

# Pituitary Volumes and Functions in Children with Growth Hormone Deficiency: Volumetric Magnetic Resonance Findings

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**Abstract:** *Purpose:* The purpose of the study was to compare pituitary volumes calculated from magnetic resonance imaging (MRI) in patients with idiopathic growth hormone deficiency (GHD) without structural abnormalities in the pituitary gland with clinical and biochemical features.

*Methods:* This study was designed as a retrospective review and the need for informed consent was waived. MRI of the head was performed for 39 male and 17 female patients ranging in age from 10 to 14 years. Pituitary volumes were calculated from sectional area and ellipsoid formula. Pituitary volumes were compared between boys and girls. Pituitary volumes were also compared with measurements of pituitary function, age, and standard deviation scores (SDS) for height.

*Results:* Whole pituitary volumes in patients were  $405.1 \pm 150.6$  mm<sup>3</sup> for the male group and  $348.6 \pm 161.1$  mm<sup>3</sup> for the female group. No significant difference was identified between mean pituitary volumes of the female and male groups. A weak correlation was found between pituitary volume and height SDS for boys ( $\rho = 0.34$ ,  $p = .03$ ). For girls, a moderate correlation was identified between pituitary volume and FSH level ( $\rho = 0.67$ ,  $p < .01$ ).

*Conclusion:* Pituitary volumes of GHD patients correlated with height SDS in boys and FSH levels in girls. Brain MRI can be used not only to rule out anatomical abnormalities of the pituitary gland in GHD patients, but also to assess pituitary functions in clinical settings.

**Keywords:** Growth Hormone Deficiency, MRI, Pituitary Gland.

## INTRODUCTION

Growth hormone (GH) deficiency (GHD) in childhood is characterized by a combination of clinical, genetic, radiological, metabolic, and hormonal abnormalities, each of which may be present to a greater or lesser extent. Confirmation of the clinical diagnosis of GHD depends on the use of specific and sensitive assays to measure the GH secretory potential of the pituitary somatotrophic cells, in addition to morphological investigation of hypothalamic-pituitary anatomy on magnetic resonance imaging (MRI). Although anatomical abnormalities of the hypothalamic-pituitary region have been described [1, 2], many cases of GHD lack a well-defined etiology and are classified as idiopathic.

The anterior pituitary and stalk are normally well-defined on MR imaging, and the posterior pituitary is

easily identifiable as a hyperintense bright spot on unenhanced T1-weighted MR images. The size of the pituitary gland increases linearly during childhood, and the height of the pituitary gland is 2-6 mm in the prepubertal period. With puberty, the gland increases in size, particularly in girls, up to 10 mm [3-8].

MRI may reveal a small to absent anterior pituitary gland in patients with idiopathic GHD [9, 10]. However, those reports included GHD patients with abnormal or absent pituitary stalk in analyses. So far, no reports have demonstrated a relationship between pituitary volume and clinical data such as age, height and pituitary functions in idiopathic GHD limited to patients with a normal neurohypophysis. The present study therefore assessed the pituitary volumes of patients showing idiopathic GHD and a normal posterior pituitary measured from MRI. We hypothesized that pituitary volumes in idiopathic GHD patients would correlate with the severity of clinical and biochemical features and have potential for assessment of pituitary functions.

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## MATERIALS AND METHODS

### Patients

This study was designed as a retrospective review. This study was approved by the Hiroshima Red Cross Hospital Committee for the Protection of the Rights of Human Subjects and the need for informed consent was waived because all personal identifying information was removed from the dataset prior to analysis. A computerized search of the radiology report databases for brain MRI examinations from December 2002 to December 2008 at Hiroshima Red Cross Hospital yielded a list of 89 patients ranging in age from 10 to 14 years with GHD diagnosed according to the criteria defined by the Study Group for Hypothalamo-Pituitary Disorder of the Ministry of Health, Labour, and Welfare of Japan (2001). These diagnostic criteria are based on major features (e.g. growth retardation, symptomatic hypoglycemia, signs indicative of an intracranial organic lesion), GH stimulation tests (with insulin, arginine, L-dopa, clonidine, etc), and minor features (e.g. perinatal abnormality, low mean serum GH level, bone age more than 80% below chronological age). All patients with GHD diagnosed in this hospital underwent brain MRI to rule out a brain tumor or an anomaly of neurohypophysis. Thirty-two patients previously administered GH replacement therapy were excluded. Another patient with ectopic posterior pituitary lobe was also excluded. No patients showed multiple pituitary hormone deficiencies or a family history of GHD.

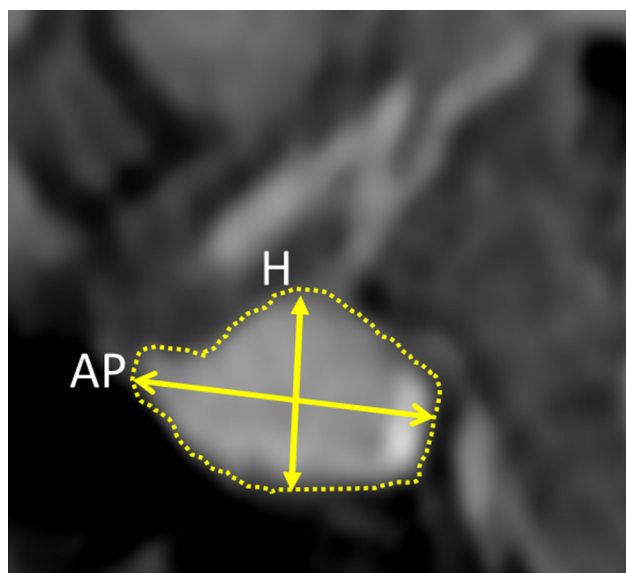
As our study cohort, we selected 39 male and 17 female patients (median age, 12.8 years for boys; median age, 10.8 years for girls) whose complete medical records were available. Information on pubertal stage was available in some patients: all six female patients were in Tanner stage 2 for breast development. Seven male patients out of 17 were in Tanner stage 1 pubic hair development and 10 out of 17 were in Tanner stage 2 pubic hair development. The delay in bone age was measured in 11 patients (median, 2.7 years; range, 1.5 to 4.2 years).

### Image Analysis

Scans were performed using a 1.5-T MR unit (Signa Horizon 1.5T; GE Healthcare, Milwaukee, Wis). T1-weighted fast spin-echo images of the pituitary gland were obtained in both sagittal and coronal planes (repetition time (TR), 400 ms; echo time (TE), 12 ms; slice thickness, 2 mm; gap, 0; field of view (FOV), 16

cm; matrix, 256 × 192; excitations, 4). T2-weighted fast spin-echo images of the pituitary gland were obtained in coronal planes (TR, 4000 ms; TE, 102 ms; slice thickness, 2 mm; gap, 0; FOV, 16 cm; matrix, 256 × 224; excitations, 4). T1-weighted fast spin echo (TR, 467 ms; TE, 16 ms; slice thickness, 6 mm; gap, 2 mm; FOV, 22 cm; matrix, 320 × 256; excitations, 2) and T2-weighted fast spin echo (TR, 3500 ms; TE, 102 ms; slice thickness, 6 mm; gap, 2 mm; FOV, 22 cm; matrix, 320 × 256 matrix; excitations 2) brain axial imaging were also performed. Normal pituitary stalks were identifiable as a hyperintense bright spot on unenhanced T1-weighted MR images in all patients.

Image analysis procedures were performed on a high-resolution monitor (Centricity; GE Healthcare). Measurements were performed retrospectively by one of the authors (M.T., with >20 years of experience as a neuroradiologist), who was blinded to subject information. Maximal pituitary height was determined from midline sagittal images by measuring the greatest distance between the superior and inferior borders of the gland (Figure 1). Lateral and anteroposterior dimensions were similarly determined by measuring the greatest dimensions on coronal and sagittal images, respectively. Cross-sectional area of the gland was measured by tracing the outline of the gland in the midsagittal image with the cursor on the offline console. Volume was estimated in two ways: 1) area × width;



**Figure 1:** Maximal anterior pituitary height (H) is determined from non-contrast enhanced midline sagittal images. Lateral and anteroposterior (AP) dimensions are determined by measuring the greatest dimensions on coronal and sagittal images, respectively. The cross-sectional area of the gland is measured by tracing the outline of the anterior gland on the midsagittal image.

and 2) using the ellipsoid formula (length × width × height)/2] [11]. The first formula tends to overestimate pituitary volume, while the latter tends to underestimate; we therefore used the average of these two measurements as the pituitary volume, as described by Murray [12].

### Assays

Plasma GH, insulin-like growth factor (IGF)-1, ACTH, cortisol, FSH, TSH, free triiodothyronine (T3), and free thyroxine (T4) concentrations were measured using radioimmunoassay methods (SRL, Tokyo, Japan). Intra- and inter-assay variances were as follows: GH, 2.56-5.76% and 2.60-3.48%; IGF-1, 2.49-3.80% and 3.08-5.96%; ACTH, 2.44-5.28% and 0.96-2.77%; cortisol, 4.31-7.98% and 0.00-2.29%; FSH, 2.41-4.99% and 1.65-2.82%; TSH, 4.62-5.21% and 1.51-3.21%; free T3, 3.48-5.33% and 0.00-4.36%; free T4, 2.82-6.06% and 0.85-2.48%, respectively.

### Comparison of Pituitary Volumes with Clinical and Biochemical Features

First, pituitary volumes were compared between boys and girls. Pituitary volumes were then compared with patient heights. Patient height values and IGF-1 concentration were converted into standard deviation scores (SDS) using the reference values reported by Ministry of Education, Culture, Sports, Science and Technology of Japan because the reference values of these measurements are considerably different according to age. Pituitary volumes were also compared with patient age (months) and parameters of pituitary function, including GH, IGF-1, ACTH, cortisol, PRL, FSH, free T4, free T3, and TSH. Both SDS were calculated as (observed serum level – normative values from the general population (standardized for age and sex)/ normative values SD). As IGF-1 did not follow normal distributions, logarithmic transformation was used.

### Statistical Analysis

All statistical analyses were performed using commercially available software (Excel 2007; Microsoft, Redmond, Wash). Values of  $p < 0.05$  were considered significant.

Welch  $t$  test was used to compare pituitary volumes between boys and girls. For evaluation of relationships between pituitary volumes and patient age, height SDS, and indices of pituitary functions, the Spearman rank correlation was used.

## RESULTS

Whole pituitary volumes in patients were  $405.1 \pm 150.6 \text{ mm}^3$  for the male group and  $348.6 \pm 161.1 \text{ mm}^3$  for the female group (Table 1). No significant difference was identified between mean pituitary volumes of the female and male groups.

**Table 1: Volumes of the Whole Pituitary**

	Pituitary Volume
Males	$405.1 \pm 150.6$ ( $423.7 \pm 110.3$ , n=22)
Females	$348.6 \pm 161.1$ ( $567.9 \pm 126.9^*$ , n=37)

Note: All values represent the mean  $\pm$  SD ( $\text{mm}^3$ ). Published norms [13] are shown in parentheses.

\*Statistically significant difference between males and females,  $p < 0.01$ .

Characteristics of the entire group are provided in Table 2. A weak correlation was found between pituitary volume and height SDS for boys ( $r = 0.34$ ,  $p = .03$ , Table 3). For girls, a moderate correlation was identified between pituitary volume and FSH level ( $r = 0.67$ ,  $p < .01$ ). Multivariate analysis was not performed because only one of the variables was significant at univariate analysis for each sex.

## DISCUSSION

GHD is a common endocrinological cause of short stature, and may be idiopathic or associated with organic causes such as tumor, surgery, or irradiation of the sellar area. In the case of idiopathic GHD, correlations between size of the gland and hormonal findings remain controversial [1, 2].

Pituitary volumes of the male and female groups were not significantly different in this study. Furthermore, female pituitary volumes were much smaller than the published value ( $567.9 \pm 126.9 \text{ mm}^3$ ) corresponding to those of the same age group published by Takano *et al.* [13] although statistical comparison could not be performed because there was a methodological difference in MR volumetry between our and their studies. They measured the whole pituitary volumes of normal children and adolescents on thin-section 3D MR images. They demonstrated that the whole pituitary in girls showed a growth spurt at the age of 10 to 14 and was significantly larger than that in boys in this age group. In addition, recent reports on relationship among pituitary volume, puberty stage, and sex hormones [14, 15] demonstrated that a larger pituitary volume was related to higher FSH production

**Table 2: Characteristics of Investigated Group**

	Sex	Patient Values	Median	IQR
Height SDS	Male	-2.67 ± 0.73	-2.75	0.53
	Female	-2.55 ± 0.57	-2.72	0.74
GH (ng/ml)	Male	1.04 ± 2.17	0.26	0.54
	Female	1.08 ± 2.08	0.39	1.24
IGF-1 SDS	Male	-1.57 ± 1.18	-1.43	1.22
	Female	-1.66 ± 2.56	-1.10	1.13
PRL (ng/ml)	Male	8.70 ± 9.88	6.37	3.98
	Female	12.16 ± 15.31	6.31	9.27
FSH (mIU/ml)	Male	2.84 ± 1.48	2.6	1.62
	Female	2.81 ± 1.62	2.22	2.11
ACTH (pg/ml)	Male	35.2 ± 43.4	25.1	14.3
	Female	42.3 ± 52.4	29.5	18.6
Cortisol µg/dl	Male	12.05 ± 6.97	9.45	3.95
	Female	15.31 ± 6.87	14.3	10.65
Free T4 (ng/dl)	Male	1.19 ± 0.16	1.19	0.19
	Female	1.14 ± 0.13	1.11	0.21
Free T3 (pg/ml)	Male	3.27 ± 0.51	3.32	0.56
	Female	3.46 ± 0.38	3.5	0.55
TSH (µU/ml)	Male	1.86 ± 0.87	1.63	1.14
	Female	2.25 ± 1.56	1.55	2.04

Note: Patient values represent mean values ± standard deviation.  
IQR: Interquartile range.

**Table 3: Association between Pituitary Volumes and Pituitary Functions**

	Boys		Girls	
	Spearman ρ	p Value	Spearman ρ	p Value
Age	-0.08	0.62	0.31	0.21
Height SDS	0.34	0.03*	0.00	0.99
GH	0.09	0.60	0.19	0.46
IGF-1 SDS	-0.03	0.86	-0.26	0.29
ACTH	0.17	0.30	0.13	0.62
Cortisol	0.20	0.23	0.17	0.52
Free T3	-0.18	0.26	0.19	0.47
Free T4	-0.02	0.86	0.10	0.73
TSH	0.03	0.87	0.00	0.99
FSH	0.01	0.93	0.67	< 0.01*

\*p values were statistically significant.

in patients in the similar age group to our study [14] and total testosterone and estradiol levels also predicted adjusted pituitary volumes in males and pre-

menarche females, respectively [15]. Therefore, our data might show that pituitary growth with puberty in female GHD patients may be impaired.

Computed tomography and MRI findings of physical hyperplasia of the pituitary gland during puberty have been reported previously [6, 7, 16]. This pubertal hyperplasia has been thought to reflect physical hypersecretion of pituitary hormones, particularly reproductive-axis related hormones such as FSH, testosterone, and estradiol [7, 14-18]. Our data identified the moderate correlation of FSH level with pituitary volume in female patients and this finding is in line with the previous study which showed significant correlation between pituitary volume and FSH level [14]. Since there is considerable evidence that GH and systemic and locally produced IGF-I exert stimulatory synergistic or permissive effects at each level of the pituitary-gonadal axis [19], we believe that the pubertal hyperplasia of female patients was hindered by the impairment of somatotrophic axis-related hormones (i.e. GH and IGF-1) in GHD.

We could not statistically compare pituitary volumes of GHD patients with those of normal subjects since MRI of normal children to obtain normative data was not performed for ethical reasons. Therefore, we could not determine if GH malfunction itself contributed to the small pituitary volumes in female patients. However, GH and IGF-1 levels in this study did not show significant correlations with pituitary volume in both sexes. Thus, we believe that impairment of somatotrophs is not reflected to the perceptible pituitary volume reduction on routine MR imaging in pubertal age group. More precise information obtained from high-resolution 3D MRI targeting the anterior pituitary may prove the relationship between somatotrophic axis-related hormone levels and the pituitary volume since somatotrophs are the most abundant cells in the anterior pituitary [20].

Pituitary volumes of the male group were weakly correlated with height SDS. This finding is not surprising when considering height SDS is merely an indirect index of GHD. The corresponding correlation was not statistically significant for female group. This could be attributed to the effect of FSH on the pituitary size which masked the relationship between pituitary volumes and height SDS.

The present study includes key limitations that must be considered. First, we did not perform MR examinations of normal children to collect normative data for ethical reasons. Instead, we compared pituitary volumes with reported normative values [13] which used 3D volumetric data of pituitary gland. We used Murray's method [12] to measure pituitary volume

because 3D volumetric data of pituitary gland were not obtained. As described before, pituitary volume was determined as the average value of the solutions of two different equations in this study. Both estimates calculated from the equations were consistent with volumes reported previously in MRI [21] and postmortem study [22]. Therefore, we considered that the comparison of pituitary volumes in this study to the results from 3D volumetry was fairly acceptable, although some uncertainty may exist regarding the results of obtaining gland volumes. Second, the posterior pituitary gland was included in measurements to compare pituitary volumes with published norms. Since posterior pituitary volumes were much smaller than whole pituitary volumes and showed gradual growth without spurt in this age group [13], we do not believe this had no significant effect on our results. A comparative study of the anterior pituitary volume and the pituitary function should be performed to determine the effect of GHD on the pituitary volume.

In conclusion, pituitary volumes of GHD patients significantly correlated with height SDS in boys and FSH levels in girls. To our knowledge, this is the first study to compare the pituitary volume of GHD patients without anatomical abnormalities in the posterior pituitary with clinical and functional parameters. Pituitary volumes between boys and girls of GHD were statistically identical in pubertal age. Brain MRI can be used not only to rule out anatomical abnormalities of the pituitary gland in GHD patients, but also to assess pituitary functions in clinical settings.

## ACKNOWLEDGEMENTS

We wish to acknowledge all the staff in the Department of Radiology of Hiroshima Red Cross Hospital for their endless support.

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Received on 02-02-2014

Accepted on 24-03-2014

Published on 04-04-2014

DOI: <http://dx.doi.org/10.12970/2310-9971.2014.02.01.7>