Age-Related Pituitary Volumes in Prepubertal Children with Normal Endocrine Function: Volumetric Magnetic Resonance Data

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Background: Evaluation of the size of the pituitary gland on magnetic resonance imaging (MRI) may be difficult, considering the wide variation in normal gland morphology. Given the paucity of age-related biometric data, our purpose was to obtain standard normal reference values for pituitary volumes in prepubertal children using three-dimensional MRI data.

Methods: Children under the age of 10 yr undergoing brain MRI for seizures or idiopathic developmental delay and who had no endocrine abnormality were recruited prospectively over 2 yr. All MRI studies included a three-dimensional sequence. Only subjects with normal studies were included. One hundred thirty-nine children were eligible (mean age, 5.2 yr). Direct pituitary volumes were measured from contiguous 1-mm thick reconstructed coronal and sagittal images. Estimated pituitary volumes were calculated using pituitary height, width, and length.

Results: Volumes obtained from reconstructions in either plane were essentially identical. There was a linear increase in log-transformed pituitary volume with age, but relatively weak correlations with height or body mass index. There was no gender difference and only weak correlations between pituitary height and pituitary volume and between estimated pituitary volume calculation and measured pituitary volume. We provide age-related reference ranges for pituitary volumes in graphical and tabular forms. (J Clin Endocrinol Metab 90: 3274–3278, 2005)

THE USE OF magnetic resonance imaging (MRI) for the evaluation of neurological and endocrine disorders in children has increased dramatically over the last 10 yr. This has coincided with a rapid evolution of MRI technology, with fast sequences and increasing image resolution allowing accurate visualization of even small structures. Three-dimensional (3D) data acquisition now allows the direct evaluation rather than estimated calculations of volumes. Despite this, there is an absence of useful reference data for the normal range of pituitary volumes in children (1, 2).

MRI of the pituitary is advocated as part of the baseline evaluation of neurological and endocrine disorders in children based on true volumetric measurements in an ethnoclinically diverse population.

Subjects and Methods

Subjects

After receiving ethics approval from the ethics in human research committee of Royal Children’s Hospital, we recruited 254 children up to the age of 10 yr. The study period extended from July 2001 to Sep-
TABLE 1. Clinical characteristics of the subjects included in the study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>5.2</td>
<td>2.9</td>
<td>0.4 to 10.0</td>
</tr>
<tr>
<td>BMI (z-score)</td>
<td>0.17</td>
<td>1.22</td>
<td>-2.48 to 2.37</td>
</tr>
<tr>
<td>Height (z-score)</td>
<td>0.06</td>
<td>1.05</td>
<td>-2.16 to 2.16</td>
</tr>
</tbody>
</table>

Height and BMI were expressed as z-scores, with standardization for age and sex.

Exclusion criteria

Any patient with a history or clinical evidence of endocrine abnormality, genetic syndrome, preterm delivery at less than 35 wk gestation, birth asphyxia, hospitalization for head injury, craniospinal irradiation, or abnormal MRI of the brain was excluded from the study. Any patient who was peri- or postpubertal on examination was also excluded from the study. After application of these exclusion criteria, 143 children were considered for inclusion.

Clinical assessment

All subjects were clinically assessed by one of two endocrinologists (C.C.P. or S.K.) before the MRI. Information regarding signs and symptoms of endocrine disorders, use of endocrine therapies, genital abnormalities, and genetic syndromes was recorded. Weight was assessed by digital scale, and height was determined by Harpenden stadiometer. Body mass index (BMI) was calculated as the ratio of weight to height$^2$ (kg/m$^2$). Patients with extreme values of height were excluded, because height was considered the most appropriate auxological indicator of subclinical endocrinopathy. In addition to this, all patients studied were clinically euthyroid and had a normal (prepubertal) genital appearance.

MRI evaluation

MRI examinations were performed using a GE 1.5 T Echospeed LX system. Thin section volumetric studies were obtained using T1-weighted sagittal 3D fast spoiled gradient echo (SPGR) data acquisition according to our protocol for the investigation of seizures and congenital brain abnormalities. The following parameters were used: minimum echo time and repetition time, inversion time of 350 msec for children over 2 yr increasing up to 850 msec for infants under 6 months of age, 320 × 192 matrix (zero filled to 512 × 512), 25° flip angle, 8.3-Hz bandwidth, 1- to 1.4-mm slice thickness (interpolated to 0.5–0.7 mm), and 21- to 23-cm field of view. For infants under 6 months of age, the parameters were as follows: 3D T1-weighted SPGR with minimum full echo time, 35-msec repetition time, 45° flip angle, 8.93-Hz bandwidth, 20- to 26-cm field of view, 0.8- to 1.2-mm slice thickness, and 256 × 192 matrix. This conventional spoiled gradient echo (SPGR) sequence was used because it was determined in clinical studies that the inherent tissue contrast of the fast SPGR was not appropriate for gray/white matter differentiation in this younger age group.

To obtain the pituitary volumes, additionally targeted sagittal and coronal reformats with 1-mm contiguous slices were obtained from the 3D dataset. The cross-sectional areas of the pituitary gland were measured manually using a surface area mark-up tool on the contiguous 1-mm sections in both sagittal and coronal planes. The volume (in cubic millimeters) was obtained by adding the areas (in square millimeters) for each plane. In addition, the maximum height and length of the gland were measured from the midsagittal image, and the maximum width of the gland was measured from the coronal images. The hypertense posterior pituitary was included in all measurements of the entire gland. Indirect volume calculations were performed using the formula most commonly used by previous researchers: $V = \frac{(\text{length} \times \text{height} \times \text{width})}{2}$ (2, 8, 10, 28, 29). This formula was originally derived from the formula of an ellipsoid $V = \frac{4}{3} \pi \frac{\text{length} \times \text{height} \times \text{width}}{2}$ to estimate the volume of the sella turcica on plain radiographs in 1960 (30).

All volume measurements were performed by one radiologist (S.K.), who was blinded to demographic data of the subjects. Volume measurements for 21 children were repeated after an interval of a minimum of 3 months to assess intraobserver reliability.

Statistical analysis

Height and BMI were converted to z-scores, adjusting for age and sex using the 1990 British growth reference (31). The concordance correlation coefficient (CCC) was calculated to assess the agreement between pituitary volume measured on coronal and sagittal planes (32). Spearman’s correlation was used to measure the association between pituitary volume and pituitary height, width, and thickness. Reference values with 95% ranges were obtained by regression analysis, using fractional polynomials where necessary to handle nonlinearity (33, 34). Because the distribution of pituitary volumes was skewed, analysis was performed on the logarithms, with resulting summaries given as geometric means for the volume. Stata software were used for all statistical analyses (release 8.0, Stata Corp., College Station, TX).

Results

Subjects

Of the 143 children thought to be eligible for inclusion, four children with height z-score absolute values greater than 2.2 were excluded; in the remaining sample, 5.0% (seven of 139) had heights outside the normal 95% range. The remaining total of 139 children up to the age of 10 yr, with 82 males and 57 females, were included in the study. Table 1 summarizes the clinical characteristics of the children.

Pituitary morphology

We observed extremely wide variation in the morphology of the pituitary gland on high resolution MRI regardless of subject age. No two pituitaries were identical in shape or size. The pituitary gland varied from crescentic to globular, with pituitary shape varying from crescentic to globular.

![Fig. 1. Range of pituitary morphology encountered. Midsagittal (top) and mid-coronal (bottom) images in seven patients (A–G), with pituitary shape varying from crescentic to globular.](https://example.com/fig1.png)
distribution of the isointense anterior gland and the hyper-
intense posterior gland. They varied in their relative antero-
posterior length and relative height, whereas the shape var-
tied from crescent-like to hemispherical and near-spherical. In
some, the anterior height was greater; in others, the posterior
height was greater; and some were dumbbell-shaped. The
posterior pituitary bright spot could be elongated or flat-
tened and extended variably in the anterior direction, often
beneath the anterior portion of the gland (Fig. 1).

Pituitary volume data analysis

Intraobserver reliability was high in the 21 repeated vol-
ume measurements, with a CCC of 0.986 [95% confidence
interval (CI), 0.967–0.994].

There was very strong agreement between the volumes
measured from the coronal and sagittal reconstructions
(CCC, 0.986; 95% CI, 0.981–0.990; Fig. 2). Because there was
no substantial difference between the volumes obtained from
the coronal and sagittal reconstructions, the coronal value
was used for subsequent analysis.

There was a gradual linear increase in log pituitary volume
over the first 10 yr of life (Fig. 3). The estimated geometric
mean and 95% reference interval for pituitary gland volume
by year of age are presented in Table 2. When separate
regression models were fitted for males and females, the
estimated geometric mean pituitary volumes were almost
identical (Fig. 4). Weak correlations were found between
pituitary volume and height, and BMI z-score (Spearman
correlations, 0.20, and 0.17, respectively). There was also only
a weak correlation between pituitary volume and pituitary
height, with a Spearman correlation coefficient of 0.35 (95%
CI, 0.20–0.49; Fig. 5).

The calculated volume using the formula derived from
that for the volume of an ellipsoid showed only modest
agreement with measured pituitary volume (CCC, 0.46; CI,
0.37–0.54).

Discussion

There is a recognized need for more normative data on
pituitary size in the pediatric population (1, 2). In this study
we reported MRI data on measured pituitary volumes in an
ethnically diverse group of prepubertal children with mor-
phologically normal brains and no clinical evidence of en-
docrinopathy. For ease of reference, we have tabulated these
data as mean values and both 90% and 95% reference ranges.
Volumetric data acquisition with MRI means that true vol-
umes can be measured from the imaging obtained. In our
experience, the manual technique for volume measurement
is not difficult, usually taking about 5 min/study. Our results
demonstrate that our method of volume measurement is
robust, providing a true volume that is independent of the
plane (sagittal or coronal) in which the data are
reconstructed.

Prepubertal pituitary volumes were found to increase with
age and appeared to be independent of gender. Independent
of age, there was no correlation found between either height
or BMI and pituitary volume.

Direct 3D assessment of pituitary volume represents a
significant advance over methods used in the past with 2D
datasets. In these studies, pituitary size was estimated using
a single linear measurement (usually pituitary height) (11–
14, 16–18, 20) or by volumes crudely calculated using for-

![FIG. 2. Concordance of volumes of the whole pituitary gland obtained from measurements from coronal vs. sagittal MRI reconstructions (the dashed line represents perfect concordance).](https://academic.oup.com/jcem/article/90/6/3274/2870556)

![TABLE 2. Geometric mean and reference intervals for pituitary gland volume by year of age (derived from mean regression model for log volume).](https://academic.oup.com/jcem/article/90/6/3274/2870556)
mulas adapted from the formula for the volume of an ellipsoid and originally used to estimate the volume of the sella turcica on plain films (10, 30). The vast variation in the shape of the normal pituitary gland, which we confirmed, means that neither linear measurements nor calculated volumes can give a true estimate of pituitary size. This is substantiated by the weak correlation we found between pituitary height and measured pituitary volume and between calculated volume and measured pituitary volume.

To date, the only other published normal data on whole pituitary volumes measured directly from volumetric data are the study by Takano et al. (23). This study included 199 Japanese children, 121 of whom were under the age of 10 yr. The mean prepubertal values and sds given were reported in relatively broad age groupings of 0–1, 1–4, and 5–9 yr. There appears to be a slight discrepancy compared with our results, in that the measured pituitary volume values reported by Takano et al. are slightly higher, particularly in the 5–9 yr age group. We are unable to explain the variability between these two studies other than to note that there were several differences between the two studies, namely, the different ethnic compositions of the study populations and the grouped age intervals. Data for anterior pituitary volumes have also recently been published (35) in a European cohort. This cross-sectional study by Marziali et al. (35) included 95 children under 10 yr of age, again plotted according to age. The volumes reported by Marziali et al. are only slightly greater than the pituitary volumes described in this study, notwithstanding the fact that only anterior pituitary volumes were measured. The significance of this is unknown given the limited data presented by Marziali et al. about the number of patients in each yearly age grouping and the variability noted in their volume by age (i.e. pituitary volume was reported to decrease between ages 2–3 and 7–8 yr). The difference may simply reflect wide CIs due to low patient numbers when substratified at yearly age intervals.

When using normal reference values, it is important to ensure that study data acquisition has been performed in a similar fashion as reference data. A recent publication (2) calculated pituitary volumes from 2D images using the DiChiro-derived formula and compared these crude estimates with the 3D true volumetric normative data reported by Takano et al. (23). We advocate using only volumetric MRI techniques and direct volume measurements when evaluating pituitary gland size, because these give the most reliable results.

In summary, we have presented normative, directly measured, 3D volumetric data for pituitary size in prepubertal children. Pituitary gland shape in this age group is highly variable; hence, we found that direct measures of pituitary volume do not correlate with either one-dimensional estimates (height) or 2D, indirectly calculated volumes. Our approach to direct measurement of pituitary volume appears to be robust, with assessment using either sagittal or coronal data reconstructions giving practically identical results. We recommend that with the advent of improved MRI technology and 3D data acquisition, indirect estimates of pituitary size and volume should be replaced by direct volumetric analysis.

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References
