Original Article

MRI-Based Evaluation of Pituitary Size and Volume in Children with Idiopathic Growth Hormone Deficiency

İ Kaba, G Yanarates[1], HNP Kendirci[2]

Departments of Pediatrics and [2]Pediartic Endocrinology, Faculty of Medicine, Hitit University, Corum, [1]Department of Radiology, Erol Olcok Training and Research Hospital, Hitit University, Corum, Turkey

Abstract

Background: Growth hormone deficiency (GHD) is the most common cause of pathological short stature of endocrine origin. Among the causes of pathological short stature, pathologies in the hypothalamic–pituitary region, especially the pituitary gland, have an important place, and imaging the region with pituitary magnetic resonance imaging (MRI) is a frequently used method in the diagnosis process and guides the diagnosis and treatment process. It is known that hypoplasia or aplasia of the pituitary gland, which plays a role in the synthesis and release of many hormones in addition to GH, causes short stature. **Aim:** This study aims to evaluate pituitary size and volume as potential diagnostic markers in children with idiopathic growth hormone deficiency (IGHD) compared with healthy controls. **Methods:** The study included children who presented to our hospital's pediatric endocrinology outpatient clinic with complaints of short stature/growth retardation and was diagnosed with IGHD, for whom MRI of the pituitary had been performed. Pituitary MRI examinations were retrospectively reviewed to measure the, adenohypophysis height, anterior–posterior diameter, width, and volume, and these measurements were compared with those of an age- and gender-matched control group. **Results:** A total of 55 patients diagnosed with IGHD were included, with a mean chronological age of 9.8 ± 3.4 years, of whom 58.2% (n = 32) were male. The control group consisted of 42 healthy children with a mean chronological age of 9.3 ± 3.4 years, with 47.6% (n = 20) being male. No significant differences in age and gender were found between the groups (P = 0.523, P = 0.306, respectively). Although the adenohypophysis height, anterior–posterior diameter, width, and volume of patients with IGHD were lower than those in the control group, no statistical differences were observed between the two groups (P > 0.05). There were no differences in pituitary size and volume based on gender in either group (P > 0.05). A positive correlation was found between pituitary height, width, and volume with age, insulin-like growth factor-1 (IGF-1) standard deviations (SD), and insulin-like growth factor binding protein-3 (IGFBP-3) SD (P < 0.05), whereas no correlation was found between stimulated peak GH levels and pituitary size and volume (P > 0.05).

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Introduction

Growth is the most objective indicator of a child's overall health status, influenced by genetic, hormonal, and environmental factors.[1,2] Growth velocity is the most significant marker of growth and development. In children with short stature, the etiological cause is often a variant of normal short stature, while GHD is the most frequent cause of pathological short stature, accounting for 1–3% of pathological cases.[3,4] The prevalence of GHD is estimated at 1/3500–1/4000.[3,5] Patients can be classified based on the presence of isolated GHD or panhypopituitarism (multiple

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Address for correspondence: Dr. İ Kaba, Department of Pediatrics, Faculty of Medicine, Hitit University, Corum, Turkey.
E-mail: ilknurkaba@yahoo.com

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Conclusion: We found that the size and volume of the adenohypophysis in patients with IGHD are not different from those of healthy peers; however, they showed a correlation particularly with IGF-1 and IGFBP-3 standard deviations.

Keywords: *Child, idiopathic growth hormone deficiency, MRI, pituitary dimensions*

pituitary hormone deficiencies) depending on whether they have GHD alone or in conjunction with other pituitary hormone deficiencies.[5,6]

In childhood, although growth hormone stimulation tests evaluating the GH and IGF axis are considered the gold standard for diagnosing GHD, a comprehensive process involving thorough clinical and biochemical evaluations, as well as radiological assessment, is essential.[7,8] These growth hormone stimulation tests are limited by issues such as reproducibility, standardization, and patient compliance. MRI is recommended for visualizing the pituitary gland because it is both noninvasive and best imaging method, aiding in determining the etiology of cases diagnosed with GHD.[9,10]

Arslanoğlu and colleagues demonstrated that the height and volume of the pituitary gland differ between patients with IGHD and healthy controls, underscoring the potential contribution of pituitary size and morphology to understanding the pathogenesis of GHD.[11] This study aims to determine the differences in MRI-based pituitary size and volume as potential diagnostic markers between children with IGHD and their healthy peers and explore correlations with biochemical markers.

Materials and Methods

Subjects

Between July 2015 and June 2022, children who admitted to our hospital's pediatric endocrinology outpatient clinic with complaints of short stature/failure to thrive, received a diagnosis of IGHD, and underwent pituitary imaging via MRI were included in the study. Patients' chronological age, bone age, anthropometric variables, growth velocity, stimulated growth hormone levels, and MRI findings of the pituitary gland were retrospectively examined from the hospital information management system. The pituitary MRI examinations were evaluated retrospectively, and measurements of the pituitary's anteroposterior diameter, height, width, and volume were compared with those of an age- and gender-matched control group. MRI evaluations were performed by the same experienced radiologist. Patients with suboptimal quality MRI scans, those diagnosed with lesions in the pituitary gland or brain, individuals who had received hormone replacement therapy for any reason, and those with questionable diagnoses based on retrospective clinical data were excluded from the study. In addition, patients with disorders of puberty are excluded because these diseases affect pituitary size.[12]

The most important limiting factor of our study is that it was conducted retrospectively. Patients whose data could not be accessed due to insufficient records had to be excluded from the study and as a result, a limited number of patients could be included in the study. The control group consisted of healthy Turkish children whose pituitary dimensions were used.[12]

Ethical considerations

The study was approved by the ethical board of Hitit University Medical Faculty (25.05.2022/2022-56) and conducted in accordance with the Helsinki Declaration.

Diagnosis of growth hormone deficiency

Patient's weight was measured using a SECA brand scale with 0.1 kg sensitivity, and a Harpenden stadiometer (Holtain Instruments Ltd., UK) was used for height measurement. All measurements were performed by the same nurse. Height and weight SDS were calculated in accordance with the accepted standards in Turkey.[13] Bone ages were assessed using the Greulich-Pyle method on left wrist radiographs.[14] After monitoring growth rate for at least 6 months by a pediatric endocrinology specialist, it was determined that there was no systematic disease or nutritional disorder affecting growth, height deviation was less than -2.0 standard deviation (SD) for that age and gender, annual growth rate was <25 percentile, bone age was 2 years or more behind chronological age, serum IGF-1 and IGFBP-3 levels were low for age and gender, and there was inadequate growth hormone response to at least two pharmacological stimulation tests (L-Dopa and Clonidine) (peak GH response to growth hormone stimulation test was <10 ng/mL).[15,16]

Imaging PROTOCOL

MRI scans of patients were obtained using a Philips MR Systems Achieva dStream 1.5 Tesla MRI machine (Philips Healthcare/Philips Medical Systems B.V., The Netherlands). All patients underwent a routine pituitary MRI protocol for the imaging procedures. A Philips SENSE-head-8 coil was used for signal acquisition. For pituitary MRI examination, precontrast T1-weighted (T1A) sagittal and coronal series, precontrast T2-weighted (T2A) coronal series, and postcontrast T1A sagittal and coronal series were

acquired, along with dynamic series in T1A coronal plane. The slice thickness for both precontrast and postcontrast T1A series was 2 mm with a slice interval of 2.2 mm; TR was set to 550 ms, TE to 10 ms, and FOV to 120 mm. For the precontrast T2A series, the slice thickness was also 2 mm with a slice interval of 2.2 mm; TR was 3000 ms, TE 120 ms, and FOV 120 mm. The slice thickness for dynamic series is specified as 3 mm, with a slice interval of 3.3 mm. The TR time is 518 ms, the TE time is 10 ms, and the FOV is set to 200 mm. A total of 15 consecutive dynamic series have been obtained. Gadolinium-based contrast agents were administered intravenously at a dose of 0.2 mL/kg (0.1 mmol/kg) at a rate of 2 mL/s, with a maximum of 20 mL used.

MRI measurement

Pituitary MRI was conducted on all patients following the diagnosis of GHD. The volume of the pituitary gland (PG) was measured on thin-section three-dimensional MR images using an electronic cursor on a workstation by an experienced radiologist, who was blinded to the hormonal results analyzed. The width and height of the PG were assessed on coronal images at the location of stalk insertion, while the length of the PG was evaluated on midsagittal images. Height was defined as the maximum vertical distance between the upper and lower borders of the PG; width was the maximum transverse diameter, and length was the maximum anteroposterior extent of the PG. Pituitary volume was calculated using Di Chiro's formula, specifically volume = 1/2 × height × length × width[17] [Figures 1–3]. The Di Chiro-Nelson method used in MRI to determine the pituitary volume is based on the measurement of three parameters: or its anteroposterior dimension, its width (lateral dimension), and its height—craniocaudal dimension. This method of detection hypophysis volume is used successfully by clinicians and specialists in radio diagnostics up to present day in spite of its antiquity.[18] The pituitary gland volume observed in GHD children via MRI was compared with that of age- and gender-matched control subjects. Data from a study where Sarı *et al*.[12] examined the pituitary volumes of Turkish children aged 0–18 years served as the control group.[14] In addition, cranial MRIs of patients with GHD were evaluated when feasible and assessed for the presence of any additional intracranial abnormalities or space-occupying lesions; such patients were excluded from the study.

Statistics

Statistical analyses were conducted using IBM SPSS Statistics for Windows version 22.0. For comparing categorical variables, the Pearson Chi-square test was used, and Fisher's exact test was employed when expected frequencies were less than 5. The normality of numerical variables was assessed using the Shapiro–Wilk test; the independent samples *t*-test was applied for comparing normally distributed variables in two groups. The Mann–Whitney U test was used for non-normally distributed variables. Relationships between normally distributed variables were examined using the Pearson correlation coefficient, while the relationship between non-normally distributed variables was analyzed using the Spearman rank correlation coefficient. A *P* value of < 0.05 was considered statistically significant.

Results

The study included 55 patients with GHD, with a mean chronological age of 9.8 ± 3.4 years, of whom

Table 1: Oxological and pubertal data of cases diagnosed with IGH at the time of diagnosis

	Mean±SD	Min–Max
Age (years)	9.8±3.4	3.08-15.66
Body Weight SDS	-1.65±0.92	-5.05-0.2
Height SDS	-2.99±0.7	-6.62-(-2.06)
BMI SDS	0.12±0.81	1.32-1.67
Puberty stage (median)	1	1-5

SD: Standard deviation, SDS: Standard deviation score, BMI: Body mass index

Table 2: Pituitary sizes and volumes of the IBHE and control groups

Pituitary dimensions	İBHE (*n*=55) (Mean±SD) (min-max)	Control (*n*=42) (Mean±SD) (min-max)	*P*
Pituitary height (mm)	4.2±1.0 (1.6-7.0)	4.6±1.2 (2.7-7.2)	0.08
Pituitary length (mm)	5.8±1.2 (4.0-10.0)	6.1±1.1 (9.3-16.5)	0.27
Pituitary width (mm)	11.7±2.2 (5.2-16.3)	12.4±1.9 (9.3-16.5)	0.09
Pituitary volume (mm^3)	151.6±72.5 (28.1-336.4)	183.7±86.4 (76.1-434.7)	0.05

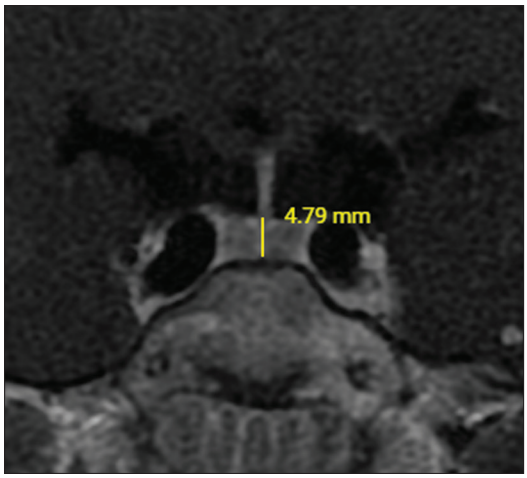

Figure 1: Measurement of height on coronal image at the site of insertion of stalk

Table 3: Correlation of pituitary size and volume in GHD cases with age, gender, IGF-1 SD, IGFBP-3 SD, and stimulated peak BH levels

Pituitary Gland	Age		Gender		IGF-1 SD		IGFBP-3 SD		Pik GH	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Height	0.491	0.001	0.05	0.717	0.308	0.030	0.425	0.006	0.076	0.593
Width	0.315	0.020	0.130	0.349	0.411	0.003	0.412	0.007	0.152	0.497
Length	0.475	0.001	0.158	0.254	0.114	0.430	0.147	0.359	0.242	0.084
Volume	0.584	0.001	0.145	0.297	0.324	0.022	0.460	0.003	0.194	0.169

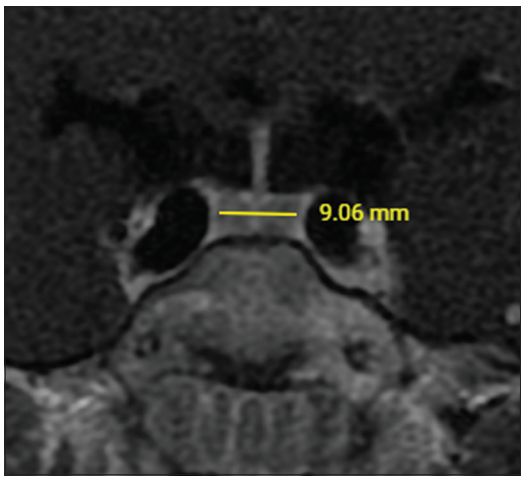

Figure 2: Measurement of width on coronal images at the site of insertion of stalk

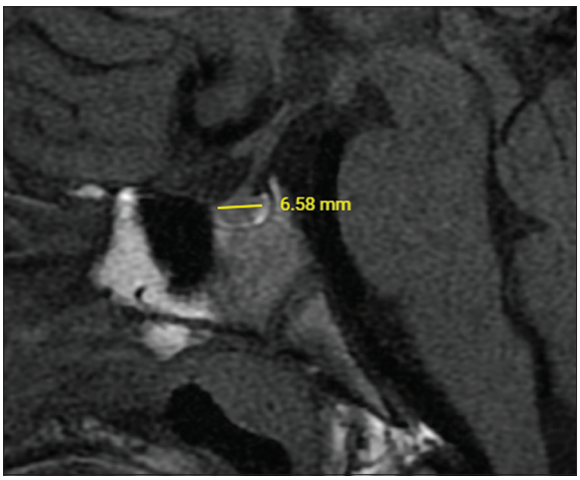

Figure 3: Measurement of length on midsagittal images

58.2% (n = 32) were boys. The control group consisted of 42 healthy children with a mean chronological age of 9.3 ± 3.4 years, of whom 47.6% (n = 20) were boys, whose pituitary MRI measurements were used. No significant differences were found between the groups in terms of age and gender (P = 0.523, P = 0.306, respectively). Table 1 presents the clinical and pubertal data at diagnosis for the cases of GHD.

While the adenohypophysis height, length, width, and volume of patients with GHD were lower compared with the control group, no statistically significant difference was detected between the two groups (P > 0.05) [Table 2]. A positive correlation was found between pituitary height, width and volume with age, IGF-1 SD, and IGFBP-3 SD (P < 0.05). There was no correlation between stimulated peak BH levels and pituitary size and volume (P > 0.05) [Table 3]. In both groups, no differences in pituitary size and volume were observed based on gender (P > 0.05).

Discussion

GHD leads to reduced growth rates during childhood and can result in significant short stature in adulthood if untreated. Diagnosis is made through the examination of auxological data, comprehensive clinical evaluations, and provocative testing.[1-4] Radiological imaging plays a significant role in assessing hypothalamic–pituitary structures in patients diagnosed with IGHD. In these patients, the pituitary gland may have a normal structure or may present with pathologies such as "empty sella," pituitary hypoplasia, or ectopic pituitary gland.[19-21] In a study conducted in our country, cranial MRI of 185 patients diagnosed with IGHD was examined, revealing normal findings in 79.5% of cases, while various cranial pathologies were detected in 20.5%, with pituitary hypoplasia being the most frequently noted (10.3%).[22] In the research conducted by Jagtab and colleagues, ectopic posterior pituitary and interrupted pituitary stalk were found in 48.6% of IGHD patients and 93.5% of congenital GHD patients.[23] In addition, over a follow-up period of 4.5 years, 5.4% of patients with IGHD and abnormal MRI progressed to congenital GHD, whereas none of those with normal MRI developed congenital GHD.[23] In our study, we found no structural anomalies of the pituitary gland in any of our patients.

In the literature, it has been reported that patients with GHD have smaller pituitary volumes compared with healthy control groups, which may be related to a lower number of somatotrop cells.[9,24] In the study by Garel and colleagues, it was noted that patients with IGHD and multiple hormone deficiencies, who also presented with short stature, had smaller adenohypophysis

dimensions.[25] The research by Deep and colleagues concluded that there is a significant relationship between pituitary gland size and IGHD. It was found that individuals with IGHD had significantly smaller pituitary height and volume compared with controls; however, due to the considerable overlap in the pituitary size data between patients and controls, it has been suggested that using this parameter alone would be less effective than considering it alongside other criteria for GHD.[24] In our study, although pituitary size and volume in patients with IGHD were smaller compared with the control group, no statistically significant difference was detected between the two groups. This inconsistency may be attributed to ethnic differences or the relatively smaller sample size of our study.

Some studies suggest that the size of the pituitary gland could be used as a criterion for diagnosing GHD.[7,8] In our study, we aimed to evaluate the contribution of comparing the size and volume of the pituitary gland in patients diagnosed with IGHD to healthy peers. It was found that the adenohypophysis size and volume in patients with IGHD were not different from healthy counterparts but showed correlation specifically with IGF-1 and IGFBP-3 standard deviations [Table 3]. Some studies have shown that pituitary volume correlates with IGF-1 and IGFBP-3 levels, as well as peak GH levels in growth hormone stimulation tests.[9] In the study by Sharma *et al*.,[26] it was reported that the height SDS of the pituitary is correlated with peak GH, basal IGF I SDS, and height SDS. It has been suggested that the pituitary height measured by MRI could serve as an indicator of the severity of idiopathic short stature (ISS). Similarly, in our study, positive correlations were found between pituitary height, width, volume, age, IGF-1 SD, and IGFBP-3 SD. However, no correlation was observed between stimulated peak GH levels and pituitary sizes and volume. This difference is due to the fact that the patient group examined by Nagel included patients with much more severe growth retardation (below -3SD) than the patient group examined by us.

In conclusion, it has been determined that MRI is an excellent method for diagnosing structural anomalies in children with IGHD. However, the evaluation of pituitary size and volume remains important as a useful complementary marker for the demonstration of the severity of GHD rather than for the diagnosis of IGHD.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Hitit University Medical Faculty (decision no: 2022/56 date: 25/05/2022).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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