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Importance of Magnetic Resonance Imaging in Pituitary Stalk Interruption Syndrome

Hipofiz Sapı Kesinti Sendromunda Manyetik Rezonans Görüntülemenin Önemi

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Abstract

Objective: To evaluate the importance of magnetic resonance imaging in the treatment and follow-up of patients with pituitary stalk interruption syndrome. **Material and Methods:** The study included patients who were admitted to the Endocrinology and Metabolism Clinic of our hospital from 2009 to 2013. Pituitary functions, growth and development curves, and magnetic resonance imaging findings of the patients were evaluated during the follow-up period. **Results:** The study included three men and two women. Four patients had multiple pituitary hormone deficiency. All cases were diagnosed with short stature with respect to their chronological age. Four patients were diagnosed with pituitary stalk interruption syndrome in their childhood. Isolated growth hormone deficiency was observed only in one patient. **Conclusion:** Pituitary insufficiency should be considered when evaluating pituitary stalk interruption syndrome. The presence of pituitary stalk and the change in the size of the anterior pituitary gland are crucial magnetic resonance imaging findings in monitoring pituitary functions. In addition, evaluating the size of the pituitary gland may allow early detection of pituitary insufficiency in adult patients with pituitary stalk interruption syndrome.

Keywords: Hypopituitarism; ectopic neurohypophysis; isolated growth hormone deficiency; magnetic resonance imaging; short stature; pituitary stalk interruption syndrome

Özet

Amaç: Hipofiz sapı kesinti sendromu hastalarının takip ve tedavisinde manyetik rezonans görüntülemenin önemini değerlendirmektir. **Gereç ve Yöntemler:** Çalışma grubumuz, 2009-2013 yılları arasında endokrinoloji ve metabolizma hastalıkları polikliniğimize başvuran hastalardan oluşmaktadır. Hasta takibinde hipofiz fonksiyonları, büyüme ve gelişme eğrileri ve manyetik rezonans görüntüleme bulguları değerlendirmeye alındı. **Bulgular:** Çalışma grubumuz üç erkek ve iki kadın hastadan oluşmaktadır. Dört hastamızda çoklu hipofizer hormon yetmezliği saptandı. Hastalarımızın hepsi kronolojik yaşlarına göre kısa boylu olmaları nedeni ile değerlendirilirken tanı konuldu. Dört hastamıza çocuk yaş grubunda tanı konulmuştu. Sadece bir hastada izole büyüme hormon eksikliği mevcuttu. **Sonuç:** Hipofiz sapı kesinti sendromlu olguları değerlendirirken hipofiz yetmezliği dikkate alınmalıdır. Manyetik rezonans görüntülemede hipofiz sapının varlığı ve ön hipofiz bezinin büyüklüğünün zaman içinde değişimi, hipofiz bezinin fonksiyonlarının takibinde önemlidir. Ayrıca, hipofiz sapı kesinti sendromlu erişkin yaştaki hastalarda, hipofiz bezinin büyüklüğünün değerlendirilmesi, hipofiz yetmezliğinin erken tanısına olanak sağlayabilmektedir.

Anahtar kelimeler: Hipofiz yetmezliği; ektopik nörohipofiz; izole büyüme hormon yetmezliği; manyetik rezonans görüntüleme; boy kısalığı; hipofiz sapı kesinti sendromu

Introduction

Pituitary insufficiency occurs because of isolated or multiple anterior pituitary hormone deficiency (MPHD). The diagnosis of pituitary insufficiency is based on clinical features including growth retardation, central hypothyroidism, or delay of secondary sexual characteristics. One of the rare causes of pituitary insufficiency is pituitary stalk interruption syndrome (PSIS). Although the etiology of PSIS remains unclear, organogenesis defects caused by a traumatic birth

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and by genetic and environmental factors are supposed to play a role (1-4). The clinical features and magnetic resonance imaging (MRI) findings of PSIS have been known for a long time. The characteristics of MRI findings in PSIS include a decrease in the size of the anterior pituitary gland, increase in or disappearance of the signal in the ectopic location of the neurohypophysis, hypoplasia, or absence of the pituitary stalk (5-8). This study aimed to investigate the importance of MRI in the treatment and follow-up of patients with PSIS.

Material and Methods

This study included patients with PSIS who were admitted to the Endocrinology and Metabolism Clinic of our hospital from 2009 to 2013. In addition, this is a retrospective clinical observation study; therefore, no ethics committee approval was obtained. But, this study was carried out adherence to guidance for ethics review of health-related research with human participants of the WHO (2011), and the Declaration of Helsinki of the World Medical Association (2013). The hormonal levels having a role in the growth and development processes and MRI findings were evaluated. Growth hormone (GH) deficiency was demonstrated with at least two growth hormone stimulation tests (with insulin, clonidine, or L-dopa). Cortisol deficiency was determined on the basis of the measurement of cortisol level in the same tests or the measurements of baseline plasma adrenocorticotropic hormone (ACTH) and cortisol levels, which were performed in the morning (at 08:00 am). A low-dose ACTH stimulation test was performed in required cases. Thyroid hormone deficiency was determined on the basis of low serum-free thyroxine level that was incompatible with the thyroid-stimulating hormone level (<5 μU/mL). Gonadal insufficiency was determined by measuring estradiol and testosterone in relation to follicle-stimulating hormone and luteinizing hormone.

During childhood and adolescence, the diagnosis of GH insufficiency is based on the following criteria (9): 1) height of a child being less than 2 standard deviation (SD) or 3 percentile as compared with a healthy children; 2) annual growth rate of less than 7 cm/year (for those less than three years), of less than 5 cm/year (from three years to puberty), and of less than 6 cm/year (for puberty); 3) child-like facial appearance and small and short symmetrical body structure; 4) normal intelligence; 5) backbone age relative to chronological age; and 6) the plasma level of GH being less than 6 μg/L in at least two GH stimulation tests and the plasma level of insulin-like growth factor 1 (IGF-1) being lower than the normal range according to age and gender. In adult patients, the diagnosis of GH deficiency was based on the plasma level of GH (less than 3 μg/L) in insulin tolerance test and IGF-1 being lower than the normal range according to age and gender (10).

Magnetic Resonance Imaging Technique

All patients were scanned in the supine position using 3 Tesla MRI systems with a head coil. The images were obtained in the sagittal and coronal planes using T1, T2 and sagittal fat-suppressed T1 sequences, coronal planar dynamic imaging, and postcontrast T1 sagittal and coronal planes. The cross-sectional thicknesses were 1 mm in dynamic images and 3 mm in other sequences. The assessments of the images were performed by the same neuroradiologist. The anterior pituitary gland, pituitary stalk size, and location of the neurohypophysis, as well as the presence and localization of accompanying malformations, were assessed. Normal height of the pituitary gland was accepted as 6 mm (upper surface plain or slightly concave) for patients less than 12 years of age, 10 mm for patients in puberty (upper surface convex, more convex in girls), 9 mm for women and 8 mm for men in young adulthood, and 12 mm for women in gestation (11). Hypoplastic pituitary gland could be described as a half-moon-shaped gland observed on the sella with a maximum measurable height of 2 mm. Radiological empty sella was defined in cases for which the pituitary gland was not visible but the cerebrospinal fluid cavity invaded the sella.

Results

This study included five patients with PSIS: Case 1: an 18-year-old man diagnosed with MPHD while being examined for short stature; Case 2: an 18-year-old man diagnosed with MPHD while being examined be-

cause of short stature at the age of eight years; Case 3: a 27-year-old woman diagnosed with MPHD as a result of the evaluation after primary amenorrhea; Case 4: a 19-year old woman diagnosed with isolated growth hormone deficiency (IGHD) while being examined because of short stature at the age of ten years; and Case 5: a man diagnosed with hypogonadism and short stature at the age of 35 years. Therefore, patients were diagnosed with short stature with respect to their chronological age. MPHD was observed in our four patients, except for Case 4. The features of the patients are presented in Table 1. One case of IGHD and three cases of MPHD were diagnosed during childhood. MRI findings of the patients according to the type of their hormone deficiency are presented in Table 2. Accordingly, midline defect was observed only in one patient with MPHD. Ectopic neurohypophysis was present in all patients. Adenohypophysis size was normal from the childhood of the patient with IGHD. In addition, there was a thin stalk in the same patient (Table 3).

In all patients, the neurohypophysis was detected in an ectopic location. In addition, it was localized in the hypothalamus or its surroundings in Cases 1, 2, and 3 (Figure 1, Figure 2, Figure 3). Moreover, it was in the pituitary stalk in Case 4 (Figure 4) and was localized in the surrounding of the hypothalamus in Case 5 (Figure 5). In most of our cases, the height of adenohypophysis was considerably decreased. Adenohypophysis

Table 1. Age, gender, and pattern of hormone deficiency in the studied cases.

Case Number	Age	Sex	Hormone deficiency
Case 1	18	Male	GH, FSH, LH, ACTH, TSH
Case 2	18	Male	GH, FSH, LH, ACTH, TSH
Case 3	27	Female	GH, FSH, LH, ACTH, TSH
Case 4	19	Female	GH
Case 5	35	Male	GH, FSH, LH, ACTH, TSH

GH: Growth hormone; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; ACTH: Adrenocorticotropic hormone; TSH: Thyroid stimulating hormone.

Table 2. Distribution of magnetic resonance imaging findings according to the type of hormonal deficiency in the studied cases.

	IGHD	MPHD
Hypoplastic pituitary gland	0	4
Absent stalk	0	4
Thin stalk	1	0
EPPBS (median eminence)	0	4
EPPBS (stalk)	1	0
Midline brain anomalies	0	1

IGHD: Isolated growth hormone deficiency; MPHD: Multiple pituitary hormone deficiencies; EPPBS: Ectopic posterior pituitary bright spot.

Table 3. Features of the studied cases according to the magnetic resonance imaging findings.

	IGHD (n=1)	MPHD (children) (n=3)	MPHD (adult) (n=1)
Adenohypophysis size	Normal	Small	Small
Visualization of a thin stalk	Yes	No	No
EPPBS (Median eminence)	Normal	Yes	Yes
EPPBS (stalk)	Yes	No	No

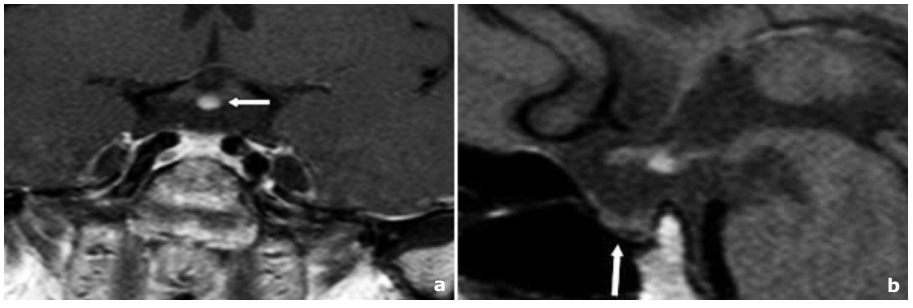

Figure 1: a) Coronal post-contrast T1 section, **b)** sagittal fat-suppressed T1 section. Hyperintensity of the neurohypophysis is observed in the vicinity of the ectopically located hypothalamus. Sella has not developed, the height of the adenohypophysis has markedly decreased, and the pituitary stalk is not visible. Cerebellar tonsils are ectopic and the Arnold-Chiari type 1 malformation is observed (Case 1).

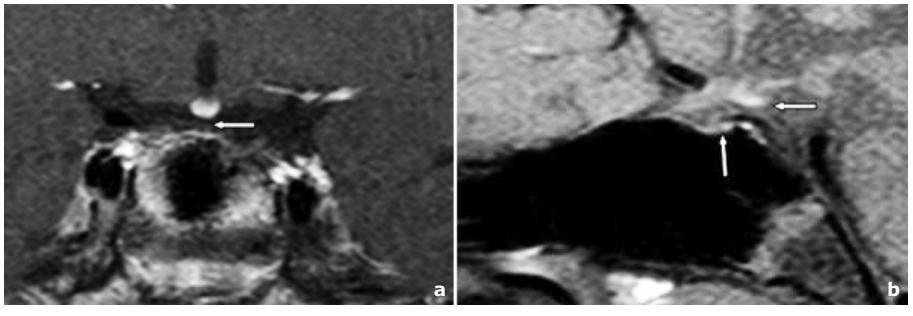

Figure 2: a) Coronal post-contrast T1 section, **b)** Sagittal fat-suppressed T1 section. Pituitary stalk does not appear in the coronal section. Neurohypophysis hyperintense signal is observed in the vicinity of the hypothalamus in sagittal section. The height of adenohypophysis is observed to be decreased in both sections (Case 2).

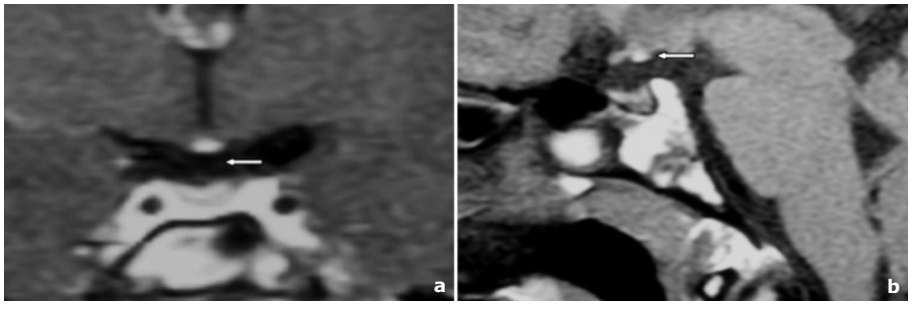

Figure 3: a) Coronal post-contrast T1 section, **b)** Sagittal fat-suppressed T1 section. The pituitary gland is not visible in coronal section. Neurohypophysis is ectopically located in the vicinity of the hypothalamus in the sagittal section (Case 3).

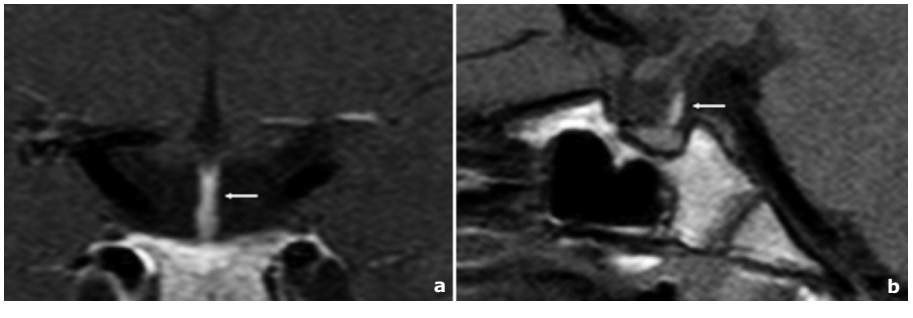

Figure 4: a) Coronal post-contrast T1 section, **b)** Sagittal fat-suppressed T1 section. The neurohypophyseal hyperintense signal is observed to be ectopic and located posterior to the pituitary stalk in the sagittal section. In addition, the pituitary stalk is observed to be long and thin in the coronal section (Case 4).

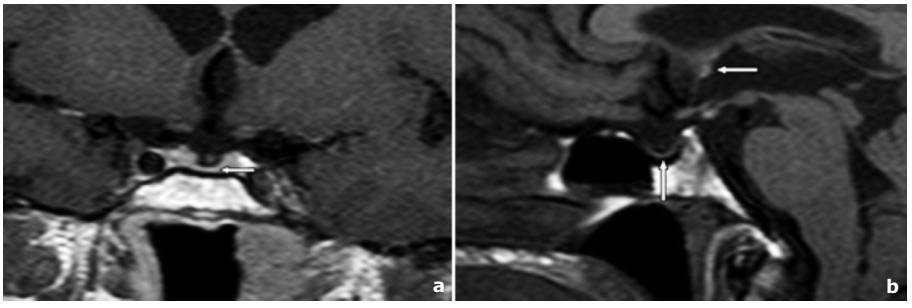

Figure 5: a) Coronal post-contrast T1 section, **b)** sagittal fat-suppressed T1 section. The height of the adenohypophysis has decreased extremely and the neurohypophyseal hyperintensity signal can be observed in the ectopic location adjacent to the hypothalamus in sagittal section. Pituitary stalk is observed to have interrupted in coronal section (Case 5).

was not observed only in Case 3 (Figure 3), and it was normal in size in Case 4 (Figure 4). Pituitary stalk was not observed in patients with MPHD (Figure 1, Figure 2, Figure 3 and Figure 5). Long and thin pituitary stalk was noted in the patient with IGHD (Figure 4). Moreover, in Case 1, cerebellar tonsils were ectopic and Arnold-Chiari type 1 malformation was observed (Figure 1).

Discussion

The pituitary gland originates from different embryonic structures and comprises adenohypophysis and neurohypophysis (12). Factors such as genetic defects, pituitary stalk injury, and perinatal trauma may lead to an incomplete downward migration of neurohypophysis which in turn results in infusion defects (13). Several hypotheses have been proposed to explain PSIS. The first hypothesis is exposure of the pituitary stalk to ischemia during breech (14). In this study, four of five patients were born by breech. However, the lack of hypoxic damage to the organs and the structures having the same vascular support, as well as the lack of pathological evidence, weakens the first hypothesis. Second, head trauma during breech delivery may cause mechanical rupture of the pituitary stalk and stretching of the pituitary stalk, pituitary gland, and mobile brain structures. This hypothesis seems to be widely accepted because of the certain incidence of breech delivery in the published studies. Most of these study groups have no genetic analysis. In addition, MPHD develops in patients with breech presentation who were delivered via cesarean section (15); this also weakens the second hypothesis. The third hypothesis, on which a consensus has been most commonly reached, is congenital hypoplasia or dysplasia because of genetic or organogenesis defects of the pituitary gland and resulting pituitary insufficiency (2,15).

In the study by Bar et al. (16), severe hormonal abnormalities and radiological findings were reported in the PSIS cases diagnosed during the neonatal period. In addition, they have reported MPHD at a rate of 100% and a nonvisible anterior pituitary lobe at a rate of 33% in this group. In this study, MPHD was present in four of five childhood cases. PSIS is associated with several midline malformations such as septal agenesis, partial corpus callosum agenesis, aqueductal stenosis, optic nerve hypoplasia, and the Arnold-Chiari type 1 malformation. The presence of extra-pituitary malformations is not associated with more severe hormonal and radiological characteristics (16, 17). In this study, the patient with Arnold-Chiari type 1 malformation was consistent with the literature.

In a study on the relationship between pituitary gland visibility and pituitary hormone deficiency, 74 patients with PSIS in whom the most common presenting symptoms were short stature and absence of pubertal development were evaluated and panhypopituitarism was reported to be considerably more common in those with an invisible pituitary stalk (18). Accordingly, it has been suggested that invisible pituitary stalk on contrast-enhanced pituitary MRI may be an indicator of clinical severity in PSIS (18-20). The absence of the pituitary stalk in our case series was the most crucial indicator for MPHD. This finding was consistent with those reported in

the previous studies. Maghnie et al. (21) and Genovese et al. (22) emphasized the importance of contrast injection to obtain an optimal image of a thin pituitary stalk. They observed that the pituitary stalk could be overlooked with the use of unenhanced pituitary MRI. In cases of isolated pituitary hormone deficiency (IPHD), the visualization of the stalk in contrast-enhanced images is considered a sign of partial preservation of the hypothalamo-hypophyseal portal blood (23). In our IGHD case, the integrity of the pituitary stalk was observed to be preserved.

In addition to the clinical findings related to the absence of the pituitary stalk, thinning of the pituitary stalk demonstrates disease progression from IPHD to MPHD and the anterior pituitary function is associated with the changes in the size of the anterior pituitary gland. These may allow early detection of hormone deficiency, particularly during puberty (17, 24). In this study, PSIS diagnosis was established in adulthood in Case 5, and all these radiological findings were demonstrated in this case.

In a large series of PSIS, clinical and hormonal features and neuroradiological appearances, as well as PIT1, PROP1, HESX1, LHX3/LHX4, PROKR, TGIF, OTX2, and SOX3 mutations, which were thought to affect these characteristics, were investigated. LHX4 and HESX1 mutations were detected in a group with familial or consanguineous marriage. The possible genetic variants may occur during early embryogenesis and are demonstrated in Figure 6 (25, 26).

In a study conducted to demonstrate an underlying genetic etiology in PSIS, GPR161 mutations were detected in the mutation analysis of two affected siblings and one unaffected sibling in a consanguineous family. HESX1, LHX4, OTX2, SOX3, and PROKR2 mutations were detected in approximately 5% of patients with PSIS (27). The multigenic pattern was found in PSIS using whole-exome sequencing technique (28). According to our opinion, PSIS has multigenic etiology. The evidence is needed to show the functional significance of the genes mentioned in the published studies.

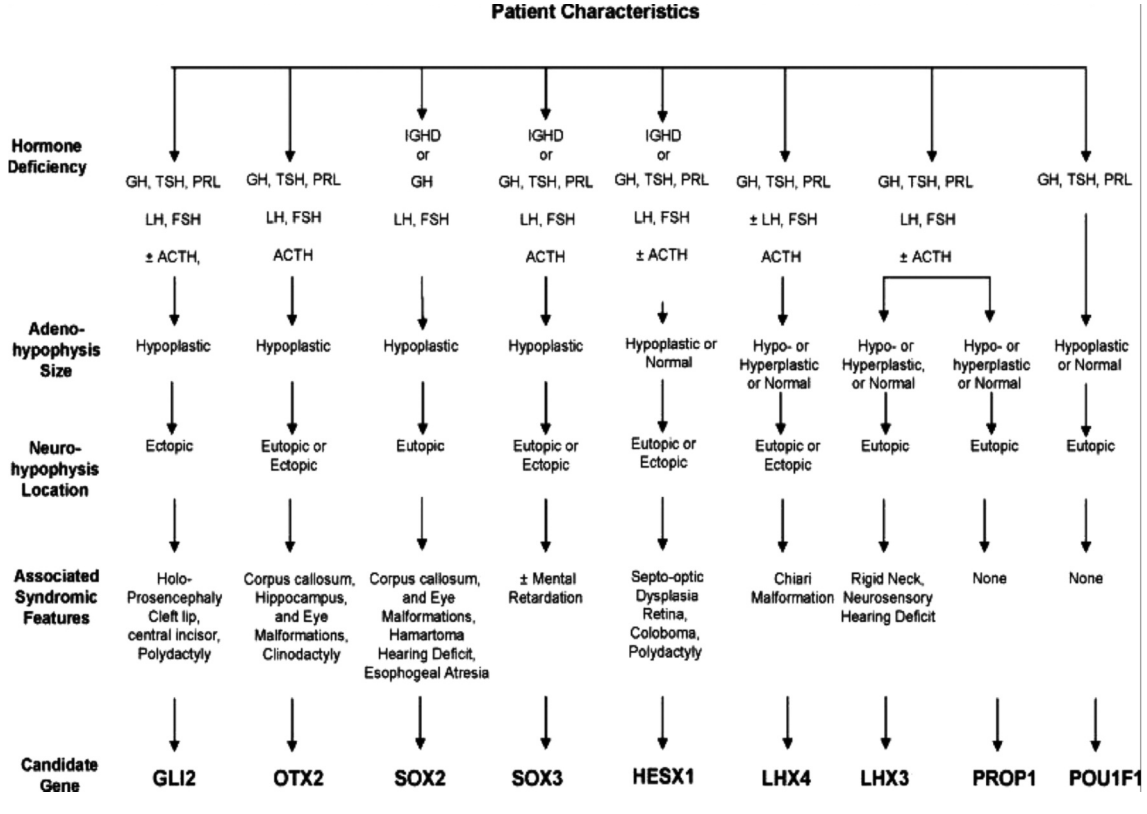

Figure 6: A guide for planning genetic screening for hypopituitary patients based on clinical findings (26).

Study limitation

One of the main limitations of this study is the lack of genetic evaluation. Another limitation is the small sample size. However, our rare group of patients with PSIS is interesting as they have different findings.

Conclusion

PSIS is rare but a crucial syndrome because of its clinical outcomes. MRI findings will continue to assist in the diagnosis and follow-up of patients with PSIS until the functional significance of the genes that have been detected is understood. Therefore, pituitary insufficiency should be considered when evaluating patients with PSIS. When the MRI findings are consistent with PSIS, the presence of pituitary stalk and change in the size of the anterior pituitary gland are accepted, as crucial imaging findings reflect the pituitary gland function. Evaluating the size of the pituitary gland may provide early detection of anterior pituitary hormone deficiency in adult patients with PSIS.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflicts of interest

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authorship Contributions

Idea/Concept: Eren Gürkan, Yonca Anık; Design: Eren Gürkan, Özlem Zeynep Akyay, Berrin Çetinarslan, Mine Filiz Çizmecioğlu; Control/Supervision: Eren Gürkan, Yonca Anık, Mine Filiz Çizmecioğlu; Data Collection and/or Processing: Eren Gürkan, Özlem Zeynep Akyay, Yonca Anık, Berrin Çetinarslan, Mine Filiz Çizmecioğlu; Analysis and/or Interpretation: Eren Gürkan, Yonca Anık, Filiz Çizmecioğlu; Literature Review: Eren Gürkan, Mine Filiz Çizmecioğlu, Özlem Zeynep Akyay, Berrin Çetinarslan; Writing the Article: Eren Gürkan, Yonca Anık; Critical Review: Eren Gürkan, Yonca Anık; References and Fundings: Eren Gürkan, Özlem Zeynep Akyay, Berrin Çetinarslan; Materials: Eren Gürkan.

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