

# Pituitary volumes and functions in children with growth hormone deficiency: Volumetric magnetic resonance data

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## Introduction

Since human pituitary growth hormone (GH) became available for treatment in 1960, followed in 1985 by recombinant human GH, the diagnosis of GH deficiency (GHD) has been the subject of many debates and controversies. The diagnosis of GHD in childhood is a complicated issue involving both clinical and laboratory aspects and also health and insurance policies. Although anatomical abnormalities of the hypothalamic-pituitary region are currently described, and mutations or deletions of the genes involved in the GH axis increasingly recognized, many cases of GHD do not have a well-defined etiology and are classified as idiopathic. MR imaging can show a small to absent anterior pituitary gland in patients with idiopathic GHD. We hypothesized that pituitary volumes measured from 3D volumetric MR imaging would correlate with the severity of the clinical and biochemical features.

## Subjects and methods

A computerized search of medical records from December 2002 to December 2008 yielded a list of 69 patients (47 males and 22 females, age range of 5-21 years) with GHD or suspicion of GHD. The scans were performed on a 1.5-Tesla MR unit (General Electric Signa). T1 weighted spin-echo images of the pituitary gland were obtained in both sagittal and coronal planes (TR/TE 400/12, 2mm slice thickness/0 gap, 16cm FOV, 256 x 192 matrix, 4 excitations). T2 weighted spin-echo images of the pituitary gland were obtained in coronal planes (TR/TE 4000/102, 2mm slice thickness/0 gap, 16cm FOV, 256 x 224 matrix, 4 excitations). Routine T1- and T2-weighted brain axial imaging was also performed. Maximal pituitary height was determined from midline sagittal T1 weighted images by measuring the greatest distance between the superior and inferior borders of the gland. Lateral and anteroposterior dimensions were similarly determined by measuring the greatest dimensions on the coronal and sagittal images, respectively. Estimates of pituitary volume were derived from these measurements using the cubic (length x width x height) and the ellipsoid [(length x width x height)/2] formulae. The first formula tends to overestimate and the latter to underestimate pituitary volume; therefore, the average of both measurements was taken as the best approximation of pituitary volume (1).

The study population was divided into two groups, prepubertal (5-11 years) and pubertal or postpubertal (12-16 years) to compare pituitary volumes with published normal values (2) matched for age group and sex using two-sided t test. Correlations of pituitary volumes and height standard deviation scores (SDS) were examined. Pituitary volumes were also compared with patients' pituitary functions. They include GH, IGF-1 (insulin-like growth factor-1), IGFBP-3 (insulin-like growth factor binding protein-3), urinary GH, ACTH, cortisol, testosterone, PRL, FSH, LH, free T4, free T3, TSH, peak GH values to insulin tolerance test, arginine test, glucagon test, clonidine test, and levodopa test.

## Results

Estimates of whole pituitary volumes were demonstrated in the figure. Pituitary volumes in the patients were  $267.4 \pm 35.5 \text{ mm}^3$  in male prepubertal group,  $399.8 \pm 148.8 \text{ mm}^3$  in male pubertal or postpubertal group,  $225.7 \pm 74.7 \text{ mm}^3$  in female prepubertal group, and  $326.9 \pm 166.6 \text{ mm}^3$  in female pubertal or postpubertal group. Pituitary volumes of all patient groups were smaller than the age-matched published norms (Figure). Pituitary volumes of both female groups were significantly smaller ( $P < .001$ , t tests) than that of controls. Pituitary volumes of male pubertal or postpubertal group were significantly larger than that of prepubertal one ( $P < .001$ , t tests), but this difference was not significant between female groups. There was no significant correlation between patients' pituitary volumes and height SDS.

Endocrine evaluation revealed that IGF-1 levels (males;  $183.32 \pm 90.8 \text{ ng/ml}$ , females;  $180.37 \pm 73.43 \text{ ng/ml}$ ) and IGFBP-3 levels (males;  $2.24 \pm 0.53 \mu\text{g/ml}$ , females;  $2.28 \pm 0.38 \mu\text{g/ml}$ ) appeared to be rather low within normal ranges.

Endocrine evaluation revealed that IGF-1 levels were significantly correlated with pituitary volumes in both genders (multiple regression analysis, males;  $P < .001$ , females;  $P = .01$ ). IGFBP-3 and urine GH (males;  $17.14 \pm 12.04 \text{ pg/mg} \cdot \text{Cr}$ , females;  $18.45 \pm 6.53 \text{ pg/mg} \cdot \text{Cr}$ ) showed weak correlation with pituitary volumes in female and male patients respectively, but these were not statistically significant. LH levels (males;  $0.90 \pm 0.93 \text{ mIU/ml}$ , females;  $0.29 \pm 0.73 \text{ mIU/ml}$ ) were significantly correlated with pituitary volumes in male patients (Spearman rank-correlation coefficient,  $P = .04$ ).

## Discussion

Since pubertal growth is much more prominent in girls, the pituitary gland is much larger in teenage girls than in teenage boys. Our results showed that the growth spurt of pituitary size in GHD was more prominent in males than in females, which is contradictory to normal development pattern. This is consistent with the report that showed the absence or low levels of GH and IGF-1 have clinical effects on the reproductive system in women (3). GH levels of our patients were not dependent on patients' pituitary volumes. It can be explained by the fact that as GH is secreted in a pulsatile manner, random measurements of serum GH are of little value for the diagnosis of GHD. On the other hand, IGF-1 levels of our patients showed significant correlation with pituitary volumes. The potential advantage of measuring IGF-1 is that their serum level shows little diurnal variation and therefore a single basal sample will suffice for assessment. Our results showed only weak correlation of pituitary volumes with IGFBP-3 in female patients. This may in part be related to the fact that IGFBP-3 is a binding protein for IGF-2 as well as IGF-1. The IGFBP-3 level is also lowered in GHD but needs to act as a binding protein to the relatively upregulated proportion of IGF-II. There was also weak correlation of pituitary volumes with urinary GH levels in only male patients. It could be related with high day to day variability of urinary GH. Since GH, directly or indirectly via IGF-1, regulates reproductive functions at all levels of the hypothalamic-pituitary-gonadal, it could be speculated that the pituitary volume dependent decline of LH was associated with IGF-1 levels with similar declining trend in male patients.

## Conclusion

Pituitary volumes of patients with GHD were smaller than those of controls. The growth spurt of pituitary size in GHD was more prominent in males than in females. IGF-1 and LH which was partly regulated by IGF-1 showed correlation with pituitary volumes.

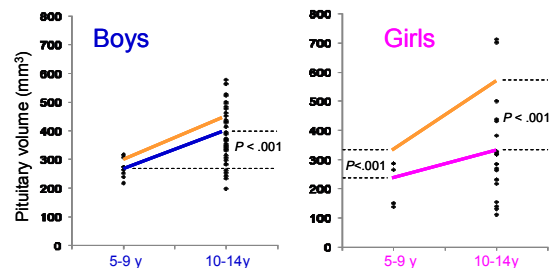


Figure 1 The relationship between patients' age and pituitary volumes in GHD. Note.- published normal mean values are shown in orange

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