Original article

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RADIOMORPHOMETRIC ANALYSIS OF HUMAN PITUITARY GLAND DURING THE AGING PROCESS

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During life, there are significant changes in the function of the hypothalamic-pituitary axis and its relationship to other endocrine glands in the body, which can affect the external and internal gland morphology. Also, the wide range of pathological changes shows the change in pituitary volume. The knowledge of dimensions and volume of the pituitary gland is very important for the correct diagnosis and prognosis of pituitary diseases.

The aim of our study was to perform radiomorphometric analysis of size and volume of human pituitary gland according to age and gender on MRI.

Our study represents a retrospective study which included 144 subjects (60 male (41.6 %) and 84 female (58.3 %)) with age range 20-80 years, who underwent magnetic resonance imaging (MRI) of the endocranium. Subjects were divided based on age: first (20-39), second (40-59) and the third group (60-80). Three pituitary diameters were measured: anteroposterior (AP), latero-lateral (LL) and craniocaudal (CC). Pituitary volume (V) was calculated based on the formula: V = AP x LL x CC /2.

Our study showed a statistically significant difference for the parameters AP-H ($p < 0.037$) and AP-A ($p < 0.040$) in patients of the first and second age group. In addition, the parameter CC showed a statistically significant difference between the first and third age group ($p < 0.031$). The value of AP-H parameter in females was 10.99 ± 1.16 mm, while in males it was 10.43 ± 1.31 mm, indicating a statistically significant difference for AP-H parameter in both genders ($p < 0.008$). The AP-N parameter in female subjects was 2.21 ± 0.72 mm, and in male subjects 1.91 ± 0.67 mm, which also indicates that there was a statistically significant difference of AP-N parameter between genders ($p < 0.012$).

The pituitary gland parameter values that were obtained in our study show normal values of pituitary gland dimensions in the Serbian population. During the aging process, the morphology of the pituitary gland changes, AP parameter increases, and parameter CC decreases. In addition, differences between genders were recorded which should be kept in mind during the analyses of pathological conditions or injury of the pituitary gland.

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Introduction

Pituitary gland (PG) is an endocrine gland that has a central role in body growth, metabolism, and reproductive function. PG is located in a special osteofibrous lodge – pituitary fossa within the sphenoid bone and is surrounded by the Turkish saddle (sella turcica), covered by a dural fold (diaphragma sellae). The pituitary gland consists of two separate parts, different in origin, histological structure and function: neurohypophysis and adenohypophysis (1).

The pituitary gland size depends on age, gender and other conditions. During life, there are significant changes in the function of the hypothalamic-pituitary axis and its relationship to other endocrine glands in the body, which can affect the external and internal gland morphology (2, 3). Age and some physiological conditions can change pituitary morphology as well as its physiology, for example, pituitary enlargement during hormonally active conditions – puberty, pregnancy etc. (4-8). Also, some pathological changes show the change in pituitary

volume such as psychiatric disorders (9, 10). There is not enough literature data which show normal pituitary gland dimensions and volume depending on age and gender.

The modality of choice for visualization of pituitary morphology and detection of pathological changes of the pituitary gland is the magnetic resonance imaging (MRI). The optimal MRI technique includes thin section T1–weighted sequences with and without contrast enhancing medium (i.e. gadolinium) in the sagittal and coronal planes (11). The most common pituitary gland pathological changes that can be diagnosed with magnetic resonance imaging are congenital anomalies, dysontogenetic expansive formations, inflammatory and vascular lesions, and tumors, of which the most common are pituitary adenomas and craniopharyngiomas (11). The aim of our study was to perform radiomorphometric analysis of size and volume of human pituitary gland according to age and gender on MRI.

Materials and methods

Our research is a retrospective study which included patients who underwent the MRI examination of the endocranium in the Center for Radiology, Clinical Center Niš, in the period between January 2017 and December 2017. This study involved all examined subjects, whose MRI examination did not show any pathological findings. Patients with any kind of pituitary gland pathology were excluded from the study, as well as the patients with pathological process of endocranium, endocrinologic abnormalities, acute trauma patients, patients with any type of systemic diseases or other abnormal MRI findings. None of the examined female patients were pregnant and lactating. The total number of examinations was 144 patients, 60 males (41.6 %) and 84 females (58.3 %). The average age of all examined patients was 46.44 ± 15.58 years (range: 20-80 years). Study groups were divided according to age into group I (20-39 years), group II (40-59 years) and group III (60-80 years).

MRI examinations were performed on the Siemens Avanto 1.5 T MRI scanner (Siemens Medical Systems, Erlangen, Germany). The processing of reconstructed MRI scans was done at the Leonardo workstation in the Syringe program. The measurement was performed on MRI tomograms in coronal, sagittal and axial plane. The sequences that were used were a T1-weighted (T1w) sequences before and after Gadolinium contrast enhancement. Sequence parameters included TR – 550 ms, TE – 11 ms, FoV – 150 mm, slice thickness – 3 mm. All measurements were performed by the same radiologist.

The analysis parameters included diameters of the pituitary gland as well as the pituitary volume. Three diameters of the pituitary gland were measured: anterior-posterior (AP), latero-lateral (LL) and cranio-caudal (CC) diameter. AP diameter (length) determined the maximum distance between the anterior and posterior points of the pituitary gland at the sagittal level. In this projection, the diameters of adenohypophysis and neurohypophysis (AP-A and AP-N, respectively) were also measured (Figure 1a). LL diameter (weight) was determined by the maximum distance of the lateral points of the pituitary gland in the coronal plane (Figure 1b). CC diameter (height) was determined as the maximum distance of the points in the mediosagittal line, measured in the coronal plane (Figure 1c). Patients were analyzed by gender and age. The pituitary volume (V) was calculated according to the formula V = AP x LL x CC / 2 (12).

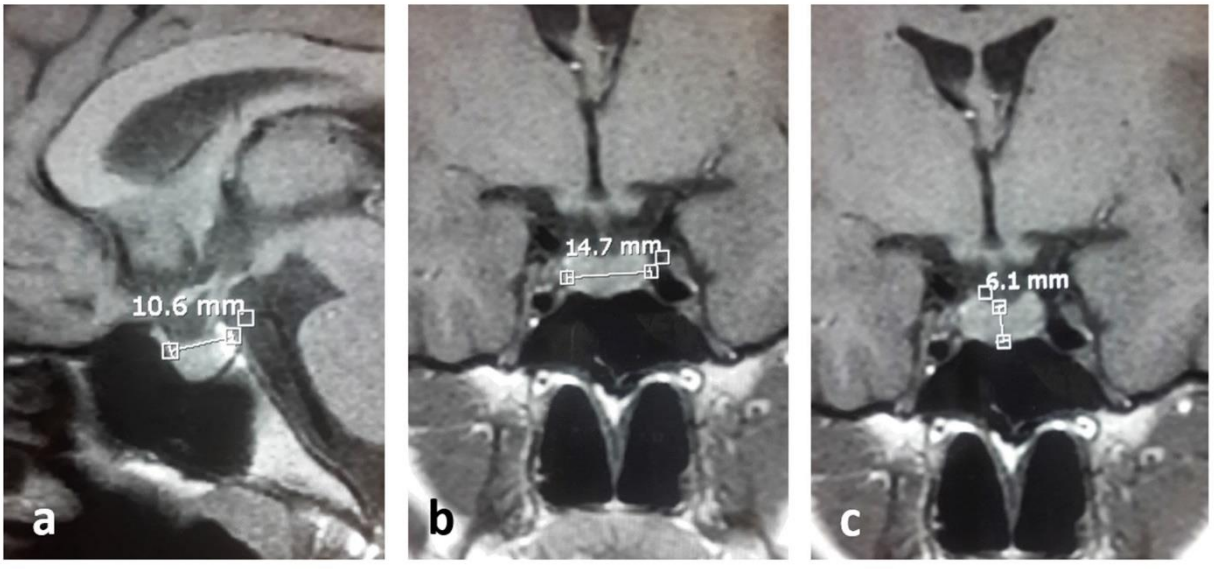
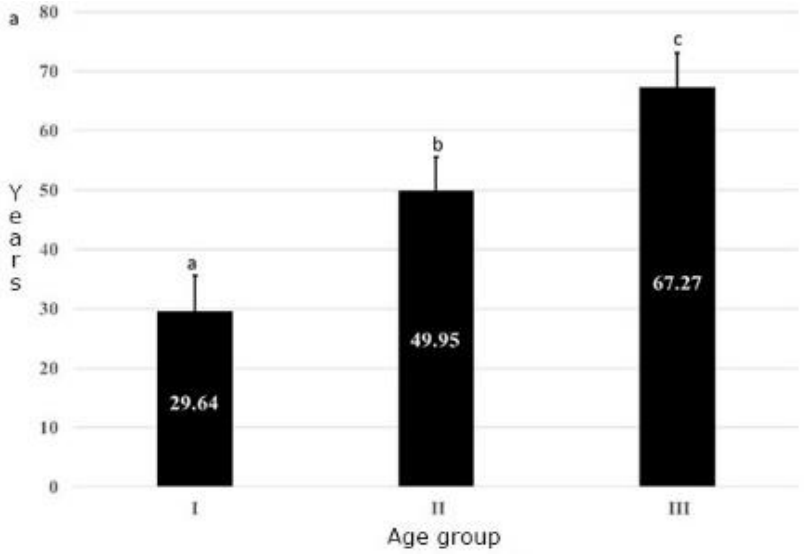


Figure 1. a - AP diameter of the hypophysis, measured in T1w sequence at the sagittal level; b - LL diameter of the pituitary gland, measured in T1w sequence at the coronal level, and c - CC diameter of the pituitary, measured in T1w sequence at the coronal level.

Statistical analysis. The Microsoft Excel program (Windows 10; Microsoft Office Excel, version 2016) was used to collect data, and statistical processing was done in the Statistical Package for the Social Sciences - SPSS version 22.0 (SPSS Inc, Chicago, IL, USA). The relationship between pituitary diameters was observed according to the age and sex of the patients and half of the subjects were analyzed by a Tukey-Kramer post hoc assay; $p < 0.05$ was considered statistically significant.

Results

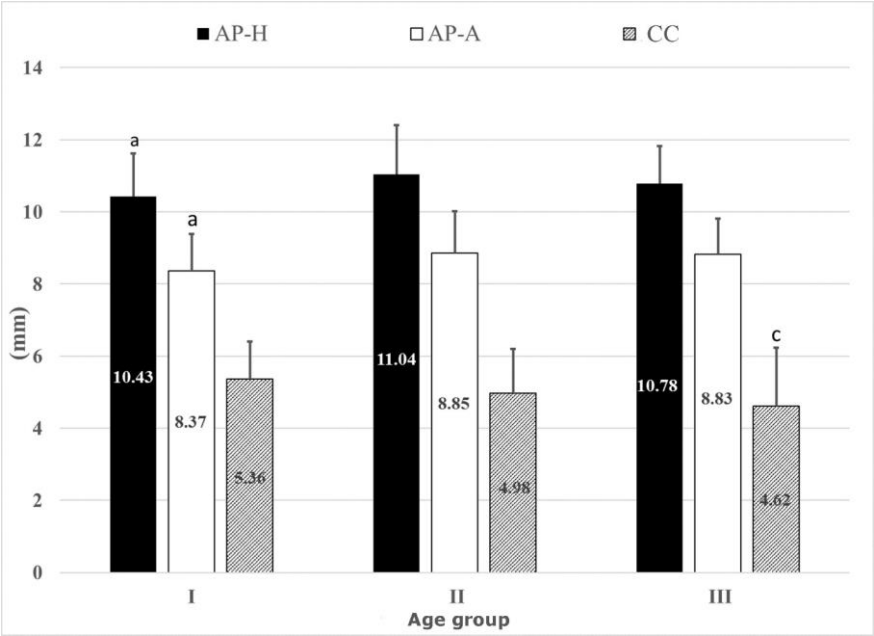
Our study included 144 patients; 60 male (41.6 %) and 84 female patients (58.3 %). The average age of all examined subjects was 46.44 ± 15.58 years (range: 20-80 years). The average age in group I was 29.64 ± 5.96 years; in group II 49.95 ± 5.58 years and in group III 67.27 ± 5.83 years (Graph 1, Table 1). There was a statistically significant difference in the age groups I, II and III (a, b, c).



Graph 1. Age groups of the patients presented with the mean value of years

Table 1. Distribution of patient groups by age: group I (20-39 years), II (40-59 years) and III (60-80 years) in relation to the diameter and volume of the pituitary gland

Parameter	Age	N	Average	SD	SE	95% CI (DG)	95% CI (GG)	F	p	Tukey - Kramer post hoc
Age	I	53	29.64	5.96	0.82	28.00	31.28	448.58	<0.0001	a
	II	58	49.95	5.58	0.73	48.48	51.42			b
	III	33	67.27	5.83	1.02	65.20	69.34			c
AP-H (mm)	I	53	10.43	1.19	0.16	10.11	10.76	3.37	0.037	a
	II	58	11.04	1.36	0.18	10.68	11.40			/
	III	33	10.78	1.04	0.18	10.41	11.15			/
AP-A (mm)	I	53	8.37	1.02	0.14	8.09	8.65	3.31	0.040	a
	II	58	8.85	1.17	0.15	8.54	9.16			/
	III	33	8.83	0.98	0.17	8.48	9.18			/
AP-N (mm)	I	53	2.07	0.64	0.09	1.89	2.24	2.52	0.084	/
	II	58	2.22	0.76	0.10	2.02	2.42			/
	III	33	1.88	0.71	0.12	1.62	2.13			/
LL (mm)	I	53	13.99	2.21	0.30	13.38	14.59	0.70	0.498	/
	II	58	13.95	2.30	0.30	13.35	14.56			/
	III	33	13.44	2.19	0.38	12.67	14.22			/
CC (mm)	I	53	5.36	1.04	0.14	5.07	5.64	3.58	0.031	/
	II	58	4.98	1.22	0.16	4.66	5.30			/
	III	33	4.62	1.60	0.28	4.05	5.19			c
Volume (mm^3)	I	53	391.67	111.01	15.25	361.07	422.27	2.27	0.107	/
	II	58	377.17	109.72	14.41	348.32	406.02			/
	III	33	336.17	144.60	25.17	284.90	387.44			/
a – I:II, p<0.05; b – II:III, p<0.05; c – I:III, p<0.05										



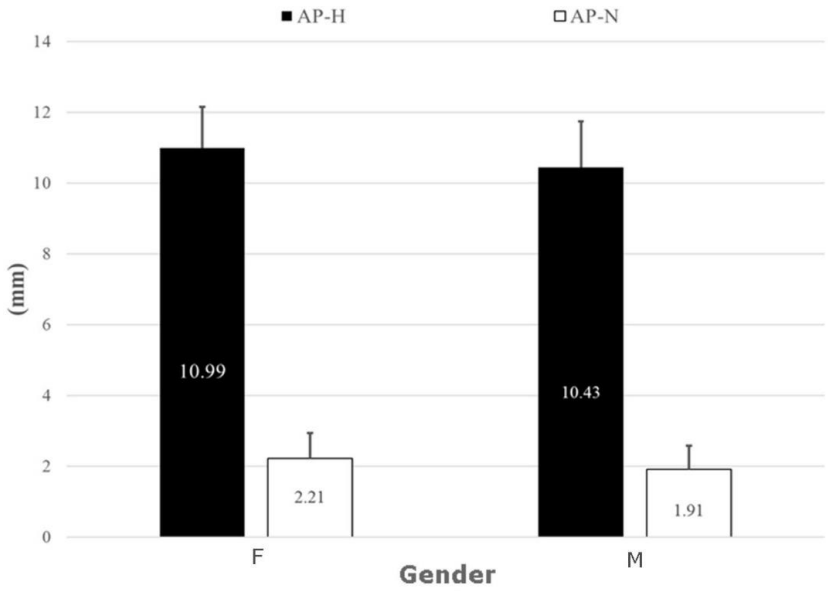
Graph 2. Relation of the pituitary gland parameters according to the age groups

Table 2. Relation of the pituitary gland dimensions in three projections and pituitary gland volume according to the genders

Parameter	Gender	N	Mean	SD	SE	T	SS	p
Age	female	84	45.18	15.45	1.69	-1.16	142	0.250
	male	60	48.22	15.72	2.03			
AP-H (mm)	female	84	10.99*	1.16	0.13	2.68	142	0.008
	male	60	10.43	1.31	0.17			
AP-A (mm)	female	84	8.80	1.08	0.12	1.77	142	0.079
	male	60	8.48	1.08	0.14			
AP-N (mm)	female	84	2.21*	0.72	0.08	2.55	142	0.012
	male	60	1.91	0.67	0.09			
LL (mm)	female	84	13.96	2.44	0.27	0.69	142	0.492
	male	60	13.70	1.92	0.25			
CC (mm)	female	84	5.05	1.41	0.15	0.14	142	0.887
	male	60	5.02	1.09	0.14			
Volume (mm^3)	female	84	383.24	125.68	13.71	1.20	142	0.232
	male	60	358.92	111.14	14.35			

In our work, a statistically significant difference was obtained for the parameters AP-H ($p < 0.037$) and AP-A ($p < 0.040$) in patients from group I and group II (a). Also, for the CC parameter, there was a statistically significant difference between I and III age groups (c, $p < 0.031$) (Table 1, Graph 2). Other parameters (AP-N, LL, and volume) did not show a statistically significant difference in age ($p > 0.05$).

The values of AP-H parameter in female patients was 10.99 ± 1.16 mm, while in male patients it was 10.43 ± 1.31 mm, which indicated a statistically significant difference in the AP-H parameter between genders ($p < 0.008$). The value of AP-N parameter in female patients was 2.21 ± 0.72 mm, and in male patients 1.91 ± 0.67 mm, which also indicated a statistically significant difference in the AP-N parameter between the genders ($p < 0.012$) (Table 2, Graph 3). Other parameters (AP-A, LL, CC, and volume) did not show a statistical significance between the genders ($p > 0.05$).



Graph 3. The relation between total AP pituitary gland diameter and AP diameter of neurohypophysis according to the gender distribution

Discussion

Knowledge of dimensions and volume of the pituitary gland is very important for the diagnosis and prognosis of pituitary diseases in everyday clinical practice. Magnetic resonance imaging is a reliable, non-invasive and highly sensitive method for the visualization of the pituitary gland. During the aging process, there is a physiological change in the size and volume of the pituitary gland due to an increase or decrease in the secretory function (3). The increase in the size of the pituitary gland occurs during puberty, pregnancy, lactation and early postpartum period (4-8, 13, 14). In the early stages of traumatic brain injury, there is an increase in the pituitary gland volume that persists in the chronic phase (15). Also, some drugs such as antipsychotic drugs can increase the pituitary size in the first 12 months of therapy due to dysregulation of hypothalamus-pituitary-adrenal (HPA) axis function (16). In addition, some recent studies showed the presence of pituitary volume enlargement in first-episode psychosis (10). The reduction occurs in a wide number of pathological conditions, as well as in psychiatric diseases such as anorexia nervosa, bipolar disorders and established psychosis (16-18). Also, the reduction of pituitary volume has been noticed in women who take oral hormonal therapy (13). The aging process involves all the endocrine glands, including a pituitary gland. During aging, the size of the gland itself is reduced, as well as its secretory activity. There is proliferation of connective tissue, pituitary fibrosis, and vascular network reduction (19). It is very important to know these oscillations (peaks) in order to give the right diagnosis and treatment.

An increasing number of various studies have been done for the evaluation and establishment of normal pituitary gland range values and have found a wide variation of pituitary gland size and volume according to age and gender. In literature, we did not find any morphometric study of this type in the Serbian population. This study attempted to gain further insight into the range of normal dimensions of the human pituitary gland in the Serbian population. This study can also be used in further larger studies.

In our study, the value of the pituitary length (AP-H) was statistically significantly lower in the age group of 20 to 39 years (10.43 mm) compared to patients aged 40-59 years (11.04 mm). Our data are consistent with other literature data (20, 21). In addition, the value of adenohypophysis length (AP-A) was statistically significantly lower in subjects of the same age groups (8.37 mm and 8.85 mm, res-

pectively). According to these results, we consider that the length of the pituitary gland changes depending on the length of the adenohypophysis. The main peak of the increase in the length of the pituitary gland occurs between the age of 40 and 59 years, which we consider as the result of a negative feedback due to a decrease in the levels of hormones of certain organs. Literature data show a similar peak in the length of the pituitary gland in the sixth decade of life (22).

By comparing the length of the pituitary gland between the genders, a statistically significant difference was obtained in the length of the pituitary gland (AP-H) and in the length of neurohypophysis (AP-N) in both males and females. The mean pituitary height (CC parameter) in our study was 5.02 mm in men and 5.05 mm in women. Our values correspond to the height of the pituitary gland from the literature: in the work of Lurie et al. (5.18 mm and 5.25 mm, respectively) (23), Ikram et al. (6.3 mm and 5.9 mm, respectively) (2), Denk et al. (5.7 mm and 5.6 mm, respectively) (24), Elster et al. (25) and Tsunoda et al. (3) (5.33 mm and 4.93 mm, respectively), while the values in Ibinaiye et al. (22) were slightly higher (7.62 mm and 7.81 mm, respectively). The pituitary height values in our work showed a statistically significant reduction in older patients (60-80 years) compared to the patients aged 20-39 years, which corresponds to the literature data (23).

Depending on hormonal status, pituitary gland volume changes during life. The pituitary gland volume was slightly higher in females - 383.24 mm^3, while in men it was 358.92 mm^3 and did not show statistical significance between genders. Our data correspond to the most publications data which reported a larger pituitary gland in females (3, 8, 16, 24-26). There was no statistically significant difference in pituitary volumes among age groups, but overall gland volume decreases with age. The development of the human body is followed by pituitary gland changes. The results of the study by Ibinaiye et al. (22) are in agreement with our results (29, 3), while Lurie at al. (23) state that there was a statistically significant difference in the pituitary volume in younger patients compared to the older ones. The differences between the measured pituitary volumes can be explained considering different volume examinations due to different volume formulas and technical parameters, such as the strength of the magnetic field, sequence parameters etc. Depending on the pituitary shape, different formulas should be used as well as correction factors for these formulas (30). The evaluation of pituitary measurements can be assessed using 2D and 3D-MRI examination. In the present study, we used 2D-MRI examination, but we consider that it would be useful to compare both methods in future studies. Pituitary gland volumes are individual and can vary depending on age and gender, but it is the most important to compare the volume in the context of clinical manifestations and all factors that can lead to pituitary volume change.

Comparison of the pituitary parameters on the cadaver with the results of our study showed that the data coincide (31) with the study of Rahman et al. where the values of all the parameters (length, height and width) of the pituitary were much lower, with the author suggesting that this was a possible reason for variation among different races (32). Determining the size of the pituitary post-mortem is, in the opinion of Ju et al. more precisely (31), but certainly, morphometry on MRI is more significant for diagnostics and prognosis in everyday clinical practice.

We consider that our study data are limited to a Serbian adult population and further studies are needed to assess pituitary measurements in pediatric patients. In addition, the number of examined subjects should be increased in order to have more precise and accurate sample data. Further evaluation with better technical improvements such as the higher strength of the magnetic field or thinner slice thickness in larger patients sample is necessary for the establishment of a normal range of pituitary gland values in everyday clinical diagnostics.

Conclusion

Based on statistically significant differences in the parameters that were analyzed, it can be concluded that the pituitary morphology changes over the course of life in terms of an increase in the anterior-posterior and reduction of the cranio-caudal dimension, with the overall gland volume showing a downward trend but without statistical significance. The differences between the genders showed that the anterior-posterior diameter was significantly higher in females than in the male patients, based on a statistically significant difference in the dimensions of the neurohypophysis. The identified differences in age and gender should be kept in mind when diagnosing pathological changes of this gland.

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RADIOMORFOMETRIJSKA ANALIZA HIPOFIZE ČOVEKA U PROCESU STARENJA

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Tokom života postoje značajne promene u funkcionisanju hipotalamo-hipofizarne ose i ostalih endokrinih žlezdi u organizmu, što utiče na unutrašnju i spoljašnju morfologiju same žlezde. Takođe, veliki broj patoloških stanja pokazuje promenu u volumenu hipofize. Poznavanje dimenzija i volumena hipofize veoma je značajno za dijagnostiku i prognozu bolesti hipofize.

Cilj našeg istraživanja bio je izvršiti morfometrijsku analizu hipofize osoba različite starosti i različitog pola.

Naše istraživanje predstavlja retrospektivnu studiju koja obuhvata 144 ispitanika (60 muškaraca (41,6 %) i 84 žene (58,3 %)), starosti od 20 do 80 godina, koji su upućeni na pregled endokranijuma na magnetnoj rezonanci (MR). Ispitanici su podeljeni na osnovu godina starosti na: I grupu (20-39 godina), II grupu (40-59 godina) i III grupu (60-80 godina). Merena su tri dijametra hipofize: anteroposteriorni (AP), latero-lateralni (LL) i kranio-kaudalni (KK). Zapremina hipofize (V) izračunavana je na osnovu formule V = AP x LL x KK/2.

U našem radu dobijena je statistički značajna razlika za parametre AP-H ($p < 0,037$) i AP-A ($p < 0,04$) kod bolesnika I i II grupe. Takođe, kod parametra KK postoji statistički značajna razlika između I i III starosne grupe ($p < 0,031$). Kod ispitanika ženskog pola vrednost AP-H parametra iznosi 10,99 ± 1,16 mm, dok kod ispitanika muškog pola iznosi 10,43 ± 1,31 mm, što ukazuje na postojanje statistički značajne razlike AP-H parametra u odnosu na pol ($p < 0,008$). AP-N paremetar kod ispitanika ženskog pola iznosi 2,21 ± 0,72 mm, a kod ispitanika muškog pola 1,91 ± 0,67 mm, što takođe ukazuje na postojanje statisti-čki značajne razlike AP-N parametra u odnosu na pol ($p < 0,012$).

Vrednosti parametara hipofize dobijene u našem radu ukazuju na normalne vrednosti dimenzija hipofize u srpskoj populaciji. Tokom života dolazi do promene morfologije hipofize u smislu povećanja AP dimenzije, a smanjenja KK dimenzije. Takođe su utvrđene razlike prema polu što sve zajedno treba imati na umu prilikom ispitivanja patoloških promena ili povrede hipofize.

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Ključne reči: *hipofiza, MR, radiomorfometrijska analiza, starenje, zapremina*