip measurements (R1) were made by the radiologist (R) with the USG device, and they were classified according to alpha and beta angles; two printouts were made. The first orthopedic specialist (OS1) and the second orthopedic specialist (OS2) made their measurements with printouts. Subsequently, the results from the physicians were compared.

Results: A statistically significant difference was found between R1-OS2 ($P < 0.001$) and OS1-OS2 ($P < 0.001$) in terms of the Graf classifications. No statistically significant difference was found between R1 and OS1 in terms of the Graf classification ($P = 0.562$). A statistically significant difference was found between R1-OS2 ($P < 0.001$) and OS1-OS2 ($P = 0.048$) angles (alpha and beta) measurements. While R1 and OS1 measurements were compatible with each other, OS2 measurements were found to be inconsistent.

Conclusion: We think that there may be differences in angle measurements and the Graf classification among physicians who perform hip ultrasonography in newborns, and the most important way to correct this is through regular participation of physicians in subject-specific trainings.

Keywords: Hip, Ultrasonography, Newborn

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Introduction

Developmental hip dysplasia (DHD) is a progressive disease that occurs as a result of disruption of the integrity of the acetabulum and femoral head due to many risk factors during pregnancy. In the past, the incidence of DHD was thought to be 1 in 1000 live births [1]. In the study of Kutlu et al. [2] the incidence of DHD was found to be 1.34%. The incidence of DDH may vary according to race and geographical regions. DHD can be seen at a rate of 1.5-2% in Europe and at a rate of 1-1.5% in Turkey [3, 4].

If DHD is not diagnosed and treated early, it can cause serious arthrosis and deformities in later life [5]. Early diagnosis is the basis of treatment and also increases the success of treatment. Although Barlow and Ortolani tests performed by physical examination have an important place in the diagnosis, hip ultrasonography (USG) performed in the first six months after birth is the most valuable method [6]. In children older than six months, pelvic roentgenogram has an important place in the diagnosis [7]. Combined clinical examination and USG are the most important methods in diagnosis and follow-up. USG is routinely used and accepted, because it is an internationally standardized diagnostic method, can diagnose up to the sixth month, and helps in the planning of follow-up and treatment [8, 9].

Although USG is used in diagnosis and treatment, we think that different results may be obtained according to the measurement of the radiologist or orthopedist performing the USG. It was stated in the studies of Bar-on and Zieger et al. [10, 11] that it may vary according to the person making the measurement.

Hip ultrasonography is the most important diagnostic method in developmental hip dysplasia in newborns. However, a disadvantage of the ultrasonography method is that there can be measurement differences among doctors measuring from the same hip. We aimed to investigate the causes and solutions of this situation. We further strived to measure the hip ultrasonography performed by different physicians using the Graf method and comparing the obtained values.

Materials and methods

Hip USGs of newborns admitted to our hospital between Jan. 8, 2020 and Jan. 5, 2021 were measured and classified using the Graf method. This study was carried out after obtaining the Clinical Research Ethics Committee of Malatya Turgut Özal University's approval, with the protocol number 2021/56 dated Aug. 20, 2021. Fifty five (49.5%) of the newborns were girls and 56 (50.5%) were boys. The study type is consistent with retrospective cohort studies. Newborns aged 0-22 weeks without any additional pathology were included in the study. Two printouts were obtained for each hip from each newborn. A radiologist and two orthopedists measured and interpreted the images separately in accordance with the Graf method. The first hip measurements (R1) were made by the radiologist (R) with the USG device, and they were classified according to alpha and beta angles, and two printouts were made. Five days later, participants were called, and R1 measured a second time (R2). The printouts were given to the first orthopedic specialist (OS1) and the second orthopedic specialist (OS2). The radiologist had previously had hip USG training. OS1 had a Graf method pediatric hip ultrasonography course certificate. OS2 had training only during the residency period.

They measured the hips manually with a protractor ruler in accordance with the Graf method and classified them according to alpha and beta angles. The alpha and beta angle measurements and classification according to the Graf method performed by the radiologist were compared with the alpha and beta angle measurements made by the two orthopedic specialists manually from the printout and classification according to the Graf method. In the study, the radiologist's first measurement (R1) was compared with the measurements of OS1 and OS2.

Type 3 and type 4 hips were not found in the study. In addition, hips were divided into two groups; Graf type 1 hips (Group 1), which did not need follow-up, and Graf type 2a - type 4 hips (Group 2), which required follow-up and treatment in order to calculate the agreement between the physicians.

Ultrasound scanning was performed with the Esaote Mylab Seven model 2019 linear probe manufactured in Genoa, Italy. The radiologist examined all hip joints with and without stress prior to USG (using Barlow and Ortolani). Then, USG was performed by the same radiologist to evaluate the stability of the hip structure and femoral head at rest and under stress (Figure 1). When the baby was in the lateral decubitus position, the probe was inserted using the lateral approach. Scanning was evaluated by fixing the hips in 20-30 degrees of flexion and 5-10 degrees of internal rotation in extension. The bone and cartilage components of the hip joint and the structure of the femoral head within the acetabulum were evaluated. Graf's classification was used for measurements. Alpha and beta angles were calculated on coronal images. In coronal images, an imaginary line is drawn from the baseline of the iliac bone and extended along the femoral head. The angle between the tangent drawn from the distal end of the deepest point of the acetabulum to the bony corner was calculated as alpha. Beta angle was calculated with the line drawn from the midpoint of the labrum to the acetabular corner (Figure 2). Two printouts were made for each hip.

Figure 1: USG measurement of radiologist

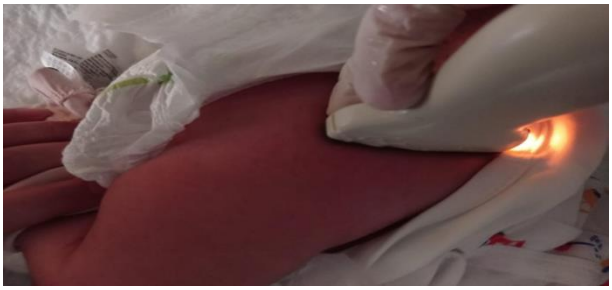

Figure 2: USG alpha and beta angle measurement

Statistical analysis

The analysis of the data included in the research was carried out using the Statistical Package for the Social Sciences (SPSS) 25 program and Kolmogorov-Smirnov test [12]. Two paired sample t-tests were used to evaluate the observers. The Pearson correlation coefficient was also calculated. Values that were frequently used in the evaluation of the findings were as follows: 0.00 – 0.19 no relationship (negligible low relationship), 0.20 – 0.39 weak relationship, 0.40 – 0.69 moderate relationship, 0.70 – 0.89 strong relationship, 0.90 – 1.00 a very strong relationship [12].

The sample of this study was determined by power analysis, using the G*Power 3.1 program. According to the power analysis, the sample was determined as 198 with an effect size of 0.25, a margin of error of 0.05, and a confidence level of 0.95.

Interobserver reliability is used to show variability between two or more raters measuring the same group of participants [13]. Observers were evaluated using the intraclass correlation coefficient (ICC). Since the participants were evaluated by the same observer, the ICC (3,2) model and two-way mixed effects model were used. ICC (3,2), standard error of measurement (SEM) and inter-measurement reliability, which is the smallest detectable difference (SDD), were evaluated [14-16]. SDD was calculated to generate random error scores. The low value of the calculated SEM indicates that the participant was consistent throughout the test trials [15, 17]. In order to compare the measurements among observers, comparisons between groups were made using the ANOVA test. The measurement values of the tests were recorded by providing similar test setups and conditions for all participants included in the study.

Results

One hundred eleven newborns were included in the study. A total of 55 (49.5%) were female and 56 (50.5%) were male. The mean age of the participants was 69.72 (30.78) days, with the youngest age being 22 days, and the highest, 155 days. A total of 222 hips of the participants, both right and left hips, were evaluated.

Mean, standard deviation, minimum and maximum values of both R1 and R2 alpha (α) and beta (β) angles taken by R, alpha (α), beta (β) angles measured by OS1, alpha (α), beta (β) angles measured by OS2 were calculated and results are given in Table 1.

The number and percentage values of R1 and R2 Graf classification (Type 1, 2A, 2B, 2C), OS1 Graf classification (Type 1, 2A, 2B, 2C) and OS2 Graf classification (Type 1, 2A, 2B, 2C) distributions of participants in the study were calculated and the results are given in Table 2. No Type 3 or Type 4 patients were found in the study.

To calculate the agreement among the physicians, measurements were divided into two groups, Group 1 (type 1) and Group 2 (type 2a to type 4). Group 1 and Group 2 classification numbers and percentage values calculated by R1, OS1 and OS2 are given in Table 3.

There was no statistically significant difference between R1 and R2 measurements made by R for alpha (α) angle variable (P^1 = 0.708, Table 4). It was observed that the values obtained with the second measurement were higher than the values obtained with the first measurement (difference = -0.05). A very high level (r = 0.872) of statistically significant correlation was found between R1 and R2 (P^1 = 0.708, Table 4).

Table 1: Alpha and beta angle measurement averages of physicians

Angle	Mean (SD)	Min	Max
R1 α angle	61.92 (3.84)	48	73
R1 β angle	55.4 (7.66)	35	72
R2 α angle	61.97 (3.95)	46	70
R2 β angle	56.36 (6.78)	40	71
OS1 α angle	60.02 (12.1)	62	71
OS1 β angle	57.9 (12.32)	55	72
OS2 α angle	59.22 (5.31)	43	75
OS2 β angle	60.64 (5.82)	42	80

SD: standard deviation, Min: lowest score received, Max: highest score

Table 2: Number of hips by Graf classification

	R1 n(%)	R2 n(%)	OS1 n(%)	OS2 n(%)
Type 1	171 (77%)	173 (77.9%)	146 (73%)	120 (54.1%)
2A	41 (18.5%)	39 (17.6%)	48 (21.6%)	76 (34.2%)
2B	9 (4.1%)	9 (4.1%)	11 (5%)	21 (9.5%)
2C	1 (0.5%)	1 (0.5%)	1 (0.5%)	5 (2.3%)

n: frequency, %: percent

Table 3: Group 1 and Group 2 distribution of physicians' measurements

	R1	OS1	OS2
Group 1	171 (77%)	162 (73%)	120 (54,1)
Group 2	51 (23%)	60 (%27%)	102 (45.9%)

%: percent, Group 1: Graf type 1 hips that do not need follow-up, Group 2: Hips between Graf type 2a + type 4 requiring follow-up and treatment

There was no statistically significant difference between R1 and R2 performed by the radiologist for the beta (β) angle variable (P^1 = 0.220, Table 4). It was observed that the values obtained with the second measurement were higher than the values obtained with the first measurement (difference = -0.95). A very high level (r = 0.952) statistically significant correlation was found between the first and second measurements (P^1 = 0.220, Table 4).

No statistically significant difference was found between R1 and R2 measurements in the Graf classification using R (P = 0.058, Table 5).

Table 4: R1 and R2 angle measurements of the radiologist

Angle	Measurement	Mean (SD)	P^1-value	r	P^2-value
Alfa (α)	R1	61.92 (3.84)	0.708	0.872	0.001*
	R2	61.97 (3.95)			
Beta (β)	R1	55.40 (7.66)	0.220	0.952	0.001*
	R2	56.36 (6.78)			

SD: standard deviation, P^1: statistical significance of two paired samples t test, r: between two observation correlation coefficients, P^2: *P <0.05. There is a statistically significant relationship between the two tests.

Table 5: Comparison of two measurements of the radiologist according to Graf classification

		R2				Total	P-value
		Type 1	2A	2B	2C		
R1	Type 1	168 (97.1%)	3	0	0	171 (77%)	0.058
	2A	5 (2.9%)	36 (92.3%)	0	0	41 (18.5%)	
	2B	0	0	9 (%100)	0	9 (4.1%)	
	2C	0	0	0	1 (100%)	1 (0.5%)	
Total		173	39	9	1	222	

%: percent, P: test statistical significance's value of kappa statistics

It was found that there was a statistically significant difference among the physicians in the alpha and beta measurements of the participants included in the study. To measure from which group the difference originates, pairwise comparisons were made with the Tukey test. According to the paired comparisons:

- No statistically significant difference was found between R1 and OS1 angle measurements (P^2 = 0.051, Table 6).
- A statistically significant difference was found between R1 and OS2 angle measurements (alpha angle: P^2 < 0.001, Table 6).
- A statistically significant difference was found between OS1 and OS2 angle measurements (P^2 = 0.048, Table 6).

Table 6: Comparison of alpha and beta angle measurements among physicians

Angle	Measurement	Mean (SD)	P^1-value	Multiple comparisons		
				First	Second	P^2-value
Alfa	R1	61.92 (3.84)	<0.003*	R1	OS1	0.051
	OS1	60.02 (4.27)			OS2	0.001**
	OS2	59.22 (5.31)		OS1	OS2	0.048**
Beta	R1	55.4 (7.66)	<0.001*	R1	OS1	0.053
	OS1	57.9 (5.96)			OS2	0.001**
	OS2	60.64 (5.85)		OS1	OS2	0.001**

SD: standard deviation, *P*: statistical significance of repeated measures of ANOVA, * P^1< 0.05: There is a statistically significant difference between observers ** P^2<0.05: There is a statistically significant difference between observers.

In the measurements made for the alpha angle, the R1 and OS1 ICC value was calculated as 0.892 (95% CI; 0.859-0.917; Table 7). The reliability between measurements was evaluated with the Standard Error of Measurement (SEM) and the smallest detectable difference (SDD). High ICC value, low SEM value indicates good inter-participant agreement [17, 18].

The R1 and OS2 ICC value was calculated as 0.327 (95% CI; 0.205-0.440). The reliability between measurements was evaluated with the Standard Error of Measurement (SEM) and the smallest detectable difference (SDD). A low ICC value and a high SEM value indicate that the agreement among participants is not good [17, 18]. OS1 and OS2 ICC values were calculated as 0.347 (95% CI; -0.226-0.458; Table 7). In the measurements made for the beta angle, the R1 and OS1 ICC value was calculated as 0.734 (95% CI; 0.654-0.796). R1 and OS2 ICC value was calculated as 0.284 (95% CI; 0.159-0.401). OS1 and OS2 ICC values were calculated as 0.389 (95% CI; 0.271-0.495; Table 7).

Table 7: ICC, SEM, and SD values of physicians' angle measurements

Angle	Measurements	Measurements	ICC (3.2)	% 95 CI		SEM	SD
				Lower Bound	Upper Bound		
Alfa	R1	OS1	0.892	0.859	0.917	0.101	0.281
		OS2	0.327	0.205	0.440	1.361	3.772
	OS1	OS2	0.347	0.226	0.458	1.257	3.484
Beta	R1	OS1	0.734	0.654	0.796	0.521	1.443
		OS2	0.284	0.159	0.401	2.767	7.670
	OS1	OS2	0.389	0.271	0.495	2.514	6.969

ICC: Intraclass Correlation Coefficient, CI: Confidence Interval, SEM: Standard Error of Measurement, SD: Smallest detectable difference.

No statistically significant difference was found between R1 and OS1 in terms of the Graf classification (P = 0.562, Table 8). A statistically significant difference was found between R1 and OS2 in terms of the Graf classification (P = 0.001, Table 8). A statistically significant difference was found between OS1 and OS2 in terms of the Graf classification (P < 0.001, Table 9). No statistically significant difference was found between Group 1 and Group 2 measurements of R1 and OS1 (P = 0.058, Table 10). A statistically significant difference was found between R1 and OS2 measurements (P = 0.001, Table 10). A statistically significant difference was found between Group 1 and Group 2 measurements of OS1 and OS2 (P < 0.001, Table 11).

Table 8: Inter-physician comparison of Graf type classification

		R1				Total	*P*-value
		Type 1	2A	2B	2C		
OS1	Type 1	160	2	0	0	162	0.562
	2A	9	39	0	0	48	
	2B	2	0	9	0	11	
	2C	0	0	0	1	1	
OS2	Type 1	108	10	1	1	120	0.001*
	2A	48	28	0	0	76	
	2B	13	0	8	0	21	
	2C	2	3	0	0	5	

* P < 0.05: There is a difference between groups. *P*: test statistical significance's value of kappa statistics.

Table 9: Inter-orthopedist comparison of Graf type classification

		OS1				Total	*P*-value
		Type 1	2A	2B	2C		
OS2	Type 1	105	11	3	1	120	<0.001*
	2A	42	34	0	0	76	
	2B	13	0	8	0	21	
	2C	2	3	0	0	5	

* P < 0.05: There is a difference between groups. *P*: test statistical significance's value of kappa statistics.

Table 10: Comparison of R1 between OS1 and OS2 in Group 1 - Group 2 classifications

		R1		Total	*P*-value
		Group 1	Group 2		
OS1	Group 1	159	3	162	0.058
	Group 2	12	48	60	
OS2	Group 1	108	12	120	0.001*
	Group 2	63	39	102	
Total		171	51	222	

* P < 0.05: There is a difference between groups. *P*: test statistical significance's value of kappa statistics, Group 1: Graf type 1 hips that do not need follow-up, Group 2: Hips between Graf type 2a + type 4 requiring follow-up and treatment

Table 11: Comparison between OS1 and OS2 in Group 1 - Group 2 classifications

			OS1		Total	*P*-value
			Group 1	Group 2		
OS2	Group 1	n	105	15	120	<0.001*
	Group 2	n	57	45	102	

n: frequency, %: percent, * P < 0.05: There is a difference between groups. *P*: test statistical significance's value of kappa statistics, Group 1: Graf type 1 hips that do not need follow-up, Group 2: Hips between Graf type 2a + type 4 requiring follow-up and treatment

Discussion

DHD is a progressive disease that occurs in newborns due to many prenatal and postnatal causes. The main deterrent of this disease is early diagnosis and treatment [19]. If the correct diagnosis and treatment is not made in the newborn, it causes permanent deformities, loss of ability to work, and a decrease in the quality of life of the patient [20]. It should be noted that 9.1% of cementless total hip prostheses and 5.2% of cemented total hip prostheses are performed due to hip dysplasia or dislocation [21]. Barlow and Ortolani examinations are also frequently used in the diagnosis of newborns. However, the specificity of these methods was found to be high >99% and the sensitivity to be 60% [22, 23]. Pelvic roentgenogram is not used for early diagnosis in children under six months, since the femoral head ossifies after four to six months [24]. For all these reasons, the importance and value of USG has been increasing.

Ultrasonography will not only prevent the occurrence of such problems in adults, but will also contribute to the reduction in surgical treatment costs of DHD [25, 26]. Although USG reduces the problems and treatment costs of the family and the child in the future, it may cause false positives and unnecessary treatments [27]. In the study of Dias et al. [28], two pediatric radiologists and three orthopedic physicians reproduced the hip ultrasound images of 209 newborns and evaluated them with the Graf method. It was stated that USG is an important diagnostic method in DHD, although the reliability among physicians is weak.

The Graf ultrasonographic hip measurement method has an important place in determining hip dislocation, as it allows us to make USG and angle measurements. In order to reduce the errors of physicians who perform USG measurements and increase the validity, reference points, drawing lines, and accurate measurement of angles were determined [29]. It has been proven in publications that errors can be minimized as a result of following these guidelines [30].

In the study of Bar-On et al. [31], hip ultrasonography was performed on 75 infants by two different physicians consecutively. Ultrasound images were printed and analyzed twice by three pediatric orthopedic surgeons and classified using

the Graf method. Intra- and inter-observer agreement between interpretations was classified as normal (types 1 to 2A) and abnormal (types 2B to 4) using the Graf classification and analyzed using kappa coefficients. When examining the same printout, the mean of intra-observer agreement kappa value for Graf classification was 0.6, but the inter-physician agreement kappa value was found to be moderate, 0.50. For normal and abnormal grouping, the mean of intra-observer agreement kappa value was 0.67 and inter-physician agreement kappa value was 0.57. According to the findings of this study, Bar-On et al. indicated that both the ultrasonography technique and the physician interpreting the image may affect the result, and that there was a weak consensus among orthopedists [31].

In the study of Roover et al. [32], 200 ultrasonography images were classified according to Graf's method by four radiographers and a radiologist. They stated that the interobserver agreement regarding the ultrasound evaluation of the hip was good enough and that observer variability did not cause any serious cases to be overlooked. In the study of Ömeroğlu et al. [33] the rates of intra-observer and inter-physician agreement in the Graf classification were 65% and 51%, respectively. Intra-observer and inter-physician agreement rates in treatment method by hip type were 76% and 64%, respectively. In the study, it was stated that having basic knowledge about the Graf method was the most important point and the number of previous examinations by the observer had no effect on the results. In a study by Roposch et al. [34] intra- and inter-observer variability in the interpretation of ultrasound was examined. Training materials developed by Graf were given to four orthopedic specialists in their last year of training. However, two physicians (Group A) attended the training courses on the technique, while the other two (Group B) did not attend the training courses. A misclassification affecting treatment was rare; one patient received unnecessary treatment and three patients did not receive the necessary treatment. In the study, it was concluded that how to do and interpret ultrasound should be done correctly through training courses and self-study is insufficient [34]. In our study, no statistically significant difference was found between R1 and OS1 in terms of Graf type and normal-abnormal classification, but a significant difference was found when these physicians were compared with OS2.

Ozgun et al. [35] treated 210 babies. Ultrasound images were evaluated by two pediatric orthopedic professors, two orthopedic specialists, and two orthopedic assistants. In their study, they stated that more importance should be given to the beta angle and cartilage labrum in the resident training program and this is directly proportional to clinical experience. In our study, a statistically significant difference was found between physicians in alpha and beta measurements. It was seen that this difference was caused by the measurements of OS2 rather than the measurements of R1 and OS1.

Simon et al. [27] evaluated 158 ultrasonographic images. There was better agreement among physicians in the assessment of immature hips compared to mature hips. The least agreement was between the least experienced and most experienced physicians. It was observed that the agreement between physicians was higher in regard to immature hips than in mature hips. Therefore, they stated that USG is important in the evaluation of immature hips. The study indicated that although there were differences between the measurements in alpha and beta angles measured among physicians, the agreement between physicians was good in the classification, and the experience and education of the researchers played an important role in the compliance [27]. Melzer et al. [36] in their study, determined a mean error of 3.2° for the alpha angle and 11.9° for the beta angle. According to Neither et al [37], it is assumed that there may be a 10° margin of error in the measurements of alpha and beta angles. Roovers et al. [32] mean standard deviations of 3.2° and 6° were reported for alpha and beta angles, respectively. According to the Graf method, the mean standard deviation for alpha and beta angles is 4° [38]. In the study of Pedrotti et al. [39] ultrasonography of 798 patients was examined by different physicians. In the study, alpha and beta angle changes were not found to be statistically significant. In our study, it was seen that the ICC values obtained as a result of alpha and beta measurement showed good agreement between R1 and OS1, but the agreement between the two physicians with OS2 was not good.

The study of Rosendhal et al. [40] aimed to determine the agreement between physicians in the evaluation of hip morphology and stability with ultrasound. Three groups of infants were examined. Intra-observer and inter-physician agreements were determined for reading and reviewing the recorded ultrasound scans. A high degree of agreement was found for the morphological classification based on repeated examinations by two physicians of the scans of 206 infants enrolled by the same physician (doctors' kappa values of 0.7 and 0.8, respectively). The degree of agreement between the physicians was found to be moderate (kappa value = 0.5). There was moderate agreement among physicians in determining hip stability in 70 infants (kappa value = 0.4). In their study, they stated that in order to achieve a high level of agreement among physicians in the evaluation of hip morphology and stability in newborns, appropriate training and attention to detail in the measurement technique should be taken [40].

We examined the variation and variables between physicians' own measurements and among physicians in the interpretation of infant hip ultrasound. There was no pediatric radiologist in our study, but we had a radiologist and two orthopedic specialists. OS1 had the Graf method pediatric hip ultrasonography course certificate. OS2 only trained for developmental dysplasia during his residency. Among the three physicians, R and OS1 were the most compatible with each other, and OS1 and OS2 were the most incompatible. We attribute this situation to the fact that OS2 did not receive hip USG training.

Limitations

The low number of patients in this study can be considered a limitation. In addition, the inclusion of more doctors in this study would have been beneficial.

Conclusion

While there was agreement between trained doctors in the Graf measurements made by more than one doctor, it was seen that there was no agreement between the doctor who was not trained and the other doctors. We think that the most

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important way to increase this compliance is that doctors should regularly attend subject-specific training courses.

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Impact of COVID-19 pandemic on births: A university hospital experience

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This study was approved by Sivas Cumhuriyet University non-interventional clinical research ethics committee (Date: 21.09.2022 No: 2022-09-01).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Many studies have focused on assessing the effects of coronavirus 2019 (COVID-19) on the general population, but insufficient data concerning the impact on vulnerable populations, such as pregnant women, are available. The aim of this study was to compare the results of births before and during the pandemic in terms of maternal and newborn health and to determine the effect of the pandemic on such births.

Methods: The population of this descriptive, retrospective cohort study consisted of women who gave birth in Sivas Cumhuriyet University Hospital Gynecology and Obstetrics Clinic between 01.03.2019–31.08.2019 and 01.03.2020–31.08.2020. No sample selection was made. As birth characteristics, the total and average number of births per month, the week of birth, whether there was a preterm birth, and the mode of delivery were evaluated. Age, number of pregnancies and births were evaluated as maternal characteristics. The birth weight and height of the newborn, number of babies with low birth weight, presence of stillbirth, Apgar 0 and 5 minute scores, and birth complications were evaluated as birth outcomes. Countable data were expressed as numbers and percentages and measurement data as mean, standard deviation, and minimum and maximum values. Inter-period means were compared with the t-test, nominal data were compared with the chi-squared test, and $P < 0.05$ was considered significant.

Results: It was observed that a 22.1% increase in the number of births during the pandemic period (n = 685) occurred when compared with the pre-pandemic period (n = 561). The difference in the increase in the number of births in both periods was not statistically significant ($P = 0.153$). The birth patterns, gender of the newborns, and the birth rates, including low birth weights, were similar during both periods. Gravidity and parity averages and minimum–maximum values were similar in both periods. When the weeks of gestation at birth were compared, it was observed that births occurred in the months before the pandemic, on average, during earlier gestational weeks. The number of births with fetal anomalies and stillbirths were compared, and it was found that the number of cases seen in both periods were similar.

Conclusion: In this study, the characteristics and results of the pre-pandemic and pandemic periods were found to be similar.

Keywords: COVID-19, Neonatal outcome, Pregnancy outcome, Preterm birth

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Introduction

Coronavirus 2019 (COVID-19) is a public health problem worldwide. that has greatly affected health systems, resulting in significant morbidity and mortality. To limit the spread of the disease, many practices were initially carried out globally , such as stay-at-home practices, social isolation, quarantine, curfews, restriction of health services provided in hospitals, closure of schools, and other aspects [1]. Although many studies that examine the effects of COVID 19 on human health are available, more data are needed to reveal its effects on populations in special groups, such as pregnant women. Due to physiological changes in pregnancy (immune system, cardiac, pulmonary, and others), the risk of developing serious diseases increases with viral infections [2]. The need for more information about the placental transmission of COVID-19 during pregnancy and how it affects pregnancy outcomes is present. These data are important for maternal and newborn health. In addition to the diseases directly caused by COVID-19 itself, the policies taken to prevent the spread of the disease, such as quarantines and the inability of people to access adequate healthcare services due to the fear of being in a crowded environment, may have adversely affected the health of pregnant woman and their fetuses [3].

The aim of this study was to compare the results of births before and during the pandemic in terms of maternal and newborn health and to determine the effect of the pandemic on such births.

Materials and methods

In the descriptive, retrospective cohort type of study, the study group consisted of women who gave birth in the Sivas Cumhuriyet University Hospital Gynecology and Obstetrics Clinic between 01.03.2019–31.08.2019 and 01.03.2020–31.08.2020 periods. Ethics committee approval dated 21.09.2022 and numbered 2022-09/01 was obtained from the ethics committee of Sivas Cumhuriyet University non-interventional clinical research. Data were obtained from Sivas Cumhuriyet University Gynecology and Obstetrics Clinic. The characteristics and birth parameters of the newborns and mothers were compared in the six-month periods covering the pandemic period (01.03.2020–31.08.2020) and the pre-pandemic period (01.03.2019–31.08.2019) between the same dates of the previous year. As the birth characteristics, the total and average number of births per month, the week of birth, whether a preterm birth (births below 37 weeks were considered preterm) had occurred, and the mode of delivery (cesarean/vaginal) were evaluated. Age and number of pregnancies and births were evaluated as maternal characteristics. The birth weight and height of the newborn, the number of babies with low birth weight (newborns under 2500 g were considered as low birth weight), the presence of stillbirth, Apgar 0 and 5 minute scores, and birth complications were evaluated as birth outcomes. Pregnancy complications were classified as the absence/presence of premature rupture of membranes, oligohydramnios, preeclampsia, placenta previa, and other fetal anomalies.

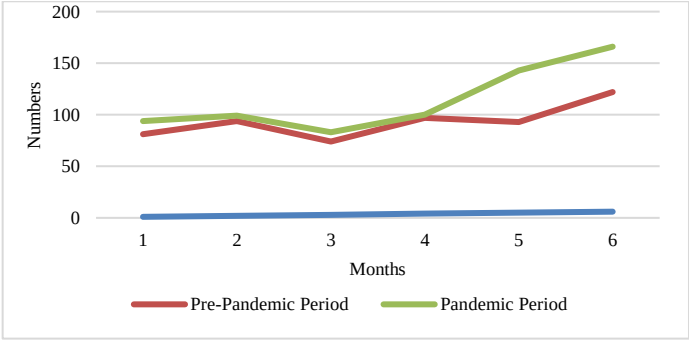
Statistical analysis

Statistical analyzes were performed with SPSS-22 (SPSS INC., Chicago, IL, USA) program. Countable data were represented as numbers and percentages and measurement data as mean, standard deviation, and minimum and maximum values. Inter-period means were compared with the t-test, nominal data were compared with the chi-squared test, and $P < 0.05$ was considered significant.

Results

When the number of births of the pre-pandemic period and the pandemic period were compared, the lowest number of births in both periods was in May (pre-pandemic period n = 74, pandemic period n = 83) and the highest birthrates were found in August (pre-pandemic period n = 122, pandemic period n = 166) as shown in Figure 1.

Figure 1: Comparison of birth numbers based on pre-pandemic and pandemic period months



A 22.1% increase in the number of births during the pandemic period compared to the pre-pandemic period was found (Table 1). The increase in the number of births in both periods is not statistically significant (n = 561 and 685, respectively; $P = 0.153$).

When the characteristics of deliveries performed during the pre-pandemic and pandemic periods were compared, it can be seen that the rate of preterm birth was significantly lower during the pandemic period ($P = 0.030$) as shown in Table 1. The birth patterns, the gender of the newborns, and the birth rates with low birth weight were similar in both periods (Table 1).

Table 1: Characteristics of pre-pandemic and pandemic-period births

	Pre-pandemic period n	%	Pandemic period n	%	*P*-value
Type of birth					0.060
Cesarean section	376	67.0	424	61.9	
Vaginal birth	185	33.0	261	38.1	
Gender					0.203
Female	258	46.0	340	49.6	
Male	303	54.0	345	50.4	
Preterm birth					0.030
Yes	178	31.7	208	30.4	
No	383	68.3	477	69.6	
Low birth weight					0.061
Yes	87	15.5	93	13.6	
No	474	84.5	592	86.4	
Birth numbers	561		685		0.153

When the characteristics of the women who gave birth in both periods were compared, it can be seen that the average ages were similar. While the youngest mother giving birth in the pre-pandemic period was 16, the youngest age was found to be 14 during the pandemic period. Gravidity and parity averages and minimum–maximum values were similar during both periods (Table 2).

When the results of deliveries performed in the pre-pandemic period and during the pandemic period were compared, the week of birth, weight and height of newborns, and

Apgar 0 and 5th minute scores were compared, and it was found that they were similar during both periods with no statistically significant difference. When the weeks of gestation at birth were compared, it was observed that births occurred in the months before the pandemic, on average, in earlier gestational weeks ($P = 0.050$) as shown in Table 3.

Table 2: Comparison of pre-pandemic and pandemic maternal characteristics

	Pre-pandemic period		Pandemic period		*P*-value
	Mean (SD)	Min–Max	Mean (SD)	Min-Max	
Age	29.1 (5.7)	16–45	28.9 (6.0)	14–48	0.210
Gravidity	2.7 (1.7)	1–14	2.7 (1.6)	1–9	0.131
Parity	1.3 (1.4)	0–9	1.2 (1.2)	0–7	0.132

SD: standard deviation

Table 3: Comparison of pre-pandemic and pandemic birth outcomes

	Pre-pandemic period		Pandemic period		*P*-value
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	
Gestational week at birth	39.4 (2.8)	22 - 41	37.8 (2.5)	(25–42)	0.050
Birth weight (gr)	3021.8 (656.5)	465 - 4420	3081.6 (633.3)	(620–5010)	0.370
Height (cm)	48.1 (4.0)	28–55	48.8 (3.6)	(31–58)	0.086
Apgar 0 minute	7.6 (1.9)	0 - 10	7.5 (1.5)	(0–10)	0.116
Apgar 5 minute	8.7 (1.7)	0 - 10	8.8 (1.4)	(0 – 10)	0.133

SD: standard deviation

The number of births with pregnancy complications in the pre-pandemic period and the corresponding number during the pandemic, and the number of births with fetal anomalies and stillbirths were compared, and it was found that the number of cases seen in both periods were similar (Table 4).

Table 4: Comparison of pregnancy complications and congenital anomalies between the pre-pandemic period and the pandemic period

	Pre-pandemic period		Pandemic period		*P*-value
	n	%	n	%	
Pregnancy Complication					0.631
Premature rupture of membranes	27	23.2	42	31.5	
Oligohydramnios	20	17.4	21	15.8	
Preeclampsia	18	15.5	30	22.6	
Placenta previa	11	9.5	12	9.0	
Other	40	34.4	28	21.1	
Fetal anomaly					
Yes	10	1.8	8	1.2	0.371
No	551	98.2	677	98.8	
Stillbirth					
Yes	11	2.0	6	0.9	0.106
No	550	98.0	679	99.1	

Discussion

Severe acute and Middle East respiratory syndrome viruses (SARS and MERS, respectively) have attracted attention as infections resulting in extremely high mortality rates and extremely serious pregnancy complications. It is known that the mortality of SARS during pregnancy is up to 25% [4]. The effects of COVID-19, which is similar to these viruses, on pregnancy and birth is also a public health problem that needs to be examined. In a study examining the data of many countries, it was reported that natural population growth rates decreased in 2020 and 2021 [5]. In our study, a 22.1% increase in the number of births occurred during the pandemic period compared to the pre-pandemic period; however, this increase was not statistically significant.

Premature birth is the leading cause of infant/child death worldwide, and most survivors face negative long-term consequences. Results on preterm birth rates during COVID-19 quarantines are conflicting. In a systematic meta-analysis review study, it was reported that the risk of preterm birth increased significantly during COVID-19 [6]. In our study, when the characteristics of deliveries performed during the pre-pandemic and pandemic periods were compared, it was found that the rates of preterm births decreased significantly during the pandemic period. The etiology of preterm births during the COVID-19 pandemic is largely unclear and possibly multifactorial thus hindering effective prevention.

In some studies, it was shown that COVID-19 causes an increase in preterm births and cesarean deliveries [7], but it seems that many pregnant women deliver by planned cesarean section with the belief that serious maternal respiratory disease will be cured by delivery. Published studies have shown that the clinical course of COVID-19 is more severe during pregnancy, but pregnancy does not increase susceptibility to COVID-19 [8]. One study included 11,078 pregnant women, and 65 of them were reported to have COVID-19. As a result of the study, it was shown that COVID-19 led to increases in adverse pregnancy outcomes, such as preterm birth and cesarean delivery, but insufficient evidence regarding placental transmission of SARS-COV-2 is available [9]. In a study conducted in Nanjing, China, it was observed that no change in preterm birth during the pandemic occurred, but a decrease in birth weight in term babies had occurred, and it was thought that anxiety and stress caused by the pandemic may also contribute to this lower weight [10]. A systematic meta-analysis review study found that low birth weight rates in neonates are more common in pregnancy with severe COVID-19 [11]. In our study, no significant difference was found in terms of birth weights of newborns between the pre-pandemic and pandemic periods. In a study examining the effect of COVID-19 on preterm birth rates, it was shown that a decrease in cesarean section and iatrogenic preterm births during the pandemic process occurred, and it was suggested that the reason for this decrease was caused by the decrease in visits to the obstetrician during childbirth and curfews [12].

In a systematic review and meta-analysis study including 40 studies, it was stated that maternal deaths, stillbirths, ruptured ectopic pregnancies, and maternal depression had increased during the COVID-19 pandemic, and the pandemic period was worse for mother and baby. It was also reported that differences between high- and low-income families in the studies included in the study were found [13]. In our study, no significant difference was found in terms of pregnancy complications in any group.

In a study, 13 states of the United States were included, and it was reported that one in four women aged 15–49 who were hospitalized for COVID-19 between August 2020 and March 2022 were pregnant, and about half of the pregnant women admitted to the hospital were asymptomatic. It was reported that 16.2% of symptomatic pregnant women were admitted to the intensive care unit, and 8.5% required mechanical ventilation. It was reported that 2.2% of all pregnancies identified during hospitalization associated with COVID-19 resulted in pregnancy loss [14].

Limitations

The limitations of this study are its single center nature, short time interval, and small sample size.

Conclusion

Although many studies have been conducted on the effects of COVID-19 during pregnancy, the long-term effects on infants are not yet clear. Although no inconvenience in terms of vaginal birth as a method of delivery has been reported, cesarean

delivery is generally preferred. Among people infected with COVID-19, pregnant women should be considered as a special group, especially due to changes in the immune system. In this study, the pre-pandemic and pandemic periods were compared in term of births, and it was seen that the number of births, birth characteristics, and birth outcomes were similar during both periods. More multidisciplinary research is needed to reveal the effects of the pandemic on births.

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The value of the optic nerve sheath diameter measured using computerized brain tomography in the evaluation of mortality status in patients admitted to the emergency department with intracranial hemorrhage

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Approval for the study was granted by the Katip Çelebi University Medical Faculty clinical research ethical committee (decision no: 675, date: May 12, 2020).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: The optic nerve sheath diameter (ONSD) measurement is a non-invasive method that can be obtained from computerized tomography (CT) images. It can therefore be a useful diagnostic tool in determining prognosis in the emergency department. The aim of this study was to investigate the relationship between ONSD and mortality status in patients with intracranial hemorrhage who presented to the emergency department by measuring ONSD on computerized brain tomography images taken during admission.

Methods: This retrospective cohort study was carried out in the emergency department of a tertiary hospital between December 1, 2018 and December 1, 2020 and included intracranial hemorrhage patients and patients with normal brain CT scans that had been obtained for any reason. Bilateral ONSDs were measured in both the intracranial hemorrhage and control groups. We first evaluated whether ONSD would differ between the two groups after which the relationship between ONSD and mortality was analyzed in the patient group who presented with bleeding.

Results: Intracranial hemorrhage was present in half the cases and midline shift in 21.5%. A statistically significant increase in ONSD was observed in cases with intracranial hemorrhage ($P < 0.001$). Similarly, a statistically significant increase in ONSD was found in cases with midline shifts and mortality ($P < 0.001$). A cut-off value of 4.19 mm for mean optic nerve diameter exhibited 100% sensitivity and 70% specificity in terms of hemorrhage detection (area under the curve [AUC]: 0.952; $P < 0.001$). A cut-off value of 6.03 mm for ONSD exhibited 76% sensitivity and 74% specificity in terms of hemorrhage detection (AUC: 0.730; $P = 0.001$). The odds ratio for prediction of mortality based on a regression analysis was 8.838 in cases with intracranial hemorrhage ($P < 0.001$).

Conclusion: ONSSD measured on CT images is a promising tool for prediction of intracranial hemorrhage, midline shift, and mortality status.

Keywords: Intracranial hemorrhage, Optic nerve sheath diameter, Computerized tomography, Mortality

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Introduction

The optic nerve is part of the central nervous system (CNS) and is surrounded by cerebrospinal fluid (CSF) and the dura mater. Changes in the optic nerve sheath diameter (ONSD) parallel changes in CSF pressure. An ONSD measurement is reliable method for showing increased intracranial pressure (ICP) [1]. Identifying an increase in ICP is as vitally important for the patient as it is difficult. An Increase in ICP following intracranial hemorrhage causes an increase in the ONSD. To date, clinical studies have observed high correlation between ONSD and symptoms, bedside ocular ultrasonography (USG), and computerized tomography (CT) scans of brain abnormalities with all three reported of being capable of indicating an increase in intracranial pressure (ICP) [2].

Patients presenting to the emergency department with traumatic or non-traumatic causes and in whom intracranial hemorrhage is suspected are diagnosed using a CT scan of the brain. Although ONSD can be measured with ultrasonography (USG), this procedure is not appropriate in patients with orbital trauma, and the fact that measurements may vary depending on individual operator performance leads to a reduction in the reliability of the procedure. Considering that tomography is performed on the majority of patients with head trauma in particular, ONSD measurement based on tomography results may be an appropriate diagnostic method since it is non-invasive and can be measured on the CT images of the brain that are obtained without any additional procedure.

The purpose of this study was to evaluate the effects of ONSD that was measured using computerized brain tomography on mortality and morbidity in patients with intracranial hemorrhage who presented to the emergency department.

Materials and methods

Study design and setting

This retrospective, observational study was performed in the emergency department of the Katip Çelebi University Training and Research Hospital in Izmir, Turkey, between December 1, 2018 and December 1, 2020. Approval for the study was granted by the Katip Çelebi University Medical Faculty Clinical Research Ethics committee (decision no: 675, date: May 12, 2020).

Study population

This study included the patients with intracranial hemorrhage and those who presented to the emergency department for any reason and obtained normal brain CT scans.

Inclusion criteria

- Age 18 or over

Exclusion criteria

- Age under 18
- Presence of glaucoma
- Presence of orbital trauma
- Presence of hydrocephaly
- Presence of intracranial space-occupying formations
- Diagnosis of intracranial hemorrhage
- Diagnosis of pseudotumor cerebri
- Presence of cerebral vein thrombosis

Study protocol and data collection

ONSD was measured by measuring transverse sections 3 mm distal to the point where the nerve exits from the globe (Figure 1) on the tomography images captured with a Toshiba Aquilion 64-Multislice system. All ONSD measurements were obtained separately for each eye with mean right and left eye diameters recorded for each patient. Statistical data were calculated using mean values. Patient information was retrieved by scanning electronic records in the hospital's data management system. Patient age, gender, chronic disease status, presence or absence of intracranial hemorrhage, history of trauma if applicable, hemorrhage site, and presence of midline shift were recorded by evaluating in-hospital mortality and morbidity records.

Figure 1: Optic nerve sheath diameter measurement from axial sections

Outcome measure

The primary outcome was the ONSD width.

Research sample

Vaiman et al. [3] examined the effectiveness of ONSD measurement for an evaluation of intracranial pressure in traumatic cerebral hemorrhage. Based on that study, a total sample size of 64 with 32 in each group was calculated using G-Power 3.1.9.2. software with mean and standard deviation values for the left ONSD that was measured 3 mm behind the globe. A study group consisting of 100 patients who developed intracranial hemorrhage for any reason and a control group of 100 patients who underwent brain CT for any indication and whose results were interpreted as normal were also included in the study.

Statistical analysis

The study data were analyzed on SPSS 20.0 software for Windows (IBM Corporation, Armonk, NY, USA). Numerical variables were subject to a normality of distribution test using parametric or non-parametric tests depending on the results. Categorical variables were expressed as frequency distribution (number and percentage) and numerical variables as descriptive statistics (mean, standard deviation, and interquartile range [IQR]). A type 1 error rate of $\alpha = 0.05$ was used to determine statistical significance. Descriptive statistics were expressed as frequency, percentage, mean, standard deviation, median, minimum, and maximum values. Numbers and percentages were calculated for categorical variables and as mean, standard deviation, minimum, maximum and IQR for numerical variables. Histogram curves, kurtosis and skewness values, and the Shapiro–Wilk test were used to determine whether data were

normally distributed. Normally distributed parameters were expressed as mean plus standard deviation and non-normally distributed parameters as median and minimum-maximum values.

A Student's t-test was applied in two-group comparisons of means of normally distributed data normal and the Mann–Whitney U test in case of non-normally distributed data. A one way analysis of variance (ANOVA) was applied for the comparison of means between more than two groups since the data were normally distributed.

Results

Two hundred patients were included in the study, 57.5% (n = 115) were men, and 42.5% (n = 85) were women. The mean age of the total study group was 51.12 (18.65) years. Mean ages were 47.90 (19.86) in men and 55.48 (15.97) in women. Participants' demographic data are presented in Table 1.

Table 1: Patient demographic characteristics and clinical data

Parameter	ICH group (n = 100)	Control group (n = 100)
Gender		
Male	59 (59%)	NA
Female	41 (41%)	NA
History of Chronic Disease		
No	42 (42%)	67 (67%)
Yes	58 (58%)	33 (33%)
Intracranial Hemorrhage Type		
Subarachnoid hemorrhage	52 (52)	NA
Subdural hemorrhage	15 (15)	NA
Intraparenchymal hemorrhage	30 (30)	NA
Intraventricular hemorrhage	3 (3)	NA
Presence of midline Shift		
No	57 (57%)	100 (100%)
Yes	43 (43%)	0 (0%)
Mortality		
No	79 (79%)	95 (95%)
Yes	21 (21%)	5 (5%)
Morbidity		
No	80 (80%)	100 (100%)
Yes	20 (20%)	0 (0%)

NA: Not applicable, ICH: Intracranial hemorrhage

Examination of the effect of ONSD on intracranial hemorrhage showed that an increase in right- and left-side ONSD and in the mean value of the two was associated with intracranial hemorrhage independent of trauma ($P < 0.001$ for all) as shown in Table 2.

Table 2: Effect of ONSD on Intracranial Hemorrhage

Intracranial Hemorrhage	ONSD Mean (SD)	*P*-value	ONSD (Right) Mean (SD)	*P*-value	ONSD (Left) Mean (SD)	*P*-value
No	3.81 (0.86)	<0.001	3.73 (0.91)	<0.001	3.90 (0.98)	<0.001
Yes	5.76 (1.04)		5.66 (1.15)		5.91 (1.16)	

ONSD: optic nerve sheath diameter

When only the ICH group was evaluated, an increase in ONSD in patients with intracranial hemorrhage was found to be significant in terms of mortality and midline shift development ($P < 0.001$ and $P < 0.001$, respectively) but not of morbidity and ($P = 0.456$) as shown in Table 3.

Table 3: The effect of ONSD on morbidity, mortality, and midline shift development in the presence of intracranial hemorrhage

		ONSD Mean (SD)	*P*-value
Morbidity	No	5.72 (1.07)	0.456
	Yes	5.92 (0.91)	
Mortality	No	5.57 (0.92)	<0.001
	Yes	6.47 (1.18)	
Midline shift	No	5.38 (0.84)	<0.001
	Yes	6.26 (1.08)	

ONSD: optic nerve sheath diameter, SD: standard deviation

ROC analysis was performed in order to calculate the success of mean ONSD in determining intracranial hemorrhage and in determining mortality and midline shift development in patients with intracranial hemorrhage. Accordingly, a cut-off value of 4.19 mm (area under the curve [AUC]: 0.952) was determined for intracranial hemorrhage, a cut-off value of 5.67 mm (AUC: 0.737) for midline shift development in patients with intracranial hemorrhage, and a cut-off value of 6.03 mm (AUC: 0.730) for mortality (Table 4).

According to the cut-off values determined by the receiver operating characteristic (ROC) analysis, the odds ratio (OR) for ICH was 29.095, the OR for mortality was 8.838, and the OR for midline shift development was 6.078 based on the binary logistic regression analysis that was done to evaluate the relationship between ONSD and intracranial hemorrhage, mortality, and midline shift development (Table 5).

Table 4: Relationship between mean ONSD and mortality and morbidity ROC analysis

	Mean ONSD Cut-off	AUC	Sensitivity	Specificity	*P*-value	95% CI Lower Bound	Upper Bound
Intracranial hemorrhage	4.19	0.952	100	70	<0.001	0.907	0.997
Mortality	6.035	0.730	76	74	0.001	0.598	0.860
Midline Shift	5.675	0.737	72	70	<0.001	0.638	0.835

ONSD: optic nerve sheath diameter, ROC: receiver operating characteristic curve, AUC: area under the curve, CI: confidence interval

Table 5: Logistic regression analysis showing the relationship of ONSD with intracranial hemorrhage, mortality, and midline shift

	B	SE	Wald	*P*-value	Exp(B)	95% CI for EXP(B) Lower	Upper
Intracranial hemorrhage	3.371	0.470	51.346	<0.001	29.095	11.573	73.150
Mortality	2.179	0.572	14.505	<0.001	8.838	2.280	27.125
Midline shift	1.805	0.447	16.333	<0.001	6.078	2.533	14.585

SE: standard error, CI: confidence interval

Discussion

Despite developments in clinical approaches, intracranial hemorrhage is a disease with high morbidity and mortality. Mortality is observed at a rate of 50% in the first year after intracranial hemorrhage. The morbidity rate in the first six months after hemorrhage in non-fatal cases is 80% [4]. In the present study, ONSD was directly related to the presence of bleeding, independent of trauma, and to mortality and midline shift development in patients with bleeding.

ONSD has been associated with intracranial hemorrhage in most studies involving measurements performed with both USG and CT [5, 6]. However, in a study of intensive care patients, Zoerle et al. [7] reported no association between subarachnoid hemorrhage and ONSD measured based on USG. This finding may be attributable to the antiedema therapy administered to intensive care patients for a period; therefore, their intracranial pressures are not particularly high. In addition, since USG is an operator-dependent technique, measurements taken by different individuals may not be consistent. This difference may lead to inaccurate results. The increase in ONSD based on CT images in patients with intracranial hemorrhage in this study was found to be associated with the presence of bleeding. At a cut-off value of 4.19 for ONSD, every 3.371 unit increase in intracranial hemorrhage was associated with a 29.095-fold increase in ONSD.

Masquere et al. [8] reported that an increase in ONSD as viewed on the CT scan was associated with an increase in mortality following intracranial hemorrhage. Another study by

Zhao et al. [9] involving ischemic and hemorrhagic stroke patients reported a positive correlation between ONSD and mortality. In a study of patients admitted to intensive care unit (ICU) due to head trauma, Sekhon et al. [10] reported that a one unit increase in ONSD as measured on a CT scan led to a 2-fold increase in mortality. In the present study, at an ONSD cut-off value of 6.03, every 2.179 unit increase in mortality was associated with an 8.838-fold increase in ONSD.

In a study of patients presenting with head trauma and admitted to the ICU, Kazdal et al. [11] reported significantly higher ONSD in measurements that were obtained using USG in patients with intracranial hemorrhage with midline shift compared to a control group with intracranial hemorrhage without midline shift. Komut et al. [12] used USG measurements to investigate non-trauma patients who presented to the emergency department and reported that an increase in ONSD was associated with the presence of a midline shift. In that study, the authors determined an ONSD cut-off value of 5.3 mm for detecting the presence of midline shift (AUC: 0.728; 95% confidence interval [CI] 0.585–0.871). That cut-off point exhibited 70% sensitivity and 74% specificity. In the present study, an ONSD cut-off point of 5.67 mm was determined for the presence of a midline shift. That cut-off value exhibited 72% sensitivity and 71% specificity. Every 1.805 unit increase in midline shift was associated with a 6.078-fold increase in ONSD.

A number of limitations, including its retrospective nature and low patient number, can be found in this study. Its single-center nature also means that it cannot be generalized to the entire population. Further multi-center studies with larger patient groups are needed to further address this subject.

Conclusions

The findings of this study suggest that ONSD measurement is a non-invasive method that can be useful to clinicians for early detection of increased intracranial pressure and intracranial hemorrhage. It is also a promising method that could be used for predicting mortality in patients with intracranial hemorrhage. An increase in ONSD can also be added as a poor prognostic factor to newly developed scoring systems.

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Clinical presentation and endoscopic findings in adult patients with eosinophilic esophagitis

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Ethics Committee Approval
The study protocol was approved by Acibadem Mehmet Ali Aydinlar University Evaluation Committee for Medical Research (ATADEK), (no: 2022-14/5; date: September 2, 2022). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: The frequency of eosinophilic esophagitis has been rising over the last decades. It is diagnosed primarily based on symptoms and endoscopic and histopathological examination findings. Although eosinophilic esophagitis is not associated with malignancy, it remains an important condition affecting both children and adults, as it is associated with morbidity such as dysphagia, food impaction, and esophageal strictures. This study aimed to define clinical and endoscopic characteristics of adult patients diagnosed with eosinophilic esophagitis based on recently recommended histopathological criteria.

Methods: This retrospective cross-sectional descriptive study included 54 adult patients (mean age: 33.6 yr, range: 16–61 yr) who underwent upper gastrointestinal system endoscopy for dyspeptic complaints (epigastric pain, reflux, dysphagia, or food impaction) and diagnosed with eosinophilic esophagitis based on the latest histopathological criteria (≥15 eosinophils per high-power field). Patients with a history of malignancy were excluded. Patients' clinical, endoscopic, and histopathological data were examined.

Results: In patients diagnosed with eosinophilic esophagitis, the most common presenting complaint was dysphagia (61.1%), followed by dyspepsia (24.0%), regurgitation (16.6%), chest pain (16.6%), epigastric pain (12.9%), food impaction (11.1%), and halitosis (3.7%), without any age predilection for the complaints. White papules and linear furrow were the most frequent findings on endoscopic examination (35.1% each), followed by circular rings (24.0%), paleness (22.2%), normal endoscopic finding (20.3%), and small-caliber esophagus (11.1%).

Conclusion: The diagnosis of eosinophilic esophagitis remains challenging due to considerable variations in definitions and in the relative frequencies of endoscopic findings. Therefore, we recommend combining clinical, endoscopic, and histologic criteria to establish diagnosis. The identification of standards for diagnosis in future studies is warranted.

Keywords: Eosinophilic esophagitis, Endoscopic examination, Histopathological examination, Eosinophil count

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Introduction

Eosinophilic esophagitis (EoE) is a relatively rare entity first reported in 1978 by Landres et al. [1]. It is characterized by a dense infiltration of eosinophils in esophageal mucosa without similar findings in the stomach or duodenum and is associated with esophageal symptoms [2]. Although a precise etiology remains unknown, its high coincidence with atopic diseases, including atopic dermatitis, asthma, and allergic rhinitis, suggests an allergic background [3-6].

Despite initial sporadic reports, the frequency of eosinophilic esophagitis seems to rise over decades [7]. A Swedish study reported a more than 10-fold rise in its prevalence between 1989 and 2004 [8]. Similarly, a US study reported an increase to 55 per 100,000 population prevalence over the last three decades [9]. Another study showed a 6.5% prevalence among individuals who underwent endoscopy examination [10], highlighting the importance of the condition from a public health standpoint. A recent meta-analysis found that the incidence rate was 6.6/100,000 person-years in children, and 7.7/100,000 person-years in adults, and that the prevalence was 34 cases per 100,000 children and 42.2 cases per 100,000 adults [11].

It is more common in men, with a male to female ratio of 3:1, and there is a peak in the third to fifth decades of life [12].

Diagnosis of eosinophilic esophagitis is primarily based on esophageal symptoms, endoscopic appearance of esophageal mucosa, and histopathological examination findings of mucosal samples showing a dense eosinophilic infiltration [7, 13, 14]. Although some controversy exists on the extent of eosinophil infiltration [15-17], recent recommendations suggest an eosinophil count ≥15 per high-power field in at least one esophageal biopsy sample and exclusion of esophageal eosinophilia secondary to GERD to be the diagnostic criteria [6, 18-21].

This study screened a large patient sample that underwent endoscopic examination and esophageal biopsy and aimed to define clinical and endoscopic characteristics of adult patients diagnosed with eosinophilic esophagitis based on recently recommended histopathological criteria.

Materials and methods

Study population

This retrospective cross-sectional descriptive study included 54 adult patients (>18 yr. of age) with a mean age of 33.6 years (range:16–61) who underwent upper gastrointestinal system endoscopy for dyspeptic complaints (epigastric pain, reflux, dysphagia, or food impaction) between January 2010 and September 2018 and diagnosed with eosinophilic esophagitis. Patients with a history of malignancy were excluded. The majority of the patients were male (81.5%). Based on previous recommendations [19], eosinophilic esophagitis was defined as an eosinophil count ≥15 per high-power field on esophageal biopsy specimens. Fifty-four patients fulfilling this criterion were included in this study and their clinical, endoscopic, and histopathological data were extracted. The study protocol was approved by the local ethics committee (Acibadem Mehmet Ali Aydinlar University Evaluation Committee for Medical Research [ATADEK], no, 2022-14/5; date, September 2, 2022) and the study was conducted in accordance with the Declaration of Helsinki.

Endoscopic biopsy assessment

All endoscopies and biopsies were done by experienced gastroenterology specialists under mild sedation. All gross examination findings, including any mucosal abnormalities, were identified and recorded, and biopsies were obtained from the esophagus, typically from multiple sites. Formalin-fixed, paraffin-embedded biopsy samples were sectioned at a thickness of 3 μm and stained with hematoxylin and eosin and PAS-AB (pH 2.5) stains. All esophageal biopsies were evaluated for reflux esophagitis, intraepithelial eosinophil infiltration, dysplasia, columnar metaplasia, and other specific conditions [22]. When intraepithelial eosinophil infiltration was seen, eosinophils were counted at the densest region using 400x high-power field. In addition, gastric biopsies were evaluated based on the histological criteria of the Sydney System [23]. Slides were also examined for the presence of *Helicobacter pylori* infection.

Statistical analysis

The results were presented with descriptive statistics. Data were expressed as mean ± standard deviation and proportions (percent, %), where appropriate.

Results

Baseline characteristics

The majority of the study population was composed of male (n = 44, 81.5%) patients. The mean age was 33.6 years (range, 16–61). The most common presenting complaint was dysphagia (61.1%), followed by dyspepsia (24.0%), regurgitation (16.6%), chest pain (16.6%), epigastric pain (12.9%), food impaction (11.1%), and halitosis (3.7%) (Table 1). The mean duration of symptoms was 6.4 (9.7) months (range, 0.5–36). History of allergy was noted in 12 (22.2%) patients, including allergic rhinitis in 7 of 12 (58.3%) patients (Table 1).

Table 1: Baseline characteristics

Age (years), mean (range)	33.6 (16-61)
Gender, n (%)	
Female	10 (18.5)
Male	44 (81.5)
Presenting symptom, n (%)	
Dysphagia	33 (61.1)
Dyspepsia	13 (24.0)
Regurgitation	9 (16.6)
Chest pain	9 (16.6)
Epigastric pain	7 (12.9)
Food Impaction	6 (11.1)
Halitosis	2 (3.7)
Duration of symptoms [a] (months), mean (SD, range)	6.4 (9.7, 0.5-36)
History of allergy, n (%)	12 (22.2)
Allergic rhinitis	7 (58.3)
Food allergy	2 (16.7)
Drug allergy	3 (25.0)

[a] Since the six patients with food impaction attended the emergency unit immediately after the incident, the mean duration of symptoms is based on data from the remaining 48 patients.

Endoscopic findings

White papules and linear furrow were the most frequent finding on endoscopic examination (35.1%) followed by circular rings (24.0%), paleness (22.2%), normal endoscopic findings (20.3%), and small caliber esophagus (11.1%) (Table 2). Two endoscopic appearance examples are shown in Figure 1.

Histopathological findings

The mean number of biopsies obtained during endoscopic examination was 4.3 (2.8) (range, 1–14). The mean eosinophil count per high-power field was 47.6 (range, 15–102). *H. pylori* data was available in 51 patients, 15 of which were

positive (29.4%) (Table 2). Examples of histopathological appearance with eosinophilic infiltration are shown in Figure 2.

Table 2: Endoscopic and histopathological findings

Distribution of endoscopic findings	n (%)
White papules	19 (35.1)
Linear furrow	19 (35.1)
Circular rings	13 (24.0)
Paleness	12 (22.2)
Normal esophagus	11 (20.3)
Food impaction	6 (11.1)
Small caliber esophagus	6 (11.1)
Number of biopsies, mean (SD, range)	4.3 (2.8, 1-14)
Eosinophil count (per high power field mean)	47.6 (15-102)
H. pylori positivity [a], n (%)	15 (29.4)

[a] For 51 cases with available data on assessment of H. pylori positivity

Figure 1: Examples of endoscopic appearance (a: food impaction, b: linear furrow).

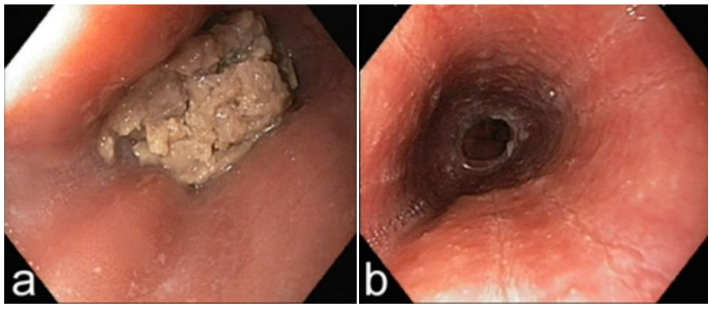
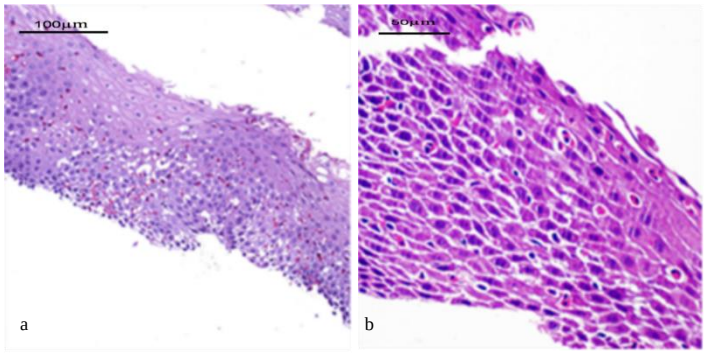


Figure 2: Histopathological appearance examples of eosinophilic infiltration (a: x40 magnification, b: x100 magnification).



Discussion

This study examined the clinical symptoms and endoscopic findings of a group of adult patients diagnosed with eosinophilic esophagitis based on the latest histopathological criteria. Our findings revealed male predominance (81.5%) in eosinophilic esophagitis and indicated dysphagia (61.1%) as the most common presenting complaint along with identification of at least two diagnostic endoscopic findings in one-third of patients.

Given that 81.5% of our cohort was composed of male patients, our findings support the male preponderance of eosinophilic esophagitis, as reported in several studies [18, 19, 24, 25], systemic reviews [26, 27], and guidelines [2, 28], although the reason remains to be specified [26].

Presenting symptoms of eosinophilic esophagitis are variable, including dysphagia, food impaction, chest pain unresponsive to anti-acids, refractory heartburn, and upper abdominal pain [2, 7, 14, 29].

Identification of dysphagia as the most prevalent complaint in our cohort is in line with several previous studies. In a US series, dysphagia was reported in 65% of patients with eosinophilic esophagitis [10]. In a Japanese study, dysphagia was the most prominent symptom reported by 46% of the patients [30]. Also, in a recent systematic review of eosinophilic esophagitis in 217 patients from Asian countries, dysphagia was reported as the primary symptom identified in 44% of the patients [26].

Nonetheless, it should be noted that most of previous studies have relatively small sample sizes along with considerable variation in the signs and symptoms reported. Being the second-most presenting complaint identified in 24.0% of our patients, dyspeptic complaints have been indicated to predominate in some patient populations [2, 29]. Also, a large Mexican study reported reflux symptoms as the most frequent presenting feature (42%) [31]. Similarly, in a Turkish study, heartburn and regurgitation was reported in 72% and 52.4% of the patients, respectively, with only 24% complaining of dysphagia [32].

Occasionally, patients may not seek help for dysphagia until food impaction occurs. The association between eosinophilic esophagitis and food impaction has been shown in previous studies, with indication of food impaction as the presenting symptom in many patients [14, 33-35].

Interestingly, in a Chinese population-based study, 1030 healthy volunteers underwent endoscopic biopsy of the esophagus, and eosinophilic esophagitis was reported in 4 (0.4%) patients [36]. Among them, only one had reflux symptoms; the remaining three patients were asymptomatic (75%). This seems to point out the fact that most eosinophilic esophagitis cases in the general population may be asymptomatic, in contrast to the findings of most previous studies, since most of clinical presentation data comes from patients who underwent endoscopic examination because of their symptoms.

Endoscopic examination with biopsy is the main diagnostic tool in eosinophilic esophagitis; however, findings are variable [2, 29]. The Eosinophilic Esophagitis Endoscopic Reference Score (EREFS; **E**dema of the mucosa, esophageal **R**ings, eosinophilic **E**xudates as white papules, linear **F**urrows, esophageal **S**tricture) has been recently validated and become an important parameter for diagnosis, clinical trials, and follow-up the patients with EoE [6, 7, 14, 20, 21, 37]. Although most patients with eosinophilic esophagitis are known to have endoscopic findings including linear furrow, circular ring, attenuation of subepithelial vascular pattern, white papules, stricture, or small caliber esophagus, many have normal esophageal appearance [35, 38]. In our study, one-third of patients had more than one endoscopic finding suggestive of the condition, emphasizing the value of gross examination of the esophagus.

Although most patients have characteristic findings, none of them were specific or pathognomonic [24, 35, 38]. Eosinophilic esophagitis may even be present in the absence of any abnormal mucosal findings [24]. In this study, approximately one-third of the patients had white papules and linear furrow; circular rings and paleness were present in 24% and 22.2% of the patients, respectively. While fibrosis in the esophageal wall with subsequent ring and stricture formation has been considered an important aspect of pathophysiology of the disease among adults [35, 38], 11.1% of our patients had a small-caliber esophagus, whereas 20% of our patients had a normal esophagus. In the study by Pasha et al., ringed esophagus was the most frequent sign (55%), followed by esophageal strictures (38%), linear furrows (33%), narrow esophagus (10%), and normal esophagus

(7%) [35]. In a Japanese study, however, longitudinal furrows were present in 35% of patients, and white papules and multiple concentric rings were found in 23% and 19%, respectively [30]. In a Turkish study, half of the patients had normal endoscopic findings, whereas the remaining cases had esophageal rings and white exudates [32].

Notably, in a systematic review of eosinophilic esophagitis in 217 patients from Asian countries, fixed concentric rings/stenosis was reported to be rare, which was likely dependent on the fact that food impaction was also a rare symptom among patients [26].

However, it should be noted that the likelihood of a normal endoscopic appearance not reflecting a truly normal esophagus has also been emphasized [36], since endoscopy has been considered to be relatively insensitive in identification of esophageal strictures, as compared with barium esophagography.

Variations in the frequency of endoscopic findings attributable to eosinophilic esophagitis in previous studies might be due to the differences in the definitions of the lesions and/or variations in the sample populations, to the stage of disease at the time of diagnosis, as well as to the relatively small sample sizes of the studies.

Allergic conditions such as allergic rhinitis, atopic dermatitis, food allergy, and asthma have been associated with esophageal esophagitis in previous studies, suggesting an allergic etiology [3-5, 39]. In the present study, twelve patients (22.2%) had a history of allergy, including food allergy, penicillin allergy, and allergic rhinitis, which supports the proposition of eosinophilic esophagitis to be categorized as an allergic disease with a genetic predisposition [2, 36, 40].

Identification *H. pylori* positivity in 29.4% of evaluated endoscopic samples in our cohort seems to align with the low rate of *H. pylori* reported among patients with eosinophilic esophagitis [26, 41, 42] and supports that eosinophilic gastrointestinal diseases have been infrequently accompanied by *H. pylori* infection [26, 43-45].

Limitations

A limitation of the present study is the small number of patients. Its retrospective design represents another limitation, where only patients with an esophageal biopsy were included, and the number of biopsies were not standardized. In addition, the retrospective design does not allow for the estimation of eosinophilic esophagitis prevalence. Future prospective studies may include all patients with esophageal complaints and a standard number of biopsies (at least four samples from mid-esophagus) may be obtained. In addition, prospective design would allow questioning allergic conditions, which may be important in early diagnosis and treatment, as well as for dietary elimination, when necessary.

Conclusions

Our findings indicate that a combination of compatible clinical, endoscopic, and histologic criteria is a mainstay in establishing the diagnosis of eosinophilic esophagitis. Given the likelihood of the prevalence of the disease to be higher than expected in the general population, along with the considerable variability in the definitions—and, thus, frequency—of endoscopic findings suggestive of the condition; the diagnosis of eosinophilic esophagitis continues to be challenging. Hence, attempts to identify a gold standard for the diagnosis seem to be one of the top priorities in the field of eosinophilic esophagitis.

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Research article

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Another perspective on lumber spinal stenosis treatment: Should exercise be added to pre-surgical treatment?

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Ethics Committee Approval
This study was approved by the Tekirdağ Namık Kemal University Ethics Committee (date: 06.02.2019 number: 2022.87.05.13).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Lumbar spinal stenosis (LSS) is a disease that affects the quality of life of elderly individuals. Most patients undergoing surgery for lumbar spinal stenosis try physical therapy before opting to undergo surgery. The effect of pre-surgical exercise treatment is unclear. This study aimed to examine the effect of pre-surgical exercise treatment on functionality, quality of life, and balance.

Methods: Patients between the ages of 40 and 70 who were scheduled for surgery based on a diagnosis of LSS were included in this cross-sectional study. The patients were randomly divided into two groups for which exercise therapy was added to the first group before the surgery, and the control group followed in the normal process. Visual Analogue Scale (VAS), Oswestry Disability Index (ODI), Beck Depression and Anxiety Inventory (BDI and BAI, respectively), Berg Balance Scale (BBS), static and dynamic balance measurements holding hands on and off on the balance device (SBHON, DBHON, DBHOFF) and the SF-36 quality of life scale tests were administered pre-operatively and eight weeks post-operatively, and the results were compared between the two groups that did and did not exercise before surgery.

Results: Post-operative SBHON values were found to be significantly lower in the exercise group compared to the other group ($P < 0.001$). While no differences between pre- and post-operative BBS, DBHON, and DBHOFF values in the non-exercising group were detected, a favorable significant difference in the exercising group was found (all $P < 0.001$).

Conclusion: The addition of pre-surgical exercise therapy to patients can lead to improvements in the success of surgery and contribute to the functionality of patients with LSS diagnosis.

Keywords: Balance, Disability, Exercise, Lumbar spinal stenosis

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Introduction

Lumbar spinal stenosis (LSS) affects the quality of life, especially in elderly patients [1]. Clinical findings include low back pain, paresthesia, and neurogenic claudication. Patients who are afraid of aggravating their symptoms do not want to walk, which negatively affects the quality of life [2].

Treatment is divided into two options: (1) surgical and (2) conservative. Decompression (with or without fusion) can be performed as a surgical treatment [3]. Conservative treatment options include physiotherapy, bracing, epidural steroid injection, medical treatment, and patient education [4]. Clear superiority of any one of these treatment methods over another one could not be determined [5]. The choice of treatment should be planned according to the patient's clinical condition, compliance with treatment, existing co-morbid conditions, and patient preference.

Although many studies in the literature comparing conservative and surgical treatment methods have been published, not enough studies evaluating the effect of adding exercise therapy before surgery are available [6]. In a study examining the effects of pre-surgical exercise, results were partially in favor of exercise; however, this issue has not yet been clarified. This study aimed to evaluate the effects of adding pre-surgical exercise therapy on the quality of life and functional parameters during the post-operative period in patients with an LSS diagnosis for whom surgical treatment was considered.

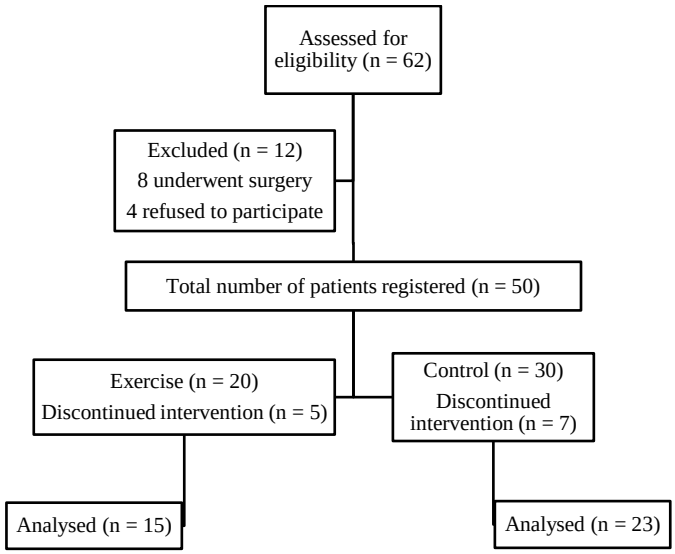
Materials and methods

Patients aged 40–70 years, who were scheduled for surgical treatment due to degenerative LSS and volunteered for the study were included in the study. Surgical indication criteria were determined as low back and/or radicular pain despite medical treatment, neurological claudication below 100 m with an antero–posterior diameter of 11.5 mm and a cross-sectional area of smaller than 1.45 cm² of spinal canal based on lumbar magnetic resonance imaging. Cases of non-degenerative LSS, those with cognitive impairment, chronic obstructive pulmonary disease, congestive heart failure, polyneuropathy, malignancy, and/or hypothyroidism, those with a history of antidepressant use, and those with advanced gonarthrosis, coxarthrosis, and/or a body mass index (BMI) greater than 30 kg/m^2 that would affect walking, stenosis more than two segments and/or scoliosis requiring osteotomy or correction during surgery were excluded from the study.

Approval for this prospective study was granted by the Namık Kemal University Ethics Committee (No: 2018.160.11.10). The research protocol was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all study subjects after the explanation of the nature of the study and possible consequences of the study.

BMI, age, and demographic characteristics were recorded for all patients and controls, and all subjects underwent a general physical examination by the same investigator. Power analysis was performed with the effect size (d) = 0.8, $\alpha = 0.05$, power (p) = 0.8, N2/N1 = 1 using the G-power 3.0.10 program, and it was calculated that the groups should consist of at least 15 people. Sixty-two patients were evaluated, and 12 patients were excluded from the study. A total of 50 patients were included: (1) 20 patients in the exercise group and (2) 30 patients in the control group. Since five patients from the surgical group and seven patients from the control group could not complete the study, the study was completed with a total of 38 patients (15 exercise, 23 control). The flowchart is presented in figure 1.

Figure 1: Flowchart of the study



All patients were referred to the physical medicine and rehabilitation clinic prior to surgery for Berg Balance Scale scoring and measurement of dynamic balance scores by, Korebalance Premiere Balance Device, CA, USA, 2007 with static hands holding (SBHON), dynamic hands holding (DBHON), and dynamic hands free (DBHOFF) on a moving platform. The Oswestry Disability Index (ODI), which was previously validated and is reliable in Turkish, was used to determine their functional status [7]. In addition, the SF-36 questionnaire form, which is valid and reliable in Turkish, was completed by patients for quality of life assessment [8]. All patients signed visual analog scales (VAS) to evaluate the pain intensity before and after the exercise treatment.

VAS was evaluated using a 10-point graded scale for which 0 indicated absence of symptoms, and 10 indicated the worst symptoms. Valid and reliable Turkish versions of Beck Depression and Beck Anxiety Inventories (BDI and BAI, respectively) were evaluated before and after the treatment [9, 10].

The patients were then randomly divided into two groups using a simple random-number drawing procedure. Those who picked odd numbers from the bag were assigned to exercise group, whereas who picked even ones were assigned to the control group.

The first group was given a pre-surgical exercise program. Lumbar flexion exercises (three times 30 s single knee-to-chest, three times 30 s double chest-to-knee), trunk raises (ten times 6-second bouts) and bridging in the supine position, and four-point knee exercise twice daily were given to patients. Three times for 30 s stretching exercises were recommended for the hamstring muscles. Strengthening exercises for lower extremity muscles were recommended using 2–3 sets,10 repetitions, and 6 s contractions. In addition, each patient was advised to take painless walks for 15 to 30 min daily. Exercise training was given to the patients by the same therapist and

visual, diagrams were provided to keep in their mind. The patients participated in this exercise program in the form of a home exercise program, and they were motivated by phone calls every week. The second group was the control group consisting of patients who were followed with a standard follow-up program.

The patients in the first group were admitted to surgical treatment 6–8 weeks after the onset of the exercise program, and the second group was promptly admitted to surgical treatment. Surgeries were performed by the same surgeon who had more than 10 years of professional experience. All patients underwent total laminectomy, bilateral foraminectomy, and rigid stabilization with a transpedicular screw via a posterior approach with preservation of the standard facet joints. All pre-operative evaluations were repeated at the eighth post-operative week.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) Version 25.0 statistical software was used to analyze the data. A Shapiro–Wilk test was used to assess conformity of the data to the normal distribution. An independent sample t-test was used to examine independent (between-group) two-group normally distributed quantitative data, whereas the paired sample t-test was used to compare two dependent (within-group) quantitative variables. A value of $P < 0.05$ was accepted as the statistical significance threshold.

Results

Thirty-eight patients, including 15 in the exercise group and 23 in the control group, were included in the study. The exercise groups had 10 women and five men in the exercise group, and 17 women and six men in the control group. No significant difference between the demographic data of the patients was found. The results are summarized in Table 1.

Table 1: Demographic characteristics of the exercise and control group

	Exercise Mean (SD) (n = 15)	Control Mean (SD) (n = 23)	*P*-value
Age (years)	55.86 (7.79)	60.34 (8.14)	0.099
Sex	10 F (66.7%), 5 M (33.3%)	17 F, (73.1%) 6 M (26.1%)	0.648
BMI (kg/m^2)	26.83 (1.89)	27.40 (1.71)	0.358

BMI: Body Mass Index, M: mean, SD: standard deviation, n: number of samples

Prior to treatment, no significant difference between the VAS, BAI, BDI, Oswestry Disability Index scores, BBS, and measurements obtained from the balance device between the patient and control groups were found. In post-treatment evaluations, a difference was found between the two groups in SBHON values, but no statistically significant difference was observed between groups in terms of other parameters. The results are presented in Table 2.

Significant improvements in VAS pain, BAI, BDI, and Oswestry Disability Index scores pre- and post-treatment in both the exercise and the control group were noted. In terms of the balance parameters, a statistically significant difference was observed in the BBS in the exercise group, while this difference was not observed in the control group ($P < 0.001$ versus $P = 0.06$). In the measurements made using the balance device, a significant difference in both static and dynamic parameters in the exercise group was found (all $P < 0.001$).

In the control group, a statistically significant difference was found in dynamic and static measurements made with holding hands ($P < 0.001$ versus $P = 0.023$), while no significant difference was found in the hands-off dynamic measurement ($P = 0.153$). All results are summarized in Table 3.

Table 2: Comparison of pain, disability, and balance parameters of the groups before and after treatment.

	Before treatment			After treatment		
	Exercise Mean (SD) (n = 15)	Control Mean (SD) (n = 23)	*P*-value	Exercise Mean (SD) (n = 15)	Control Mean (SD) (n = 23)	*P*-value
VAS	7.13 (2.92)	6.91 (1.53)	0.791	4.06 (2.05)	2.95 (2.26)	0.128
ODI	45.73 (28.1)	53 (22.95)	0.411	32.46 (22.47)	28.26 (18.42)	0.551
BBS	47.13 (14.11)	43.30 (12.16)	0.396	50.73 (11.47)	45.13 (13.72)	0.183
BAI	14.86 (9.92)	16.6 (10.65)	0.611	10.46 (7.26)	7.30 (5.12)	0.157
BDI	12.53 (8.23)	13 (9.37)	0.873	7 (4.79)	8.34 (5.54)	0.432
SBHON	649.5 (147.2)	733.3 (165.03)	0.112	421.6 (120.8)	658.9 (206.7)	<0.001
DBHON	1054,6 (215.1)	984 (230.03)	0.343	833.13 (203.6)	897.9 (286.9)	0.421
DBHOFF	1627.2 (461)	1378.3 (355.2)	0.088	1249.4 (310.4)	1340.8 (369.8)	0.417
SF-36	44 (18.04)	42.17 (19.29)	0.769	66.00 (16.49)	56.95 (17.69)	0.118

VPS: Visual Analogue Score, ODI: Oswestry Disability Index, BBS: Berg Balance Scale, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, SBHON: Static Balance Hands-ON, DBHON: Dynamic Balance Hands-ON, DBHOFF: Dynamic Balance Hands-OFF, SF-36: Short-Form 36, M: mean, SD: standard deviation, n: number of samples

Table 3: Within group comparison of changes of the pain, disability, and balance parameters of the groups before and after treatment.

	Exercise (n = 15)			Control (n = 23)		
	BT Mean (SD)	AT Mean (SD)	*P*-value	BT Mean (SD)	AT Mean (SD)	*P*-value
VAS	7.13 (2.92)	4.06 (2.05)	<0.001	6.91 (1.53)	2.95 (2.26)	<0.001
ODI	45.73 (28.1)	32.46 (22.47)	<0.001	53 (22.95)	28.26 (18.42)	<0.001
BBS	47.13 (14.11)	50.73 (11.47)	0.001	43.3 (12.16)	45.13 (13.72)	0.060
BAI	14.86 (9.92)	10.46 (7.26)	<0.001	16.6 (10.65)	7.3 (5.12)	<0.001
BDI	12.53 (8.23)	7.00 (4.79)	0.009	13.00 (9.37)	8.34 (5.54)	0.017
SBHON	649.5 (147.2)	421.6 (120.89)	<0.001	733.3 (165.03)	658.9 (206.7)	<0.001
DBHON	1054,6 (215.1)	833.13 (203.6)	<0.001	984 (230.03)	897.9 (286.9)	0.023
DBHOFF	1627.2(461.02)	1249.4(310.42)	<0.001	1378.3 (355.2)	1340.8 (369.8)	0.153
SF-36	44 (18.04)	66 (16.49)	<0.001	42.17 (19.29)	56.9 (17.69)	<0.001

BT: Before Treatment, AT: After Treatment, VPS: Visual Analogue Score, ODI: Oswestry Disability Index, BBS: Berg Balance Scale, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, SBHON: Static Balance Hands-ON, DBHON: Dynamic Balance Hands-ON, DBHOFF: Dynamic Balance Hands-OFF, SF-36: Short-Form 36,M: mean, SD: standard deviation, n: number of samples

Discussion

The current study aimed to evaluate the effect of pre-surgical exercise therapy on the quality of life and functionality during the post-operative period in patients with a diagnosis of LSS. According to the results of our study, exercise therapy for patients in the pre-operative period, even for a short time, provides positive and significant contributions in the post-operative period. Our study makes an significant contribution to the literature in terms of describing that the balance parameters are also affected by LSS and revealing these results using objective balance measurements.

Limited data are available in the literature evaluating the effect of exercise therapy before LSS surgery. Conflicting results have also been reported in these limited studies . In a study by Nielsen et al. [11], it was shown that the pre-operative rehabilitation program improves patient outcome and shortens the length of hospital stay. However, in the Nielsen study, patients were treated with protein support before and after surgery and pain control in the early rehabilitation process, and exercise efficiency was not evaluated alone. The Nielson study also evaluated all patients who underwent spinal surgery, not only LSS patients. Likewise, in the meta-analysis conducted by Janssen et al. [12], a total of 15 studies were evaluated, and most of these studies focused only on cognitive behavioral therapy. According to the results of the Janssen meta-analysis, which had a very low–moderate quality of evidence, the authors stated that pre-rehabilitation (prehabilitation) does not contribute much to analgesic use, length of hospital stay, anxiety–depression, functionality, and/or quality of life. Marchand et al. [13] evaluated the effectiveness of prehabilitation in patients with elective LSS surgery. In that study, it was found that

prehabilitation was partially effective for these patient, but this effect was found to be short-term and not been observed long-term. Similar results were found in our study, and it was shown that exercise therapy added before surgery had a positive effect on post-operative parameters in the short term, while long-term effects were not evaluated.

Similar to the other studies in the literature, our study was conducted with questionnaire forms for anxiety, depression, pain, and quality of life in addition to functional assessments, and unlike other studies, measurements obtained with a balance device and its associated objective data were also obtained. Balance disorder is a finding that frequently accompanies other parameters in LSS patients, and rates of up to 40% to 65% are reported in the literature [14, 15]. Effects on both static and dynamic balance parameters in patients have been described in which both static and dynamic balance parameters are affected in patients. Improvements in post-operative balance parameters were found in some studies [16, 17]. In our study, an increase in post-surgical balance parameters in both groups was found, but this effect was more significant in the exercise group. The dynamic balance parameter without holding hands was observed in the exercise group. Kinesiophobia, which occurs in patients who are afraid of falling and may develop after balance disorder, also impairs their quality of life, so exercise therapy for appropriate patients before surgery is very important in terms of functionality and quality of life.

Limitations

Several limitations in our study should be mentioned. The small number of patients is the first limitation. The predicted number of patients could not be included in the study due to coincidence with a period when elective surgeries could not be performed during the world wide coronavirus 2019 (COVID-19) pandemic. Post-operative evaluations of the patients were performed at the third month; however, whether exercise therapy was effective for a longer period of time was not evaluated. Due to staff limitations, patients were given a home exercise program in the exercise group, and patients did not exercise under the supervision of a physiotherapist. However, to increase the compliance of patients undergoing exercise therapy, they were asked to keep an exercise log book and were motivated by weekly phone calls. In this process, patients who were not properly exercising were excluded from the study. Many strengths of our work can be described. Although the number of patients is small, it is an important point that the surgeries were performed by a single physician. Besides tests and questionnaire forms used for pre- and post-surgical evaluation of patients, obtaining objective data using a balance device is another strength of the study.

Conclusion

In patients who were considered for surgical treatment due to a diagnosis of LSS, adding eligible exercise therapy (6–8 weeks) pre-operatively can both increase the success of the surgical treatment and contribute to the functionality of the patients.

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Is heart-type fatty acid binding protein (H-FABP) a valid marker of arterial stiffness in patients with systemic sclerosis?

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Ethics Committee Approval
Ethics approval was taken from the Selçuk University Non-Invasive Ethics Committee dated 06.01.2015 and meeting number 2015/1.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Both micro- and macro-vascular involvement has been researched in systemic sclerosis (SSc) for many years. In this study, the relationship of arterial stiffness with heart-type fatty acid binding protein (h-FABP), which is well-accepted as a cardiac marker, was investigated for the first time.
Methods: In this case-control study, 40 patients diagnosed with SSc between the ages of 18 and 65 were included. Thirty healthy individuals of similar age and gender were included as the control group. Patients were excluded from the study if they had cardiovascular risk factors, active infections, and/or malignancies. Along with detecting biochemical markers in the blood, results from methods, such as 24-h blood pressure Holter recordings, pulse-wave velocities (PWV), and echocardiograms (ECHO) were obtained from patients.
Results: The homocysteine mean level was higher in the patient group than in the control group ($P < 0.001$). H-FABP and asymmetric dimethylarginine (ADMA) means were similar between the two groups ($P = 0.286$ and $P = 0.340$, respectively). Vascular parameters, including mean arterial pressure (MAP), augmentation index normalized to the 75 /min heart rate (AIx @ 75), and PWV were also similar between the two groups ($P = 0.498$, $P = 0.382$ and $P = 0.180$, respectively).
Conclusion: It can be concluded that no ongoing myocardial damage occurs based on normotensive Holter findings, normal h-FABP levels, and ECHO findings in our patients. It is suggested that vasodilatory treatments, such as pentoxifylline and calcium channel blockers, which the patients receive for SSc treatment due to Raynaud Syndrome, may protect them from hypertension and therefore offer protection from myocardial damage.

Keywords: Systemic sclerosis, Heart fatty acid binding protein, Arterial stiffness, Pulse wave velocity, Homocysteine

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Introduction

Systemic sclerosis (SSc) is a chronic, autoimmune, multisystemic connective tissue disease of unknown etiology. SSc is characterized by functional and structural abnormalities in small blood vessels and progressive fibrosis in the skin and internal organs [1]. Other than microvascular involvement, SSc has also been recently associated with macrovascular disease [2], endothelial dysfunction, and increased arterial stiffness [3, 4]. Measurements of arterial tension and stiffness are the most important parameters in assessment of endothelial dysfunction and early atherosclerosis in patients with systemic autoimmune disease [5]. Asymmetric dimethylarginine (ADMA), a nitric oxide synthase inhibitor, is a specific marker of cardiovascular pathologies in chronic inflammatory diseases. Significantly elevated ADMA levels are considered to be an indicator of endothelial dysfunction and impaired coronary microcirculation. Heart-type fatty acid binding protein (h-FABP) is a cytoplasmic protein responsible for the intracellular transport of free fatty acids in cardiomyocytes. It has been observed that a significant relationship between carotid-femoral pulse-wave velocities (PWV) and h-FABP levels [6] exists, and this relationship has been shown to be a useful predictor for cardiovascular events in patients with stable coronary artery disease [7]. Furthermore, h-FABP appears to be a useful marker in deaths not only due to cardiovascular causes in the general population but also in deaths associated with all other causes [8]. Homocysteine is an amino acid containing a sulfhydryl group and is a component of the normal methionine and cysteine amino acid biosynthetic pathways. Homocysteine is known as an independent risk factor for atherosclerosis [9] and is associated with cardiovascular disease (CVD) [10].

Impaired coronary microcirculation, macrovascular involvement, and subclinical atherosclerosis have been demonstrated in some SSc patients who do not have CVD [11].

The aim of this study was to detect the early association of arterial stiffness in SSc patients with changes in biochemical markers, such as h-FABP, ADMA, and homocysteine in addition to methods, such as 24-h blood pressure values, Holter recordings, PWVs, and ECHO results.

Materials and methods

This study was performed as a case-control study in patients who presented to our Internal Medicine/Rheumatology outpatient clinic. Patients were evaluated by the cardiology department of our facility for cardiovascular involvement based on 24-h Holter and transthoracic ECHO results. The study was initiated after the approval of Selçuk University Non-Invasive Ethics Committee dated 06.01.2015 and meeting number 2015/1.

Inclusion criteria

Thirty-eight females and two male patients who were diagnosed with SSc between the ages of 18 and 65 and met the disease diagnosis requirement of a total score of 9 and above according to the 2013 ACR/EULAR Scleroderma Classification Criteria were included in the study. Forty patients met the study inclusion criteria. Thirty healthy individuals with similar ages and genders were included as the control group.

Exclusion criteria

Patients were excluded from the study if they had one or more of several conditions: (1) cardiovascular risk factors (coronary artery, cerebrovascular and/or peripheral arterial disease history, diabetes mellitus, hypertension, and/or obesity), active infections, and/or malignancies. Healthy controls also had no systemic disease and no signs of an acute or chronic infection.

Clinical and laboratory investigations

H-FABP, ADMA, and homocysteine levels were obtained in the biochemistry laboratory from the remaining 2 cc of the biochemistry blood taken during routine blood sampling.

MyBioSource (Lot06/2015; Cat no: MBS020502) enzyme-linked immunosorbent assay (ELISA) kit was used for the h-FABP test.

For ADMA, symmetrical dimethylarginine (SDMA), L-monomethylarginine (LMMA), arginine, and citrulline analyses, pre-prepared plasma samples were dissolved at room temperature. The ABSCIEX API 3200 High Performance Liquid Chromatography (HPLC) device in the Medicine Biochemistry Laboratory of our faculty was used in a positive mode based on electrospray ion source (ESI) using PhenomenexLuna 50x4.6,5µ C18 HPLC column to analyze the samples.

For homocysteine, after dissolving pre-prepared plasma samples at room temperature, the samples were analyzed in positive mode using ESI at ABSCIEX API 3200 triple quadrupole mass spectrometer (Canada) device at our faculty hospital.

Ambulatory blood pressure monitoring and arterial stiffness monitoring were performed using an oscillometric type Mobile O Graph NG (İ.EM GmbHStolberg, Germany) device that measures blood pressure within desired intervals as number of pulses per minute in addition to measuring arterial stiffness parameters, including augmentation pressure, augmentation index, pulse pressure. and PWV. Blood pressure measurements were obtained from both arms. If the difference of the measurements between the two arms was not more than 10 mmHg, the cuff was placed on the non-dominant arm. If the difference was more than 10 mmHg, the cuff was placed on the arm that yielded the higher value. The patients were informed about the procedure and the device, and they were told to perform their daily activities while keeping the arm with the cuff at the level of the heart during the measurements. The sleep period was determined as between 24:00 at night and 8:00 in the morning.

ECHO examination was performed using the Vivid E9 ultrasound system (General Electric, Ultrasound AS, Horten, Norway) possessing a 1.5-4.6 MHz transducer system. Measurements were obtained from the left lateral decubitus position from the standard parasternal long axis, short axis, and apical two and four chamber windows. All patients underwent standard two-dimensional (2D) and colored Doppler ECHO examinations. Septum and posterior wall thickness of the left ventricle, diastolic and end-diastolic diameters, and left atrium and aorta diameters were measured from the parasternal long-axis window. The left ventricular injection fraction was calculated from the apical four chamber and two chamber images by averaging the ejection fractions obtained by the modified Simpson method.

Statistical analysis

The statistical analysis of the data was performed by using SPSS version 22.0 (SPSS Inc. Chicago, IL, USA) and Microsoft Office Excel version 2010. One sample Kolmogorov–Smirnov Test was used for the compatibility of the data to normal distribution. A Student's t-, Mann–Whitney U, chi-squared, Fisher's exact, and Spearman's and Pearson's correlation tests were used for comparison of the data. A *P*-value of < 0.05 was accepted as statistically significant. Epi Info software was used to calculate the sample size. The minimum sample size was 15 participants at the level of α = 0.05 with 95% power.

Results

A total of 70 participants, including 40 (38 women, two men) patients and 30 (29 women, one man) control subjects, were enrolled in our study. The mean age of the patient group was 47.40 (9.91), and the mean age of the control group was 44.83 (9.53).

Evaluating the disease duration of the patients, the average duration of the disease was 6.03 (5.118). The shortest disease duration was one year, and the longest was 20 years.

The mean homocysteine level was 12.43 µmol/L (8.94) in the patient group and 7.01 µmol/L (3.99) in the control group. Homocysteine and C-reactive protein (CRP) levels were higher in the patient group than the control group (*P* < 0.001 and *P* < 0.001 respectively). The mean h-FABP in the patient group was 8.68 ng/ml (5.77) and 7.15 ng/ml (5.98) in the control group. The mean h-FABP and ADMA levels were similar between two groups (*P* = 0.286 and *P* = 0.340 respectively). Biochemistry data of the patient and control groups are summarized in Table 1.

Table 1: Comparison of biochemistry data in patient and control groups

Parameters	Patient Mean (SD)		Control Mean (SD)		*P*-value
WBC (K/uL)	7.27	(2.77)	7.00	(1.52)	0.632
NE (K/uL)	4.65	(2.26)	3.78	(1.09)	0.038
LY (K/uL)	1.80	(0.77)	2.46	(0.69)	0.001
Hg (g/dL)	12.59	(1.34)	13.23	(1.12)	0.036
PLT (K/uL)	264.73	(59.61)	267.33	(69.68)	0.867
UT LC (HPF)	5.95	(20.84)	1.57	(5.34)	0.088*
ESR (m/h)	28.05	(18.98)	17.10	(9.94)	0.003
Creatinine (mg/dL)	0.70	(0.12)	0.68	(0.07)	0.479
ALT (u/L)	14.80	(6.97)	21.43	(14.18)	0.023
Uric Acid (mg/dL)	4.73	(1.56)	4.43	(0.91)	0.363
Hcy (umol/L)	12.43	(8.94)	7.01	(3.99)	<0.001*
CRP (mg/L)	8.33	(10.83)	3.42	(0.74)	<0.001*
Glucose (mg/dL)	97.30	(17.96)	96.57	(12.22)	0.848
h-FABP (ng/ml)	8.68	(5.77)	7.15	(5.98)	0.286
ADMA (µmol/L)	0.37	(0.18)	0.33	(0.15)	0.340
Arginine (µmol/L)	246.18	(76.53)	233.95	(81.01)	0.521
Arginine /ADMA ratio	736.17	(263.83)	761.44	(224.04)	0.674
Citrulline (µmol/L)	11.49	(5.16)	16.88	(8.83)	0.001*
Citrulline/Arginine ratio	0.05	(0.03)	0.07	(0.03)	0.001
SDMA (µmol/L)	0.41	(0.16)	0.32	(0.14)	0.029
L-NMMA (µmol/L)	0.54	(0.29)	0.44	(0.20)	0.102

* Mann–Whitney U Test, in comparison of other tests, Student's t-test was used. WBC: White blood cell, NE: Neutrophil, LY: Lymphocyte, Hg: Hemoglobin, Plt: Platelet, UT LC: Leukocyte count in urine test, ALT: Alanine aminotransferase, ESR: Erythrocyte sedimentation rate, Hcy: Homocysteine, CRP: C-reactive protein, h-FABP: Heart type fatty acid binding protein, ADMA: Asymmetric dimethylarginine, SDMA: Symmetric dimethylarginine, L-NMMA: L-monomethylarginine

The mean arterial pressure (MAP) in the patient group was 88.68 mmHg (12.04) and 90.40 mmHg (7.95) in the control group. AIx@75 was detected as 28.52% (6.50%) in the patient group and 26.96% (6.59%) in the control group. PWV was determined as 6.75 (1.26) m/s in the patient group and 6.37 (1.00) m/s in the control group. No differences between the patient and control groups in terms of MAP, augmentation index normalized to 75 /min heart rate (AIx@75), and PWV (*P* = 0.498, *P* = 0.328, and *P* = 0.180 respectively) were detected. Twenty-four hour blood pressure Holter and ECHO data for patient and control groups are summarized in Table 2. Table 3 summarizes the medications used by patients in our study.

Table 2: Comparison of echocardiography and 24-h Holter data from the patient and control groups

Parameters	Patient Mean (SD)		Control Mean (SD)		*P*-value
EDD (mm)	45.53	(3.22)	44.63	(3.38)	0.265
ESD (mm)	28.98	(2.84)	28.43	(3.60)	0.484
PWDT (mm)	8.60	(1.78)	8.67	(1.32)	0.864
IVSDT (mm)	8.70	(1.91)	9.03	(1.22)	0.406
EF (%)	65.48	(3.45)	67.37	(5.37)	0.078
LAD (cm)	3.24	(0.43)	3.20	(0.38)	0.748
PAP (mmHg)	24.23	(4.90)	23.60	(3.78)	0.564
SIS (mmHg)	113.58	(14.65)	113.30	(9.21)	0.348*
DIA (mmHg)	68.28	(10.49)	71.47	(7.34)	0.159
MAP (mmHg)	88,68	(12.04)	90.40	(7.95)	0.498
PR (1/min)	80.13	(11.32)	76.17	(14.33)	0.201
PP (mmHg)	44.83	(7.85)	41.90	(5.86)	0.091
MSBP (mmHg)	103.95	(14.10)	105.87	(9.11)	0.518
MDBP (mmHg)	69.80	(10.92)	72.40	(7.34)	0.264
Alx@75 (%)	28.52	(6.50)	26.96	(6.59)	0.328
PWV (m/s)	6.75	(1.26)	6.37	(1.00)	0.180

* Mann–Whitney U Test, in comparison of other tests, Student's t-test was used. EDD: End-diastolic diameter, ESD: End-systolic diameter, PWDT: Posterior wall diastolic thickness, IVSDT: Interventricular septum diastolic thickness, EF: Ejection fraction, LAD: Left atrium diameter, PAP: Pulmonary artery pressure, SIS: Systolic pressure, DIA: Diastolic pressure, MAP: Mean arterial pressure, PR: Pulse rate, PP: Pulse Pressure, MSBP: Mid-systolic blood pressure, MDBP: Mid-diastolic blood pressure, AIx@75: Aortic augmentation index corrected for a heart rate of 75 bpm, PWV: Pulse wave velocity

Table 3: Percentages and types of drugs used in the patient group

Parameters	Drugs Non-Users n (%)	Users n (%)
Pentoxifylline	5 (12.5)	35 (87.5)
Calcium channel blocker	18 (45)	22 (55)
Methotrexate	37 (92.5)	3 (7.5)
Hydroxychloroquine	10 (25)	30 (75)
NSAID	38 (95)	2 (5)
Cyc C	35 (87.5)	5 (12.5)
Cyc P	21 (52.5)	19 (47.5)
Azathioprine	25 (62.5)	15 (37.5)
Corticosteroids	26 (65)	14 (35)
Acetylsalicylic acid	6 (15)	34 (85)
IV PG C	38 (95)	2 (5)
IV PG P	38 (95)	2 (5)

NSAID: Non-steroidal anti-inflammatory drug, Cyc C: Receiving cyclophosphamide treatment currently, Cyc P: Cyclophosphamide treatment in the past, IV PG C: Receiving intravenous prostaglandin treatment currently, IV PG P: Intravenous prostaglandin treatment in the past

Discussion

In this study, we examined arterial stiffness in SSc patients without cardiovascular risk factors by obtaining measurements of ADMA, homocysteine, and h-FABP levels, which are considered to be associated with arterial stiffness. We aimed to determine the association of the PWV and AIx@75 values used to evaluate arterial stiffness with these parameters.

No differences between the patient and control groups in terms of AIx and PWV were found. Some miscellaneous studies in the literature state PWV, AIx and other arterial stiffness methods and markers did not differ between patients and control groups in different rheumatological conditions, including SSc, in addition to studies reporting that these differs significantly [12–14]. These conflicting data in the literature may have different causes. In our study, most patients were receiving vasodilator treatments, such as pentoxifylline (87.5%) and calcium channel blockers (55%), which cause an increase in aortic distensibility [15]. In addition, differences in methods used for arterial stiffness measurements can occur for other reasons. Our Holter device only had the capability of obtaining measurements from the upper arm. In various studies, it has been shown that SSc may only affect distal small vessels rather than large vessels [16], at least during the early course of the disease [17]. Hydroxychloroquine was being taken by 75% of our patients, and this drug may have positive effects on atherosclerosis, arterial stiffness, and lipid profiles in different patient groups [18]. Besides, functional and structural vascular

abnormalities in different rheumatological diseases may respond differently to vasodilator treatments, such as calcium channel blockers [19].

Homocysteine, which is known to have a strong relationship with arterial stiffness [20, 21], was found to be significantly higher in SSc patients compared to the control group in our study.

H-FABP values, which are accepted as a sensitive marker of myocardial injury [22], did not differ between SSc patients and the control group in our study. The main reason for this result may be related to an increase in h-FABP under conditions that cause damage to the vascular endothelium rather than conditions that cause functional effects to the vascular endothelium [6, 23]. Although molecular markers in our patients that prove the presence of arterial stiffness were found, it can be concluded that no ongoing myocardial damage was occurring based on normotensive Holter findings, normal h-FABP levels, and ECHO findings. Consequently, it can be thought that vasodilator treatments, such as pentoxifylline and calcium channel blockers, which the patients take as part of their SSc treatment due to Raynaud Syndrome, may protect them from hypertension and therefore offer protection from myocardial damage. However, the available data on this issue are insufficient and further studies are needed.

Limitations

The most important limitation of our study was the lack of measurements from other non-invasive and invasive methods (such as carotid intima-media thickness, flow- and nitrate-mediated vasodilation, and angiography), which are useful methods for demonstrating arterial stiffness.

Conclusion

SSc shows an increased risk of atherosclerosis, independent of traditional cardiovascular risk factors. Therefore, careful follow-up of SSc patients is also required with regard to CVD.

Therapeutic agents, such as calcium channel blockers, pentoxifylline, and hydroxychloroquine, which SSc patients use for their SSc treatment due to Raynaud Syndrome, may also have a positive effect on arterial stiffness due to their positive effects on blood pressure and lipid profiles.

More studies are needed to demonstrate both the relationship of H-FABP with arterial stiffness and its importance as a marker of myocardial damage in SSc patients.

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Successful treatment of an adolescent patient with acute subclavian vein occlusion using the Cleaner thrombectomy device

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Informed Consent
The authors stated that the written consent was obtained from the legal guardians of the patient presented with images in the study.

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Abstract

Paget-Schroetter Syndrome is a rare condition characterized by the thrombosis of the axillary and/or subclavian vein due to repetitive activity of the upper extremity. This effect results in exertion-induced deep venous thrombosis (DVT) of the upper extremity. In the literature, it has been reported more frequently among the adult population. We aimed to introduce a 15-year-old female patient who suffered an acute DVT of the left upper extremity, and her successful treatment using the Cleaner thrombectomy device.

Keywords: Upper extremity, Deep venous thrombosis, Juvenile, Cleaner device

Introduction

Paget–Schroetter syndrome (PSS), or venous thoracic outlet syndrome, occurs due to the compression of the subclavian vein as it passes through the thoracic outlet. The compression may occur with hypertrophy of the pectoralis minor, scalenius, or subclavius muscles. Moreover, a cervical rib may be another cause of PSS. This condition typically affects the dominant arm of healthy and athletic young adults with a typical history of repeated overhead exertion. Management of PSS in adults includes anticoagulation, systemic or mechanic thrombolysis, angioplasty, and surgery for decompression of the vascular structure [1].

Symptomatic deep venous thrombosis (DVT) is rare in children, with an incidence of approximately 0.7 per 100,000 children [2]. Treatment mostly includes systemic thrombolysis; however, due to the increased practice of pharmaco-mechanic thrombolysis, experiences and favorable results encourage medical practitioners to use this in children and adolescents.

We introduce a 15-year-old female patient who suffered an acute DVT of the left upper extremity. Treatment was successful using the Cleaner thrombectomy device in its early follow-up results.

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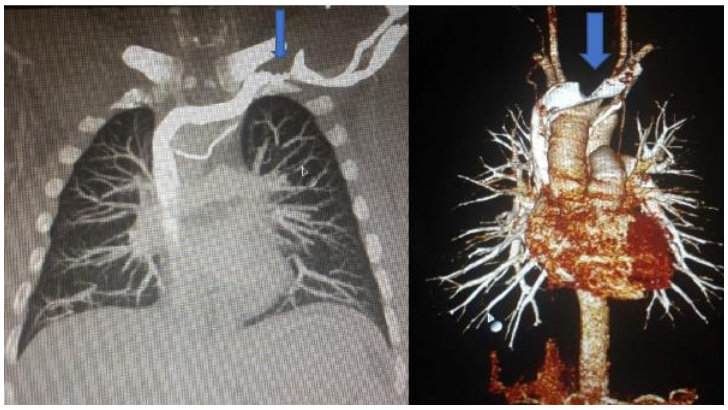
Case presentation

A 15-year-old female patient was admitted to the emergency service with pain in the left upper extremity, swelling, rash, and an increase in temperature that occurred six hours after repetitive abduction exercises in school. On physical examination, her left upper extremity was significantly swollen, with a 5 cm larger diameter and warmer, compared to the right extremity. The patient's pulse was palpable. On Doppler ultrasound, the left subclavian vein was nearly totally occluded due to acute thrombosis, and compression of the vein was diagnosed. Computed tomography angiography showed a subtotal occlusion (Figure 1). A cervical rib was visualized on X-ray. Platelet count, hematocrit, international normalized ratio (INR), partial thromboplastin, and prothrombin time were normal. Plasma D-dimer level was > 2500 ng/mL (normal, < 500 ng/mL). The patient did not possess a medical history involving thrombophilia, cancer, previous DVT of the same extremity or central venous catheterization except for the cervical rib. Doppler USG examination was performed and acute DVT caused by subtotal occluding thrombosis of the subclavian vein was detected. Informed consent was taken from relatives of the patient.

Figure 1: Pre-interventional contrast tomography view of the left subclavian vein occlusion



At the time of diagnosis, 1 mg/kg enoxaparine was administered as the first step of medical treatment. Local anesthesia was administered and a 6 Fr sheath for entry access was inserted through the cephalic vein with USG guidance. An initial venogram was performed and the diagnosis confirmed. A 6 Fr 65 cm Cleaner thrombectomy device (Argon Medical Devices, Inc.; Plano, Texas, USA) was inserted through the introducer sheath. Recombinant tissue plasminogen activator (tPA) (alteplase, Genentech, South San Francisco, California, USA) was administered intermittently (10 mg recombinant tPA diluted with 50 mL saline) through the catheter lumen. The clot material was macerated by advancing and withdrawing the device into the vessel over a period of ten minutes. By aspirating adversely through the catheter lumen, clot material and the lytic medical agent were removed. Via arterial catheter, alteplase (0.5 mg/saline over 24 hours) was infused to remove the residual clot material and avoid probable thrombosis due to possible catheter damage. When the procedure was terminated, the catheter was removed. Within the first 24 hours no bleeding occurred. Enoxaparin (0.125 mg/kh/dose) was administered twice daily to complete the anticoagulation process. The patient was discharged on the third postoperative day with warfarin. INR control was performed monthly and warfarin was administered for three months. Following treatment, symptoms, including swelling, rush, pain and edema, recovered gradually.

Discussion

DVT of the upper extremity is rare compared to the lower extremity, with an incidence rate of 4–11% [3]. The most determined etiological factors are: central venous catheter insertion, pacemaker leads, cancer, thrombophilia caused by a major surgical procedure, trauma, pregnancy, oral contraceptive medical treatment, and hyperstimulation syndrome of the ovary [3-4]. PSS may be detected at a ratio of 20% of all etiologies. Spontaneous DVT of the upper limb is extremely rare in childhood and occurs in the dominant arm, typically following repetitive abduction activity, at a ratio of 68% [3]. The condition mostly occurs due to PSS.

To evaluate for spontaneous DVT in childhood and adolescents, it has been suggested to examine for abnormalities in antithrombin III level, protein C and S activity, factor VIII level, anti-phospholipid antibodies and homocysteine level [5]. It is important to determine if thrombophilia is present to avoid the recurrence of DVT [6]. The aim of medical management is to prevent vascular insufficiency and limb edema (i.e., post-thrombotic syndrome) [5].

Catheter-directed thrombolysis (CDT), seldom used in children and adolescents, is extremely rare, particularly for DVT of the upper limb [6]. There are a few studies and case reports regarding CDT usage, but it is mostly used for pulmonary embolism. Goldenberg's study [7] reported that 3 of 16 pediatric patients suffering from upper limb DVT received CDT. The underlying reason for upper limb DVT in these three patients was PSS. In the literature, there exists a case report of a 16-year-old male patient diagnosed with bilateral upper extremity DVT caused by PSS, but treated medically. No consensus regarding PSS and upper limb DVT in pediatric and adolescent populations exists. Treatment may be medical (associated with anticoagulant and thrombolytic agents) or interventional. In some instances CDT is strongly recommended, and surgical decompression can be advised in the case of anatomical defect [2].

We did not find any thrombophilic factors, such as anomalous antithrombin III level, protein C and S activity, factor VIII level, anti-phospholipid antibodies and homocysteine level in our case post-interventionally. We would have investigated the patient by CT angiography for TOS etiology post-interventionally, but, unfortunately, the patient's parents would not allow us due to recurrent radiation exposition.

The symptoms of the patient were detected in the non-dominant left arm. This was unexpected and contradictory to the literature. We preferred CDT therapy for our patient, in this case, the upper limb DVT, and bleeding, which is a complication, did not occur. Although we did not locate involvement of a cervical rib, we detected slight compression of the venous vasculature on Doppler USG, signifying PSS. We did not advocate a massive decompression surgery, as recommended in the literature. Early during follow-up, the patient's symptoms regressed and did not recur. We continued to follow the patient for probable recurrence.

The American College of Chest Physician (ACCP) guidelines [5] advise at least three months of anticoagulant medicine. If more than one risk factor exists, anticoagulant treatment should be extended for a lifetime. This patient was treated with warfarin for three months.

Conclusion

PSS is a rare reason of essential deep vein thrombosis of the upper extremity, and it is more frequent in the young population. The main cause is repetitive and forcible arm activity and vascular compression by anatomical structures. The diagnosis can be considered if it does not present any trauma to the subclavian vein or if interventional procedure does not exist in medical history [8]. Doppler Ultrasound should be the first choice in diagnosis prior to computed tomography. We believe that this is one of the rare cases documenting non-dominant upper extremity DVT caused by repetitive abduction activity, with a background of PSS in childhood. This adolescent patient was successfully treated via CDT.

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Follicular dendritic cell sarcoma of the spleen: A case report

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Abstract

Follicular dendritic cell sarcomas (FDCS) are spindle cell lesions that are large, slow-growing masses in either nodal or extranodal regions or both and originate from B-cell follicles of the lymph nodes. Most tumors originate from the cervical lymph nodes, but retroperitoneal and mediastinal origins have also been reported. Extranodal areas include soft tissues, skin, tonsils, gastrointestinal tract, liver, and spleen. The spleen is an uncommon location for an FDCS and for this reason, the tumor may be underdiagnosed or overlooked because of confusion with other solid tumors. In this study, we present a patient with a splenic FDCS who presented clinically with abdominal pain and diarrhea. The patient underwent a splenectomy and had an uneventful remission.

Keywords: Follicular dendritic cells, Sarcoma, Spleen

Introduction

Follicular dendritic cells may demonstrate as antigen presenting cells in B-lymphocyte mediated humoral immunity. A follicular dendritic cell sarcoma (FDCS) is an uncommon type of tumor with a low incident rate. Although these tumors are primarily found in cervical lymph nodes, they can be localized in extranodal regions. Extranodal areas include soft tissue, skin, tonsil, gastrointestinal tract, liver, and spleen. FDCS have a serpiginous growth pattern of the lymph nodes that may progress by leaving residual areas between the nodules [1]. FDSCs may clinically present with regional growth of lymph nodes or intraabdominal masses. Due to their aggressive biological patterns, they are reported to have high local recurrence and metastasis rates and can cause a decrease in patient survival [2]. This article presents a case of a FDCS that was localized in spleen.

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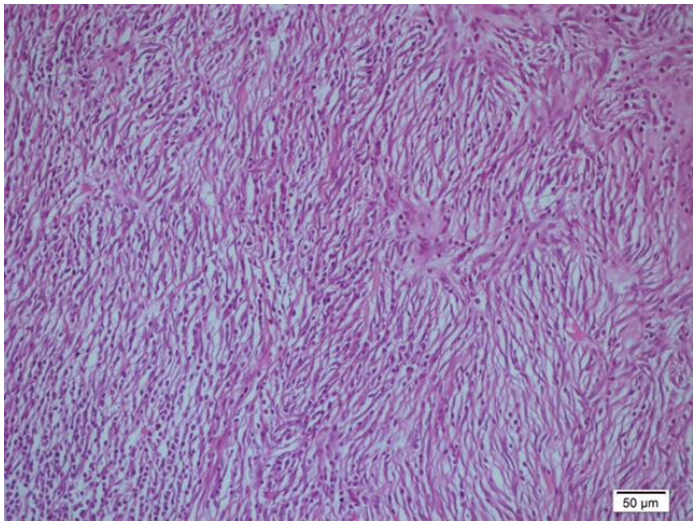
Case presentation

We received written consent from the patient after which we designed the study. A 58-year-old male with no history of chronic disease presented with ongoing abdominal pain and diarrhea over the course of one month. Physical examination revealed a closed Traube's space and splenomegaly. Laboratory investigations showed elevated levels of white blood cells (17.3 x 10^3/L), C-Reactive Protein (CRP) of 8.28 mg/L (reference range: 0-5 mg/L), cancer antigen-15-3 (CA-15-3) of 30.1 U/mL (reference: <30 U/mL), and CA-125 of 45 U/mL (reference: <35 U/mL). No other laboratory abnormalities were found. On a computed tomography (CT) scan, the long axis of the spleen was found to be remarkably increased by 168 mm. A bilobular, heterogeneously enhanced, solid lesion measuring 14 cm extending from the hilus of the spleen to the lower pole was detected, and the left kidney was compressed by the lesion inferomedially (Figure 1). Endoscopic evaluation showed no pathological findings in the upper or lower gastrointestinal tract. The patient underwent surgery for explorative laparotomy and was diagnosed with a primary splenic tumor. The tumor had not invaded the surrounding tissues and was limited to the splenic capsule. The tumor was excised with en-bloc splenectomy (Figure 2). Abdominal exploration revealed no additional macroscopic pathology. Histopathological examination confirmed that the lesion was an FDCS with spindle cell fascicles that formed a storiform pattern (Figure 3). The splenic capsule was intact, and the surgical margins were found to be negative in agreement with a macroscopic examination. Significant cytological atypia and extensive coagulative necrosis were detected in the lesion. Based on immunohistochemistry, examination showed positive cluster of differentiation (CD)-23 and -21 whereas CD-3, -20, -117, and -138 were found to be negative. The percentage of Ki-67-stained tumor in the hotspots was found to be 60%. The patient was discharged without any post-operative complications and has completely recovered. The patient was referred to the oncology clinic for follow-ups.

Figure 1: Computed tomography (CT) view of the heterogeneously enhanced, bilobular solid splenic lesion (arrow)

Figure 2: Macroscopic view of the excised tumor with en-bloc splenectomy.

Figure 3: Histopathological view of the spindle cell fascicles that formed a storiform pattern in the resected spleen material. Oval cells and lymphocytes are found between the spindle cells.



Discussion

FDCSs are recently frequently described in the literature [3]. Most of these tumors originate from the cervical lymph nodes, whereas mediastinal and retroperitoneal origins have also been reported. Retroperitoneal tumors have only been reported as sporadically developed tumors. Due to their aggressive histopathological nature, high incidence of local recurrence and metastasis and poor survival rates have been reported [2]. Although patients often present with regional enlarged lymph nodes, spleen sarcomas mostly present as a palpable mass in the abdomen [4]. FDCS are rare malignancies with heterogeneous outcomes. Patients with bulky, extranodal, and/or intra-abdominal disease at presentation usually have poor outcomes [5].

Physical examination revealed a closed Traube's space and splenomegaly. Elevated WBCs, CRP, and tumor markers were reported. Radiological evaluation revealed a bilobular, well-bordered splenic mass that had not invaded the surrounding tissues.

FDCSs have a serpiginous growth pattern of the lymph nodes that may progress by leaving residual areas between the nodules. Immunohistochemically, the tumor has a unique phenotypic profile, including follicular dendritic cell markers: (10 CD21 and (2) CD35. They also express CD23, CD68, fascin, and clusterin, whereas CD1a, S100, desmin, actin, and cytokeratin expression is not found [1].

CT imaging with focal, course, single, or multiple masses occurring intra-abdominally and/or retroperitoneally, which are relatively larger sized and have significant internal necrosis, should lead to consideration of a possible FDCS [6]. Magnetic resonance imaging is helpful in determining the extent of the lesion, its relationship with the surrounding tissues, and the tumor stage. T1-weighted sections indicated an isointense expansive mass, whereas T2-weighted sections indicated a homogeneous, slightly hyperintense mass after a gadolinium infusion was administered [6].

FDCS is a rare type of tumor with low incidence rates. No specific treatment guidelines for FDCSs are available. Resection of the tumor with a wide surgical margin is usually recommended much the same as is done for other sarcomas [7]. Currently, surgery is the primary choice of treatment, and in the case of resectable FDCS, adjuvant chemotherapy or radiotherapy can be used to improve survival rates [8].

Conclusion

In conclusion, FDCS is an uncommon tumor that can remain underdiagnosed or overlooked since it has imaging features similar to other solid tumors. The current report describes the main clinical features and discusses the diagnostic challenges and treatment options. Immunohistochemistry and specific FDCS markers are important for determining the tumor differentiation grade. Currently, complete surgical resection is warranted. After proper surgical resection, FDCS generally has a favorable prognosis.

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