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Original Article

Clinical course of primary empty sella in children: a single-center experience

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ABSTRACT

Background. Various studies, mainly conducted in adults, have examined the hormonal axis in primary empty sella (PES), and reported various forms of pituitary deficiencies. We report our experience with PES in pediatric patients in terms of pituitary function, associated impairments, and responses to treatment.

Methods. We reviewed 10,560 cranial and 325 pituitary magnetic resonance imagings (MRIs) performed at our university hospital between January 2010 and December 2020 and identified patients with PES. Patients with additional abnormal MRI findings, a history of cranial surgery or radiotherapy, autoimmunity, long-term use of chemotherapeutic or immunosuppressive agents or incomplete diagnostic evaluation were excluded. Clinical, radiological and laboratory evaluations were recorded.

Results. The study included 17 patients [9 girls, 8 boys; median age 12.4 years (7.25, 4.3 - 17)]. The median size of the pituitary was 2 mm (0.7, 1.2 - 3). Based on age-dependent pituitary height measurements, fifteen (88%) patients had pituitary gland hypoplasia. Five patients presented with short stature, two had both pubertal delay and short stature, and one had pubertal delay. Nine patients presented with neurological symptoms such as headaches, tinnitus, tics, and dizziness. Five short patients had growth hormone deficiency. None of the patients had hyper- or hypoprolactinemia, adrenal insufficiency, hypothyroidism, or diabetes insipidus. There was statistically no significant association between the size of the pituitary gland and the severity of hypopituitarism ($p = 0.42$).

Conclusions. The high incidence of pituitary dysfunctions ascertain that this entity should not be considered a normal variant but, should instead be carefully evaluated with appropriate basal and dynamic hormonal testing.

Key words: primary empty sella, hypopituitarism, pituitary, magnetic resonance imaging.

Empty sella is a neuroradiological and anatomical condition, characterized by intrasellar extension of the subarachnoid space followed by flattening of the pituitary gland.[1] The term was first described in 1951, and is often regarded as an incidental finding, with a prevalence of 5.5 to 35% in the general population.[1-3] According to the underlying etiology, related pathologies or disorders can be classified as primary and secondary.[2] In primary empty sella (PES), the underlying pathophysiology remains undetermined; however, the incompetency of the diaphragma sella, which is reported in 22-77% of all previously diagnosed patients, is accepted as the major factor in the development of PES.[2,3] Further, the defects in the pituitary or upper sella, chronic increases in intracranial pressure or derangements in cerebrospinal fluid (CSF) dynamics are the other possible causative factors.[3] In contrast, among the

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responsible mechanisms in secondary empty sella are tumors, hydrocephalus, surgery, radiotherapy, trauma, autoimmunity, infection, genetic diseases and drugs.[1,4,5] PES is commonly not associated with any signs or symptoms; however, headache, obesity, menstrual irregularities, and galactorrhea may occur.[1,2,6-8] Pituitary dysfunction ranging from isolated deficiencies, such as growth hormone (GH) deficiency, to panhypopituitarism have been reported in patients with PES.[1] Various studies, mostly conducted in adults, evaluated the hormonal axis in PES, and reported different forms of pituitary deficiencies.[4,5,7,9-11] Here, we report our 10-year experience in pediatric patients with PES with particular attention to the pituitary function, associated impairments, and responses to treatment.

Material and Methods

Study design

Regardless of chief complaints, we reviewed 10,560 cranial and 325 pituitary magnetic resonance imagings (MRIs) performed at our university hospital between January 2010 and December 2020. In this retrospective chart review study for pediatric patients, 20 scans revealed empty sella. Relevant images and files were reviewed, and one case with incomplete endocrine evaluation, one with previously diagnosed Cushing's syndrome, and one with a history of chemotherapeutic agents were excluded. Eventually, our study included 17 patients (9 girls, 8 boys). MRIs were ordered for suspected endocrine dysfunctions in eight (47%), and neurological pathologies in nine (53%) of the patients. The following variables were recorded: age at diagnosis, initial complaints, period of follow-up, size of the pituitary gland on MRI, medications, physical, and laboratory findings.

Physical evaluation

Age, sex, and anthropometric parameters such as height (cm), body weight (kg), body mass index (BMI) (kg / m^2) and the respective standard deviation scores (SDS) according to the standards set for Turkish children, and pubertal staging's, were both recorded at the time of diagnosis as well as the last follow-up visit.[12,13]

Hormonal evaluation

The hypothalamic-pituitary axis was assessed using the baseline serum levels of morning cortisol, free thyroxine (fT4), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone in boys, estradiol in girls, prolactin, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), sodium and urine osmolality. Central adrenal insufficiency was excluded when a morning (08:00) serum cortisol level was above 10 μg/dL or in the presence of a peak cortisol value higher than 18 μg/dL, following either an intravenous low dose (1-mcg) ACTH test or an insulin tolerance test (0.1 U / kg insulin).[14,15] The diagnosis of central hypothyroidism was based on low fT4, with low, normal, or slightly elevated TSH levels (reference ranges supplied by our central laboratory: TSH 0.38 - 5.33 mIU/L; fT4 0.5 - 1.5 ng / dL).[16] Delayed puberty, suggesting gonadotropin deficiency, was considered in the absence of breast tissue by age 13 in girls or testis development by age 14 in boys, and was excluded in the presence of a stimulated peak LH concentration above 5 IU / liter, following a LH-releasing test (gonadorelin 2.5 mcg / kg).[17] Moreover, both the spurious inhibitory effect of high levels of prolactin, defined as levels above 20 ng / mL in two consecutive measurements and low levels below the limits of detection were evaluated.[18,19] For patients with growth impairment, defined according to the Growth Hormone Research Society guidelines[20], GH deficiency was diagnosed when two different stimulation tests (clonidine, insulin tolerance or L-dopa test) resulted in a GH peak below < 7 ng / mL.[21] Central diabetes insipidus, which indicated posterior pituitary dysfunction, was diagnosed in the presence of polyuria (urinary

volume more than 4 - 5 mL / kg / h or 2 L /m^2 /d) and polydipsia (2 L / m^2 / d) along with low urine osmolality (≤ 300 mOsm / L) and high plasma osmolality (≥ 300 mosm / L).[22]

Radiological evaluation

All MRI examinations were performed with 1.5-T MR system (Ingenia; Philips Healthcare, USA) and all images were analyzed by an experienced pediatric radiologist. The characteristics of the pituitary gland and sella tursica were assessed using coronal, axial T2 images and coronal sagittal T1-weighted images. Patients with a cerebrospinal fluid filled sella and decreased pituitary gland height were evaluated. The vast majority of the measurements were performed on sagittal and coronal images at multiplanar reformatted images of the 3D T1 sequence. The measurements of the patients with pituitary MRI were made with sagittal and coronal T1 images. Measurements in the sagittal plane were made on the midsagittal section and the coronal plane were made on the section where the pituitary stalk is seen in T1 images. Pituitary gland hypoplasia was defined based on age-dependent pituitary height measurements.[23] Partial/complete PES were classified as partial when less than 50% of the sella was filled with CSF and the pituitary height was 3 mm or greater, and complete when more than 50% of the sella was filled with CSF and the pituitary height was less than or equal to 2 mm.[4]

Statistical analysis

Statistical analyses were performed using SPSS v.24 for Windows. The results of the study were presented as categorical or continuous variables. The homogeneity of the continuous data obtained in the study were tested using the Shapiro-Wilk and Kolmogorov-Smirnov test. The continuous variables were expressed as median [interquartile range (IQR), (minimum-maximum)], unless otherwise stated. Categorical variables were given as the number of patients and percentages (%). The bivariate associations between continuous variables were compared using the Mann-Whitney U test for pairwise comparisons. The Spearman rank correlation was used to discover the association between the pituitary size and auxological measurements. A p-value of < 0.05 was considered statistically significant.

Ethical approval

The research was complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration. Institutional approval was granted by the Ethics Committee of Dokuz Eylül University Faculty of Medicine. (Ethics approval number: 2021/14-2906052021). Informed consent was obtained from all individuals' parents or legal guardians included in this study.

Results

The study included 17 patients [9 girls, 8 boys; median age 12.4 years (7.25, 4.3 - 17)]. Clinical presentation, pituitary size, and treatments of the patients are presented in Table I. Brain MRI findings of two patients (#2 and #7 in Table I) as examples of the measurement methods are presented in Figures 1a, 1b, 2a, and 2b.

Brain MRIs were ordered for diagnostic evaluation of short stature in five patients, pubertal delay and short stature in two patients, pubertal delay in one patient and neurological symptoms including headache, tinnitus, tics, and dizziness in nine patients. The median duration of follow-up was 36 months (53, 9 - 70 months). The median size of the pituitary was 2 mm (0.7, 1.2 -3). Fifteen (88%) patients showed pituitary gland hypoplasia. Nine patients (53%) had complete empty sella. The median SD scores for weight, height, and BMI of the patients at the time of diagnosis were -0.19 (2.2, -2.5 - 1.9), -0.98 (2.9, -3.8 - 1.8), and 0.2 (1.6, -1.3 - 1.97), respectively.

Eight patients (47%) were evaluated with provocative tests (low dose ACTH test (n=2, 25%), insulin tolerance test (n=5, 63%), clonidine test (n=5, 63%), L-dopa test (n=3, 38%), LH-releasing test (n=3)) for pituitary

Table I. Clinical presentation, pituitary size and treatments of the patients.

Case number	Age, (years), gender	Follow-up, months	Initial complaints	Pituitary size, mm	Weight, SDS	Height, SDS	BMI, SDS	Stimulation tests	Treatment
1	11, F	11	H, T	2	1.9	1.33	1.62	LDST	None
2	12, F	36	S	1.2	-0.73	-3.06	1.01	C, ITT	GH
3	6, M	11	H	2	-0.12	-1.36	0.92	N/A	None
4	15, F	36	H, I	1.9	1.77	1.26	1.08	N/A	None
5	10, M	70	S	3	0.18	-2.38	1.56	C, ITT	GH
6	17, F	70	H	1.7	-0.19	-0.63	0.09	N/A	None
7	13, M	70	H	2	0.66	1.78	-0.17	N/A	None
8	7, F	12	H, N	2.8	1.23	-0.78	1.83	N/A	None
9	16, M	36	S	2.8	-2.41	-3.75	-0.35	C, ITT	GH
10	12, F	32	S	1.8	-0.93	-2.83	0.67	C, D, LHRH	None
11	5, M	48	S	2	-1.85	-2.11	-0.81	N/A	None
12	12, M	70	S	2	-2.41	-2.62	-1.27	ITT, D	GH
13	17, F	32	P	2.5	-2.53	-0.98	0.16	LHRH, LDST	E
14	13, F	60	S	2	0.93	-1.8	1.97	D, ITT, LHRH	GH
15	17, M	12	H	3	-0.52	-0.46	-0.5	N/A	None
16	4, M	9	H	2.1	0.49	1.61	-0.4	N/A	A
17	8, F	9	H	2.2	-0.44	-0.48	-0.2	N/A	None

F: female, M: male, H: headache, T: tinnitus, N:tics, S:short stature, I:menstrual irregularity, P: pubertal delay, LDST: Low-dose synacthen test, LHRH: luteinizing hormone releasing test, ITT: insulin tolerance test, C:clonidine test, N/A: not applicable, D:L-Dopa Test, GH: growth hormone, E:estradiol, A: acetazolamide

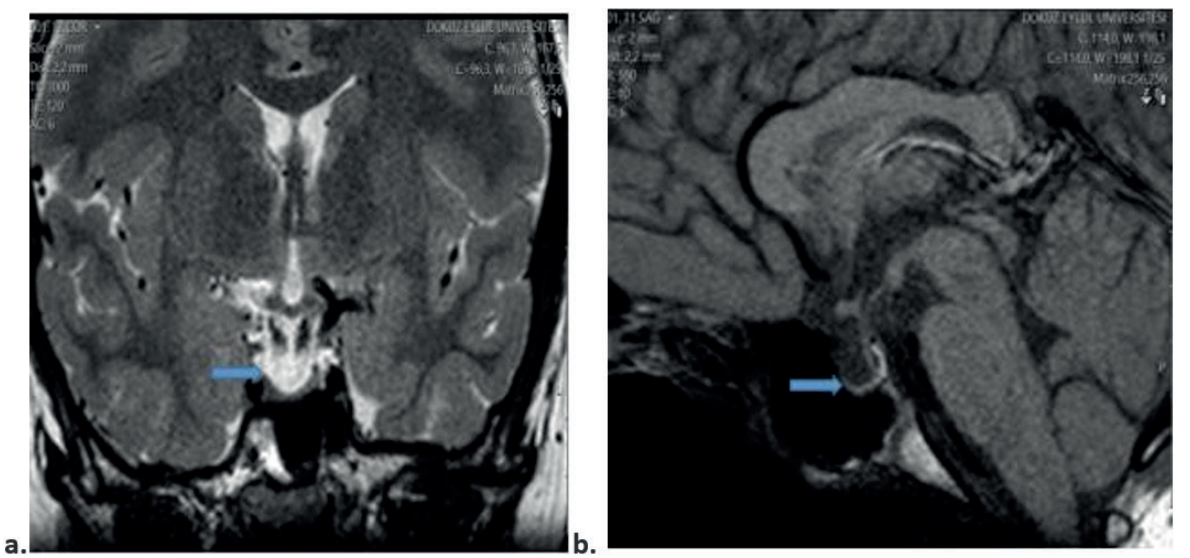

Fig. 1. MRI brain scans of patient number 2 confirming the diagnosis of empty sella. **a.** T2weighted (arrow: fluid attenuated) coronal section shows the increased signal intensity of the CSF occupying the sella turcica **b.** T1-weighted mid-sagittal section that demonstrates a fluid filled sella turcica with a flattened pituitary gland (arrow) at the base of the pituitary fossa.

dysfunctions. Five short patients (#2, #5, #9, #12 and #14) had growth deceleration and/or target height discrepancies with low to normal IGF-1 / IGFBP-3 levels [SD scores –1.2 (2, -2 - 1.2); 0.2 (3.4, -2.4 - 1.8), respectively]. All these five patients failed to achieve adequate GH

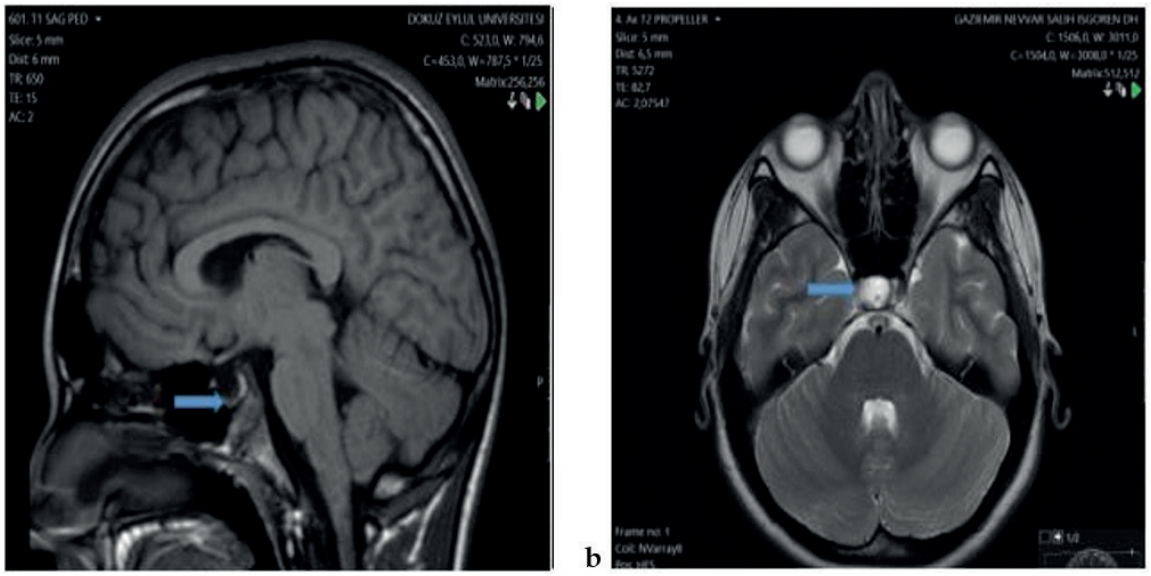

Fig. 2. MRI brain scans of patient number 7. **a.** Midsagittal T1-weighted image through the sellar region shows decreased pituitary gland (arrow) height. **b.** T2-weighted axial image shows the increased signal intensity (arrow) of the CSF at sella turcica.

responses with two GH stimulation tests; thus, GH therapy at conventional doses (25 - 35 mcg / kg / day) was initiated. The SD scores for median height at baseline and at final evaluation were -2.6 [1.3, -1.8 - (-3.75)] and -1.9 [1.3, -0.6 - (-2.6)], respectively.

Two of the six short patients (#10 and #11) lacked predisposing factors for short stature, such as a history of small-for-gestational-age births or syndromic traits. The target height SD scores of patients #10 and #11 were -1.4 and -0.5, respectively. Both patients demonstrated delayed skeletal maturation, which was consistent with their family history of constitutional delay of growth and puberty in both parents. With IGF-1 / IGFBP-3 values above the 0 SD threshold, they exhibited normal growth rates for their ages. Consequently, no GH therapy was initiated throughout the time of follow-up. At the last visit, the SD scores for height and the predicted adult heights of patients #10 and #11 were -1.8, -0.8 and -1.7, -0.5, respectively.

Two short patients (#10 and #14 in Table I) complained of delayed puberty at follow-up and one (#13 in Table I) showed no pubertal signs at 17 years of age. Their basal LH and FSH levels were 0.07, 0.8, 0.19 mIU/mL and 4.9, 4, 0.7 mIU/mL, respectively. All patients showed normal pubertal responses to GnRH test. To stimulate pubertal development in patients #10 and #13, a low dose of estrogen (5 μg/kg/day of 17-β oestradiol) was administered for a short period of time (three months). On the last examination, at age 14, with a bone age of 12, and without therapy in the previous year, patient #10 presented as tanner stages 2-3, with pubertal hormone levels and pelvic ultrasonography. Yet, one case (#13 in Table I), had no sign of breast development and her estrogen levels were below detection limits, thus low dose of estrogen was gradually increased over 3-6 months and progesterone was added to estrogen after one year. Combined estrogen and progesterone therapy facilitated her menstrual cycles. She later had normal physiological menstrual cycles. All three were considered to have transient pubertal delays.

The median cortisol levels of the patients were 10 μg/dL (9.4, 5.4 - 27). Five of the patients had a baseline cortisol levels below 10 μg/dL. All five of them showed normal cortisol responses to stimulation tests. Two patients underwent

low-dose ACTH testing and, to avoid multiple testing, three short patients underwent insulin tolerance testing to simultaneously rule out GH deficiency. None of the patients had hyper- or hypoprolactinemia [median prolactin level 7 ng/mL (8.6, 3.5 - 20)] or central hypothyroidism [fT4, 0.9 ng/dL (0.06, 0.7 - 1.7); TSH, 2.6 mIU/L (2, 0.5 - 5.6)]. Diabetes insipidus was also not observed in any of the patients.

Six patients (35%) had clinical conditions requiring pharmacological treatment. Five patients (29 %) were diagnosed with endocrine dysfunctions; all five were diagnosed with isolated GH deficiency, and GH replacement treatment was initiated. No further endocrine deficiencies were detected. One patient (#16 in Table I) with a severe headache, had papilledema without visual loss and increased intracranial pressure on lumbar puncture was detected; after acetazolamide treatment, his symptoms disappeared and surgical treatment was not required. However, on follow-up examinations, he later developed cervical lymphadenitis, and was diagnosed with Burkitt lymphoma. Control MRIs were not ordered for the other patients, since none of them developed new complaints or showed clinical progression during follow-ups.

There was no significant correlation between the size of the pituitary gland and the SD scores of weight, height, and BMI of our patients (***Spearman's Rho*** (r_s)= -0.08, p = 0.8; r_s = 0.036, p = 0.9; r_s = -0.045, p = 0.87, respectively). Also, the size of pituitary gland was similar between patients with GH deficiency and normal growth velocity (p = 0.42).

Discussion

PES is often considered an incidental finding and a normal variant, but our study showed that it may also be associated with different important neurological and endocrine problems. In the present study, empty sella was diagnosed either during the evaluation of neurological complaints or hormonal dysfunctions. Similar to prior studies[1,2], the early neurological symptoms of our patients included headache, tinnitus, tics, vertigo, and depression. As for endocrine functions in PES, endocrinological evaluation may be completely normal; however, various degrees and forms of pituitary dysfunctions, including hyperprolactinemia (4 - 37.5% of patients), GH deficiency (4 to 57% of patients), secondary defects in ACTH, TSH or gonadotropins (2.3 - 32% of patients), panhypopituitarism (2% of patients) and isolated or combined hypopituitarism (28 - 53% of patients) have also been reported.[1,4,10,24,25]

Overall, pituitary disturbances have been observed in 8 to 60% of all patients.[4,7,10,26] In our study, 29% of all our patients had isolated GH deficiency, indicating that somatotroph cells are the most vulnerable site, and so probably the most crucial screening parameter for other hormone deficiencies. Even while this incidence of GH deficiency in PES patients is consistent with previous studies[1,4,10,24,25], it should be noted that up to 57 % of all patients have been documented to have GH deficiency. Given the young ages and short follow-up duration of our patients, it would be prudent to consider the likelihood that more deficiencies may appear during the follow-up in our cohort. This prediction may be especially plausible for patients such as #10 and #11, who were considered to have constitutionally delayed growth and puberty, with delayed bone age, normal growth velocity, and predicted adult height consistent with familial patterns. Since they had not yet attained adult heights, it is questionable whether they could have benefited from GH replacement as well.

Menstrual irregularities, hirsutism, and gynecomastia are also associated with PES.[1] One patient had menstrual irregularity in our study. Obesity is also a component of the clinical spectrum, and it is involved in the pathophysiological mechanism.[1] However, none of our patients were obese, indicating that obesity could be an incidental association.

In PES, increased intracranial pressure and changes in cerebrospinal fluid dynamics, which have been reported in 60 - 77% of patients may necessitate surgical treatment.[5] Only one of our patients experienced increased intracranial pressure, which resolved with pharmacological treatment. As for the follow-up of patients, De Marinis et al.[4] suggested that patients with no abnormalities at baseline are unlikely to develop any symptoms in the future. Therefore, careful re-evaluation of symptom progression was advised for those with baseline defects. In line with this suggestion, in our study, only the patients with primary endocrine pathologies actually needed hormone replacement treatments, while those with neurological complaints had normal endocrinological assessments. This suggests that the initial clinical findings are more predictive than neuroimaging in empty sella.

Previous studies have shown conflicting results regarding the correlation between the degree of herniation, the size of the pituitary, and related dysfunctions.[25,27] Similar to Gallardo et al.[6], we also found no correlation between the pituitary size and the severity of the clinical course.

A limitation of our study is that it was conducted retrospectively on a small number of patients. Methods of radiological evaluation, laboratory tests and techniques could have changed in the past years. However, the pituitary axis was systematically assessed according to the current guidelines for each patient, and long-term follow-up examinations were presented accordingly. However, since the patients presented during childhood and the final adult assessments were unfortunately not available, various other future deficiencies may emerge over time. For this reason, it is important to monitor potential deficiencies over a longer period of time in pediatric patients.

Furthermore, among all cranial MRIs of pediatric patients ordered in our hospital in the past 10 years, only seventeen children were diagnosed with PES, which is fewer than in previous studies. This finding supports the fact that empty sella is difficult to recognize and can be easily missed without specific requests to the sellar region.

PES may be associated with different neurological and endocrinological conditions (mostly, short stature and transient delayed puberty), which may require specific treatments. The size of the pituitary gland does not relate to the severity of the symptoms. The high incidence of pituitary dysfunctions ascertains that this entity should not be considered as a normal variant, but should instead be carefully evaluated using appropriate basal and dynamic hormonal testing to identify the distinct hormonal dysfunctions.

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Ethical approval

Approval was granted by the Ethics Committee of Dokuz Eylül University Faculty of Medicine (Ethics approval number: 2021/14-2906052021).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: AA, ÖB; data collection: ÖB, EY; analysis and interpretation of results: ÖB, İME, KYA; draft manuscript preparation: AA, ÖB, KD, EB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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