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MR imaging of the pituitary gland in central precocious puberty

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Abstract. Cranial magnetic resonance imaging was performed in 17 children with central precocious puberty (CPP) and 19 aged-matched controls to compare the appearance of the pituitary gland. Gland size was measured on T1-weighted sagittal and coronal images. The gland was graded according to the concavity or convexity of the upper surface, and the signal intensity of the gland was assessed visually. The mean pituitary volume in 13 CPP children without hypothalamic tumor (292.6 mm^3) was significantly greater than that in normal controls (181.35 mm^3). The mean volume for the four CPP children with hypothalamic tumor was smaller (145.0 mm^3). Compared to controls, the upper pituitary surface in CPP patients appeared convex in a higher proportion. The anterior pituitary was isointense to pons in all patients and controls. Although the posterior pituitary bright spot was present in 14 controls and 11 CPP patients, none with hypothalamic tumor showed it.

Puberty is a transitional stage when a complex interplay of regulatory events results in reactivation of the hypothalamo-pituitary-gonadal axis, production of gonadal steroids, secondary sexual characteristics, accelerated growth, attainment of reproductive capacity, and psychosocial maturity. When the clinical features appear before the age of eight years in girls or nine years in boys, puberty is considered precocious [1, 2]. Precocious puberty is classified into heterosexual (when the physical changes are consistent with those of the opposite sex, such as virilization of female), and isosexual (changes consistent with phenotypic sex) types. The latter is further subdivided into those that are gonadotropin-releasing hormone (GnRH) independent (peripheral or incomplete type), and those that are GnRH-dependent (central or true type). In central precocious puberty (CPP), there is premature reactivation of the hypothalamo-pituitary-gonadal axis. Although the cause may not be found (80–90% in females and 50% in males), known associations include central nervous system tumors (especially hypothalamic), irradiation, infection, trauma, neurofibromatosis, and others [1, 2]. At our institution, cranial magnetic resonance (MR) imaging has been used to exclude possible intracranial abnormalities in the workup of children with CPP.

The pituitary gland has recently been shown by MR imaging to undergo transient hypertrophy during early infancy [3], normal puberty [4] and pregnancy [5, 6]. Although it has been stated that the pituitary gland is larger in precocious puberty [4], there has not been a systematic study of the appearance ot the pituitary gland in children with CPP compared with aged-matched normal controls. We report a comparative study of the appearance of the pituitary gland in a qualitative and quantitative manner in 17 children with CPP and in 19 normal age-matched controls.

Material and methods

From 1987 to 1991, 17 consecutive children with a clinical diagnosis of CPP underwent cranial MR imaging to exclude an intracranial lesion before hormonal therapy. There were 14 girls and 3 boys, ranging in age from 3.9 to 10.25 years with a mean age of 7.9 years. Five children had associated intracranial lesions including one of each with neurofibromatosis or hypothalamic hamartoma, and hypothalamic astrocytoma in three (two of whom were boys). The remaining 12 children were diagnosed with idiopathic CPP.

For the normal controls, 19 age-matched children (11 girls and 8 boys, ranging in age from 6 to 9.75 years with a mean age of 7.6 years) were found among the 324 children who had undergone cranial MR imaging between 1988–1990. Indications for their MR imaging include seizures in nine, peripheral neurologic symptoms in three, and miscellaneous in seven. All 19 MR studies were reported to be normal in the final report, and none of them presented with precocious puberty or other endocrine problems.

Eighteen studies (8 controls and 10 CPP) were performed with a 0.5-T superconducting system (Picker International, Highland-Heights, OH) and the rest (11 controls and 7 CPP) with a 1.5-T system (Signa; GE Medical Systems, Milwaukee, WI). Only the midsa-

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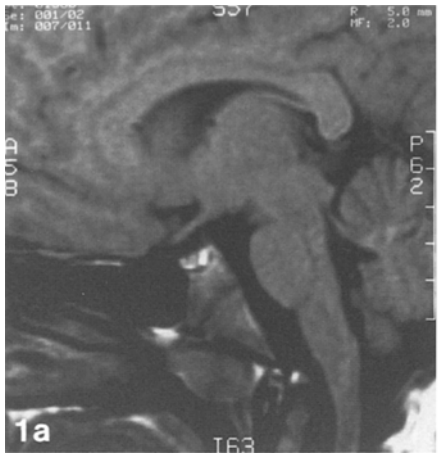

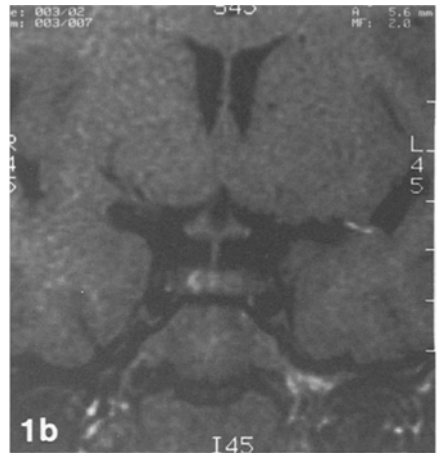

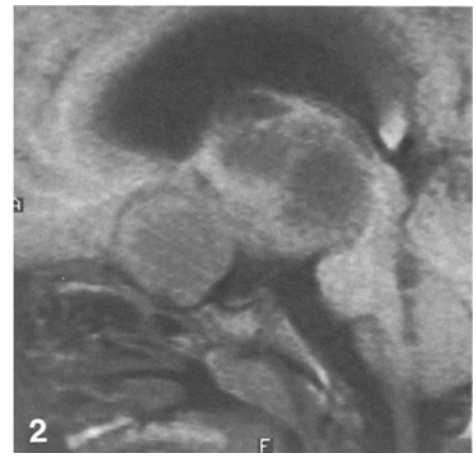

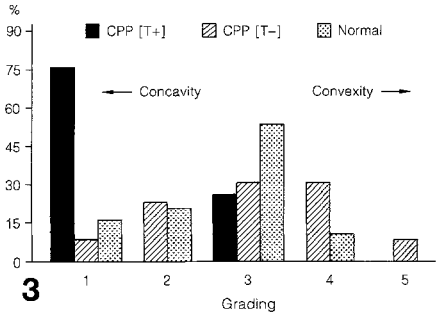

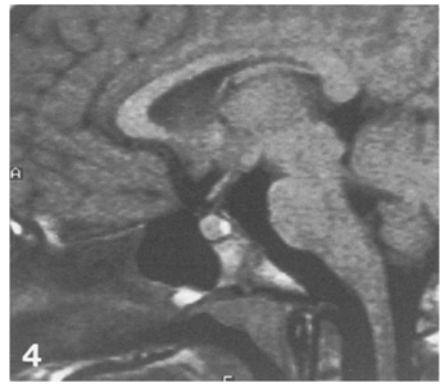

Fig. 1a, b. Sagittal (**a**) and coronal (**b**) spin-echo (SE 600/20) MR images of the pituitary in an 8-year-old girl with precocious puberty. The gland shows both the anterior (isointense with pons) and posterior lobes (bright spot) with a flat upper surface (grade 3)

Fig. 2. Sagittal spin-echo (SE 500/20) MR image of the pituitary in a 3.9-year-old boy with precocious puberty. A large hypothalamic astrocytoma is seen not directly compressing on the small pituitary (grade 1). Although the pituitary stalk is seen, the posterior bright spot is absent

Fig. 3. Comparison of the shape of the pituitary gland in CPP([T+] and [T−]) versus that in normal children on sagittal images. Percentages are computed for each of the three subgroups

Fig. 4. Sagittal spin-echo (450/20) MR image of the pituitary in a 10-year-old girl with precocious puberty. The gland is large and appears spherical (grade 5) with a well-defined posterior bright spot

gittal and coronal noncontrast T1-weighted images of the pituitary gland were used in the analysis. The spin-echo pulse sequence was used in all cases with a repetition time (TR) of 350–700 ms, an echo time (TE) of 11–26 ms, and a slice thickness of 3–5 mm.

In all cases, a radiologist (S.C.S.K) blinded to the hormonal results analysed the 2× magnified sagittal and coronal images on the image console (Fig. 1). For the size of the gland, the maximal length (L) and height (H) were measured from the sagittal image, and the maximal width (W) from the coronal image. The volume was estimated by the formula $V = {}^1/_2 L \times W \times H$. All measurements were subjected to statistical analysis using the one-way analysis of variance (ANOVA). All results were tabulated (Table 1) and expressed in mean ± SEM (standard error of the mean).

In all cases and normal controls, the shape of the gland was visually graded on the sagittal images using the scoring system described by Elster et al [4]. Using this scheme, grade 1 represents a gland with a markedly concave upper surface (> 2 mm of central depression). A grade 2 gland is minimally concave with < 2 mm of central depression. A grade 3 gland is one that is flat, and a grade 4 gland is minimally convex (< 2 mm central elevation). A grade 5 gland is markedly convex, appearing almost spherical. The relative distribution in the grading was plotted on bar graphs for all cases and controls.

In all CPP patients and controls, the signal intensity of the anterior lobe of the pituitary gland was assessed visually by using the adjacent pons as the reference. The presence or absence of a high signal intensity in the posterior lobe (posterior bright spot) was also noted.

Comparison was made between CPP patients with and without associated hypothalamic tumor. Results of these subgroups were also compared with those of normal controls.

Results

Comparing the mean size parameters of the pituitary gland in the 13 children with CPP not associated with a hypothalamic tumor (CPP[T−]) to the remaining four with associated hypothalamic tumor (CPP[T+]) and to the controls, there was no statistically significant difference in the mean L and W among the three groups (Table 1). However, the mean H and V were significantly larger ($p < 0.05$) in the CPP[T−] group when compared with the other two groups. While the mean V for the controls was 181.35 ± 14.73 cu mm (one-way ANOVA), the mean V for the 13 CPP[T−] children (12 idiopathic, and 1 with neurofibromatosis) was 292.6 ± 38.3 cu mm, and that for the four CPP[T+] children was 145.0 ± 18.18 cu mm. There was no statistically significant difference in all parameters between the CPP[T+] group and the normal controls.

To further examine the CPP[T+] group, the only patient with hypothalamic hamartoma and one of the three patients with hypothalamic astrocytoma had a normal pi-

Table 1. Size of pituitary gland in CPP versus normal (mean value in brackets)

Parameter	CPP[T +] (n = 4)	CPP[T −] (n = 13)	Normal (n = 19)
L (mm)	6.3–8.3 (7.28)	5.6–10.55 (8.52)	5.9–9.2 (7.69)
W (mm)	7.81–12.1 (10.2)	7.03–15.0 (11.5)	6.09–14.5 (9.96)
H (mm)	2.1–6.3 (4.2)	3.12–8.4 (5.84)	3.14–6.71 (4.67)
V (cu mm)	104.6–188.5 (145)	157.1–586 (292.6)	89.03–271 (181.35)

CPP[T −] = CPP not associated with hypothalamic tumor
CPP[T +] = CPP associated with hypothalamic tumor

tuitary size compared to controls. However, two children with hypothalamic astrocytoma had significantly smaller pituitary glands when compared to the controls. Although one of these two children received radiation therapy six years previously, the other had not received any treatment at the time of MR imaging (Fig. 2). In both cases, the pituitary gland was not directly compressed by the hypothalamic astrocytoma.

Children with CPP had a different relative distribution in the shape of the gland based on the grading system (Fig. 3). On sagittal images, while only 10.5% of the glands had a convex upper surface in normal controls, 38.5% of the glands were convex in the CPP[T −] subgroup (Fig. 4). None of the normal controls had a grade 5 pituitary gland. The majority (75%) in the CPP[T +] subgroup (including all three patients with hypothalamic astrocytoma) had a grade 1 pituitary gland.

The anterior lobe of the pituitary gland was visually isointense with the pons in all CPP children and normal controls. While the majority of children in the two study populations (14/19 controls and 11/17 of CPP children) showed a high signal intensity in the posterior lobe, none of the four children with associated hypothalamic tumor had this signal in the posterior pituitary or in an ectopic location.

Discussion

The advent of computed tomography (CT) and MR imaging has made it possible to study the appearance of the pituitary gland in various projections and populations [3–13]. Recent studies have shown developmental changes in the appearance of the pituitary gland with age. The gland has been shown to be relatively large in the first two months of infancy [3], during growth spurt in adolescence [4], and during pregnancy and postpartum [5]. The pituitary gland decreases in size with aging [7], and has been shown to be smaller in patients with growth hormone (GH) deficiency and in depressed patients [14–20].

Although it has been stated that the pituitary gland is larger in precocious puberty [4], there has not been a report of the appearance of the gland in CPP children compared to age-matched normal controls. In our study, the pituitary gland of the CPP[T −] group has a significantly larger mean H and V when compared to those of the CPP[T +] group and the normal controls. The size of the gland in the CPP[T +] group is either normal or small. The smaller pituitary gland can be attributed to irradiation for an astrocytoma in one and possibly a functional effect of the hypothalamic astrocytoma in the other.

Early studies of the pituitary gland using high-resolution CT suggested that a gland with a convex upper border was abnormal [21–22]. However, subsequent studies with CT and MR imaging have shown that this appearance may be seen during puberty or pregnancy probably due to physiologic hypertrophy [8, 23]. In our study, the findings of a larger gland size and a higher proportion of children with CPP showing a convex upper pituitary outline suggest that the gland in this group of children undergoes hypertrophy similar to that in normal puberty. This supports the concept that CPP results from reactivation of the hypothalamo-pituitary-gonadal axis in a manner similar to that observed in normal puberty, but occurs prematurely.

Although a precise description of the role of each of the hormonal mediators (such as GH and sex steroids) in the pubertal growth spurt remains unclear, there is an association between GH deficiency (with a smaller gland) and precocious puberty [24]. The small pituitary gland with a markedly concave upper border (grade 1) seen in our few patients presenting with precocious puberty (also shown by endocrine studies to have growth hormone deficiency) supports this clinical association. Our study also shows that the presence of a pituitary gland of normal size does not exclude CPP.

MR imaging of the pituitary gland in infancy has shown increased signal intensity in the anterior lobe of the gland (compared to that of the pons), possibly due to an increase in the amount of endoplasmic reticulum and the degree of protein synthesis during active physiologic growth [3]. Our series representing a different age range does not show this finding. The significance of the absent posterior bright spot (either orthotopic or ectopic) in CPP children associated with hypothalamic tumor is unknown. None of our case population or normal controls showed symptoms or signs of neurohypophyseal deficiency, which has been shown to be associated with absence of the posterior bright spot or with the presence of an ectopic bright spot [15–19, 25]. Since this signal intensity may not be detected in all normal controls, it is debatable whether one needs to evaluate posterior pituitary function. Further studies with particular attention paid to technique, such as slice thickness and the direction of the frequency encoding gradient, are needed to clarify this interesting question [26].

In conclusion, we have shown a significant difference in the size and shape of the pituitary gland in children with CPP[T −] compared to CPP[T +] and age-matched normal controls using MR imaging. Since hypothalamic tumors were found in two of the three boys with CPP, cranial MR imaging is particularly important in the evaluation of CPP in boys.

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