

RESEARCH ARTICLE


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Pituitary Volume in Patients with Primary Empty Sella and Clinical Relevance to Pituitary Hormone Secretion: A Retrospective Single Center Study



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Abstract: Background: According to neuroradiological findings, empty sella seems to be deprived of pituitary tissue in sella turcica. Changing size of the pituitary volume is closely related to the occurrence of primary empty sella. The aim of the study is to determine pituitary dysfunction in patients with partial or total primary empty sella and the significance of pituitary volume measurements in these patients.

Methods: This study was designed retrospectively. 67 patients (55 females, 12 males) diagnosed with primary empty sella syndrome between the years of 2015-2019 were included in the study. Patients were divided into two groups: partial (PES) and total (TES) empty sella by magnetic resonance imaging (MRI). Basal anterior pituitary and its hormones were assessed. We also included 26 healthy control subjects (19 females, 7 males) to compare the differences in pituitary volumes. Volumes were measured by using Osirix Dicom Viewer (Pixmeo SARL, Geneve, Swiss) in 3.0 Tesla scanner MRI.

Results: 82.1% (n=55) of all patients were PES and the others were (n=12) TES. Hypopituitarism, known as one or more pituitary hormones deficiency, was found in 12 patients (17.9%). While 9 of them had total PES, the others had partial PES. Secondary adrenal insufficiency and gonadotropin deficiency were more prevalent in patients with TES. Mean volume measurements of patients with TES, PES and healthy subjects were 0.23 ± 0.17 , 0.35 ± 0.15 , 0.54 ± 0.17 cm³, respectively. Except for IGF1 values (p=0.026), there was not any significant correlation found between the anterior pituitary hormones and volume measurements.

Conclusion: Although volume measurement has helped in the diagnosis of pituitary empty sella (partial or total), it does not seem to have any significant correlation with pituitary secretory function.

Keywords: Partial empty sella, total empty sella, pituitary volume, hypopituitarism, magnetic resonance imaging, herniation.

1. INTRODUCTION

Primary empty sella is an anatomical condition characterized by herniation of the subarachnoid space into the sella turcica. Primary empty sella syndrome is defined in patients with unknown etiology or patients without a history of sellar region treatment by surgical, radiotherapy or pharmacological therapies [1, 2]. Particularly, in the autopsy series, prim-

ary empty sella is described as an incidental finding in approximately 5.5% to 12.5% of cases [3]. In clinical practice, due to the increased usage of radiological imaging studies via magnetic resonance imaging (MRI), computerised tomography (CT), the prevalence of primary empty sella has increased and it has been reported from 8% to 35% in the general population [4, 5]. The peak incidence of empty sella is shown between thirties and forties, with female preponderance [6]. Although the pathogenesis of empty sella is not known clearly, numerous etiopathogenetic mechanisms including upper-sellar factors (intracranial hypertension, cerebrospinal fluid (CSF) pulsatility, obesity), and pituitary fac-

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ARTICLE HISTORY

Received: December 16, 2020
Revised: February 16, 2021
Accepted: February 23, 2021

DOI:
[10.2174/1573405617666210525111218](https://doi.org/10.2174/1573405617666210525111218)


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tors associated with variation of pituitary volume (lactation, pregnancy, hypophysitis) have been suggested up to date [7, 8]. Empty sella is divided into two categories according to the volume of CSF: partial empty sella (PES) and total empty sella (TES) [9]. The clinical scenario of empty sella is often quite complex. Primary empty sella has been reported to be associated with endocrine dysfunction (mainly based on oligomenorrhea in females and sexual dysfunction in males). While some studies [10, 11] have reported that the endocrine disturbances are more common, some [12, 13] have shown that primary empty sella is an only asymptomatic radiological finding.

In the diagnosis of primary empty sella, physiological as well as individual variability in volume and morphology of the pituitary gland and sellar cavity, particularly in infancy and adolescence, has to be taken into account [14, 15]. Especially, its largest size appears during hormonally active conditions (such as puberty and pregnancy) [16]. On the other hand, decreased volumes following the expansion of the pituitary gland in sella turcica can cause a space allowing suprasellar chiasmatic cistern herniation [17]. Although the radiological degree of empty sella is stable over time, due to progression or new-onset of pituitary dysfunction, even in the absence of clinical indications, biochemical evaluation should be done. Although many studies [18, 19] evaluating the prevalence and hormonal status in an incidental finding of primary empty sella have been published, the exact size of the pituitary in these patients or its effect on secretory function remains unclear. In this study, we aimed to evaluate the pituitary dysfunction as well as provide the measurements of the pituitary gland volumes in patients with primary empty sella. We also compared the measurements of pituitary volumes of the patients with empty sella to those of healthy control patients.

2. MATERIALS AND METHODS

2.1. Patients

67 patients (55 females, 12 males) diagnosed with empty sella between the years 2015 and 2019 were included in our study. All patients had primary empty sella confirmed by pituitary MRI. The reasons for pituitary imaging were headache (40%), neurological symptoms (30%), endocrine disorders (10%), abnormalities of sella turcica radiography (5%) and others (15%). Empty sella diagnosis and subdivisions were done according to the common consensus of the medical literature [1, 2]. We included patients with only primary empty sella syndrome and separated them into two groups: (i) partial empty sella (PES); (ii) total empty sella (TES). Total empty sella was diagnosed according to the findings of MRI before and after the contrast enhancement (more than 50% of the sella filled with CSF or pituitary gland thickness ≤ 2 mm) (9). PES was described as the pituitary thickness ≥ 3 and below 50% of the sella filled with CSF [9]. Clinical data were obtained from the medical records according to individual diagnostic criteria. Otherwise, patients with empty sella due to causes such as the history of the central nervous system/hypothalamic-pituitary diseases,

history of pituitary surgery, secondary to radiotherapy or medical treatments were excluded. As well as patients who had functional pituitary diseases including growth hormone (acromegaly), cortisol hypersecretion (Cushing disease) or prolactin (prolactinoma) were also excluded to rule out the possibility of secondary empty sella syndrome. The study was approved by the Local Ethical Committee of the University (Number: 96 on February 2020).

Endocrine functions of the pituitary were evaluated by blood levels of free thyroxine (fT4, normal range 0.61-1.12 ng/dL), thyroid stimulating hormone (TSH, normal range 0.38-5.33 mIU/L), follicle stimulating hormone (FSH), luteinising hormone (LH), growth hormone (GH, normal range 0-10 ng/mL), age and gender-adjusted-Insuline. Like Growth Factor-1 (IGF-1, normal range 45-900 ng/mL), estradiol (for women), testosterone (for men, normal range 0.14-0.76 ng/mL), cortisol (6.7-22.6 mcg/dL), adrenocorticotropic hormone (ACTH, normal range 10-50 pg/mL), and prolactine (PRL, normal range 3.34-26.7 ng/mL).

The control group (n=26, F=19, M=7) consisting of healthy subjects was recruited based on the normal endocrine functions and pituitary imaging of MRI. The indications for imaging the pituitary *via* MRI in control subjects were similar to the patients with primary empty sella syndrome. The empty sella group was selected similar to control patients in order to avoid difference in findings based on age and gender.

2.2. MRI Techniques and Pituitary Volume Measurements

All magnetic resonance imaging was performed at the Çukurova University Radiology Department. Comfortable head positioning was provided. Dynamic pituitary MRI was performed by using 3.0 Tesla scanner (Philips Achieva, Philips Medical Systems, Best, The Netherlands). The whole brain was scanned with a 3-D fast field echo (FFE) T1-weighted dataset. T1-weighted images were obtained in the coronal plane with 1.5 mm contiguous sections. TR was 25 ms, TE was 4.6 ms, and the flip angle was 30°, with a 256× 256 mm matrix used. Anatomic measurements were obtained on an independent workstation. Pituitary volume (ICV) was measured by a single rater blind to the subject's identity. Boundary definition and tracing of the pituitary were done using standard neuroanatomical measurements with methods and definitions adapted from neuroimaging studies on the pituitary. The superior border of the structure was described as the optic chiasm and infundibular recess of the third ventricle, while the inferior border was the sphenoid sinus. The volume of the pituitary (in cm³) was calculated by adding the volumes for all relevant slices (Fig. 1A-1B)

2.3. Statistical Analysis

Categorical variables have been shown as numbers and percentages, but the other continuous variables have been presented as mean and standard deviation. Chi-square test was used to compare categorical variables between the

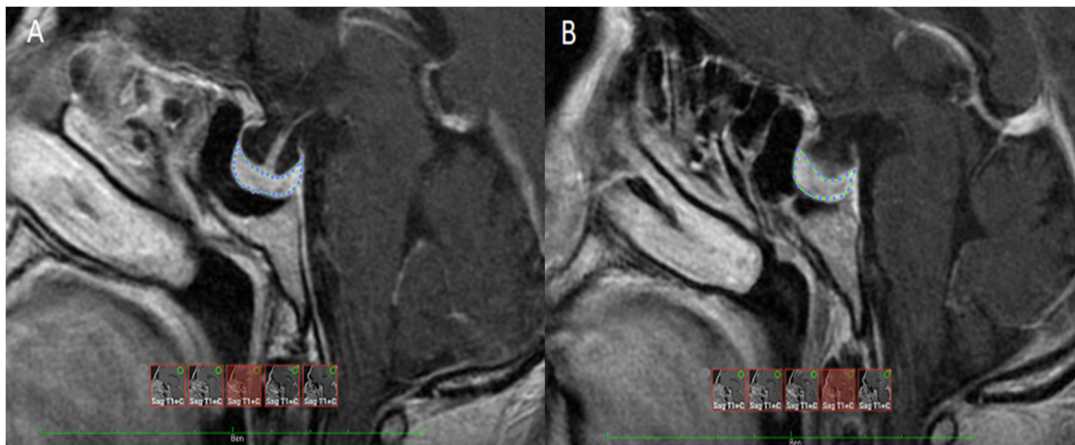


Fig. (1A-B). (left-right side): Sella area is delineated with using dashed line. Sagittal post-contrast magnetic resonance images (MRI) show partially empty sella.

groups. The normality of distinction for continuous variables was demonstrated using the Shapiro Wilk test. The Student's t-test or Mann-Whitney U test were used for continuous variables. Pearson Correlation Coefficient or Spearman Rank Correlation Coefficient were used for evaluating the correlations between measurements. All analyses were carried out by using IBM SPSS Statistics Version 20.0 statistical software package. The statistical level of significance for all tests was considered to be 0.05.

SPSS referansı: IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

3. RESULTS

55 of 67 (82.1%) patients were diagnosed as PES, whereas 12 of 67 (17.9%) were diagnosed as TES. The mean age of all female and male patients with primary (total or partial) empty sella was 45.3 ± 15.9 , 46.6 ± 14.7 , and 39.08 ± 20.1 , respectively ($p=0.136$). When we evaluated the female patients' menstrual history from the patients' files, all female patients were found to be post-menopausal. Male patients diagnosed with primary empty sella had erectile dysfunction or sexual impotence. There was not any significant correlation observed between the demographical parameters (age, gender) and the diagnosis of partial or total empty sella.

Baseline demographic characteristics and biochemical parameters of the patients with PES are summarized in Table 1.

Hypopituitarism, which is known as one or more pituitary hormones deficiency, has been found in 12 patients (17.9%). While 9 of the patients with hypopituitarism had TES, the other patients with hypopituitarism had PES.

More specifically, isolated gonadotropin deficiency was found in 6 patients (3 males, 3 females, 8.9%). Isolated secondary adrenal insufficiency was found in 4 (5.9%) and isolated GH deficiency was found in 2 patients (2.9%).

Based on the hormonal evaluation, plasma FSH, LH, ACTH, cortisol and ft4 levels were significantly decreased

in patients with TES than PES ($p<0.05$). Secondary adrenal insufficiency and gonadotropin deficiency were more prevalent in patients with TES (Table 1).

Mean volume levels of all patients ($n=67$) with empty sella syndrome were $0.33 \pm 0.16 \text{ cm}^3$ (range $0.03-0.75 \text{ cm}^3$). Mean volume levels of TES patients' pituitary (0.23 ± 0.17 vs. $0.35 \pm 0.15 \text{ cm}^3$, $p=0.02$) were more decreased than the patients with PES (Table 2 and Figs. 2A-B, 3). We did not observe any significant correlation between the volume measurements and gender differences in patients with PES or TES (Table 2, $p>0.05$). A negative correlation was observed between volume and age of all patients with empty sella ($r=-0.552$, $p=0.008$). In terms of hormone parameters and volume measurements, only basal IGF1 values were correlated with the pituitary volumes ($p=0.026$) (Fig. 3).

The mean age of the control group was 40.2 ± 12.7 (females 43.1 ± 9.6 , males 36.6 ± 13.2). Parameters of age and gender were similar between patient and control groups ($p>0.05$). When we compared the volume levels of TES and PES (0.23 ± 0.17 vs. 0.35 ± 0.15) and control patients' pituitary (0.54 ± 0.17), there was a significant difference in terms of pituitary volumes ($p=0.00$). Detailed results of patients and control subjects are shown in Table 2.

4. DISCUSSION

In this study, 82.1% of the patients were PES and the others (17.9%) were diagnosed as TES. As mentioned in results section, secondary adrenal insufficiency and gonadotropin deficiency were more prevalent in patients with TES. Although hypopituitarism was seen only in the minority of patients with PES and TES, volume measurements of them (0.23 ± 0.17 vs. $0.35 \pm 0.15 \text{ cm}^3$) were found to be severely decreased than healthy control subjects (0.54 ± 0.17 , $p=0.00$). In our study, we emphasized that empty sella is an incidental finding in neuroradiological imaging with decreased pituitary volume. And we also determined that the pituitary volume has no significant effect on the deficiency of hormonal status.

Table 1. Demographical, biochemical parameters and volume measurements of the patients with partial or total empty sella.

-	PES(n=55)	TES(n=12)	p
Female	46 (83.6%)	9 (75%)	0.43
Male	9 (16.4%)	3 (25%)	0.43
Age (year)	44.87±16.32	47.33±14.45	0.63
Pituitary Volume (cm ³)	0.35±0.15	0.23±0.17	0.00
FSH (mIU/mL) (1.27-19.26)	26.8±31.9	2.7±2.05	0.016
LH (mIU/mL) (1.24-8.62)	13.8±14.7	2.6±2.9	0.011
TSH (mIU/L) (0.38-5.33)	1.8±1.4	1.2±0.9	0.11
fT4 (ng/dL) (0.61-1.12)	0.77±0.18	0.89±0.22	0.041
GH (ng/mL) (0-1)	0.58±1.15	0.30±0.43	0.25
IGF1(ng/mL)* (94-252)	154.5±92.8	102.7±76.5	0.12
ACTH (pg/mL) (10-50)	23.08±8.7	15.8±5.9	0.022
Cortisol (mcg/dL) (6.7-22.6)	10.03±4.3	6.3±4.1	0.013
Prolactine (ng/mL) (2.64-13.13)	17.2±33.5	19.2±23.7	0.23
Total Testosterone** (ng/mL) (2.41-8.27)	3.5±2.6	1.9±0.2	0.32

Abbreviations: PES: Partial Empty Sella, TES: Total Empty Sella, FSH: Follicle Stimulating Hormone, LH: Luteinizing Hormone, TSH: Thyroid Stimulating Hormone, ACTH: Adrenocorticotroph hormone, IGF1: Insuline Growth factor 1.
IGF1*: Matched for age and gender, Total Testosterone**: in male subjects.

Table 2. Comparement of the volume measurements in patients with empty sella or control subjects.

-	Volume of PES (n=55)	Volume of TES (n=12)	P*	Volume of healthy controls (n=26)	P**
Female	0.33±0.16	0.21±0.17	0.00	0.56±0.17	0.00
Male	0.35±0.16	0.24±0.16	0.022	0.48±0.19	0.00
Total 0.35±0.15 0.23±0.17 0.001 0.54±0.17 0.002					

PES: Partial Empty Sella, TES: Total Empty Sella.
p*: p value shows comparement between the volumes of partial and total empty sella.
p**: p value shows comparement between the volumes of empty sella and healthy control subjects.

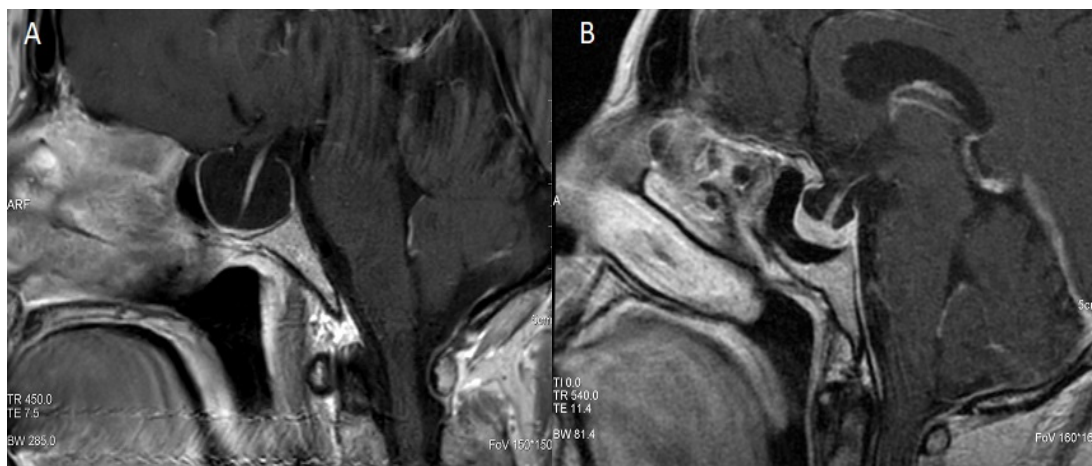


Fig. (2A-B). (left side): Sagittal post-contrast image shows enlarged sella with marked of the pituitary gland of the stalk. (right side): Sagittal post-contrast magnetic resonance image (MRI) shows partially empty sella.

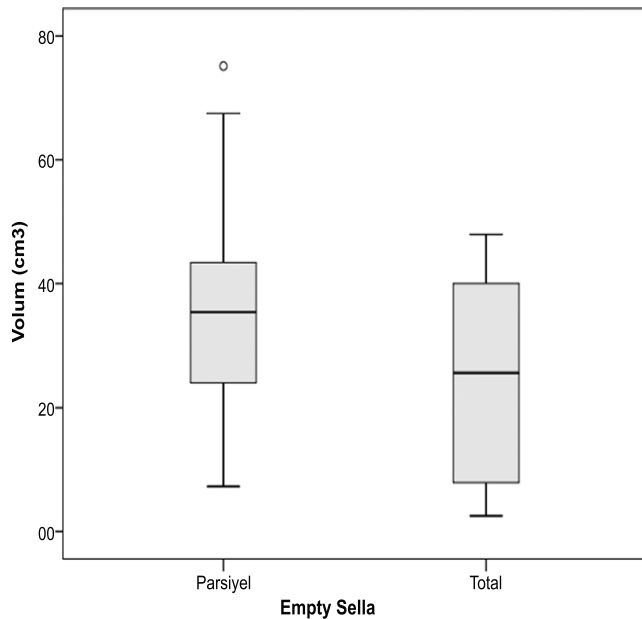


Fig. (3). Volume measurements of partial and total empty sella (PES, TES).

In daily practice, the widespread usage of neuro-imaging techniques, particularly MRI, has increased the frequency of incidental diagnosis of empty sella [20]. Although the pathogenesis of empty sella is quite complicated in many patients, incompetence of sellar diaphragm is commonly considered in the formation of empty sella [21]. The role of intracranial hypertension has been proposed by many authors and elevated CSF pressure is found in up to 84% of patients [22]. Related to intracranial hypertension, 10% of these patients were referred to hospital with headache and visual-field defects [23]. Data from autopsy series and neuroradiological studies reported that primary empty sella accounted for about 5.5% to 35% of those subjects, and it was observed four times frequently in women [24, 25]. The peak incidence of PES occurred between the third and fourth decades [26]. In the current study, the mean age of the patients was 45.3 ± 15.9 with the preponderance of females. There was no significant correlation observed in terms of age between female and male patients with PES (46.6 ± 14.7 vs. 39.08 ± 20.1). The most common clinical complaint of our patients was headache (40%). When the demographical parameters (age, gender, *etc.*) were compared between patients with partial and total empty sella, both groups had female preponderance (83.6% vs. 75%; respectively) and similar age (44.87 ± 16.32 vs. 47.33 ± 14.45 ; respectively, $p=0.63$).

The endocrinological picture is quite complicated in patients with empty sella and it is not always possible to differentiate clinical findings or hormonal parameters that are consequences of partial or total empty sella [27, 28]. Different degrees of hypopituitarism ranging from 8 to 60% have been reported. Pituitary insufficiency can be diagnosed in various degrees ranging from total hypopituitarism to isolat-

ed hormonal deficiency, with increased or normal prolactin values [29]. In the case control study, including 85 patients (59 PES, 26 TES), reported by Lupi *et al.* [30], pituitary insufficiency was diagnosed in 49% of patients. They also showed the results of PES and TES to be similar, except for the preponderance of secondary hypothyroidism in the TES group; however, this was not significant. Zuhur *et al.* [31] reported 81 (47 partial, 34 total) patients' results with empty sella and documented the gonadotropin deficiency in 29.6% and GH deficiency in 29.6%. They also found a significant difference in pituitary function in patients with PES compared to those with TES. In contrast to previous results, hypopituitarism was not common ($n=12, 17.9\%$) in our study ($n=67$). Isolated gonadotropin insufficiency (8.9%) was more common than the other hormone deficiencies. According to hormonal evaluation, measurements of ACTH, cortisol, LH, and FSH levels were found to be significantly decreased in patients with TES compared to PES. Hence, we argued that hormonal alterations were not sharply demarcated; moreover, it could be a variable related to individual differences.

Pituitary gland is a dynamic organ that changes in response to different factors such as age, gender, *etc.* [32]. Although previous studies have reported pituitary gland volumes for various disease groups (schizophrenia, obsessive-compulsive disorder, polycystic ovarian syndrome), there has been only one study found in the literature that has investigated pituitary volumes in patients with empty sella syndrome [33-35]. Fleckman *et al.* [36] reported the mean pituitary volume from 13 women with postpartum hypopituitarism (Sheehan's Syndrome) as 0.5 ± 0.6 cm³ (range 0.2-1.09 cm³) and 85% of them were in the normal range. Terrano *et al.* [37] reported pituitary volumes in 59 elderly healthy subjects (70-95 years, average 81.8 ± 5.9) and 41 younger healthy subjects (19-59 years, average 34.7 ± 10.7). They reported that the pituitary gland volume of elderly subjects (0.2 ± 0.13 cm³) was significantly smaller than the younger group (0.4 ± 0.11 cm³). While empty sella was diagnosed in 19% of all elderly subjects ($n=59$), no significant relationship between hormone parameters and pituitary properties (empty sella or pituitary volume measurements) was found. The results of our study indicate that the mean pituitary volume of patients with total or partial empty sella (0.23 ± 0.17 vs. 0.35 ± 0.15) was remarkably decreased than the volumes of age and gender-matched control patients (0.54 ± 0.17 $p=0.00$). Our study also demonstrated age to be negatively correlated with pituitary volume ($p=0.008$), but serum IGF1 values were positively correlated with pituitary volume ($p=0.026$). Although measurements of pituitary volume helped in the diagnosis of empty sella, we could not find any significant relationship between the anterior pituitary hormones and volume measurements.

This study has several limitations. Pituitary stimulation tests were not performed as the study was retrospective. Hence, it has been impossible to specify the exact frequency of GH, TSH and gonadotropin deficiency. The second limitation is the small sample size. Another limitation is that the

hormonal values were not followed up in the patients probably due to the retrospective nature of the study. Finally, we could not evaluate hormone parameters of healthy control subjects. But the current study is the first study in terms of pituitary volume evaluation in patients with empty sella and their comparison with healthy control subjects.

CONCLUSION

In conclusion, in the majority of the cases, empty sella was the only neuroradiological finding without any clinical implication. Primary empty sella (partial or total) should be carefully identified and properly managed since clinical characterization shows peculiar entities. The results of the study suggest that the primary empty sella displayed a characteristic appearance with decreased pituitary volume, previously not reported, compared to age- and sex-matched healthy controls. Although pituitary insufficiency in our patients was less common than that found in previous studies, all subjects with empty sella, especially with TES, should be evaluated carefully for pituitary hormone deficiency.

AUTHORS' CONTRIBUTIONS

Gamze Akkuş wrote the manuscript. Mehtap Evran and Bilen Onan designed the study. Editing was done by Gamze Akkuş, Murat Sert and Tamer Tetiker. Collection of materials was done by Barış Karagün, Fulya Odabaş and Sinan Sözütok. All authors have read and approved the final version of the manuscript.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Local Ethical Committee of the Cukurova University, Turkey. (Number: 96 on February 2020).

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

CONSENT FOR PUBLICATION

The consent was obtained from the patients for this study.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise..

ACKNOWLEDGEMENTS

The authors wish to thank Dr. Oğuz Akkuş for English editing of this paper.

REFERENCES

- [1] Maira G, Anile C, Mangiola A. Primary empty sella syndrome in a series of 142 patients. *J Neurosurg* 2005; 103(5): 831-6. <http://dx.doi.org/10.3171/jns.2005.103.5.0831> PMID: 16304986
- [2] Guitelman M, Garcia Basavilbaso N, Vitale M, *et al.* Primary empty sella (PES): a review of 175 cases. *Pituitary* 2013; 16(2): 270-4. <http://dx.doi.org/10.1007/s11102-012-0416-6> PMID: 22875743
- [3] Bergland RM, Ray BS, Torack RM. Anatomical variations in the pituitary gland and adjacent structures in 225 human autopsy cases. *J Neurosurg* 1968; 28(2): 93-9. <http://dx.doi.org/10.3171/jns.1968.28.2.0093> PMID: 5638016
- [4] Foresti M, Guidali A, Susanna P. Primary empty sella. Incidence in 500 asymptomatic subjects examined with magnetic resonance. *Radiol Med (Torino)* 1991; 81(6): 803-7. PMID: 1857785
- [5] Gallardo E, Schächter D, Cáceres E, *et al.* The empty sella: Results of treatment in 76 successive cases and high frequency of endocrine and neurological disturbances. *Clin Endocrinol (Oxf)* 1992; 37(6): 529-33. <http://dx.doi.org/10.1111/j.1365-2265.1992.tb01484.x> PMID: 1286523
- [6] Chiloiro S, Giampietro A, Bianchi A, *et al.* Diagnosis of endocrine disease: Primary empty sella: A comprehensive review. *Eur J Endocrinol* 2017; 177(6): R275-85. <http://dx.doi.org/10.1530/EJE-17-0505> PMID: 28780516
- [7] Morris PP, Lachman N, Black DF, Carter RA, Port J, Campeau N. Increased curvature of the tentorium cerebelli in idiopathic intracranial hypertension. *AJNR Am J Neuroradiol* 2017; 38(9): 1789-93. <http://dx.doi.org/10.3174/ajnr.A5289> PMID: 28663268
- [8] Loh WA, Sittampalam K, Tan SC, Chandran M. Symptomatic empty sella syndrome: an unusual manifestation of Erdheim-Chester disease. *Endocrinol Diabetes Metab Case Rep* 2015; 140122.
- [9] De Marinis L, Bonadonna S, Bianchi A, Maira G, Giustina A. Primary empty sella. *J Clin Endocrinol Metab* 2005; 90(9): 5471-7. <http://dx.doi.org/10.1210/jc.2005-0288> PMID: 15972577
- [10] Xu P, He H, Chen Y, Wang C, Zhu Y, Ye X. Osteoporotic fractures and persistent non-fusion of the hand epiphyses caused by empty sella syndrome in an adult: a case report. *J Int Med Res* 2013; 41(5): 1768-72. <http://dx.doi.org/10.1177/0300060513490609> PMID: 24029021
- [11] Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology* 2013; 81(13): 1159-65. <http://dx.doi.org/10.1212/WNL.0b013e3182a55f17> PMID: 23966248
- [12] Pompili A, Calvosa F, Appetecchia M. Evolution of primary empty sella syndrome. *Lancet* 1990; 336(8725): 1249. [http://dx.doi.org/10.1016/0140-6736\(90\)92862-C](http://dx.doi.org/10.1016/0140-6736(90)92862-C) PMID: 1978086
- [13] Cannavò S, Curtò L, Venturino M, *et al.* Abnormalities of hypothalamic-pituitary-thyroid axis in patients with primary empty sella. *J Endocrinol Invest* 2002; 25(3): 236-9. <http://dx.doi.org/10.1007/BF03343996> PMID: 11936465
- [14] Atmaca M, Baykara S, Mermi O, Yildirim H, Akaslan U. Pituitary volumes are changed in patients with conversion disorder. *Brain Imaging Behav* 2016; 10(1): 92-5. <http://dx.doi.org/10.1007/s11682-015-9368-6> PMID: 25877743
- [15] Peper JS, Brouwer RM, van Leeuwen M, *et al.* HPG-axis hormones during puberty: a study on the association with hypothalamic and pituitary volumes. *Psychoneuroendocrinology* 2010; 35(1): 133-40. <http://dx.doi.org/10.1016/j.psyneuen.2009.05.025> PMID: 19570613
- [16] Simmons JG, Whittle SL, Patton GC, *et al.* Study protocol: imaging brain development in the Childhood to Adolescence Transition Study (iCATS). *BMC Pediatr* 2014; 14(1): 115. <http://dx.doi.org/10.1186/1471-2431-14-115> PMID: 24779869

- [17] Takano K, Utsunomiya H, Ono H, Ohfu M, Okazaki M. Normal development of the pituitary gland: assessment with three-dimensional MR volumetry. *AJNR Am J Neuroradiol* 1999; 20(2): 312-5. PMID: 10094362
- [18] Giustina A, Aimaretti G, Bondanelli M, *et al.* Primary empty sella: Why and when to investigate hypothalamic-pituitary function. *J Endocrinol Invest* 2010; 33(5): 343-6. <http://dx.doi.org/10.1080/BF03346597> PMID: 20208457
- [19] Karaca Z, Tanriverdi F, Unluhizarci K, Kelestimur F, Donmez H. Empty sella may be the final outcome in lymphocytic hypophysitis. *Endocr Res* 2009; 34(1-2): 10-7. <http://dx.doi.org/10.1080/07435800902841306> PMID: 19557587
- [20] Del Monte P, Foppiani L, Cafferata C, Marugo A, Bernasconi D. Primary "empty sella" in adults: endocrine findings. *Endocr J* 2006; 53(6): 803-9. <http://dx.doi.org/10.1507/endocrj.K06-024> PMID: 16983177
- [21] Julayanont P, Karukote A, Ruthirago D, Panikkath D, Panikkath R. Idiopathic intracranial hypertension: ongoing clinical challenges and future prospects. *J Pain Res* 2016; 9: 87-99. PMID: 26929666
- [22] Ghatnatti V, Sarma D, Saikia U. Empty sella syndrome - beyond being an incidental finding. *Indian J Endocrinol Metab* 2012; 16 (Suppl. 2): S321-3. PMID: 23565413
- [23] Gruner P, Christian C, Robinson DG, *et al.* Pituitary volume in first-episode schizophrenia. *Psychiatry Res* 2012; 203(1): 100-2. <http://dx.doi.org/10.1016/j.psychres.2011.09.017> PMID: 22858406
- [24] Poggi M, Monti S, Lauri C, Pascucci C, Bisogni V, Toscano V. Primary empty sella and GH deficiency: prevalence and clinical implications. *Ann Ist Super Sanita* 2012; 48(1): 91-6. PMID: 22456022
- [25] Dange N, Redhu R, Kawale J, Mahore A. Primary amenorrhea due to empty sella: an underestimated entity. *Turk Neurosurg* 2012; 22(4): 499-501. PMID: 22843475
- [26] Beressi N, Beressi JP, Cohen R, Modigliani E. Lymphocytic hypophysitis. A review of 145 cases. *Ann Med Interne (Paris)* 1999; 150(4): 327-41. PMID: 10519020
- [27] Petersenn S, Quabbe HJ, Schöfl C, Stalla GK, von Werder K, Buchfelder M. The rational use of pituitary stimulation tests. *Dtsch Arztebl Int* 2010; 107(25): 437-43. <http://dx.doi.org/10.3238/arztebl.2010.0437> PMID: 20644702
- [28] Colao A, Cotta OR, Ferone D, *et al.* Role of pituitary dysfunction on cardiovascular risk in primary empty sella patients. *Clin Endocrinol (Oxf)* 2013; 79(2): 211-6. <http://dx.doi.org/10.1111/cen.12122> PMID: 23215853
- [29] Caplan RH, Dobben GD. Endocrine studies in patients with the "empty sella syndrome". *Arch Intern Med* 1969; 123(6): 611-9. <http://dx.doi.org/10.1001/archinte.1969.00300160001001> PMID: 4181579
- [30] Lupi I, Manetti L, Raffaelli V, *et al.* Pituitary autoimmunity is associated with hypopituitarism in patients with primary empty sella. *J Endocrinol Invest* 2011; 34(8): e240-4. PMID: 21623153
- [31] Zuhur SS, Kuzu I, Ozturk FY, Uysal E, Altuntas Y. Anterior pituitary hormone deficiency in subjects with total and partial primary empty sella: do all cases need endocrinological evaluation? *Turk Neurosurg* 2014; 24(3): 374-9. <http://dx.doi.org/10.5137/1019-5149.JTN.8671-13.0> PMID: 24848177
- [32] Grams AE, Gempt J, Stahl A, Förschler A. Female pituitary size in relation to age and hormonal factors. *Neuroendocrinology* 2010; 92(2): 128-32. <http://dx.doi.org/10.1159/000314196> PMID: 20523033
- [33] Garner B, Berger GE, Nicolo JP, *et al.* Pituitary volume and early treatment response in drug-naïve first-episode psychosis patients. *Schizophr Res* 2009; 113(1): 65-71. <http://dx.doi.org/10.1016/j.schres.2009.05.008> PMID: 19515535
- [34] Kaess M, Simmons JG, Whittle S, *et al.* Sex-specific prediction of hypothalamic-pituitary-adrenal axis activity by pituitary volume during adolescence: a longitudinal study from 12 to 17 years of age. *Psychoneuroendocrinology* 2013; 38(11): 2694-704. <http://dx.doi.org/10.1016/j.psyneuen.2013.06.028> PMID: 23906875
- [35] Bozkurt Koseoglu S, Dinc Elibol F. Does the pituitary gland volume change in polycystic ovary syndrome? *Gynecol Obstet Invest* 2018; 83(5): 515-9. <http://dx.doi.org/10.1159/000489495> PMID: 29763897
- [36] Fleckman AM, Schubart UK, Danziger A, Fleischer N. Empty sella of normal size in Sheehan's syndrome. *Am J Med* 1983; 75(4): 585-91. [http://dx.doi.org/10.1016/0002-9343\(83\)90437-0](http://dx.doi.org/10.1016/0002-9343(83)90437-0) PMID: 6605088
- [37] Terano T, Seya A, Tamura Y, Yoshida S, Hirayama T. Characteristics of the pituitary gland in elderly subjects from magnetic resonance images: relationship to pituitary hormone secretion. *Clin Endocrinol (Oxf)* 1996; 45(3): 273-9. <http://dx.doi.org/10.1046/j.1365-2265.1996.00555.x> PMID: 8949564