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Female Pituitary Size in Relation to Age and Hormonal Factors

Astrid Ellen Grams[a] Jens Gempt[c] Alexander Stahl[b] Annette Förschler[d]

Departments of [a]Diagnostic and Interventional Radiology and Neuroradiology, and [b]Nuclear Medicine, University Hospital Essen, University Duisburg-Essen, Essen, and Departments of [c]Neurosurgery, and [d]Neuroradiology, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

Key Words
Pituitary volume · Cranio-caudal diameter · Sella turcica · Contraceptives

Abstract
Background: It is well known that pituitary volume decreases with age; little is known about the influences of female cycle, intake of oral contraceptives, number of given births and duration of menopause on pituitary morphology. Furthermore, these contexts have never been examined with 3-tesla MRI, from which a high spatial resolution is expected. ***Methods:*** Ninety-four women from 18 to 80 years (mean 64 years) had to answer a questionnaire concerning their cycle situation, menopause, hormone intake and childbirths before receiving a 3-tesla MRI scan (Achieva, Philips, N.V.), including a T_1-weighted TSE sequence of the sella turcica. Pituitary volumes and diameters were measured with the software iplan® (BrainLAB, Feldkirchen, Germany). ***Results:*** A significant reverse correlation was found between age and pituitary volume ($p < 0.0001$)/cranio-caudal diameter ($p = 0.02$). In addition, an age-independent influence of oral contraceptives was found, indicating smaller pituitary sizes with hormone intake ($p = 0.003$). Cycle phase, number of given births and onset or duration of menopause had no effects on pituitary size. ***Conclusion:*** Three-tesla MRI suggests that pituitary volume not only decreases with age, it also seems to be related to long-term hormonal changes such as intake of oral contraceptives.

Introduction

In magnetic resonance imaging, especially in young female patients, the pituitary gland is often found with borderline large size. The perception of a borderline large or slightly enlarged pituitary may lead to a misdiagnosis of pituitary adenoma [1, 2]. This in turn may unsettle the patient and entail unnecessary diagnostics. For this reason, it is important to gather more knowledge concerning pituitary size variability in healthy women.

It is known that pituitary size depends on age, gender, certain diseases and even race [3]. Furthermore, hormone-related factors such as the intake of estrogens and pregnancy are known to influence pituitary morphology [4–7]. However, little is known about pituitary size variations with short-term, transient and long-term changes of the hormonal status in women.

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Astrid Ellen Grams
Department of Diagnostic and Interventional Radiology and Neuroradiology
University Hospital Essen, Hufelandstrasse 55
DE–45122 Essen (Germany)
Tel. +49 201 723 84512, Fax +49 201 723 1548, E-Mail astrid.grams@uk-essen.de

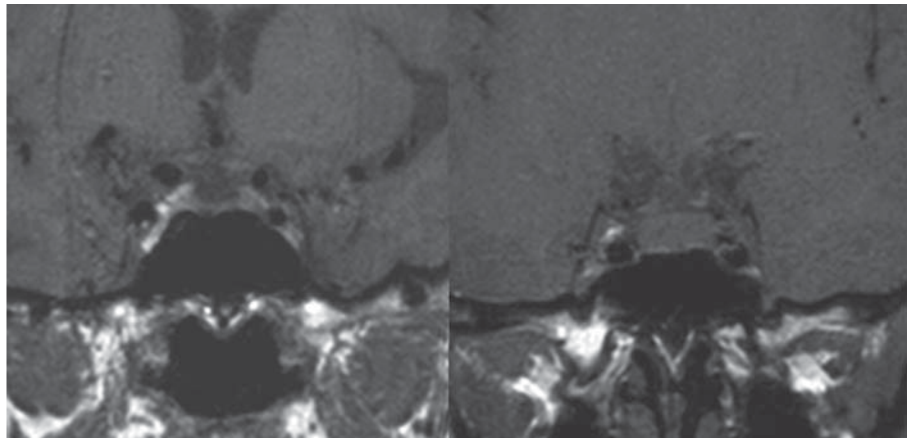

Fig. 1. Coronal T_1-weighted sequence covering the region of the sella turcica.

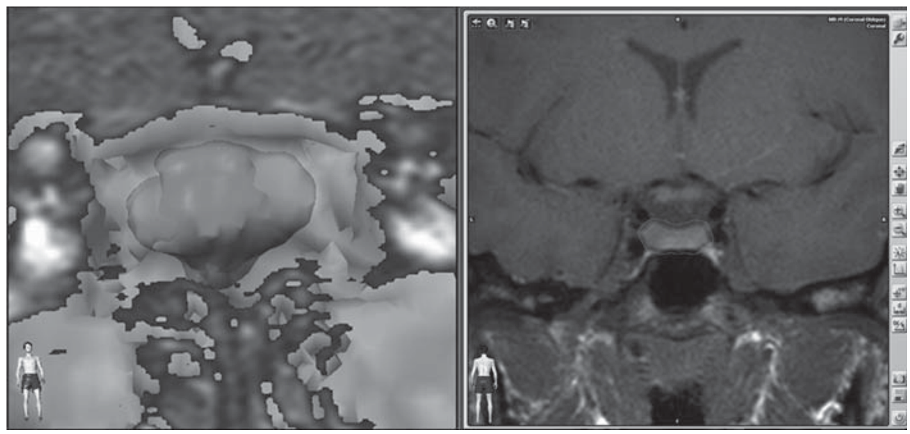

Fig. 2. Semiautomatic voxel-based pituitary volumetry with the software iplan cranial.

Table 1. Indications for clinical MRI scans

Diagnosis/question	Cases
Multiple sclerosis	26
Question for ischemia (without relevant territorial infarction)	26
Mild cognitive impairment (without relevant brain atrophy)	15
Headaches (without pathologies on MRI)	14
Meningioma (without relevant space occupation)	7
Cavernoma (without relevant prior bleeding)	6

This study investigates hormone-related factors which may have an influence on pituitary size including the female cycle, the number of given births and the intake of contraceptives. In addition, the known influence of age on pituitary size is evaluated and compared to other time-dependent factors including time since menopause and time since last giving birth.

Materials and Methods

Ninety-four women underwent an MRI scan for routine assessment of different symptoms and diseases (table 1) with the exclusion of prior brain surgery, symptoms of pituitary disease, hydrocephalus, thyroid disease, psychiatric disorders.

Age ranged from 18 to 80 years (mean 64 years). All women gave written informed consent and had to answer a short questionnaire concerning their menstrual cycle situation, time of menopause, hormone intake and given births.

Pituitary sizes were assessed for the following factors: cycle phase (eumenorrheic women only: menstrual phase day 1–4, proliferative stage day 5–14, secretory phase day 15–28); intake of oral contraceptives for more than 6 months; nulli-, uni-, di- and multiparous women; years since menopause, and years since last giving birth.

Pituitary size was assessed according to the following MRI technique: A T_1-weighted TSE sequence (TR/TE: 500/10 ms, slices: 12 × 2 mm, resolution: 0.35 mm^2, voxel size: 0.7 mm, scan time: 1:26 min) covering the region of the sella turcica (fig. 1) was performed with a 3-tesla MRI scanner (Achieva, Philips, N.V.). Pituitary dimensions (cranio-caudal diameter, right-left diameter and anterior-posterior diameter) were measured and pituitary volumes were calculated with the software iplan® cranial (BrainLAB, Feldkirchen, Germany) via a semiautomatic voxel-based

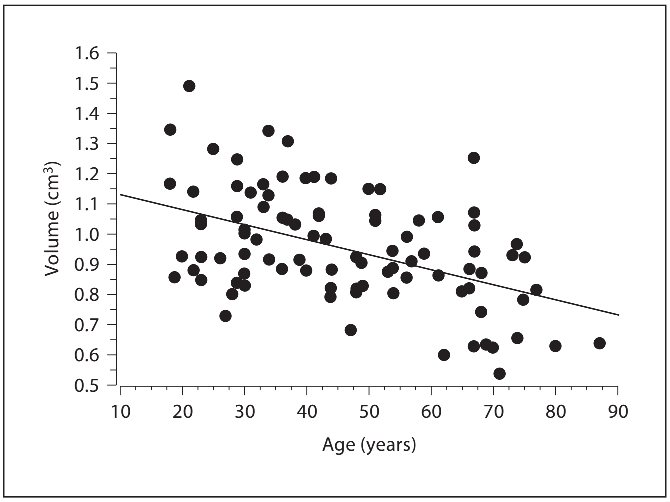

Fig. 3. Pituitary volume displays a significant decrease with age. Equation for line of regression: volume (cm^3) = 1.186 – 0.005 · age (years); $r^2 = 0.228$.

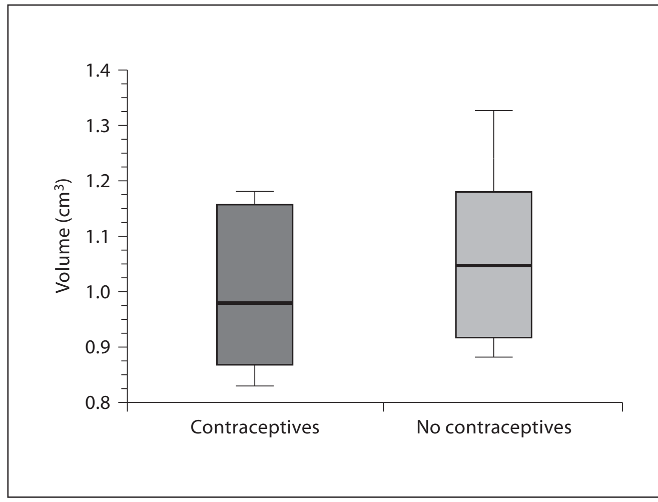

Fig. 4. Boxplots of pituitary volumes in women with and without intake of contraceptives, showing higher values in the 'no intake' group.

segmentation method (fig. 2), which is, for example, frequently used for tumor volumetry in radiation therapy planning [8]. Measurement was performed by 2 experienced neuroradiologists. With the Spearman correlation, an interrater reliability of r = 0.72 was achieved with a significance of $p < 0.0001$.

For statistical analysis, the software StatView (SAS Institute Inc., version 5.0.1) was used. ANOVA tests were applied to assess significant relationships between pituitary size and possible influencing factors. Where appropriate, age was entered as a cofactor into ANCOVA analysis in order to account for age-dependent influences. Furthermore, regressions, averages and standard deviations were calculated.

Results

A mean pituitary volume of 0.957 cm^3 (±0.184) and mean anterior-posterior, cranio-caudal and right-left diameters of 10.374 (±1.836), 5.336 (±1.466) and 14.239 mm (±1.943), respectively, were found. Pituitary volume correlated significantly with anterior-posterior, cranio-caudal and right-left diameters ($p < 0.01$ each).

A significantly negative correlation was found between age and pituitary volume ($p < 0.0001$; fig. 3) and – to a lower degree (p = 0.02) – between age and cranio-caudal diameter. No significant relationship was found between age and anterior-posterior or right-left diameters. For further analysis, pituitary volumes were used as the single target (dependent) parameter.

A significant difference for pituitary volumes was found between the two groups, one taking and one not taking contraceptives. Women with intake of contraceptives had slightly smaller pituitary volumes than women without (table 2; fig. 4). This influence was independent of age-related effects since women with intake were even younger than patients without (31 vs. 34 years).

When we corrected for age-dependent effects, no significant influence on pituitary volumes was found for: women in eumenorrhea versus women in amenorrhea; the three cycle phases; the groups nullipara, unipara, dipara and multipara; the time interval since the last childbirth, and the duration of menopause.

Table 2. Hormone-related group comparisons

	Cases	Pituitary volume cm^3 ± SD	Group comparisons
Intake of birth control pill (premenopausal only)			
Intake of contraceptives	18	0.995 ± 0.149	
No intake of contraceptives	31	1.055 ± 0.191	p = 0.003
Cycle phase			
I	7	1.087 ± 0.229	
II	27	1.034 ± 0.134	
III	13	1.072 ± 0.180	p = 0.35
Given births			
Nullipara	49	1.006 ± 0.210	
Unipara	26	0.885 ± 0.206	
Dipara	15	0.958 ± 0.152	
Multipara	4	0.729 ± 0.106	p = 0.32

Discussion

In this study, a significant decrease in pituitary volume with age was found. This relationship has also been described by other investigators [9–11]. The loss of volume is generally attributed to the decreasing levels of gonadal steroids after puberty [3]; furthermore, a loss of sensitivity of the hypothalamic-pituitary system to ovarian sex steroid feedback has been described, which might display a reason for this [12]. Although less close than pituitary volumes, cranio-caudal diameters of pituitary glands also decreased with age, as shown in the present study and prior ones [10]. Anterior-posterior and right-left diameters did not show correlation with age. Consequently, we considered pituitary volumes as the most useful target (dependent) parameter for the investigation of factors possibly influencing pituitary size.

Time-related factors other than age – such as years after menopause or years since last giving birth – had no influence on pituitary volumes when corrected for age. Thus, they were not considered as independent factors. For this reason, age was assumed to be the only known influence on pituitary volume in this study and used as a cofactor for the analysis of hormonal factors on pituitary volumes.

A significant reduction in pituitary volume was found in women who took oral contraceptives. However, this difference was marginal in a range of about 0.06 cm^3. In contrast, other hormonal factors such as female cycle phase and the number of given births had no significant influence on pituitary volumes. In earlier studies, an increase in pituitary volumes between 120 and 136% during pregnancy was found [6] (in comparison to nulliparous patients), with the largest volumes found immediately postpartum. A return to normal size between the first week and 6 months postpartum has been described [4, 5]. Furthermore, an alteration of pituitary function by some drugs, which are frequently applied in late pregnancy, was found [13]. In postmenopausal women, cranio-caudal diameters were found to be significantly larger in individuals with estrogen substitution, compared to no substitution [7]. These results seem to contradict present results as we described a volume loss with hormone intake. One explanation for this might be that most birth control pills do not only contain estrogens. However, as our sample of young women taking a birth control pill was small (n = 18), we did not try to distinguish different preparations; a larger sample should be examined to prove this correlation.

In addition to the above factors, pituitary hypertrophy was described in patients with hypothyroidism [14, 15]. In patients with depression and schizophrenia, influences on pituitary morphology were also described and attributed to a hypothalamic-pituitary-adrenal dysfunction [3, 16, 17]. Therefore, women with known thyroidal dysfunction or psychiatric diseases were excluded from the present study.

In addition, the applied slice thickness of 2 mm might have led to an inaccuracy of volume measurement, as the pituitary gland showed mean diameters of only $10 \times 5 \times 14$ mm; a sequence with a higher and isotropic resolution might have eliminated this limitation.

In conclusion, 3-tesla MRI suggests that hormone-related factors influence pituitary size. Based on our results and those in the literature, long-term hormonal changes such as hormone intake or pregnancy have an influence on pituitary volume. These changes in pituitary sizes seem to be reversible. Short-term changes such as the female cycle did not have any influence on pituitary volume.

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