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Age and sex related differences in normal pituitary gland and fossa volumes

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1. ABSTRACT

This study investigates the influence of age and sex on the volumes of the pituitary fossa and gland in 91 males and 108 females from Croatia who underwent magnetic resonance imaging of the endocranium for complaints not related to the pituitary gland. Isometric 3DT1 MPRAGE and 3DT1 MPR sequences were obtained on 1.5. Tesla and analysed on ISSA software. The volumes were obtained from the sum of all the areas multiplied by the thickness of the section. The mean volume of the pituitary fossa for males was 1111.1.4 mm^3, for females 1354.4.2 mm^3. Correlation analysis showed a significant negative correlation (P=0.0.09) between age of the patient, and pituitary volume. Age of the patient and free volume demonstrate a significant positive correlation (P=0.0.01) indicating that the amount of unoccupied space in the pituitary fossa significantly increases with age. Determining general morphological values, as well as variations of pituitary depth and the occupation of the fossa with the pituitary gland is of great help in everyday diagnostic and therapeutic approach.

2. INTRODUCTION

Dimensions and interactions of neighbouring anatomic structures i.e. the pituitary fossa (*fossa hypophyseos*) and pituitary gland (*hypophysis*) in relation to basic demographic characteristics such as age and sex is significant in clinical practice. This research is now possible owing to MR imaging and procedures, and is useful primarily because of safer neurosurgical access to the pituitary gland, particularly in pituitary gland tumour treatment. Defining a range of normal dimensions for the pituitary gland and fossa in healthy individuals is also essential for recognizing potential pathological changes in the pituitary gland.

So far, research has been carried out mostly on anatomical tissue samples. Veineratos *et al*. (1) measured the volume of the *sellae turcica* in 20 samples by making silicon moulds and placing them into gauge glass. The volume ranged between 460 mm^3 - 1570 mm^3, with a mean value of 835 mm^3. Sahni *et al*. (2) determined the weight of the pituitary gland while performing post mortem analyses. In males the measured weight increased until the 36 to 45 years old age group after which it decreased. In females, the weight of the pituitary gland increased from subadults to the age group of 16 to 17 years, after which it fluctuated. In females up to 35 year of age the weight of the pituitary gland was always higher than in men of the same age.

Computed tomography (3,4) and magnetic resonance allow functional testing of the changes in size (height, width, length, volume) of the pituitary gland in relation to age and sex (5-12). Lurie *et al*. (7) on a small number of individuals (aged 26 to 79 years) measured height, width and length of the pituitary gland on the sagittal and coronal MR T-1. Individuals above 50 years of age had a significantly lower height and volume of the pituitary gland compared to younger age groups. Interestingly, no significant differences in the size of the pituitary gland were found between males and females. Doraiswamy *et al*. (13) used High-field MR imaging at 1.5. T to determine the effects of age and sex on pituitary size and shape in a sample of 71 adults (40 females) aged between 21 to 82 years and in all of their subjects age was inversely correlated with pituitary height and cross-sectional area. Additionally, a convex upper pituitary margin was more common in females. Terano *et al*. (14) conducted research on the size of the pituitary gland in two groups of adult individuals. The mean age for the younger age group was 34, for the older age group 82 years. Their results showed that the size of the pituitary gland decreases with age. Similarly, they recorded a higher incidence of 'empty sella' in the older age category. Through MR imaging of 78 pregnant women Dinc *et al*. (15) found that the volume, height, width, and length of the pituitary gland, as well as the pituitary shaft increases during pregnancy. The highest values were recorded three days after childbirth. The highest increase was noted in the volume of the pituitary gland (as much as 120%), while the height of the pituitary gland showed a strong correlation to the stage of pregnancy. During normal development of the pituitary gland the measured pituitary volumes showed a growth spurt during puberty, which was more prominent in girls (16). Studies dealing with the size of the pituitary gland and fossa in various hormonal disorders, either of the pituitary, thyroid or adrenal gland, have also been published (17,18). In recent times more research has been conducted on the correlations between pituitary gland size and mental illnesses such as depression, schizophrenia, psychosis (19-22).

The previously mentioned research is uniform in the sense that there was always a control group of healthy individuals, and that females always exhibited a larger volume of the pituitary gland than males. In their large scale study DiChiro and Nelson (23) stated that the mean volume of the pituitary fossa is 654 mm^3, ranging from 450-1092 mm^3, but they did not define or quantify potential differences between males and females. The same authors state that the pituitary gland fills 81% of the pituitary fossa in adults, but only 76% in subadults. Using specialized software, MacMaster *et al*. (24) tested 77 males and 77 females aged from 7-35 years for MR voluminometry and concluded that females have a larger pituitary volume in the age group from 14-17 years, while in other age groups there were no differences between the sexes.

As is clear from these data, there is a consensus that pituitary fossa and gland dimensions vary between adults and subadults, as well as between males and females, and possibly that these differences are not uniformly present in all populations. With this in mind, the aims of this research are as follows: to analyze the effects of age and sex on the volume of the pituitary fossa, the volume of the pituitary gland, and on the amount of unoccupied space in the pituitary fossa (the so called "free volume") in a Croatian sample. This is the first time that such a demographic analysis of pituitary gland and fossa dimensions will be carried out on a Croatian sample, and the hope is that it will define sex and age specific anatomical standards for pituitary gland and fossa dimensions that will be useful in clinical and diagnostic procedures.

3. PATIENTS AND METHODS

3.1. Patients

Patients undergoing neuroradiological brain MR imaging in the University Hospital Center "Sestre Milosrdnice" in Zagreb, Croatia, form the study group for this analysis. Individuals diagnosed with tumours of any aetiology or localisation, as well as patients diagnosed with any kind of pituitary gland pathology were excluded from the research group. Additionally, patients suffering from any type of systemic disease such as rheumatoid arthritis, lupus etc. (in other words patients receiving corticosteroid therapy) were also excluded. None of the analyzed female patient were pregnant or breastfeeding. The group did not include acute trauma patients either. If during the MRI diagnostic procedure any pathological condition in the cranial cavity was suspected, the patients were excluded from the research group. All of the patients gave informed written consent for their MR imaging to be used in the research.

3.2. Methods

All patients underwent neuroradiological imaging of the endocranium on a 1.5. Tesla (Siemens Avanto) MR device. Isometric 3D T1 MPRAGE sequence was obtained. Minimal protocol of MR sellar region included T-1 weighted image in sagittal and coronal plane without contrast, with the thickness of the section of 1.0. mm in high resolution (image section 16 – 20 cm, matrix 256-512) applied. On given sagittal layers T1 MPR thickness of 1.0. mm the bone borders of the pituitary fossa and border of pituitary gland were marked. ISSA software was used to determine the surface area in square mm. The volume of the fossa was obtained by multiplying the sum of all measured areas

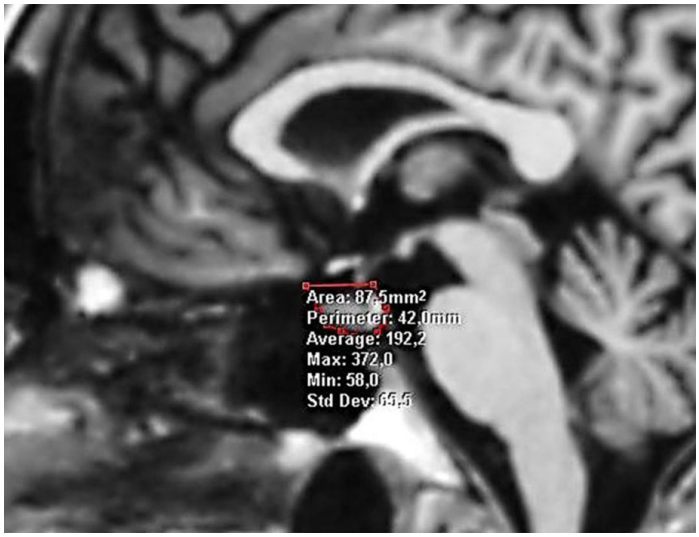

Figure 1. On given sagittal layers T1 MPR thickness of 1.0. mm the borders of the pituitary fossa were marked. ISSA software was used to determine the surface area in square mm. The volumes of pituitary fossa were obtained from the sum of all the areas measured multiplied by the thickness of the section.

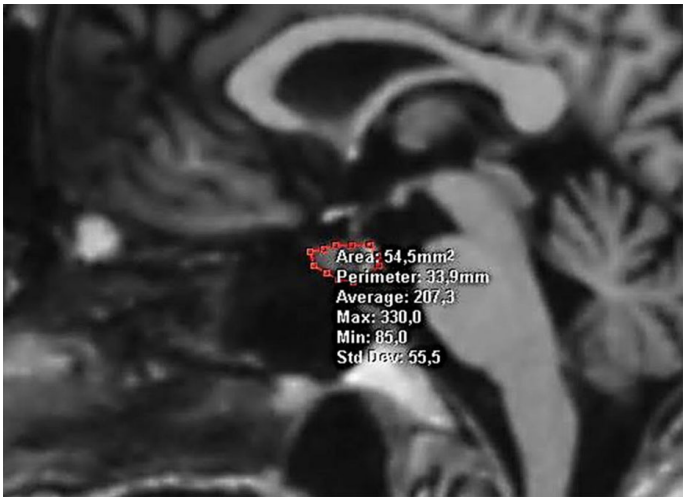

Figure 2. On sagittal T1 MPR images (thickness of the layer 1 mm) the borders of the pituitary gland were marked. ISSA software was used to determine the surface area in square mm. The volumes of pituitary gland were obtained from the sum of all the areas measured multiplied by the thickness of the section.

by the thickness of the section/layer (fig. 1). The volume of the pituitary gland was obtained in the same way as the volume of the fossa (fig. 2).

3.3. Statistical analyses

SAS 9.1.3. (SAS Inc. Cary, NC, USA) statistical software was used for data analysis. All measurements gathered during the research were summarised with descriptive statistics. All dependent variables were analysed with multivariate tests. Fossa volume, pituitary gland volume and occupations of the fossa with the pituitary gland were analyzed with multiple linear regression analysis. Analyses were done by treating age as a continuous variable, as well as a discrete variable (age groups). Statistical significance was set at 0.0.5.

4. RESULTS

The research was conducted on a group of 199 adults (91 males and 108 females) between 20 and 79 years of age. Patients were selected within a specific time period of two years.

Age categories were determined in the following way: 20-29 years old, 30-39, 40-49, 50-59, 60-69 and 70-79 (Table 1).

Table 1. Total sample according to sex and age

Age (yrs)	Males	Females	Total
20-29	12	18	30
30-39	17	20	37
40-49	19	18	37
50-59	19	24	43
60-69	14	20	34
70-79	10	8	18
Total	91	108	199

Table 2. Descriptive statistics for pituitary fossa, pituitary gland and free volume by sex

Site	Sex	N	Mean value (in mm^3)	SD	Minimum (in mm^3)	Maximum (in mm^3)
Pituitary fossa	Males	91	1111.14	327.37	466	2094
	Females	108	1354.88	365.09	680	2365
	Total	199	1243.42	368.19	466	2365
Pituitary gland	Males	91	505.40	140.57	207	1050
	Females	108	643.31	172.62	264	1031
	Total	199	580.24	172.71	207	1050
Free volume	Males	91	605.74	248.18	244	1421
	Females	108	711.58	292.26	221	1603
	Total	199	663.18	277.40	221	1603

Table 3. ANOVA analysis of the differences between males and females

Volumes		Sum of squared errors	DS	Median of squared errors	F	Significance
Pituitary fossa	Between samples	2934226.7	1	2934226.685	24.178	0.000
	Within a sample	23907913	197	121359.962		
	Total	26842139	198			
Pituitary gland	Between samples	939264.19	1	939264.192	37.252	0.000
	Within a sample	4967052.2	197	25213.463		
	Total	5906316.4	198			
Free volume	Between samples	553241.45	1	553241.455	7.423	0.007
	Within a sample	14682836	197	74532.164		
	Total	15236078	198			

F: ???? F is the 'F' statistic commonly used in ANOVA analysis to determine if a test is significant. It is if the Significance is less than 0.05. It's value corresponds to the = variance of the group means / mean of the within group variances. It is very commonly used and in my opinion should not need an explanation.

4.1. The volume of pituitary fossa, pituitary gland and free volume by sex

The mean volume of the pituitary fossa for males was 1111.1.4 mm^3, for females 1354.4.2 mm^3. The mean volume of the pituitary gland for males was 505.4.0 mm^3 and for females 643.3.1mm^3. That mean free volume for males was 605.7.4 mm^3 while females had 711.5.8 mm^3. At the level of the complete sample, females exhibited significantly higher mean values for the volumes of pituitary fossa, pituitary gland and free volume (Tables 2 and 3).

4.2. Volume of the pituitary fossa, pituitary gland and free volume by age

Analysis of the total sample (Table 4) shows that there was a slight positive correlation between the age of patients and the volume of the pituitary fossa in other words that the volume of the fossa increased

Table 4. Volumes of the pituitary fossa, pituitary gland and free volume for the total sample by age groups

Age (yrs)		Volumes (in mm^3)		
		Pituitary fossa	Pituitary gland	Free volume
20 – 29	Mean value	1169.27	623.67	545.60
	N	30	30	30
	SD	268.439	145.801	175.652
30 – 39	Mean value	1259.93	609.87	650.07
	N	37	37	37
	SD	262.521	163.218	188.854
40 – 49	Mean value	1234.71	599.45	635.27
	N	37	37	37
	SD	324.868	174.374	222.764
50 – 59	Mean value	1227.53	549.15	678.38
	N	43	43	43
	SD	432.430	199.126	310.267
60 – 69	Mean value	1253.81	553.11	700.70
	N	34	34	34
	SD	453.587	170.731	361.664
70 - 79	Mean value	1369.31	533.01	836.30
	N	18	18	18
	SD	443.982	153.287	331.138
Total	Mean value	1243.42	580.24	663.18
	N	199	199	199
	SD	368.193	172.713	277.398

with age, but this trend was not significant (Pearson's correlation= 0.0.83, P = 0.2.44). However, correlation analysis at the level of the complete sample did indicate a significant negative correlation (Pearson's correlation = -0.1.85, P = 0.0.09) between the age of the patients and pituitary gland volume. Similarly, analysis between age and the "free volume" in the pituitary fossa demonstrated a significant positive correlation (Pearson's correlation = 0.2.25, P = 0.0.01), indicating that the "free volume" in the pituitary fossa significantly increased with age. At the level of the total sample, pituitary gland volume decreased from 623.6.7 mm^3 in the youngest age group (individuals aged from 20-29 years of age) to 533.0.1 mm^3 in the oldest age group from 70-79 years of age (Table 4). ANOVA analysis showed that this decrease of pituitary gland volume is significant (P = 0.0.13 and P = 0.0.01).

Correlation analyses between fossa and pituitary gland volumes, and the specified age groups (Table 5) show a weak negative correlation between these variables in males that is not significant. In contrast to this, correlation analyses between pituitary gland, fossa, and free volume and age categories in females (Table 6) show a significant increase of the volume of the pituitary fossa with age, accompanied by a significant decrease of pituitary gland volume and a corresponding significant increase of unoccupied volume in the pituitary fossa.

5. DISCUSSION

Defining normal biological variation in the morphological shape and size of the pituitary gland and fossa is crucial for identifying potential pathological changes. Discrepancies in pituitary gland and fossa measurements and dimensions resulting from the ways in which particular analysis have been designed, the age composition of the sample, and the populations on which the analysis was performed are present in the available medical literature. To this end we have measured and analyzed the dimensions and volumes of the pituitary gland and fossa, and the space between them in a modern Croatian sample in order to determine standards for clinical investigations that will be applicable in Croatia (25). Our results are then compared to the results of studies conducted by other authors (23, 26-29) in order to determine potential dissimilarities or congruence. In the available studies the volume of the pituitary fossa ranged from 754 mm^3 to as much as 1230 mm^3 (26-29). De Chiro and Nelson (23) reported a range from

Table 5. Volumes of the pituitary fossa, pituitary gland and free volume for males by age groups

Age (yrs)		Volumes (in mm^3)		
		Pituitary fossa	Pituitary gland	Free volume
	Mean value	1054.40	539.20	515.20
	N	12	12	12
20 – 29	SD	246.776	106.490	206.677
	Mean value	1195.02	508.03	686.99
	N	17	17	17
30 – 39	SD	228.278	124.310	189.672
	Mean value	1113.32	535.62	577.70
	N	19	19	19
40 – 49	SD	264.461	126.156	172.005
	Mean value	1142.31	503.80	638.51
	N	19	19	19
50 – 59	SD	475.303	200.665	350.087
	Mean value	1007.48	473.69	533.79
	N	14	14	14
60 – 69	SD	390.050	143.091	277.583
	Mean value	1118.37	450.37	668.00
	N	10	10	10
70 – 79	SD	238.275	77.089	210.884
	Mean value	1111.14	505.40	605.74
	N	91	91	91
Total	SD	327.372	140.575	248.176

Table 6. Volumes of the pituitary fossa, pituitary gland and free volume for females by age groups

Age (yrs)		Volumes in mm^3		
		Pituitary fossa	Pituitary gland	Free volume
	Mean value	1245.86	679.99	565.87
	N	18	18	18
20 – 29	SD	260.759	143.288	154.615
	Mean value	1315.11	696.43	618.68
	N	20	20	20
30 – 39	SD	282.3.2	142.469	187.152
	Mean value	1362.85	666.82	696.03
	N	18	18	18
40 – 49	SD	339.982	195.397	257.188
	Mean value	1295.00	585.06	709.94
	N	24	24	24
50 – 59	SD	392.327	194.549	278.423
	Mean value	1426.24	608.71	817.53
	N	20	20	20
60 – 69	SD	420.995	169.457	373.586
	Mean value	1683.00	636.31	1046.69
	N	8	8	8
70 - 79	SD	450.894	165.744	343.613
	Mean value	1354.88	643.31	711.58
	N	108	108	108
Total	SD	365.093	172.625	292.262

489 to 1229 mm^3 (466 to 2094 mm^3 for males and 680-2365 mm^3 for females).

The results of our measurements of the volume of the pituitary gland in a Croatian sample fall within this broad range and therefore coincide with results published by other authors. The mean value of the pituitary gland according to Ottaviani (27) is 570 mm^3, according to Busch (30) 660 mm^3, while De Chiro and Nelson (23) report the mean value of 608 mm^3. Patients included in our study exhibit a mean value for the volume of the pituitary gland of the whole sample is 580.2.4 mm^3 (505.4.0 mm^3 for males and 643.3.1 mm^3 for females). It is of interest to note that the results obtained from our study of the volume of the pituitary gland are similar to previously published results in medical literature, while the published results pertaining to the volume of the pituitary fossa show a range of values that is too large to be suitable for comparison with the results obtained in our study.

With regards to the occupied space in the pituitary fossa, there are conflicting opinions in the available medical literature (23, 27, 30). Ottaviani (27) found that the mean volume of the pituitary fossa was 1230 mm^3, while the mean volume for the pituitary gland was 570 mm^3, indicating that the pituitary gland occupies slightly less than half of the pituitary fossa. Marx *et al*. (29) report a mean value of pituitary fossa volume of 950 mm^3 with a mean value of pituitary gland volume of 600 mm^3, which would mean that the pituitary gland occupies roughly 63% of the pituitary fossa. In our research the mean value for the volume of the pituitary fossa was 1234.4.2 mm^3 that coupled with a mean pituitary gland volume of 663,18 mm^3, indicated that the pituitary gland occupies approximately 50% of the pituitary fossa.

Basic descriptive statistics of the sample analyzed in our study showed that, at the level of the complete entire sample, females exhibited higher mean values for the volume of the pituitary fossa, the pituitary gland, as well as for the free volume.

Results differing form this can be found in the available medical literature. Most authors report no differences between the sizes of the pituitary fossa in the sexes (31-34). With respect to the size of the pituitary gland, most publications report larger pituitary glands in females (2, 13, 15, 20, 35-37). Our research additionally shows a correlation between the age of the individual and the volume of the pituitary fossa, gland and free volume that results from a significantly decreases of the volume of the pituitary gland with age. This is in contrast to some publications that noticed no increase of the pituitary fossa with age (31-34). Additionally, several publications have dealt with the problem of the decrease of the volume of the pituitary gland in correlation to age (14,35). Related to this phenomenon is Terano *et al*. (14) assertion that the so-called 'empty sella' is more often found in older individuals. The 'empty sella' syndrome has previously been described in neuroradiological publications (38,39). A completely empty pituitary fossa is defined as a pituitary fossa in which there is no pituitary tissue, but rather the fossa is completely or partially filled with cerebrospinal fluid. This can be interpreted as a depletion of neurosecretory granules of the posterior pituitary lobe and the disappearance of the T1 measuring signal. Empty fossa raises the problem of whether this represents a normal anatomical phenomenon, potentially related to advanced age, or if the condition is the result of a disease process such as idiopathic intracranial hypertension.

What is obvious is that that pituitary gland volume is subject to dynamic changes in response to different factors. The volume increases in puberty, pregnancy or because of the exogenous estrogens (40) and there is some evidence that it increases in psychotic disorders (40). The clinical meaning of the differences that we observed in our study are beyond the scope of this paper but the knowledge that dimensions vary with age holds major potential interest.

6. CONCLUSION

Magnetic Resonance Imaging proved to be an appropriate radiological method in the investigations of the volumes of the pituitary fossa and gland as well as the relationship of the surrounding anatomical structures. Our analysis showed that at the level of the complete Croatian sample females have higher mean values for pituitary fossa volume, volume of the pituitary gland and volume of the unoccupied space left in the pituitary fossa. Our results also demonstrate that pituitary gland volume decreases with age, which simultaneously increases the unoccupied space within the pituitary fossa. This is the first time that these measurements were performed for a Croatian population. Determining general morphological values, as well as variations of pituitary depth and the occupation of the pituitary fossa with the pituitary gland is of importance in everyday diagnostic and therapeutic approaches to ailments of the pituitary gland, and the sellar region in general.

7. ACKNOWLEDGEMENT

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