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# Patients with Ectopic Posterior Pituitary: Report of Six Cases

## Ektopik Posterior Hipofizi Olan Hastalar: Altı Olgunun Sunumu

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### Abstract

**Objective:** Ectopic posterior pituitary (EPP) can occur because of a migration defect or neurodegeneration of the hypothalamic nuclei. EPP is typically rarely diagnosed. Therefore, we aimed to report our patients with EPP. **Material and Methods:** This is a retrospective study (approved by the Ege University Ethical Committee, protocol 20-7T/49) that included 6 patients with EPP who were followed up between 2012 and 2019. We collected information on age, sex, height, weight, body mass index, age at the diagnosis, history of traumatic delivery, consanguinity, multiple hormone deficiency and treatment. We examined laboratory levels and medical records, and, magnetic resonance imaging (MRI) reports. **Results:** The mean age of patients was 25.83 years, and the age at diagnosis was 11.16 years. One patient was female, and the others were male. They were receiving hormone replacement treatment. The patients were diagnosed with EPP during their childhood. All patients, except 2, were taking growth hormone replacement therapy. Only one patient had a history of consanguinity. Additional information about the patients is described in the patient sections. **Conclusion:** Patients with EPP are rarely seen, and this rare condition should be considered when a patient has panhypopituitarism. MRI is the gold standard imaging modality for hypophysis to identify this condition. In addition, patients who have EPP in MRI should be screened for hypopituitarism.

**Keywords:** Hypopituitarism; combined pituitary hormone deficiency; posterior pituitary gland; ectopic neurohypophysis

### Özet

**Amaç:** Ektopik posterior hipofiz [ectopic posterior pituitary (EPP)] migrasyon defektinden ya da hipotalamik nükleusun nörodejenerasyonundan kaynaklanabilir. EPP, genellikle nadiren teşhis edilir. Bu nedenle EPP'li hastalarımızı paylaşmak istedik. **Gereç ve Yöntemler:** Bu çalışma, (Ege Üniversitesi Etik Komitesi tarafından onaylanan, protokol 20-7T/49) 2012 ile 2019 arasında takip edilen 6 EPP hastasını içeren retrospektif bir çalışmadır. Yaş, cinsiyet, boy, kilo, beden kitle indeksi, tanı yaşı, travmatik doğum öyküsü, akrabalık, çoklu hormon eksikliği ve tedavisi hakkında bilgi topladık. Laboratuvar değerlerini ve tıbbi kayıtları, manyetik rezonans görüntüleme (MRG) raporlarını inceledik. **Bulgular:** Hastalarımızın yaş ortalaması 25,83 ve tanı yaşı ortaması ise 11,16'ydı. Hastalarımızdan 1'i kadın, diğerleri erkekti. Hipofizer yetmezlikleri olması nedeniyle hormon replasman tedavisi alıyorlardı ve çocukluk çağında tanı almışlardı. İki hasta dışında diğerleri büyüme hormonu tedavisi almaktaydı. Sadece 1 hastamızın öyküsünde akraba evliliği vardı. Hastaların yarısında, travmatik doğum öyküsü vardı. Hastalar hakkında ek bilgiler, hasta bölümlerinde anlatılmıştır. **Sonuç:** EPP'li hastalar nadiren görülür ve bir hastada panhipopituitarizm olduğunda bu nadir durumu dikkate almalıyız. MRG, bu durumu tanımlamak için hipofiz için altın standart görüntüleme yöntemidir. Ek olarak, MRG'de EPP'si olan hastalar hipopituitarizm açısından taranmalıdır.

**Anahtar kelimeler:** Hipopituitarizm; kombine hipofizer hormon eksikliği; pituiter bez, posterior; ektopik nörohipofiz

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## Introduction

Ectopic posterior pituitary (EPP) can occur because of a migration defect or neurodegeneration of the hypothalamic nuclei (1). EPP can be identified by magnetic resonance imaging (MRI) and found at the median eminence or along the pituitary stalk, with complete or partial pituitary stalk agenesis and anterior pituitary hypoplasia (2).

Although the etiology is uncertain, traumatic birth, breech delivery and genetic factors may lead to EPP. Antenatal environmental factors such as birth trauma may cause hypopituitarism and EPP (3,4). Genetic factors may result in these developmental abnormalities and EPP (5,6). The formation and differentiation of the pituitary gland are regulated by specific transcription factors such as *Prop-1, Pit-1, HESX1, Pitx1, Pitx2, LHX3,* and *LHX4* (7). Mutations in the *HESX1, LHX4,* and *SOX3* genes may cause EPP (8-10).

The clinical presentation of EPP is variable and may range from isolated growth hormone (GH) deficiency (IGHD) to multiple pituitary hormone deficiency (MPHD) because of the normal posterior pituitary functions (2,11,12). The pathogenesis of hormone deficiency associated with EPP is not well understood. Previous studies have demonstrated the relationship between EPP and the severity of hormone dysfunction (13).

EPP is typically diagnosed in childhood by pediatric endocrinologists, and adult endocrinologists come across these patients rarely. Therefore, we aimed to report our patients who were transferred to our department from the pediatric endocrinology of our university.

## Material and Methods

The study was conducted in accordance with the Declaration of Helsinki Principles. Six patients were enrolled who were transferred to our department from the pediatric endocrinology of our university between 2012 and 2019. All patients were included after signing the informed consent. Ethical approval was obtained from Ege University (approved by the ethical committee, protocol 20-7T/49, 08.07.2020).

We collected information on age, sex, height, weight, body mass index (BMI), age at the diagnosis, history of traumatic delivery, consanguinity, multiple hormone deficiency and treatment. We examined laboratory levels, and medical records, and, MRI reports. MRIs were performed on 1.5 Tesla (Siemens Amira, Erlangen, Germany) or 3 Tesla (Siemens Verio, Erlangen, Germany) scanners. Fast spin-echo, pre-contrast and dynamic post-contrast multiplanar T1 and T2-weighted sequences were obtained from all the patients.

## Results

Table 1 demonstrated the baseline characteristics of the patients. Table 2 shows the laboratory levels of the patients at the last appointment. Additional information about the patients is described in the patient sections.

### Patient 1

A 19 year-old male patient was diagnosed at the age of nine years. He had a history of breech presentation. Pituitary MRI revealed a hypoplastic pituitary gland, complete pituitary stalk agenesis and ectopic posterior pituitary (Figure 1). He was receiving hormone replacement treatment when he started to follow up at our department, and we continued his treatment.

### Patient 2

She had applied to the pediatric endocrinology department because of her short stature when she was ten years old. MRI revealed ectopic posterior pituitary. She initiated hormone replacement treatment because of multiple hormone deficiency. In addition, in the follow up period, she was first initiated with estrogen treatment to provide thelarche, and after one year, she continued with combined estrogen and progesterone. We continued her replacement treatment.

### Patient 3

He was diagnosed with EPP when he was ten years old**.** Pituitary MRI demonstrated pituitary stalk agenesis, ectopic neurohypophysis, corpus callosum dysgenesis and neurohypophysis located in the hypothalamic region (Figure 2). He had multiple hormone deficiency and was taking hormone replacement treatment. Although he had received GH treatment for eight years, he de-

Table 1. Baseline characteristics of the patients with ectopic posterior pituitary.

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| Age (y) | 19 | 35 | 19 | 32 | 25 | 25 |
| Sex (F/M) | M | F | M | M | M | M |
| Height (cm) | 174 | 165 | 172 | 168 | 170 | 176 |
| Weight (kg) | 62 | 54 | 60 | 115 | 63 | 65 |
| BMI (kg/m$^2$) | 20.48 | 19.83 | 20.28 | 40.75 | 21.8 | 20.98 |
| Age of the diagnosis (y) | 9 | 10 | 10 | 19 | 9 | 10 |
| History of traumatic delivery | Yes | No | No | Yes | Yes | No |
| Consanguity | Yes | No | No | No | No | No |
| Multiple Hormone deficiency | Yes | Yes | Yes | Yes | Yes | Yes |
| Treatment | GH, T4, hydrocortisone, testesterone | GH, T4, hydrocortisone Estrogen+ progesterone | T4, hydrocortisoneestosterone | GH, T4, hydrocortisone testosterone, desmopressin | GH, T4, hydrocortisonetestosterone | T4, hydrocortisone testosterone |

BMI: Body mass index; GH: Growth hormone.

veloped epileptic seizures in the follow-up period. Therefore, the neurology department suggested stopping GH treatment. After stopping GH, he never developed epileptic seizures and his insulin-like growth factor-1 (IGF-1) level was normal. Furthermore, we did not initiate GH but continued the other hormone replacement treatments.

### Patient 4

He was diagnosed with tuberculosis meningitis when he was three years old. He developed hydrocephalus and had ventriculoperitoneal shunt insertion. When he was six years old, he had diabetes insipidus and initiated desmopressin treatment. At the age of 19 years, a pituitary MRI revealed hypoplastic pituitary gland and, EPP. He was started with hormone replacement treatment because of multiple hormone deficiency. In the follow-up period, we continued his treatment.

### Patient 5

He presented with short stature when he was nine years old. Cranial MRI showed ectopic neurohypophysis and incision of the corpus callosum. We continued hormone replacement treatment in the follow-up period.

### Patient 6

At the age of ten years, he was diagnosed with EPP. Cranial MRI revealed ectopic neurohypophysis, located in the hypothalamic region. He did not want to continue GH replacement treatment, thus he only took other hormone replacement treatments. In the follow-up period, although he did not take GH, he had no hypoglycemia and central adiposity.

## Discussion

A summary of the patients with EPP is provided. The EPP can occur because of defective embryogenesis during neuronal migration. EPP may be isolated or be associated with stalk anomalies. The pituitary stalk interruption syndrome consists of stalk hypoplasia, absence or interruption of the stalk, hypoplastic anterior pituitary, and EPP (14,15). Antenatal factors such as breech deliveries, neonatal hypoxia, and hypoglycemia play significant roles in the

Table 2. Laboratory levels of the patients at the last appointment.

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| ALT (U/L) | 10 | 16 | 13 | 23 | 14 | 6 |
| FPG(mg/dL) | 72 | 83 | 71 | 80 | 84 | 65 |
| GH (µg/L) | 0.109 | 0.265 | 0.311 | 0.224 | 0.730 | 0.068 |
| IGF-1(µg/L) | 74.1 | 160 | 204 | 115 | 82.5 | 68.5 |
| TSH (mU/L) | 0.01 | 0.01 | 0.93 | 0.42 | 0.53 | 0.27 |
| FT4 (ng/dL) | 1.27 | 1.11 | 0.77 | 1.64 | 1.22 | 1.08 |
| Cortisol (µg/dL) | 1.31 | 3.38 | 1.63 | 1.65 | 1.31 | 2.99 |
| T. testosterone (ng/dL) | 631 | | 400 | 580 | 316 | 800 |
| Estradiol (ng/L) | | 38.34 | | | | |

ALT: Alanine aminotransferase; FPG: Fasting plasma glucose; GH: Growth hormone (normal range: <3); IGF-1: Insulin-like growth factor 1 (normal range: 117-323); TSH: Thyroid stimulating hormone (normal range: 0.27-4.2); FT4: Free thyroxine (normal range: 0.89-1.76); T. testosterone: Total testosterone (normal range: 280-800).

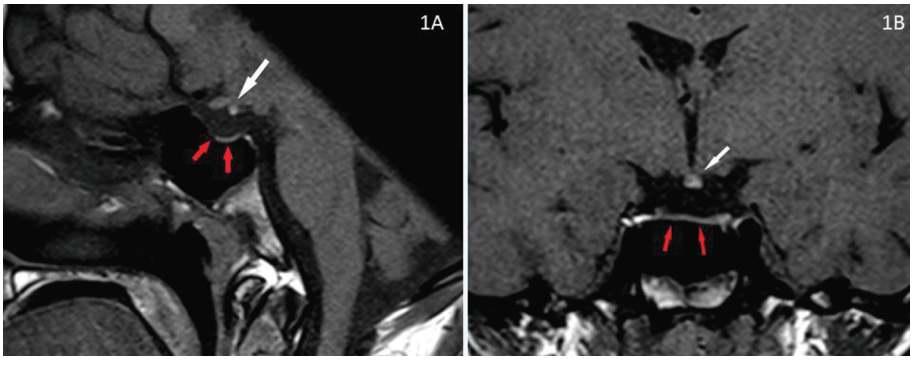


**Figure 1:** The non-contrast T1-weighted sagittal **(A)** and coronal **(B)** magnetic resonance (MR) images demonstrate ectopic neurohypophysis as a bright spot (white arrow) that is located adjacent to the optic chiasm and the hypothalamus. In addition, shallow sellae turcica and thin/hypoplastic adenohypophysis (red arrows) are seen on the same MR images.

development of EPP and stalk anomalies (15). In this study, three out of six patients had a history of a traumatic delivery. Genetic factors may cause EPP, and several genes are reported to be involved in the EPP development such *as PROP1, IFT172, LHX4, HESX1, OTX2* and *SOX3* (5,10,16,17). Phenotypes of these mutations are variable and affect patients in different ways. Some patients had only pituitary hormone deficiencies in their adulthood (18).

All our patients could reach their estimated height when they became adults. In their follow-up, they did not have any osteoporotic fracture. Although Pubarche was normal, male patients did not have normal testes volumes. In additon, they had received gonadotropins in their chidhood but still did not have normal testes volumes and had azoospermia. All our patients were not mentally retarded.

Although some patients with an EPP may have a normal pituitary function, EPP typically presents with IGHD or multiple anterior MPHD. It depends on the severity of the structural abnormality (19,20). Murray et al. (1) demonstrated that small EPP surface area was predictive of MPHD development. In addition, hypothalamic sited EPP was predictive of MPHD (1,21). The absence of the stalk was also reported as a risk factor (2,22). All of our patients had MPHD and were receiving hormone replacement treatments. Although receiving GH treatment in adulthood is controversial, the 2019 guideline suggests it in patients with genetic defects affecting the hypothalamic-pituitary

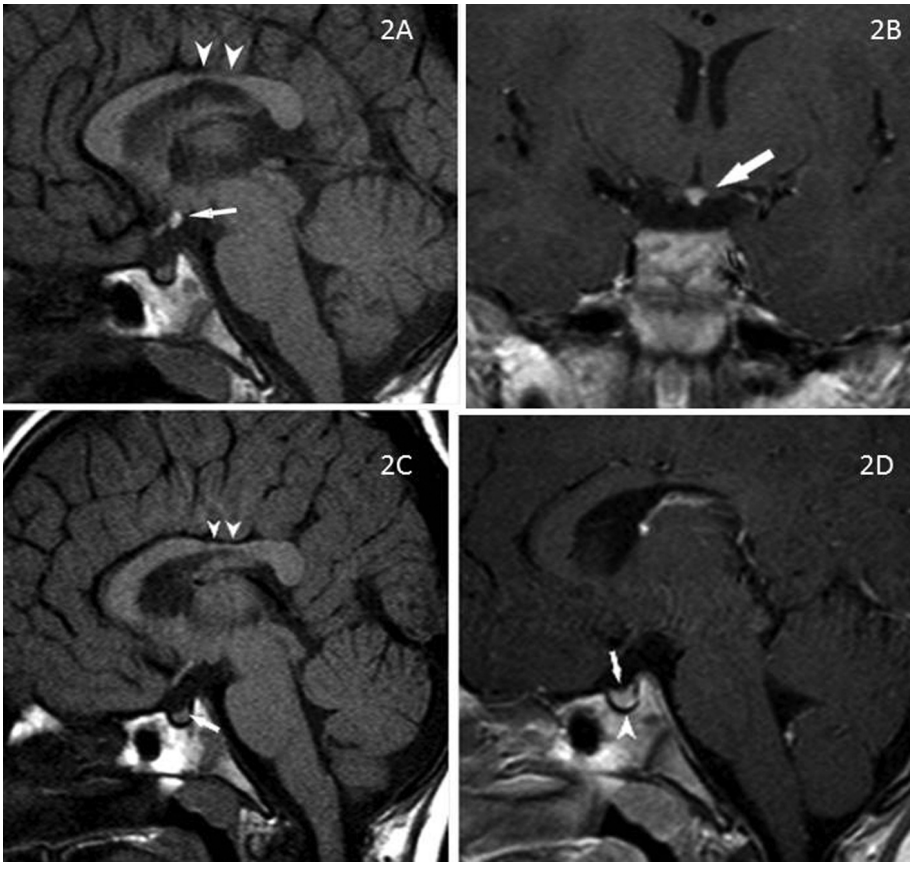


**Figure 2: A, B)** Turbo spin-echo T1-weighted images show hyperintense dot (arrow) in the hypothalamic region that is consistent with ectopic neurohypophysis. There is also thinning of the corpus callosum (arrow heads). **C)** The non-contrast T1 weighted sagittal image, which is next slice to Fig2A, well depicts the corpus callosum dysgenesis (arrow heads) and lack of normal posterior pituitary bright spot (arrow). **D)** The size of the sellae turcica and adenohypophysis (arrow) is normal.

axes, and hypothalamic-pituitary structural brain defects without performing GH stimulation tests in adults.(23) On the contrary, Leger et al.(21) demonstrated that 22 % of patients with EPP and childhood -onset GH deficiency presented normal GH secretion after GH withdrawal.

Although the roles of GH in the brain, including cognitive functions, neural development and neuroprotection were reported, Kato et al. demonstrated that GH enhances epilepsy progression by increasing and signaling the hormone itself in neural circuits. (24-26) In our third patient, we stopped GH because of epileptic seizures. In the follow-up period, he never developed epileptic seizures and his IGF-1 level was normal despite stopping GH treatment.

Our study was limited because of the small number of patients. Furthermore, no pathology proof was found, and genetic testing was not available for any of our patients.

In conclusion, patients with EPP are rarely seen and this rare condition should be considered when a patient has panhypopituitarism. MRI is the gold standard imaging modality for hypophysis to identify this condition. In addition, patients who have EPP in MRI should be screened for hypopituitarism.

## 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.

## Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

## Authorship Contributions

Idea/Concept: Hatice Özışık, Banu Sarer Yürekli; Design: Hatice Özışık, Banu Sarer Yürekli; Control/Supervision: Füsun Saygılı; Data Collection and/or Processing: Hatice Özışık, Banu Sarer Yürekli, Ömer Kitiş, Mehmet Erdoğan; Analysis and/or Interpretation: Hatice Özışık; Literature Review: Hatice Özışık, Banu Sarer Yürekli; Writing the Article: Hatice Özışık; Critical Review: Mehmet Erdoğan, Füsun Saygılı; Materials: Hatice Özışık.

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