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**ORIGINAL ARTICLE**

# Intracranial Pathologies and Endocrine Results: Single Pediatric Endocrinology Center Experience

# İntrakraniyal Patolojiler ve Endokrin Sonuçları: Tek Çocuk Endokrinoloji Merkezi Tecrübesi

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**ABSTRACT**

Intracranial pathologies can affect pituitary hormone levels whether they are primarily related to the pituitary gland or not. In pituitary hormone deficiencies, the size and location of the pituitary gland may be normal, as well as one or more hormone effects may be observed after hypoplasia, partial empty sella, ectopic neurohypophysis, Rathke's cleft cyst, adenomas and other pituitary masses or surgeries. In early puberty, the pituitary dimensions usually increase and, rarely hypoplasia and rathke cleft cyst are seen as MRI findings. Non-pituitary pathologies cause especially early puberty, single or multiple pituitary hormone deficiency.
In this study, we aimed to categorize the patients with pituitary/cranial lesions and hormonal pathology and to determine their frequency and distribution in the single pediatric endocrinology clinic for ten years.
The data of 485 patients, 186 (38.3%) male, were retrospectively analyzed. Their mean age was 9.3 ± 3.2 years. The incidental pituitary lesion was found in 28 (5.77%) of all cases. There was no hormonal influence in 20 (71.4%) of them. In most of the 454 cases with hormonal disorders, MRI (Magnetic Resonance Imaging) findings were normal in most of the 454 cases with hormonal disorders (71.8%). The most common hormonal pathologies were precocious puberty and isolated Growth Hormone deficiency, 57.9% and 26.4% respectively. Non-pituitary lesions (n=23, 5%) were most frequently accompanied by early puberty (39.1%).
The hypothalamus-pituitary axis may be affected by primary lesions in its own region, or it may be seen as a result of other cranial pathologies. Cranial evaluation is also important in addition to pituitary imaging in pituitary hormone disorders.

**Keywords:** Pituitary Hormone Disorders, Central Nervous System Lesions, Precocious Puberty, Magnetic Resonance Imaging.

**ÖZ**

İntrakranial patolojiler hipofiz beziyle primer bağlantılı olsun veya olmasın hipofizer hormon düzeylerini etkileyebilirler. Hipofizer hormon eksikliklerinde hipofiz bezi boyutları ve yerleşimi normal olabildiği gibi hipoplazi, parsiyel empty sella, ektopik nörohipofiz, rathke kleft kisti, adenomlar ve hipofiz yerleşimli diğer kitleler veya cerrahilerinden sonra da bir veya birçok hormon etkilenmesi görülebilir. Erken pubertede hipofiz boyutları genellikle artar, nadiren hipoplazi ve rathke yarık kisti Manyetik Rezonans Görüntüleme (MRG) bulguları olarak görülür. Hipofiz dışı patolojiler özellikle erken ergenliğe, tek veya çoklu hipofiz hormon eksikliğine neden olur.
Bu çalışmada, tek pediatrik endokrinoloji kliniğinde on yıl boyunca hipofiz/kraniyal lezyonları ve hormonal patolojisi olan hastaların kategorize edilmesi, sıklık ve dağılımlarını belirlenmesi amaçlanmıştır.
186'sı (%38,3) erkek 485 hastanın verileri geriye dönük olarak incelendi. Ortalama yaşları 9.3 ± 3.2 yıldı. Tüm olguların 28'inde (%5.77) tesadüfi hipofiz lezyonu saptandı. Bunların 20'sinde (%71,4) hormonal etki yoktu. Hormonal bozukluğu olan 454 olgunun çoğunda MRG bulguları normaldi (%71.8). En sık görülen hormonal patolojiler sırasıyla %57.9 ve %26.4 ile erken ergenlik ve izole büyüme hormonu eksikliği idi. Hipofiz dışı lezyonlara (n=23, %5) en sık erken ergenlik (%39.1) eşlik ediyordu.
Hipotalamus-hipofiz ekseni kendi bölgesindeki primer lezyonlardan etkilenebileceği gibi diğer kraniyal patolojilerin sonucu olarak da görülebilir. Hipofiz hormon bozukluklarında hipofiz MRG'yle birlikte kraniyal değerlendirme de yapılmalıdır.

**Anahtar Kelimeler:** Hipofizer Hormon Bozuklukları, Santral Sinir Sistemi Lezyonları, Puberte Prekoks, Manyetik Rezonans Görüntüleme

## Introduction

Neuroimaging is an essential tool in diagnosing various clinical conditions, particularly in pediatric endocrinology. Advanced Magnetic Resonance Imaging (MRI) technology can be used to definitively characterize structural brain abnormalities, including those related to the pituitary gland and hypothalamus. Intracranial pathologies can affect pituitary hormone levels whether they are primarily related to the pituitary gland or not.

Pituitary adenoma can be functioning, causing an overproduction of hormones. Sometimes, because of the mass effect, it impairs the function of other cells, leading to hypopituitarism. The pituitary hormonal deficiency can accompany with the normal size and location of the pituitary gland. However, isolated or multiple hormones deficiency can occur due to hypoplasia, partial empty sella (PES), ectopic neurohypophysis, Rathke cleft cyst (RCC), adenomas and other pituitary masses, or complications after surgery. Pituitary gland size is expected to increase with puberty even if hypoplasia and RCC can be rarely found through MRI in early adolescence. Non-pituitary pathologies such as arachnoid cysts, hydrocephalus,

and cortical atrophy can eliminate factors involved in gonadotropin suppression, resulting in early puberty.

The aim of this study is to examine pituitary hormone disorders in all patients who underwent cranial and/or pituitary MRI for 10 years in a single pediatric endocrinology center.

## Methods

Patients admitted to our pediatric endocrinology clinic between January 2011 and December 2020 and had pituitary and/or cranial MRIs were included in the study (Ethics committee approval no. 2022/706). Patient files were reviewed retrospectively. The patient with brain tumors that cause the sellar extension and primary pituitary masses referred to pediatric endocrinology after surgery were excluded, considering the probable hormonal impact of the surgery. Patients who underwent shunt procedures for non-pituitary masses or hydrocephalus remained in the study. Our study cohort consisted of 485 patients, 186 male, and 299 female.

Patient clinical data included age at presentation, gender, hormonal deficiency (according to the results of hormone and dynamic endocrine testing), and brain/pituitary MRI findings. Growth Hormone Deficiency (GHD) diagnosis was based on low growth velocity and low growth hormone (GH) response in two sequential GH stimulation tests (1). Central precocious puberty (CPP) was diagnosed in the presence of clinical and laboratory evidence of hypothalamic-pituitary-gonadal axis activation before the age of 8 in girls and 9 in boys (2). In patients with clinical symptoms of polyuria and polydipsia, water restriction test was made in accordance with the guidelines to determine a diagnosis of central diabetes insipidus (DI) (3). Delayed puberty was defined as the absence of pubertal signs at 13 years of age in girls and 14 in boys, with laboratory evidence of prepubertal gonadotropin levels after a dynamic test (4). Inadequate cortisol response with low-dose ACTH test was considered secondary to adrenal insufficiency. The presence of two or more pituitary hormone deficiencies were interpreted as multiple pituitary hormone deficiency (MPHD) (5, 6). The diagnosis of hyperprolactinemia was confirmed by repeated measurements (7). A patient with excessive height and accelerated growth, and insufficient GH suppression by oral glucose test, was regarded as GH hypersecretion (8). Pituitary gland and stalk sizes were evaluated according to normal values for patient age and gender (9). An anomaly usually characterized by the triad of a very thin or interrupted pituitary stalk, an ectopic/absent posterior pituitary, and anterior pituitary hypoplasia in MR results was interpreted as PSIS (5).

## Statistical Analysis

SPSS software package (SPSS Statistics, Version 23) was used in the statistical analysis. Descriptive statistical methods were used. The prevalence of each brain finding was calculated for all endocrine diagnosis groups. The distribution of MRI findings was also shown for the groups.

## Results

The study cohort included 485 patients, 186 (38.3%) male, and 299 (61.7%) female, with a mean age of 9.3 ± 3.2 years (range: 1.5 months to 18 years). The youngest case was a 1.5-month-old male MPHD patient with a midline defect. Eleven (2.26%) patients had active pituitary adenomas; 10 of these were prolactin secreting, and one was GH-secreting. Cystic components were present in two of the prolactinomas.

Among the patients with pituitary pathology diagnosed incidentally by brain MRI, 20 (4.1%) had no hormonal deficiency. Their findings of MRI were that 6 of them had RCC, 4 arachnoid cysts, 3 PES, 2 PES and hydrocephalus, 3 non-functioning adenomas (NFA), and 2 had hypoplasia. Eight (1.64%) patients with pituitary pathology diagnosed incidentally by brain MRI had hormonal deficiency. Two of these had RCC and PP, 2 had RCC and GHD, 1 NFA and GHD, 1 arachnoid cyst and PP, 1 PES and GHD, and 1 had hypoplasia and MPHD. Overall, out of 28 (5.77%) patients with pituitary pathology diagnosed incidentally, 28.57% had a hormonal deficiency. The distribution of patients with and without hormone deficiency among the patients with coincidental lesions is given in Table 1.

The distribution of 454 hormonal deficiency cases was analyzed in terms of pituitary hormone pathologies and MRI findings. Fifty-seven point nine percent had PP, 26.4% had isolated GHD, 7.26% MPHD, 2.2% hypogonadotropic hypogonadism (HH), 1.4% isolated ACTH deficiency, 1.76% isolated central hypothyroidism, 1.32% central DI, and 1.98% had GHD and PP. In the PP group, which constituted the majority of the patients, pituitary pathologies were generally absent, and among the 85.17% (n=224) with normal MRI, RCC was the most common (46.87%, n=15). Eighty-three of GHD cases had normal brain MRI, and 7.5% (n=9) had hypoplasia. PP and GHD were present in 1 PES case with no visual field defects and neurological findings, 1 RCC with a size of 1.6 cm, 1 developmental brain anomaly, 1 hydrocephalus, and 1 arachnoid cyst. Four cases with PP and GHD had normal MRI findings (Table 2).

**Table 1.** Incidental lesions

| | Without Hormonal Deficiency | With Hormonal Deficiency | | |
|---|---|---|---|---|
| | | PP | GHD | MPHD |
| Rathke Cleft Cyst | 6 | 2 | 2 | |
| Arachnoid Cyst | 4 | 1 | | |
| Partial Empty Sella | 3 | | 1 | |
| Non-functioning Adenoma | 3 | | 1 | |
| PES+ Hydrocephalus | 2 | | | |
| Hypoplasia | 2 | | | 1 |
| Total | 20 | | 8 | |

PP: Precocious Puberty, GHD: Growth Hormone Deficiency, MPHD: Multiple Pituitary Hormone Deficiency, PES: Partial Empty Sella

**Table 2.** Hormonal Pathologies and MRI Findings

| | MRI Pathology | IGHD *(%) **(%) | GHD+PP *(%) **(%) | ICH *(%) **(%) | IACTHD *(%) **(%) | MPHD *(%) **(%) | HH *(%) **(%) | DI *(%) **(%) | Total *(%) **(%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| PP *(%) **(%) | Normal | 224 (85.17%) (98.7%) | 83 (69.16%) (25.46%) | 4 (44.44%) (1.23%) | 2 (25%) (0.61%) | 2 (40%) (0.61%) | 6 (18.18%) (1.84%) | 3 (30%) (0.92%) | 2 (33.33%) (0.61%) | 326 (71.8%) (100%) |
| Pituitary | Hypoplasia | 8 (3.04%) (34.78%) | 9 (7.5%) (39.13%) | | | | 4 (12.12%) (17.39%) | 2 (20%) (8.7%) | | 23 (5%) (100%) |
| Pituitary | Partial Empty Sella | 6 (2.28%) (28.57%) | 7 (5.83%) (33.33%) | 1 (11.11%) (4.76%) | 2 (25%) (9.52%) | | 3 (9.09%) (14.29%) | 1 (10%) (4.76%) | 1 (16.67%) (4.76%) | 21 (4.62%) (100%) |
| Pituitary | Non-functioning Adenoma | | 4 (3.33%) (57.14%) | | 1 (12,5%) (14.28%) | | 2 (6.06%) (28.57%) | | | 7 (1.54%) (100%) |
| Pituitary | Craniopharyngioma | | 3 (2.5%) (27.27%) | | 1 (12.5%) (9.09%) | | 4 (12.12%) (36.36%) | 3 (30%) (27.27%) | | 11 (2.42%) (100%) |
| Pituitary | Ectopic Neurohypophysis | | | | | | 1 (3.03%) (33.33%) | | 2 (3.33%) (6.67%) | 3 (0.66%) (100%) |
| Pituitary | PSIS | | 2 (1.67%) (33.3%) | | | | 3 (9.09%) (50%) | | 1 (16.67%) (16.67%) | 6 (1.32%) (100%) |
| Pituitary | Rathke Cleft Cyst | 15 (5.7%) (46.87%) | 8 (6.68%) (25%) | 1 (11.11%) (3.13%) | 2 (25%) (6.25%) | 3 (60%) (9.37%) | 2 (6.06%) (6.25%) | 1 (10%) (3.13%) | | 32 (7%) (100%) |
| Pituitary | Pituitary Invasive Germinoma | | 1 (0.83%) (100%) | | | | | | | 1 (0.02%) (100%) |
| Pituitary | Pituitary Invasive Arachnoid Cyst | 1 (0.38%) (100%) | | | | | | | | 1 (0.02%) (100%) |
| Non-.Pituitary | Arachnoid Cyst | 4 (1.52%) (44.45%) | 2 (1.67%) (22.22%) | 1 (11.11%) (11.11%) | | | 2 (6.06%) (22.22%) | | | 9 (1.98%) (100%) |
| Non-.Pituitary | Hydrocephalus | 3 (1.14%) (42.86%) | 1 (0.83%) (14.29%) | 1 (11.11%) (14.28%) | | | 2 (6.06%) (28.57%) | | | 7 (1.54%) (100%) |
| Non-.Pituitary | Developmental Brain Anomaly | 2 (0.77%) (28.57%) | | 1 (11.11%) (14.28%) | | | 4 (12.12%) (57.14%) | | | 7 (1.54%) (100%) |
| | Total | 263 (100%) (57.9%) | 120 (100%) (26.4%) | 9 (100%) (1.98%) | 8 (100%) (1.76%) | 5 (100%) (1.1%) | 33 (100%) (7.26%) | 10 (100%) (2.2%) | 6 (100%) (1.32%) | 454 |

ACTH: Adrenocorticotropic Hormone, PP: Precocious Puberty, GHD: Growth Hormone Deficiency, MPHD: Multiple Pituitary Hormone Deficiency, DI: Diabetes İnsipidus. ICH: İsolated Central Hypothyroidism, IACTHD: İsolated ACTH Deficiency. * Percentage of hormonal pathology, ** Percentage of MRI finding

**Discussion**

When pituitary hormone deficiency is suspected in pediatric endocrinology practice, the first examination to be performed is pituitary-hypothalamus MRI. Conversely, brain MRI findings are highly common in pituitary disorders such as adenohypophyseal hypoplasia, pituitary stalk interruption syndrome, ectopic neurohypophysis, partial or total empty sella, Rathke cleft cyst, pituitary adenoma, and craniopharyngioma. Non-pituitary pathologies such as arachnoid cyst, pineal cyst, choroid plexus cyst, and vascular anomalies may also entail hormonal deficiency, though rarely (10, 11).

In the literature, there are numerous cases of incidentally detected pituitary pathologies in patients who underwent brain MRI for non-endocrine reasons. In a study on pediatric patients who underwent brain MRI for general symptoms, principally headache, 41 patients with incidentalomas were identified. In the same study, the most common findings were pituitary hypertrophy (29.3%), arachnoid cysts (17.1%), pituitary adenomas (14.6%), and RCC (12.2%). 56.1% of these patients were re-evaluated radiologically, but none showed dimensional progression (12). A similar study identified 31 incidental lesions, primarily RCC (67.7%), followed by pituitary cysts (19.4%), and microadenomas (12.9%) (13). In our study, 20 (71.42%) of the 28 patients with incidental lesions had no hormonal deficiency. RCC (35.71%) was the most common type of lesion, followed by arachnoid cysts (17.85%). Detailed findings are given in Table 1.

RCCs are non-neoplastic sellar lesions originating from embryonic Rathke cleft remnants. In general, these are clinically silent throughout life and increase gradually with age (14). In the pediatric population, RRCs are known as a rare cause of headache, visual impairment, and pituitary dysfunction. In a study conducted in Korea, 26 of the 34 patients diagnosed with RCCs had endocrine disorders, with idiopathic short stature in 7 (27%) patients, GHD in 7 (27%), and CPP in 12 (46%) cases. CPP and GHD patients with small RCCs (<20 mm) can be managed medically, but close radiological monitoring is essential to assess dimensional progression (15). In the present study, 38 (7.8%) patients in our cohort had RCC, and 6 of them (15.78%) had no hormonal deficiency. The most common endocrine pathology among our RCC cases was CPP (39.47%). In a large-scale study examining brain MRI data of 12 414 patients, empty sella was detected in 241 (1.94%) patients, with 3.31% of these having pituitary hormone pathologies (16). Unlike this study, 26 (5.3%) of our patients had PES, and 21 of them had hormonal disorders.

CPP and GHD are the most common disorders for which brain MRI is performed in pediatric endocrinology practice, and anomalies and malformations hence detected are not uncommon (17, 18). Precocious puberty in girls is usually idiopathic. The prevalence of central nervous system (CNS) abnormalities is reported as approximately 40-75% higher among boys (19, 20). International guidelines recommend neuroimaging in all-male CPP patients, and female CPP patients under 6 years, since these are likely to have brain lesions causing the disorder (2, 14). MRI in girls aged 6-8 years is still debated because the incidence of cranial abnormalities in this age group is minimal (21-26). The most prevalent CNS lesions are hypothalamic hamartomas in the tuber cinereum, which are typically asymptomatic (27, 28). In a study in Taiwan on 251 girls with CPP, 190 (75.70%) of the patients had normal MRIs. Abnormalities were observed in the hypothalamic-pituitary (HP) area in 54 (21.51%) patients, and in non-HP areas in 7 (2.79%) patients. Hypothalamic hamartoma was detected only in one patient under 6 years old (29). In our cohort, CPP patients most commonly underwent brain MRI. Two hundred and five of the 263 CPP cases were female. Also, there were no cases of pineal gland cysts or hamartoma. Pituitary and brain MRI findings are generally normal in isolated GHD cases, except in those with severe GHD (peak GH<3 ng/mL) (30). A study in 2019 evaluating brain MRI findings in isolated GHD mostly reported normal pituitary findings (67.5%). The most common pathological findings were adenohypophysial hypoplasia (20.6%), followed by the ectopic neurohypophysis, and pars intermedia cysts (31). In our study, 83 (69.16%) of the 120 isolated GHD cases had normal MRIs. Non-pituitary pathologies were more frequent than isolated CPP (3.42%-33.33%).

The congenital etiologies of MPHD are associated with structural pituitary abnormalities, eye and optic nerve disorders, hearing disorders, and midline craniofacial defects such as cleft palate and/or lip. Secondary hypopituitarism can result from any damage to the pituitary gland due to tumor mass effect, autoimmune disease, infiltrative disease, infection, chemotherapy, and radiation exposure, as well as trauma. Our 33 MPHD cases mostly had normal pituitary MRI (18.8%). The most common pathologies were hypoplasia (12.22%), craniopharyngioma (12.12%), PES (9.09%), and PSIS (9.09%). 24.24% of the MPHD cases had non-pituitary MRI findings.

A significant rate of endocrine disorders is caused by the pituitary and hypothalamic conditions. As were observed in our study, anatomical structures can seem normal on MRI despite pituitary or hypothalamic hormone pathologies. Nevertheless, we recommend imaging hypothalamic-pituitary and other intracranial structures, following complete endocrine examination and dynamic testing, in order to reveal the underlying organic etiology.

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