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Original Article

Prognosis of Hormonal Deficits in Empty Sella Syndrome Using Neuroimaging

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Abstract

Aim: We have evaluated the anatomic measurements on sellar area of patients who were radiologically diagnosed with empty sella to determine the relation between the amount of pressure on the adenohypophysis and hormonal imbalances. **Materials and Methods:** Sixty-one cases were diagnosed with empty sella and had hormone tests and hypophysis magnetic resonance (MR). The cases were categorized into two groups – patients with hypophyseal hormone anomaly and patients without hormone anomaly. We have measured interclinoid distance, anteroposterior distance from the anterior diaphragm sella to the pituitary stalk, depth of the sella turcica, craniocaudal distance of the optic chiasm from the diaphragm sella, the heights of the right and left adenohypophysis, subcutaneous fat thickness measured orthogonal to the coronal suture and posteriorly at the level of C2–C3 for two groups on hypophysis and cranial MR imaging MRI. **Results:** Twenty-five hormone-positive cases (40.9%) (hormone test were abnormal) and 36 hormone-negative cases (59.1%) (hormone tests were normal) were included in the study. The most common hormone abnormality was thyroid-stimulating hormone, T3 and T4 deficiency in 12 cases (48%) and increase in prolactin level in 7 cases (28%). Right adenohypophysis height was 1.54 ± 0.840 mm for the 1st group, and 1.96 ± 0.83 mm for the 2nd group. The left adenohypophysis height was 1.66 ± 0.80 mm for the 1st group, and 1.94 ± 0.94 mm for the 2nd group. It was found out that the thickness at right and left side in the hormone-positive group diminished significantly. **Conclusion:** Adenohypophysis height and distance between stalk and optic nerve were good determiner for hormone defect.

Keywords: *Empty sella syndrome, magnetic resonance imaging, pituitary, pituitary hormones*

Introduction

Empty sella syndrome (ESS) is a radiological and anatomical term in which the pituitary stalk is compressed, due to the inward herniation of the suprasellar subarachnoid space through the diaphragma sella and displacement of the pituitary gland toward the sellar floor. ESS is observed at a rate of 5.5% in the general population, but the incidence rate is lower in men.[1] It can frequently be observed in overweight, hypertensive, and middle-aged women. The reported prevalence has increased as a consequence of the increased availability of neuroimaging as part of outpatient practice; a prevalence of 8%–38% has been shown in neuroradiologic case series.[2,3] Radiologically, the partial and total types of ESS has been described.

Although partial and total ESS can occur without any signs, they can sometimes be found with headache, visual defects, and photophobia in more severe cases with increased intracranial pressure and with rhinorrhea.

Symptoms arising from endocrine dysfunction are rarely observed in adults with ESS compared with the pediatric age group. The most typical characteristics are symptoms that may evolve as a result of secondary amenorrhea, loss of libido, and loss of hypophysis reserve. Nevertheless, in some series, panhypopituitarism has been observed at a rate of 10%.

The present study aimed to conduct anatomical measurements on the sellar area of patients who had been radiologically diagnosed with ESS, to determine the amount of pressure on the adenohypophysis, and to estimate the relationship between pressure on the adenohypophysis pressure and hormonal disturbances.

Materials and Methods

We retrospectively reviewed the images of the outpatient clinic of the neurosurgery

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department of Istanbul Education and Research Hospital between 2015 and 2017 and selected those which were diagnosed to have ESS (partial or total) by the neuroradiology service.

We excluded patients with a history of sellar surgery and/or radiotherapy, previous history of hypophysis-related disease (infarction, infection, and tumor), and pregnant or lactating women, traumatic brain injury, a prolactin level of over 100 ngr/dl, long-term endocrinological treatment and those who were taking drugs affecting pituitary function.

Sixty-one eligible patients were enrolled with complete pituitary axis hormonal tests, brain magnetic resonance imaging (MRI) and visual status test. According to the hormonal tests, the patients were classified into two groups: Those with normal hormonal test (hormone positive) and those with hormonal disturbance (hormone negative).

A neuroradiologist evaluated the MRI images of the patients. All MRIs were taken by the same imaging system. (1.5 tesla, Avanto, Siemens Healthcare; or Signa, GE Healthcare) using a standard head coil. We used a the following measurements on the midsagittal T1-weighted images were done: Distance between anterior clinoid and posterior clinoid (in mm), anteroposterior distance from the anterior diaphragm sella to the pituitary stalk (in mm) and depth of the sella turcica and craniocaudal distance of the optic chiasm from the diaphragm sella [Figure 1]. We then measured and recorded the height of the adenohypophysis right and left hemispheres in mm in the coronal section T2 images [Figure 2], and measured subcutaneous fat thickness orthogonal to the coronal suture and posteriorly at the level of C2–C3 [Figure 3].

The radiological parameters were compared between the two groups of normal and abnormal hormonal status.

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.

For this type of study, formal consent is not required.

Results

We evaluated 61 cases - 25 (40.9%) hormone-positive patients (whose hormone tests were abnormal) and 36 (59.1%) hormone-negative patients (whose hormone tests were normal). Of the 25 hormone-positive patients (Group 1), 24 were females and one was male, and 34 of the 36 hormone-negative cases (Group 2) were females, with two being males. In Group 1, the lowest and highest ages were 21 and 83 years, respectively, and the median age was 48.23 years. In Group 2, the lowest and highest ages were 36 and 85 years, respectively, and the median age was 56.8 years.

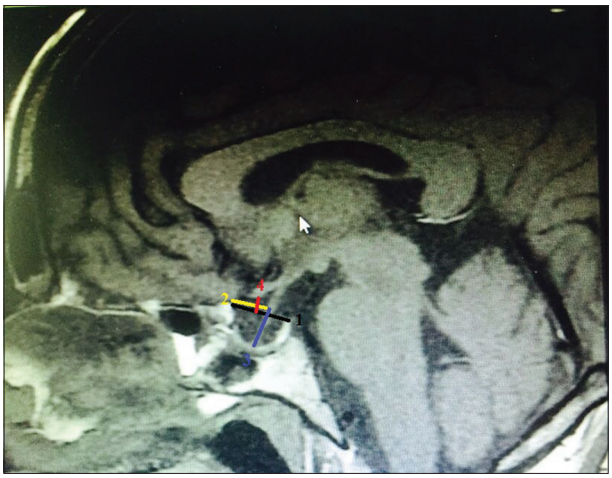

Figure 1: (1) Hypophysis sagittal T1-weighted images; distance between anterior clinoid and posterior clinoid (2) anteroposterior distance from the anterior diaphragm sella to the pituitary stalk (3) depth of the sella turcica (4) cranio caudal distance of the optic chiasm from the diaphragm sella

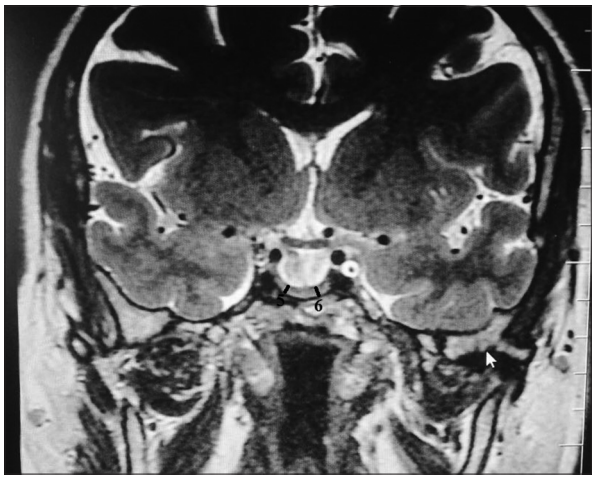

Figure 2: (5 and-6) Adenohypophysis right and left hemisphere heights in coronal section T2 images

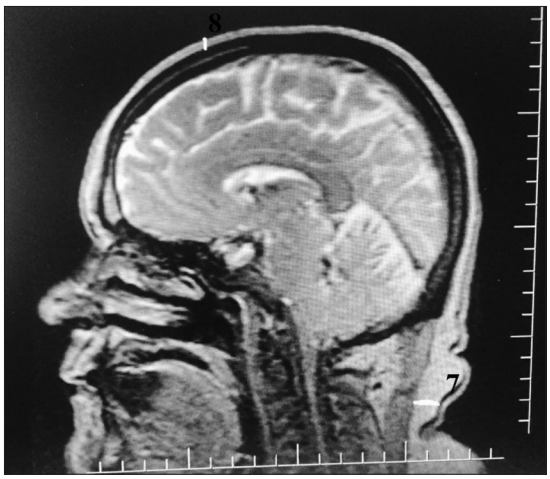

Figure 3: (7 and 8) Subcutaneous fat thickness was measured orthogonal to the coronal suture and posteriorly at the level of C2–C3

The hormone examinations showed that the thyroid-stimulating hormone (TSH), T3 and T4 values were

below the lower limit values, determined according to age and gender profiles, in 12 (48%) patients. The TSH values were low in 2 (8%) patients, while prolactin values were high. The prolactin, FSH, and luteinizing hormone (LH) values were high in 1 (4%) patient, and the prolactin values were high in 7 (28%) patients. Adrenocorticotropic hormone (ACTH) and cortisol levels were high in 2 (8%) patients, while the TSH value was low. In 1 (4%) patient, ACTH, cortisol, and prolactin values were high. Neither growth hormone (GH) nor insulin-like growth factor 1 (IGF-1) disorder was identified in any patient [Table 1].

Radiologically, we first measured the distance between the anterior clinoid and the posterior clinoid. The distances were 13.25 ± 3.88 mm in Group 1 and 12.15 ± 1.72 mm in Group 2. There was no statistically significant difference between the average values of the interclinoid distances of the two groups (t = 1.35; P > 0.05). Subsequently, we measured the distance between the stalk and anterior clinoid, and the values obtained were 8.53 ± 1.69 mm for Group 1 and 8.43 ± 1.53 mm for Group 2. We statistically evaluated the average values of the two groups, and no significant difference was observed (t = 0.48; P > 0.05). We also evaluated the bone sella depth of the two groups; the average value of Group 1 was 11.6 ± 3.254 mm, while the average value of Group 2 was 10.9 ± 2.45 mm. There was no statistically significant difference between the average bone sella depth values of the two groups (t = value, 0.92; P > 0.05).

We measured right adenohypophysis height using coronal section hypophysis MRI. The average value was 1.54 ± 0.840 mm for Group 1 and 1.96 ± 0.83 mm for Group 2. We statistically evaluated the average values of the two groups, and it was shown that the thickness of right adenohypophysis had significantly diminished in Group 1 (t = 2.05; P < 0.05). We also measured left adenohypophysis height using coronal section hypophysis MRI. The average values were 1.66 ± 0.80 mm for Group 1 and 1.94 ± 0.94 mm for Group 2.

We statistically evaluated the average values and found that the thickness of left adenohypophysis had diminished significantly in Group 1 (t = 2.01; P < 0.05). This indicates that the hypophysis-based hormone disorder was a significant cause of the reduction of hypophysis height observed in the MRIs of the ESS patients.

We measured the distance between the stalk and optic nerves using hypophysis MRI. The average values were 1.33 ± 1.22 mm for Group 1 and 2 ± 1.26 mm for Group 2. We statistically evaluated the average values and found that the distance between stalk and optic nerves was significantly reduced in Group 1 (t = 2.05; P < 0.05).

We radiologically measured neck-fat thickness on a level that corresponded to the C2–3 disc gap in the sagittal section of the cranial MRI. The average value was 12.44 ± 5.93 mm for Group 1 and 11.55 ± 5.49 mm for Group 2. We evaluated the average values and found no statistically significant difference between the two groups (t = 0.59; P > 0.05). We measured scalp subcutaneous fat thickness on a level that corresponded to the vertex in the sagittal section. The average value was 2.28 ± 0.75 mm in Group 1 and 3.02 ± 1.08 mm for Group 2. We statistically evaluated the average values, and found no statistically significant difference between the two groups (t = 0.47; P > 0.05) [Table 2].

Table 1: Hormone analysis results of hormone positive group.

Hormone positive group	TSH	T3	T4	PL	FSH	LH	ACTH	Kortizol
12 cases (48%)	Low	Low	Low	Normal	Normal	Normal	Normal	Normal
7 cases (28%)	Normal	Normal	Normal	High	Normal	Normal	Normal	Normal
2 cases (8%)	Low	Normal	Normal	High	Normal	Normal	Normal	Normal
2 cases (8%)	Low	Normal	Normal	Normal	Normal	Normal	High	High
1 case (4%)	Normal	Normal	Normal	High	High	High	Normal	Normal
1 case (4%)	Normal	Normal	Normal	High	Normal	Normal	High	High

TSH – Thyroid-stimulatinghormone; FSH – Follicle-stimulating hormone; LH – Luteinizing hormone; PL – Prolactinp; ACTH – Adrenocorticotropic hormone

Table 2: Average values of the two groups for 8 radiological points and statistical analysis of the two groups.

Radiological measurement points	Average values of the 1st group (of which hormone values are abnormal)	Average values of the 2nd group (of which hormone values are normal)	account (passessed in company with table)
Interclinoid distance	13,25±3,88 mm	12,15±1,72 mm	t:1,35 (P>0.05)
The distance betweens talk and anteriorclinoid	8,53±1,69 mm	8,43±1,53 mm	t:0,48 (P>0.05)
Bone selladepth	11,6±3,254 mm	10,9±2,45 mm	t:0,92 (P>0.05).
Right adenohypophysis height	1,54±0,840 mm	1,96±0,83 mm	t:2,05 (P<0.05)
Left adenohypophysis height	1,66±0,80 mm	1,94±0,94 mm	t:2,01 (P<0.05)
The distance between stalk and opticnerve	1,33±1,22 mm	2±1,26 mm	t:2,05 (P<0.05)
Neck fat thickness at C2-3 level	12,44±5,937mm	11,55±5,49 mm	t:0,59 (P>0.05)
Subcutaneous fat thickness at vertex level	2,28±0,75 mm	3,02±1,08mm	t:0,47(P>0.05)

Discussion

The term empty sella was first coined by Busch in 1951 with regard to a patient on which he conducted an autopsy.[4] In 1968, Kaufman gave the name ESS to the clinical entity in which the supracerebellar cistern caused a vision defect due to hypophysis pressure, and which could be accompanied by headache, and reported two cases.[5] Although more than one hypothesis of pathogenesis has attempted to explain it, it is thought that the suprasellar cistern is herniated with cerebrospinal fluid (CSF) pulsations through a defect and gap, which frequently form on the diaphragmatic sella. When the diaphragmatic sella is incomplete, the pressure caused by cerebrospinal pulsations is directly exerted on the hypophysis. While the hypophysis gradually diminishes, CSF takes its place. In addition, previously published evidence has revealed that necrosis and infarct, pituitary apoplexia and intrasellar cyst rupture can be observed as a result of recurrent pregnancy-based volumetric changes of the hypophysis and aging.[6] There are two types of ESS: In primary cases, it occurs as a result of idiopathic and intracranial pressure; and in secondary cases, it is observed due to cerebrospinal effusion within the sella following hypophyseal infection, radiotherapy, trauma, spontaneous regression of hypophyseal adenoma, multiparity, the menopause, diabetes mellitus, and vascular-based infarcts. It can also arise from postpartum pituitary necrosis (Sheehan's syndrome) or lymphocytic hypophysitis; the latter occurs due to the accumulation of lymphocytes in the hypophysis. The length of the sella space is 17 mm and its depth is 3 mm. However, it can be clearly evaluated through cranial MRI; sella diameter, hypophysis volume, and pressure rates can be explicitly observed in this manner. The way in which the suprasella cistern is placed within the sella under coronal sections, lateral walls and the gland, which changes place towards the sella base, can be seen.

When 50% of the sella area is filled with CSF and the pituitary gland thickness is 3 mm or more, the condition is called partial ESS, and when over 50% of the sella is filled with CSF and the pituitary gland thickness is <2 mm, the condition is called total ESS.[1,7]

Previous studies have shown that syndromic vision defects occur at a rate of 1.6%–16%, frequently showing as bitemporal hemianopsia and restricted area of vision.[8] It has been asserted that symptoms concerning vision are due to kinking of the optic nerves toward the sella.

In ESS cases, hypophyseal pressure-based hormonal disorders, such as hyperprolactinemia, hypopituitarism, central diabetes insipidus, hypothalemic hypothyroidism, and ACTH hypersecretion, may also be present.[2,9] Explicit changes can found in up to 30%–50% of patients following hypophysis stimulation tests. Insufficient GH levels have been observed in 30%–50% of the patients tested, and anomalies related to ACTH secretion and LH and TSH secretion have been found in 11% and 15% of these patients, respectively.[10,11]

Although some studies have observed hypopituitarism at a rate of 25% in their series, global hypopituitarism is rare (range 2–8%).[1,13]

Some previous studies have stated that the suprasellar cistern rate and the clinical findings are not correlated.[9] In addition, some investigations have remarked that pituitary gland pressure and stalk compression could cause a hormonal deficit in ESS. When we considered these studies, we observed that the clinical studies and neuroradiology were not correlated and statistically compared.[13] In our study, our main aim was to reveal the relationship between the adenohypophysis pressure rate and hormonal anomalies using anatomical measures. De Marinis *et al*. showed that hypophyseal endocrine disorders accompanied ESS in 18.7% of cases diagnosed, while Cacciari *et al*. observed ESS in 10.9 (37 cases) of 339 cases of hypothalamo-hypophyseal disorder.[2,14] These studies particularly emphasized the fact that ESS investigations should be carried out through the neuroimaging of pediatric cases that include hypothalamo-hypophyseal disease and growth deficiency.

When we consider hormonal disorders separately, we observed prolactin hormone anomaly at a frequency of 10%–37.5%.[2,10,15] The previously conducted studies primarily found empty sella-based prolactin hormone disorders, and they generally emerged as hyperprolactinemia.

However, others have specified that hypophyseal adenoma escapes the attention in prolactin blood values that are over 100 ngr/dl. High prolactin levels in patients with ESS can take the form of pituitary stalk compression and failure of prolactin inhibitory factor, rather than hypophysis compression. In addition to the prolactin anomaly, other hormone defects may also accompany cases of ESS. Since the prolactin blood value is particularly affected by various factors, serial measurements are also required in cases in which high prolactin values are observed. In our study, we found prolactin hormone disorder in 11 (18%) patients.

Previous studies have observed gonadotropin defects at a rate of 6%. However, in our study, we found this defect in only 1 (1.6%) patient. Previous investigations have shown evidence of GH-IGF 1 axis disorders. An emphasis should be placed on high levels of GH since it not only causes extremity and appearance anomalies but also results in heart failure and multiple organ dysfunction. In addition, defect-based deficiencies of the IGF 1-GH axis result in growth deficiency and retarded development. A high level of abnormalities (8%–60%) was found on the IGF1 and BH axis with regard to empty sella.[16] These were generally GH deficiencies, which previous studies have described, particularly in children. In the examinations performed on the patients, who were followed up due to retarded development, the authors identified GH deficiency

and detected ESS with neuroimaging.[16] However, we do not believe that this was at a high rate. In our study, we found A GH deficiency in 61 patients with ESS. Possibly, the high levels which were detected in the previous study in relation to GH adenoma were also included in the study.

With regard to other hormone anomalies, some studies have reported high levels of secondary hypothyroidism and adrenal insufficiency. In our study, we detected secondary hypothyroidism in 12 (19.6%) patients, and this rate was high compared to other hormone deficits. There are a variety of possible reasons for this, among which are the ages of patients and hormone anomalies, and the fact that we did not conduct thyroid and inhibition tests.

The previous studies conducted, in addition to our study, observed hypophyseal hormone defects in cases of ESS. The reasons for this have not been analyzed in detail, and it has been stated that hypophyseal pressure and stalk compression can cause such defects. No previous study has statistically compared neuroradiological and endocrinological tests in terms of various parameters. In our study, we attempted to obtain a result by comparing the patients who did and did not have hormone defects by measuring eight-parameters through hypophysis MRIs. We believe that our study is important since it showed that hormone defects increased at a statistically significant rate, particularly in patients in whom adenohypophysis thickness decreased due to suprasellar cistern pressure, and in which the distance between the stalk and optic nerves shortened. The fact that we included an insufficient number of patients and that we did not use hormone examinations in conjunction with suppression and stimulation tests can be regarded as limitations of our study.

Conclusion

ESS is a disease that can follow a course of a headache and vision anomalies, and it can cause various clinical disorders, hormone defects, and high hormone levels. If an adenohypophysis height of <2 mm is observed in neuroimaging, we believe that hormone parameters should be necessarily measured, even in nonsymptomatic patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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