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# Relevance of Pituitary Gland Magnetic Resonance Imaging Results with Clinical and Laboratory Findings in Growth Hormone Deficiency

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**Background:** The present study investigated the relationship between detection of organic pathologies with magnetic resonance imaging of the pituitary gland, clinical and laboratory findings, and treatment response.

**Material/Methods:** The study included a total of 183 patients who had isolated growth hormone deficiency, received at least 1 year of treatment, returned regularly for follow-ups, and whose pituitary magnetic resonance images were available. The patients were divided into 2 groups: those with and without pathological evidence with magnetic resonance imaging. Clinical and laboratory features and treatment responses were compared between patients with and without pathological evidence with magnetic resonance imaging.

**Results:** Of the 183 patients, 105 were females and 78 were males, and 114 patients (62.2%) were prepubertal and 69 patients (37.8%) were pubertal. Their mean age was 10.01±3.25 years (1–17.6 years). Pituitary images of 153 (83.6%) patients were normal. Of the patients with detected pathologies (16.4%), 19 (10,4%) had pituitary hypoplasia, 5 (2.7%) had partial empty sella, 3 (1.7%) had ectopic neurohypophysis and 3 (1.7%) had empty sella, pineal, and arachnoid cyst. A statistically significant increase was observed in the height increase rate after treatment compared to before treatment in both groups (p<0.001). However, the group with pathology had a statistically significant (p=0. 007) post-treatment increase height rate. Although in the group with pathology there was a lower L-DOPA and clonidine peak GH response, there was not any statistically significant difference between the 2 groups (p=0.051, p=0.113). Pituitary gland length was also shorter in the group with pathology compared to the group without pathology (P<0.001).

**Conclusions:** Magnetic resonance imaging is a useful tool in assessing GH deficiency pathogenesis and in predicting treatment response.

**MeSH Keywords:** Dwarfism, Pituitary • Growth Hormone • Magnetic Resonance Imaging

**Abbreviations:** **MR** – magnetic resonance; **IGF-1** – insulin like growth factor-1; **IGF-BP3** – insulin like growth factor binding protein 3

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## Background

Growth hormone deficiency is a common endocrinological cause of pathologically short stature in children. Its incidence is 1 in every 3500–4000 births [1]. Growth hormone deficiency may be idiopathic or may develop as a consequence of congenital or acquired organic pathology of the hypothalamo-pituitary axis [2]. Growth hormone deficiency (GHD) diagnosis is based on auxologic assessment, particularly in the presence of low height increase rate with short stature and low growth hormone response in growth hormone stimulation tests [3]. However, these criteria are not always helpful in predicting the disease course (e.g., transient/permanent, isolated/multiple pituitary hormone deficiency) and in determining the underlying cause (organic pathology/idiopathic), and additional assays are therefore needed [4]. Neuroradiological analyses can reveal pathologies at the hypothalamo-pituitary axis in patients previously assessed as having idiopathic growth hormone deficiency [5–7]. MR is a good imaging method for assessing the anatomic characteristics of the hypothalamo-pituitary axis and alternations such as pituitary hypoplasia, ectopic neurohypophysis, and pituitary stem agenesis [8,9]. Recent studies have shown that individuals with pathologies at the hypothalamo-pituitary axis respond better to growth hormone therapy compared to those with no pathologies [10]. Similarly, patients with growth hormone deficiency had smaller pituitary glands [11,12].

In conclusion, there is a close relationship between structural changes in the pituitary gland and clinical status [13]. In light of these data, we aimed in this study to investigate the relationship between clinical and laboratory findings of patients with and without growth hormone-associated pathologies in the pituitary gland and their response to treatment.

## Material and Methods

### Patients and method

We included a total of 183 patients who presented to our hospital between 2009 and 2012 and who were found to have isolated growth hormone deficiency, received at least 1 year of treatment, returned regularly for follow-ups, and whose pituitary MR images were available. All patients used 0.25 mg/kg/week of growth hormone therapy. Diagnosis of growth hormone deficiency was based on the following criteria:

- Pre-treatment height SDS <–2 SDS
- Pre-treatment growth rate <10 percentile
- Bone age *vs.* chronological age <2 SDS
- Growth hormone peak response according to at least 2 growth hormone stimulation tests <10 ng/ml (L-DOPA and Clonidine) complete growth hormone deficiency if <5 ng/ml, and partial growth hormone deficiency if 5–10 ng/ml).

Patients with multiple pituitary hormone deficiencies were excluded. Patients who had a history of head injuries or radiation exposure were not included in the study. The files of all patients with isolated growth hormone deficiency were reviewed retrospectively for clinical characteristics, including chronological age at treatment start, bone age, target height, predicted height, height, height SDS, body weight, body mass index, puberty status, pre-treatment growth rate, and post-treatment one-year growth rate. As laboratory analyses, IGF-1, IGFBP3 levels before and 1 year after treatment with standard deviations, and L-Dopa and growth hormone peak levels according to clonidine stimulation tests were recorded. Pituitary MR images were evaluated. Pituitary gland height <–2 SDS was defined as pituitary hypoplasia [14]. Pathological findings in MRI were recorded as pituitary hypoplasia, ectopic posterior pituitary, empty sella, partial empty sella, and other (e.g., pineal cyst, arachnoid cyst). Patients were divided into 2 groups: those with and without pathological findings with MRI. Patients' height was measured with a stadiometer and puberty was assessed based on Tanner staging (stage 2 and above values were recorded as pubertal). Bone age was interpreted based on the Greulich and Pyle atlas. The predicted height (adult height) was calculated according to Bayley-Pinneau (B-P) method. This method assumes that every bone age represents a certain percentage of the adult height reached by the child.

### MR evaluation

Dynamic contrast pituitary MR images were studies using head bandages with the Philips Infinion model 1.5 T magnetic resonance device in our hospital. Contrast was used for imaging. Gadoterate meglumine (Dotarem; Guerbet, Aulnay-sous-Bois, France) was administered at a single dose of 0.1 mmol/kg of body weight (0.2 mL/kg for gadoterate meglumine) by intravenous bolus injection at a rate of 2 mL/s with an automatic injector. Small FOV (16–20 cm), high-resolution (matrix 256×256), and thin sections (2–3 mm) were used during the analysis. T1- and T2-weighed spin echo sequences were obtained from the sagittal and coronal planes prior to contrast substance administration. Following intravenous contrast substance administration, a coronal plane TSE T1-weighed dynamic phase examination was performed. SE T1-weighed images were obtained post-contrast at the coronal and sagittal planes.

### Statistical evaluation

All statistical analyses were performed using the SPSS version 17.0 (IBM Corporation, Armonk, NY, USA). The variables used in the present study were either continuous or categorical. Continuous variables are reported as mean ± standard deviation (SD) or median (interquartile range), while categorical variables are reported as number of cases and frequencies (%). Whether the distributions of continuous variables were normally





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**Table 1.** Clinical findings of the patients in the study.

| | Pathology (–) 153 (%83.6) | Pathology (+) 30 (%16.4) | p |
|---|---|---|---|
| Gender | | | 0.908# |
| Male | 66 (%43.1) | 12 (%40.0) | |
| Female | 87 (%56.9) | 18 (%60.0) | |
| Age (year)* | 10.10±3.16 | 9.53±3.70 | 0.433## |
| Bone age (year)* | 8.28±3.15 | 7.16±3.82 | 0.142## |
| Puberty status | | | 0.455# |
| Pubertal | 60 (%39.2) | 9 (%30.0) | |
| Prepubertal | 93 (%60.8) | 21 (%70.0) | |
| Weight (kg)** | 25.2 (20.7–32.3) | 21.6 (14.8–34.1) | 0.239@ |
| Height (cm)** | 126.4 (113.9–134.7) | 122.5 (101.1–136.2) | 0.240@ |
| Height SDS* | –3.16±0.95 | –3.52±0.81 | 0.057## |
| BMI (kg/m$^2$)** | 16.3 (15.1–18.1) | 16.1 (15.0–20.0) | 0.562@ |
| BMI SDS* | –0.62±1.19 | –0.56±1.19 | 0.796## |
| Target height (cm)** | 158.0 (154.0–16.0) | 157.6 (154.6–165.0) | 0.747@ |
| Predicted final height (cm)** | 153.8 (147.0–163.9) | 156.1 (146.8–165.6) | 0.762@ |

* Data were shown in mean ± standard deviation; ** data were expressed as median (interquartile range); # continuity correction chi square test; ## Student's t test; @ Mann Whitney U test.

or not was determined by Kolmogorov-Smirnov test. Levene test was used for the evaluation of homogeneity of variances. The bivariate associations between continuous variables were examined using the *t* test with the Mann-Whitney U test applied for pairwise comparisons of proportions between groups. Whether the mean differences in SDS levels for IGF-1 and IGFBP3 between pre- and post-treatment within each group were statistically significant or not was evaluated by paired *t* test. Wilcoxon signed rank test was applied for examining the effect of treatment on the level of body height, IGF-1, and IGFBP3 measurements. Categorical variables were assessed using the continuity-corrected chi-square test. P values <0.05 were considered statistically significant.

### Ethics

The study protocol was approved by the Ethics Committee of Ankara Pediatric Diseases and Health Hematology Oncology Training and Research Hospital (2014-079). This study was performed in accordance with the Helsinki Declaration and Good Clinical Practices.

## Results

The study included 183 patients who were found to have growth hormone deficiency and whose pituitary gland magnetic resonance images were available. Their mean age was 10.01±3.25 years (1–17.6 years), and 105 (57.3%) were girls and 78 (42.6%) were boys. Patients were divided into 2 groups: those with and without pathological findings, with pituitary gland MRI. There were 153 patients (83.6%) with normal pituitary imaging.

- Etiologies in 30 (16.4%) patients with pathologies:
  - Pituitary hypoplasia: 19 cases (10.4%),
  - Partial empty sella: 5 cases (2.7%),
  - Ectopic neurohypophysis: 3 cases (1.7%),
  - Empty sella: 1 case (0.55%),
  - Pineal cyst: 1 case (0.55%),
  - Arachnoid cyst: 1 case (0.55%).

Rathke's cleft cysts did not occur in any patient. Rathke's cleft cysts are benign sellar and suprasellar lesions arising from epithelial remnants of Rathke's pouch with a peak incidence at 30–50 years of age (15). Pediatric cases are rare. Pituitary cysts suggestive of Rathke's cleft cysts were observed in 1.2% of patients between 1 and 4 years old who underwent MRI





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**Table 2.** Height increase rate, IGF-1 and IGFBP3 measurements before and after treatment.

| | Pre-treatment | Post-treatment | P value* | Variation | P value** |
|---|---|---|---|---|---|
| Height increase[a] | | | | | 0.007[##] |
| Pathoology (–) | 4.0 (3.3–4.6) | 8.0 (7.0–9.4) | **<0.001**[#] | 4.1 (2.9–5.7) | |
| Pathology (+) | 3.7 (2.9–4.2) | 8.9 (7.3–10.5) | **<0.001**[#] | 5.3 (3.8–6.6) | |
| IGF-1[a] | | | | | 0.293[##] |
| Pathoology (–) | 143.0 (87.2–225.0) | 313.0 (189.0–442.0) | **<0.001**[#] | 148.0 (63.5–256.0) | |
| Pathology (+) | 116.0 (47.3–262.5) | 244.0 (125.2–423.7) | **<0.001**[#] | 114.5 (40.0–226.0) | |
| IGF-1 SDS[b] | | | | | 0.302[@@] |
| Pathoology (–) | –1.48±0.95 | –0.35±1.38 | **<0.001**[@] | 1.13±1.24 | |
| Pathology (+) | –1.39±1.21 | –0.50±1.46 | **<0.001**[@] | 0.89±1.06 | |
| IGFBP3[a] | | | | | 0.804[##] |
| Pathoology (–) | 3750.0 (2980.0–4650.0) | 4600.0 (4050.0–5520.0) | **<0.001**[#] | 895.0 (–149.0–1850.0) | |
| Pathology (+) | 4175.0 (2465.7–4889.7) | 4524.5 (3457.5–5837.5) | **<0.001**[#] | 1050.5 (87.7–1461.7) | |
| IGFBP3 SDS[b] | | | | | 0.594[@@] |
| Pathoology (–) | –0.79±1.11 | –0.33±1.09 | **<0.001**[@] | 0.46±1.18 | |
| Pathology (+) | –0.75±1.36 | –0.41±1.01 | **<0.001**[@] | 0.34±0.91 | |

* The comparisons between pre- and post-treatment within groups; ** the comparisons between groups in terms of the levels of variations; [a] data were expressed as median (interquartile range); [b] data were shown in mean ± standard deviation; [#] Wilcoxon Sign Rank test; [##] Mann Whitney U test; [@] Paired t-test; [@@] Student's t test.

**Table 3.** Other clinical findings of the patients in the study.

| | Pathology (–) | Pathology (+) | p-Value* |
|---|---|---|---|
| L-DOPA peak GH response (ng/ml) | 2.9 (1.4–5.1) | 1.7 (0.6–4.5) | 0.051 |
| Klonidin peak GH response (ng/ml) | 4.8 (3.2–7.1) | 4.2 (2.1–6.4) | 0.113 |
| Pituitary gland height (mm) | 4.5 (4.0–5.0) | 2.5 (2.0–4.0) | **<0.001** |

Data were expressed as median; * Mann Whitney U test.

following presentation with epilepsy, psychomotor retardation, or headache [16].

Table 1 shows that there was no statistically significant difference between the study populations in terms of sex, chronological age, bone age, or puberty status (p>0.05), and there were also no statistically significant differences between the study populations in terms of body weight, height, body mass index, target height, or predicted height (p>0.05).

Table 2 shows that in both populations, increasing levels of IGF-1 and IGFBP3 after the treatment were significantly different compared to the levels before the treatment (p<0.001). The levels of IGF-1 and IGFBP3 after the treatment were similar in both populations (p=0.293, p=0.804). Also, there was a statistically significant height increase in both populations (p<0.001), but this was significantly higher in the pathology (+) group (p=0.007).

Table 3 shows that although there was a lower L-DOPA peak GH response and Clonidine peak GH response in the pathology (+) group, there was no statistically significant difference between the 2 groups (p=0.051, p=0.113). Table 3 shows that pituitary gland length was lower in the group with pathologies compared to the group without pathologies.





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## Discussion

Of the 183 patients with isolated growth hormone deficiency in our study, 16.4% had pathologies in pituitary gland images. The incidence of detecting pathologies in the pituitary gland ranged from 12% to 86% in other studies [7,12,17,18]. Such a wide range may be due to the differences in interpreting pituitary MRIs and use of contrast substances.

Pituitary pathologies detected in the patients included in our study were pituitary hypoplasia, partial empty sella, ectopic neurohypophysis, empty sella, pineal cyst, and arachnoid cyst. In a study by Kemp et al. with children with short stature, pituitary hypoplasia was the most common pathological finding. Other concomitant pituitary pathologies were ectopic neurohypophysis, pituitary stem abnormality, and increased pituitary gland size [19]. Ectopic neurohypophysis results from local neuronal migration defect, and there is a strong relationship between ectopic neurohypophysis and anterior pituitary development. In our study, 2 of the 3 patients with ectopic neurohypophysis had pituitary hypoplasia. This relationship was determined in many previous studies [8,20,21], but the pathogenesis is not fully elucidated [22].

In both populations, increasing levels of IGF-1 and IGFBP3 after the treatment were significantly different from levels before treatment. The levels of IGF-1 and IGFBP3 after the treatment were similar in both populations. The study by Zenaty et al. suggested that there is no correlation of IGF-1 levels between pathology (+) and pathology (–) groups [23], but another study suggested that IGF-1 level is lower in pathology (+) groups [20]. Serum IGF-1 and IGFBP3 levels are used widely to evaluate growth hormone secretion. However, studies may yield different results because this may be affected by other factors, including nutrition [19].

Pre-treatment IGF-1 level was significantly lower in the group with pathologies. IGF-1 levels were not different between patients with and without pathologies in a study by Zenaty et al. [24], while another study found lower IGF-1 levels in the group with pathologies [19].

Although there was a lower L-DOPA peak GH response and Clonidine peak GH response in the pathology (+) group, there was no significant difference between the 2 populations. Similar studies have arrived at the same conclusion [23,24]. It is believed that response to growth hormone stimulation is lower due to the pituitary gland pathology.

Pituitary gland length was also lower in the group with pathologies compared to the group without pathologies. Measurement of pituitary gland length enables determination of the width of the pituitary gland, as increasing pituitary gland width with increasing ages is associated with length increase, especially in the pituitary gland. Therefore, there is a strong relationship between pituitary gland length and pituitary volume [25]. In our study, we used pituitary gland length to determine pituitary gland size. Growth hormone-releasing cells are abundant in the pituitary gland. Thus, a direct relationship between growth hormone level and anterior pituitary width is to be expected [26]. In similar studies previously performed, there was also a positive correlation between pituitary gland size and peak growth hormone response to growth hormone stimulation tests [20,21]. However, some relevant studies in the literature have found no relationship between the 2 parameters [8,17,18].

The pathologic group had a better post-treatment growth rate. Remarkably, previous studies reported similar results [10,23,27]. The main cause of short stature in individuals with pituitary gland pathologies is growth hormone deficiency, but in individuals without pathologies, growth hormone deficiency is only a part of the cause of short stature. Thus, it is believed that the group with pathologies responded better to growth hormone therapy [10].

## Conclusions

In conclusion, magnetic resonance imaging is a useful tool in elucidating the pathogenesis of GH deficiency and in predicting treatment response.

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