MR Assessment of Pituitary Gland Morphology in Healthy Volunteers: Age- and Gender-Related Differences

P. Murali Doraiswamy,[1] Jonathan M. Potts,[3] David A. Axelson,[1] Mustafa M. Husain,[5] Scott N. Lurie,[1] Chul Na,[1] P. Rodrigo Escalona,[1] William M. McDonald,[1] Gary S. Figiel,[4] Everett H. Ellinwood, Jr.,[1] Orest B. Boyko,[2] and K. Ranga Krishnan[1,6]

PURPOSE AND METHODS: High-field MR images at 1.5 T were used to characterize the effects of age and gender on pituitary size and shape in a sample of 71 adult volunteers (40 females), aged 21 to 82 years. **FINDINGS:** For all subjects, age was inversely correlated with pituitary height ($r = -.43$, $P < .0002$) and cross-sectional area ($r = -.35$, $P < .0028$). Age-specific gender differences were also present in pituitary height and area. A convex upper pituitary margin was more common in females ($P = .002$) and younger subjects ($P = .009$). **CONCLUSIONS:** This study confirms that aging is accompanied by gender-specific changes in pituitary size and shape, and provides normative data that may facilitate evaluation of the pituitary gland in neuroendocrine disorders.

Index terms: Pituitary gland; Pituitary gland, magnetic resonance

AJNR 13:1295–1299, Sep/Oct 1992

MR is important in assessing the in vivo shape (1–4), dimensions (2, 5–7), and pathology (8) of the pituitary gland. Prior MR studies have characterized the maturation of the pituitary gland during early childhood (7) as well as during puberty (1). Hayakawa et al (7) studied 94 patients, newborn to 15 years old, and showed that, except for growth spurts in the 1st year and between the 10th and 15th years, the pituitary gland showed linear growth. Elster et al (1), in an elegant study of 169 children and adolescents, confirmed Peyster's hypothesis (9) that the pituitary gland undergoes physiologic hypertrophy during puberty. This, they suggested, is manifested in girls by a significant enlargement in pituitary size and the frequent presence of a spherical or convex upper pituitary margin, whereas the glands of teenage boys undergo a transformation in size only.

Two recent MR studies (7, 10) have examined age-related changes in the adult pituitary gland. Using a low field (0.35 T) MR, Hayakawa et al (7), in 49 patients and seven volunteers aged 16–60 years, found that pituitary gland height and cross-sectional area were both less for subjects over 50 years of age than for those under 40 years of age. Suzuki et al (10) studied a group of 213 patients and showed that pituitary height decreases with increasing age after the age of 20 years.

Since both these studies were based on patient populations rather than healthy volunteers, we undertook a large cross-sectional MR study of pituitary morphology in adult community volunteers. In a preliminary report on 35 healthy volunteers (5), we found a significant age-related decline in pituitary gland cross-sectional area and height, although the limited sample size did not permit age-specific subgroup comparisons.

The present study provides normative data on pituitary size and shape in an expanded sample

Received May 1, 1991; revision requested July 31; revision received on August 21; accepted after additional revision November 27.

This work was supported by NIMH Grant MH-44716, MH-42210, and the Stanley Fellowship.

[1] Department of Psychiatry, Duke University Medical Center, Durham, NC.

[2] Department of Radiology, Duke University Medical Center, Durham, NC.

[3] Department of Radiology and Nuclear Medicine, Medical University of South Carolina, Charleston, SC.

[4] Department of Psychiatry, Washington University School of Medicine, St. Louis, MO.

[5] Department of Psychiatry, UT-Southwestern School of Medicine, Dallas, TX.

[6] Address reprint requests to Ranga Krishnan, MD, Box 3215, Duke University Medical Center, Durham, NC 27710.

AJNR 13:1295–1299, Sep/Oct 1992 0195-6108/92/1305-1295

of 71 adult volunteers and further characterizes age- and gender-related differences in pituitary size and morphology.

Methods

Subjects

The study was approved by the Duke University Medical Center Institutional Review Board. Written informed consent was obtained from all subjects prior to their participation. All premenopausal women had a negative β-hCG test to rule out pregnancy. We studied 71 volunteers (40 females and 31 males), aged 21–82 years, recruited from the community and medical center health staff. None of the subjects had a current clinical indication for a brain MR and all were scanned for ongoing research studies. Efforts were made to recruit approximately equal numbers of males and females in each decade. All subjects were free of significant current neuroendocrine (except as specified below), neurologic, and psychiatric disorders as determined by history and physical examination. Ten subjects who had undergone a hysterectomy and two postmenopausal women on replacement estrogen were not excluded. One subject had thyroiditis 2 years ago, but his recent thyroid function tests and clinical exam were within normal limits. Four women had been (or were being) treated for hypothyroidism, one of whom (a 59-year-old) also reported a past history of amenorrhea following pregnancy. These subjects were included since all were judged on clinical grounds to be currently euthyroid and since reanalysis after exclusion of the latter four subjects revealed an essentially identical and highly significant relationship between age and pituitary height ($r = -.46$, $P < .0001$). The overall group of 71 subjects consists of 35 subjects who were included in our preliminary report (5) and an additional 36 subjects. Table 1 presents the composition of this group.

MR Acquisition and Pituitary Gland Measurements

MR was performed on a 1.5-T system. Sagittal images obtained using T1-weighted spin-echo pulse sequences were used for all measurements and data analysis. TR/TE/excitations/matrix/field of view/thickness (mm)/interscan gap (mm) were as follows: For the 36 new volunteer subjects, pulse sequence parameters were 500/20/.5/256×128/20/4/1. Parameters for 23 of the original 35 subjects were 500/20/1/256×128/20/5/2.5. For the remaining 12 subjects, parameters varied as shown below and as reported previously (5). Parameters were 500/20/2/256×128/20/5/2.5 for four subjects; 500/20/4/256×256/20/5/2.5 for two subjects; 500/20/1/256×192/20/5/2.5 for three subjects; 500/20/2/256×192/20/5/2.5 for one subject; 500/20/4/256×256/20/3/0 for one subject; 500/20/1/256×128/20/4/1 for one subject. The variations in the original group of subjects resulted from initial efforts to minimize acquisition time and improve visualization of other structures. These variations were unrelated to age (5). The imaging protocol for all 71 subjects also included a T1- and T2-weighted axial series. A T1-weighted contiguous coronal series was also obtained for the original 35 subjects, but not for the additional 36. All scans available were evaluated by a neuroradiologist to rule out macroadenomas and mass lesions. The lack of coronal images in some subjects or contrast enhancement prevented complete exclusion of microadenomas.

The sagittal and midsagittal images were graphically prescribed and selected at the time of image acquisition by identifying the sella using an axial series. The pituitary gland was measured for height, length, and cross-sectional area on the midsagittal image as shown in Figure 1 and as reported previously (2, 5). Pituitary height was measured as the maximum height drawn perpendicular to the floor of the sella. Length was the maximum anteroposterior diameter parallel to the floor of the sella. Linear measurements were obtained using the Measure Distance program available with GE Signa software on an offline console with twofold magnification of images. Pituitary area was measured using the ROI program on Signa software, without magnification, by manually tracing the outline of the gland with a tracball controlled cursor. The hyperintense area in the posterior portion of the gland (routinely seen on T1-weighted images) was included in the measurements (7). Subjects with a partially empty sella were not excluded since this condition is common in normal subjects (5, 6, 8).

TABLE 1: Distribution of volunteers by age and gender

Subject Age Range	No. of Females	No. of Males	Total No. of Subjects
20–29	5	6	11
30–39	7	5	12
40–49	5	5	10
50–59	6	2	8
60–69	8	5	13
70–82	9	8	17
Total	40	31	71

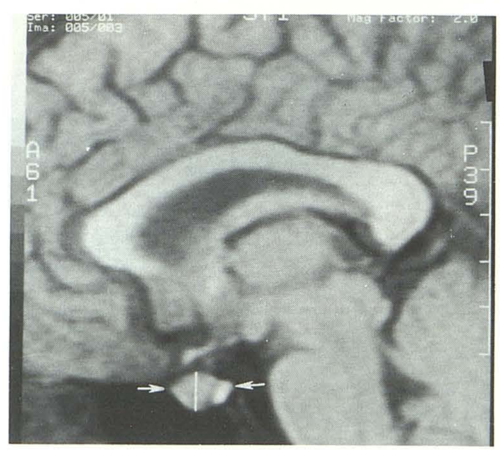

Fig. 1. *Central line* indicates pituitary height. *Arrows* indicate pituitary length. (Reproduced from Lurie et al (5).)

All measurements were obtained blinded to the age and gender of the subjects and represent the average of two independent ratings (P.M.D./S.N.L. for the initial 35 subjects and P.M.D./J.M.P. for the rest). Interrater reliability as assessed by Pearsons correlation coefficients was excellent: for pituitary height $r = .96$, $P < .0001$ (P.M.D./S.N.L. and P.M.D./J.M.P.); pituitary length $r = .93$ (P.M.D./S.N.L.) and .85 (P.M.D./J.M.P.), $P < .0001$; pituitary area $r = .88$ (P.M.D./S.N.L.) and $r = .92$ (P.M.D./J.M.P.), $P < .0001$. The superior margin (upper border) of the pituitary gland was classified into one of two categories: flat/concave (Elster grades 1/2/3) or convex/spherical (Elster grades 4/5) as per Elster et al (1). This was done by the consensus judgment of the raters who were blinded to the subject's age and gender. Similar methods have been used by the rater(s) in several previous studies (2, 4–6).

Statistical Analyses

Data was analyzed using PC-SAS (SAS Institute, Cary, NC). Pearson correlation coefficients were used to examine correlations between pituitary measurements and age. Spearman correlation coefficients were almost identical. Subjects were divided into under 50 years and over 50 years to enable comparison with our previous study. Differences between these two groups were analyzed using the Student's two-tailed *t*-test (since variances were almost identical). The nonparametric Kruskal-Wallis (χ^2 approximation) test yielded essentially identical results. We then further subdivided the sample into three groups: 21–40 years ("young or premenopausal"), 41–64 years ("transitional period or perimenopausal"), and 65 years or older ("elderly or postmenopausal"). Between groups, differences were tested using analysis of variance (ANOVA) (NPAR 1 WAY). Gender differences within each of the three groups were tested using the nonparametric Wilcoxon's 2-sample test (normal approximation with continuity correction of .5) because pituitary heights and areas showed greater variability in women than in men. The Fisher's Exact test (two-tailed) was used to compare the shape of the pituitary between those under 50 and those older, and between males and females.

Results

The mean (±SD) for age, pituitary height, length, and cross-sectional area for all subjects was 52 years (±18), 5.1 mm (±1.5), 10.6 mm (±1.5), and 38.3 mm^2 (±12), respectively. For all subjects, age was inversely correlated with pituitary height ($r = -.43$, $P < .0002$) and area ($r = -.35$, $P < .003$), but not length ($r = -0.12$, $P < .32$). Pituitary area correlated well with pituitary height ($r = .80$, $P < .0001$). Subjects under 50 years of age had larger pituitary height ($t = 3.2$, $df = 69$, $P < .003$) and area ($t = 2.5$, $df = 69$, $P < .01$) than subjects over 50 years (Table 2). Pituitary length did not differ between the young and old groups. Tables 3 and 4 show gender-specific comparisons. In male subjects, the age effects did not reach significance.

In female subjects, pituitary height declined between the ages of 20 and 65. This relationship was nonlinear beyond 65 years (Fig. 2). Eighteen of 40 women had pituitary heights greater than

TABLE 2: Pituitary gland morphology: the effect of age[a]

	Young (<50 yr)	Old (>50 yr)	*df*	t^b	*P*
Sample size	33	38			
Male/female	16/17	15/23	1		.45[c]
Mean (± SD) age (years)	34.2 ± 7.8	67.6 ± 7.2	−18.8	69	.000
Pituitary height (mm)	5.7 ± 1.4	4.6 ± 1.4	3.2	69	.002
Pituitary length (mm)	10.8 ± 1.2	10.5 ± 1.7	0.8	69	.42
Pituitary area (mm^2)	42.2 ± 12	34.9 ± 12	2.5	69	.01
Number of subjects with a convex pituitary	10 (30%)	2 (5%)			.009[d]

[a] All data are mean ± SD.
[b] Student's two-tailed *t*-test.
[c] χ^2 test ($\chi^2 = 0.58$).
[d] Two-tailed Fisher's Exact test.

TABLE 3: Pituitary gland morphology: the effect of age in females[a]

	Young (<50 yr)	Old (≤50 yr)	*df*	t^b	*P*
Sample size	17	23			
Age (years)	34.1 ± 7.8	66.6 ± 7.5			
Pituitary height (mm)	6.1 ± 1.7	4.7 ± 1.5	38	2.8	.01
Pituitary length (mm)	10.8 ± 1.1	10.4 ± 1.7	37.2	0.8	.44
Pituitary area (mm^2)	45.8 ± 13.7	36.5 ± 13.3	38	2.2	.04

[a] All data are mean ± SD.
[b] Student's two-tailed *t*-test.

TABLE 4: Pituitary gland morphology: the effect of age in males[a]

	Young (<50 years)	Old (≤50 years)	*df*	t^b	*P*
Sample size	16	15			
Age (years)	34.3 ± 8.0	69.1 ± 6.6			
Pituitary height (mm)	5.2 ± 0.9	4.4 ± 1.2	29	2.0	.06
Pituitary length (mm)	10.8 ± 1.4	10.7 ± 1.7	29	0.3	.76
Pituitary area (mm^2)	38.3 ± 9.3	32.5 ± 8.5	29	1.8	.08

[a] All data are mean ± SD.
[b] Student's two-tailed *t*-test.

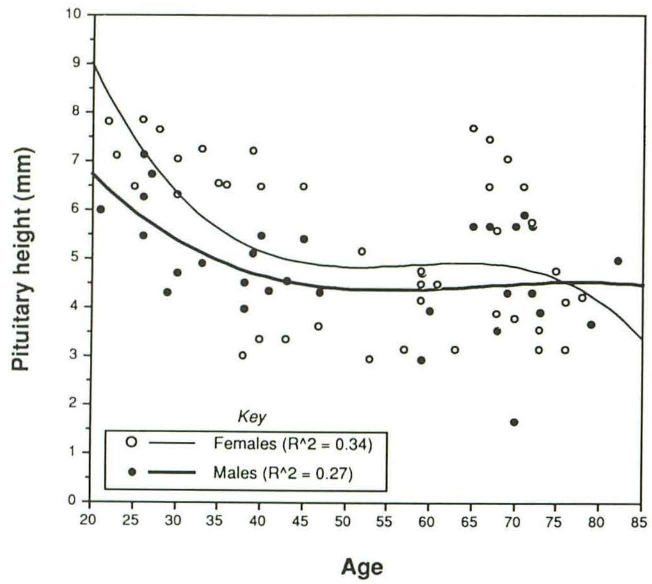

Fig. 2. Age versus pituitary height.

6 mm and of these, 10 (25%) exceeded 7 mm. Twelve of 14 (81%) women in the 20–40 year range had pituitaries that exceeded 6 mm in height and of these, seven (58%) exceeded 7 mm. In the 41–64 year range, only one (10%) of 11 exceeded 6 mm. Five of 15 women (33%) in the 65–78 year range had pituitary heights that exceeded 6 mm and of these, three (20%) exceeded 7 mm. ANOVA confirmed the highly significant differences in pituitary height between the three groups ($f = 8.3$, $P < .001$). Pituitary heights for women in the 20–40 year ranges were larger than women in the older age groups ($P < .05$). Pituitary heights in women age 30–39, 40–49, and 60–69 years showed considerably greater variability than males of similar age (Table 5).

In male subjects, also, pituitary height declined between the ages of 20 and 65 (Fig. 2), although age effects were clearly less prominent than that observed among women. Only three of 31 (10%) males (all three within the 20–30 age range) had pituitary heights greater than 6 mm and of these, only one exceeded 7 mm. Differences in pituitary heights between the 20–40, 41–64, and 65 plus groups did not reach significance ($f = 2.8$, $P < .08$).

Age-specific gender differences were significant in the 20–40 age group (Rank Sum = 114; Wilcoxon's test, $P < .01$) with larger pituitary heights among female subjects. Visual examination of the upper pituitary margin revealed gender differences. A convex upper pituitary margin was present in 11 females, but in only one male ($P < .0016$). Nine females below 50 years (53%) had a convex upper margin compared with two females over 50 years (9%) of age.

There were no group differences between the original 35 subjects and the additional 36 in pituitary measurements.

DISCUSSION

The main findings were as follows: Pituitary height and cross-sectional area declined with increasing age in both males and females between the ages of 20 and 65. This decline was highly significant in women, but not in men. Female subjects in the 20–40 age group had larger pituitaries than males of similar age. Young female subjects also showed a greater prevalence of a convex upper pituitary margin than males of all ages and older females. In the 30–39 and 40–49 age groups, the variability in pituitary heights was approximately threefold greater in female than in male subjects.

These results are consistent with our preliminary report (5). The mean dimensions of pituitary height in our volunteer subjects are similar to those reported from coronal CT (9, 11, 13) and midsagittal MR (7) studies in adult populations. The age-related decline in pituitary height and area is consistent with prior midsagittal MR studies in patient populations (7, 10). The prevalence of a convex upper pituitary border in female subjects under 50 years in the present study is similar to that reported previously by our group (5), by Swartz et al (44% of 50 women of childbearing age) (11), and recently by Elster et al (1). Our protocol, by not including coronal images in some subjects or contrast enhancement, was not optimal to completely excluding pituitary microadenomas. Coronal images for the two older women with pituitary convexity were normal, although we cannot exclude the presence of an associated microadenoma (probably nonfunctional) in these two subjects.

The functional significance of our findings remains speculative. Two previous studies have suggested that changes in the endocrine milieu may be reflected in pituitary morphology (6, 12). The increased prevalence of pituitary convexity and the larger pituitary heights in young women may reflect physiologic neuroendocrine differences between young women and men. This is further supported by the lower prevalence of pituitary convexity in older women than younger women. As Elster et al (1) and Peyster et al (9) suggest, puberty and adolescence are periods of

TABLE 5: Age- and gender-specific pituitary heights

Age Range (yr)	Pituitary Gland Height (mm) (mean ± SD)					
	n	Females	n	Males	n	Combined
20–29	5	7.4 ± 0.6	6	6.0 ± 1.0	11	6.6 ± 1.1
30–39	7	6.3 ± 1.5	5	4.6 ± 0.4	12	5.6 ± 1.4
40–49	5	4.6 ± 1.7	5	4.8 ± 0.6	10	4.7 ± 1.2
50–59	6	4.1 ± 0.9	2	3.8 ± 1.3	8	4.0 ± 0.9
60–69	8	5.7 ± 1.7	5	4.6 ± 1.0	13	5.3 ± 1.5
70–82	9	4.3 ± 1.2	8	4.5 ± 1.4	17	4.4 ± 1.2

physiologic pituitary "hypertrophy." This hyperplasia in young adult females appears to be related to endocrine changes associated with normal menarche and is relatively uncommon in older females or in males (1).

The decline in pituitary gland size between the second and sixth decades of life may likewise reflect the neuroendocrinology of aging and a physiologic pituitary "atrophy." We speculate that this may also be related to chronologic changes in the activity of the hypothalamo-pituitary-gonadal axis. It has been reported that basal serum concentrations of gonadotropic hormones (luteinizing hormone and follicle-stimulating hormone) decline after puberty up to the fifth decade (14). However, concentrations of these hormones then begin to increase dramatically in the fifth and sixth decades (14), apparently due to an age-related decline in circulating gonadal steroids (loss of feedback) and an increased "drive" from gonadotrophic-releasing hormone. Thus, speculatively, the larger pituitary heights observed in some of the elderly subjects over 65 years could reflect a compensatory hypertrophy following a greater loss of gonadal steroid feedback. Correlative endocrine studies as well as longitudinal MR studies are clearly needed to test this hypothesis and to elucidate the functional significance of differences in pituitary size and shape.

The neuroendocrine milieu reflects an important pathway in which patterns of diet, weight, activity, stress, and mood, as well as hypothalamic function are expressed (4). Whether such endocrine changes are reflected in pituitary size and shape deserves further study. MR provides a useful noninvasive means to help test such hypotheses. In conclusion, our study provides normative data on pituitary size and shape for a group of 71 adult volunteers. These data should facilitate further evaluation of pituitary morphology in neuroendocrine disorders.

Acknowledgments

We are grateful to Robert A. Burn, RT and the MR staff for their expert technical assistance.

References

1. Elster AD, Chen MY, Williams DW, Key LL. Pituitary gland: MR imaging of physiologic hypertrophy in adolescence. *Radiology* 1990;174:681–685
2. Doraiswamy PM, Krishnan KRR, Figiel GS, et al. A brain magnetic resonance imaging study of pituitary gland morphology in anorexia nervosa and bulimia. *Biol Psychiatry* 1990;28:110–116
3. Doraiswamy PM, Potts JM, Figiel GS, Boyko OB, Krishnan KR. MR imaging of physiologic pituitary gland hypertrophy in adolescence. *Radiology* 1991;178:284–285
4. Doraiswamy PM, Krishnan KRR, Boyko OB, et al. Pituitary abnormalities in eating disorders: further evidence from MRI studies. *Prog Neuropsychopharmacol Biol Psychiatry* 1991;15:351–356
5. Lurie SN, Doraiswamy PM, Husain MM, et al. In vivo assessment of pituitary gland volume with MRI: effect of age. *J Clin Endocrinol Metab* 1990;71:505–508
6. Krishnan KRR, Doraiswamy PM, Lurie SN, et al. Pituitary size in depression. *J Clin Endocrinol Metab* 1991;72:256–259
7. Hayakawa K, Konishi Y, Matsuda T, et al. Development and aging of brain midline structures: assessment with MR imaging. *Radiology* 1989;172:171–177
8. Chakeres DW, Curtin A, Ford G. Magnetic resonance imaging of pituitary and parasellar abnormalities. *Radiol Clin North Am* 1989;27:265–281
9. Peyster RG, Hoover ED, Viscarello RR, Moshang T, Haskin ME. CT appearance of the adolescent and preadolescent pituitary gland. *AJNR* 1983;4:411–414
10. Suzuki M, Takashima T, Kadoya M, et al. Height of the normal pituitary gland on MR imaging: age and sex differentiation. *J Comput Assist Tomogr* 1990;1491:36–39
11. Swartz JD, Russell KB, Basile BA, O'Donnell PC, Popky GL. High resolution CT appearance of the intrasellar contents in women of child bearing age. *Radiology* 1983;147:115–117
12. Gonzalez J, Elizondo G, Saldivar D, et al. Pituitary gland growth during normal pregnancy: an in vivo study using magnetic resonance imaging. *Am J Med* 1988;85:217–220
13. Wolpert SM, Molitch ME, Goldman JA, Wood JB. Size, shape and appearance of the normal female pituitary gland. *AJNR* 1984;5:263–267
14. Simpkins JW, Estes KS. Role of Monoaminergic Neurons in the age-related alterations in anterior pituitary secretion. In: Nemeroff CB, Dunn AJ, eds. *Peptides, hormones and behavior.* New York: Spectrum Press, 1984:823–863.