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Incidence of Pituitary Tumors in the Human Population of Croatia

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A B S T R A C T

Pituitary tumors are rare tumors (less then 10%) of the central nervous system (CNS), which malignicity depends on their localization, meanwhile, their biological nature is benign. The diameter they have is mostly less then 10 mm (microadenomas), but sometimes could be 10 mm (macroadenomas) to 5 cm and more and then are usually nonfunctional (about 20% of all pituitary tumors). Clinical presence depends on their localisation and hormonal activity. In the Center for Clinical Neuroendocrinology and Pituitary Diseases, in the last working 10 years, there were treated and examined 504 patients from Croatia, all with pituitary tumors: 182 patients with prolactinomas, 137 with acromegaly, 70 with Morbus Cushing (Mb. Cushing), and 115 patients with nonfunctional pituitary tumors. The patient's classification is based on regional (Mediterranean and continental region, 20 counties) and the state level. In our analysis we haven't found difference in incidence of tumors between Mediterranean and continental region.

***Key words**: pituitary tumor, functional adenomas, nonfunctional adenomas, Croatia*

Introduction

A large number of diseases may affect the pituitary, the most frequent are benign tumors or adenomas that are either hormonally functional or nonfunctional, making up more then 90% of all pituitary neoplasms. Also, we can divided them into microadenomas (<10 mm in diameter) and macroadenomas (>10 mm in diameter). They are frequently occurring tumors representing approximately 15% or even more of the operated intracranial neoplasms. Studies using unselected adult autopsy material show that pituitary adenomas can be incidentally identified in approximately 20% of men and women dying of different non-endocrine diseases. These results indicate that in North America millions of adults harbor adenomas in their pituitaries. Most of these tumors are small, unassociated with clinical symptoms and usually of no significance. Many pituitary adenomas secrete various hormones in excess and are associated with elevated blood hormone levels as well as different endocrine signs and symptoms. Several pituitary nonfunctional adenomas are unassociated with increased blood hormone levels and endocrine alterations. These tumors, if they reach a large size, can cause local symptoms[1–3].

About 40% of these small tumors produce prolactin (PRL), the remaining ones most likely secrete other peptides or proteins whose biologic function is obscure.

Hyperprolactinaemia is the most common pituitary disorder, and the prolactinoma is the most common pituitary tumor. Prolactin-producting tumors exist "silently" in up to 5–10% of population. In both sexes prolactinomas are the most common secretory tumors of the pituitary, producing excessive quantities of prolactin[4].

Clinically significant prolactinoma affects the health subjects approximately 14 out of 100,000 individuals. The majority of tumors in women are microadenomas (<10 mm in diameter), but in a small percentage there are macroadenomas (>10 mm) at the time of diagnosis. The frequency of microadenomas is much lower in men, perhaps because of later recognition[5–8].

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Acromegaly is a serious systemic condition caused in over 98% of cases by a well-demarcated acidophilic or chromophobic growth hormone- secreting adenoma located in the anterior lobe of the pituitary gland that secrete excessive growth hormone (GH). The classification of GH-secreting pituitary tumors, based on their hormonal content, ultrastructural features, and cytogenesis includes densely and sparsely granulated GH cell adenomas, mixed GH and PRL cell adenomas, acidophil stem cell adenomas, mammosomatotroph cell adenomas, plurihormonal adenomas and GH cell carcinomas. It is relatively uncommon disease, which has been estimated to affect about 40 cases per million. An annual incidence of 3 cases per million has been estimated in English and Swedish surveys. A recent epidemiologic study, performed in Italy, confirmed a prevalence of 42 cases per million, and an annual incidence of 3.3 cases per million. There is a slight preponderance of women, and the onset of the disease is more frequent between the third and the fifth decades. Growth hormone-secreting pituitary tumors generally grow more rapidly in patients younger then 35[9–11].

Cushing's disease affects 10 to 15 of every million people every year, and most commonly affects adults aged between 20 to 50 years. Incidence is 0.1 to 1 new clinically case per year. Women account for over 70% of cases, and the ratio between men and women is from 3:1 to 10:1. Children in Morbus Cushing (Mb. Cushing) participate in 30% and mostly are older then 9 years, with similar sex distribution. Patients with Cushing's disease may have a basophilic adenoma of the pituitary or a chromophobic adenoma. The cause of Cushing's syndrome is a pituitary adenoma in over 70% of adults and in approximately 60–70% of children and adolescents. Most pituitary adrenocorticotropic- secreting adenomas are small in size (microadenoma)[12,13].

Nonfunctional tumors of intra- or parasellar region are craniopharyngiomas, meningiomas, hamartomas, gliomas, germinomas and nonfunctional hypophiseal adenomas. They are usually not discovered until they press on important structures around them. For this reasons, although they are almost always benign tumors, they are frequently quite large when detected, ranging from an average of about one inch across to more than four inches. Nonfunctional pituitary adenomas participate in 25–30% of all hypophiseal adenomas. Craniopharyngiomas are intracranial tumors that can occur at any age, most commonly in childhood and adolescence and in later adult life, after 50 years. The median age is 22 years. They account for about 10% of CNS tumors in these younger age groups and 2 to 4% of primary brain tumors. There is similar classification among sexes. Hypothalamic hamartomas are not true neoplasms, but

TABLE 1
THE PITUITARY TUMORS SEPARATED BY TUMOR TYPE AND COUNTIES IN CROATIA

County	Cushing		Prolactinoma		Acromegaly		Nonfunctional		Total	
	N	%	N	%	N	%	N	%	N	%
1. Zagrebačka	12	6	87	42	50	25	54	27	203	40
2. Krapinsko-zagorska	4	16	12	48	8	32	1	4	25	5
3. Sisačko-moslavačka	6	35	4	24	6	35	1	6	17	3
4. Karlovačka	6	23	5	19	7	27	8	31	26	5
5. Varaždinska	1	13	2	25	2	25	3	37	8	1.6
6. Koprivničko-križevačka	2	22	3	34	2	22	2	2	9	1.8
7. Bjelovarsko-bilogorska	2	40	3	60	0	0	0	0	5	0.9
8. Primorsko-goranska	1	25	2	50	1	25	0	0	4	0.8
9. Ličko-senjska	1	25	0	0	2	50	1	25	4	0.8
10. Virovitičko-podravska	4	49	3	38	1	13	0	0	8	1.6
11. Požeško-slavonska	1	7	3	21	7	51	3	21	14	2.8
12. Brodsko-posavska	2	18	3	27	1	9	5	46	11	2.2
13. Zadarska	5	22	7	31	7	30	4	17	23	4.6
14. Osječko-baranjska	2	9	8	36	7	32	5	23	22	4.4
15. Šibensko-kninska	0	0	6	60	1	10	3	30	10	2
16. Vukovarsko-srijemska	5	26	5	26	6	32	3	16	18	3.6
17. Splitsko-dalmatinska	8	12	19	30	19	29	19	29	65	13
18. Istarska	3	27	6	55	2	18	0	0	11	22
19. Dubrovačko-neretvanska	1	10	2	20	4	40	3	30	10	2
20. Međimurska	4	40	2	20	4	40	0	0	10	2
TOTAL	70	14	182	36	137	27	115	23	504	100
Mediterranean	19	37.25	42	30	36	35.64	30	35.29	128	33.78
Continental	51	62.75	140	70	101	64.36	85	64.71	376	66.22

rather congenital malformations, mostly discovered in age before 2 years (69.8%), 2 to 4 years (17.5%) and 5 to 8 years (7.9%). They occure in men in 55.4% and in women in 44.6% of cases. Meningiomas arise in the presellar and parasellar region, usually occurring in adult women in age between 40 and 50 years. The ratio between men and women is 3:1. Optic chiasm gliomas usually occur in children[14].

Frequent monitoring of endocrine status and evaluation of the sella turcica, at least yearly, are indicated for the remainder of a patient's life following therapy of a macroadenoma[15].

Subjects and Methods

In Center for Clinical Neuroendocrinology and Pituitary diseases, University Hospital "Sestre milosrdnice", Zagreb, there have been analyzed and cured 504 patients with pituitary tumor in total in the last working 10 years. The patients from the Republic of Croatia have been cured in Center (Table 1):

- 182 patients with prolactinomas
- 137 patients with acromegaly
- 70 patients with Cushing's disease
- 115 patients with non-functional pituitary tumors.

All patients have been analyzed by tumor type. The regional pituitary tumor incidence is analyzed by solitary regions and the whole territory of Republic of Croatia. All regions are also analyzed based on the Mediterranean and continental position (Table 1, Figure 1).

Continental Croatia: County of Zagreb, County of Krapina-Zagorje, County of Sisak-Moslavina, County of Karlovac, County of Varaždin, County of Koprivnica – Križevci, County of Bjelovar-Bilogora, County of Virovitica-Podravina, County of Požega-Slavonia, County of Slavonski Brod-Posavina, County of Osijek-Baranja, County of Vukovar-Srijem and County of Međimurje.

Mediterranean Croatia: County of Split-Dalmatia, County of Istria, County of Dubrovnik-Neretva, County of Zadar and County of Šibenik-Knin.

Fig. 1. Mediterranean and Continental regions in Republic of Croatia.

Results

The largest account of Cushing's disease is found in Count of Virovitičko-Podravska (49%), the smallest account in Šibensko-Kninska County (0%).

The largest account of prolactinomas is in Bjelovarsko-Bilogorska and Šibensko-Kninska County (60%) and the smallest in Ličko-Senjska County (0%).

Acromegaly is the leading pituitary tumor in Ličko-Senjska (50%) and almost never found in Bjelovarsko-Bilogorska County (0%).

The largest account of non-functional tumors is in Brodsko-Posavska County (46%), and the smallest in Bjelovarsko-Bilogorska, Primorsko-Goranska, Virovitičko--Podravska, Istarska and Međimurska County.

In total, the largest number of tumors is numbered in Zagrebačka county (203, or 40%), because there is the largest number of inhabitants. Primorsko-Goranska and Ličko-Senjska County had the smallest percent of tumors (4 or 0.8%), because there is the smallest number of inhabitants.

Also, based on our documents, in Croatia the prolactinomas are the leading pituitary tumor (36%). Acromegaly is on the second place (27%), non-functional tumors are on the third place (23%) and Cushing's disease is the last (14%, Figure 2).

These results, compared to worldwide published results, show the same incidence of pituitary tumors in Croatia and the world itself.

We didn't separate the patients only according to counties. We separate them on the regional base: Mediterranean (coast) and continental Croatia, to see if the natural conditions and different life style (including food, water, or war events) have any impact on appearance of pituitary tumors. These two groups showed very similar results. In Mediterranean region of Croatia there were found 127 patients with pituitary tumors; Cushing's disease had 19 (15%), prolactinoma 42 (34%), acromegaly 36 (28%) and nonfunctional tumor 30 (23%) patients (Table 2, Figure 3).

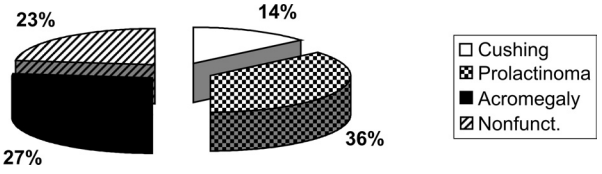

Fig. 2. Representation of pituitary tumors in Croatia. Nonfunct. – nonfunctional.

TABLE 2
PITUITARY TUMORS IN MEDITERRANEAN REGION OF CROATIA

Cushing		Prolactinoma		Acromegaly		Nonfunctional		TOTAL
N	%	N	%	N	%	N	%	N
19	15	42	34	36	28	30	23	127

Nonfunct. – nonfunctional

TABLE 3
PITUITARY TUMORS IN CONTINENTAL REGION OF CROATIA

Cushing		Prolactinoma		Acromegaly		Nonfunctional		TOTAL
N	%	N	%	N	%	N	%	N
51	14	140	37	101	27	85	22	377

Nonfunct. – nonfunctional

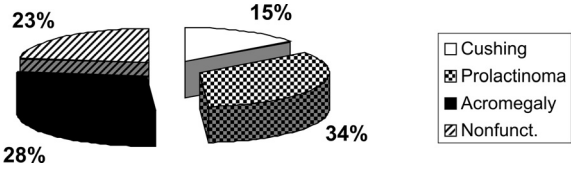

Fig. 3. Representation of pituitary tumors in Mediterranean regions of Croatia. Nonfunct. – nonfunctional.

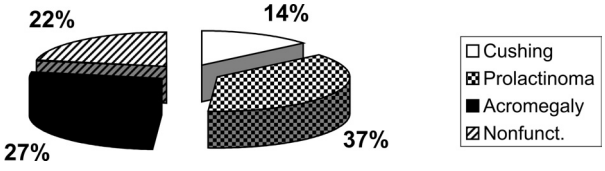

Fig. 4. Representation of pituitary tumors in continental regions of Croatia. Nonfunct. – nonfunctional.

In Continental region of Croatia there were found 377 patients with pituitary tumors: 51 patient (14%) had Cushing's disease, prolactinoma 140 (37%), acromegaly 101 (27%) and nonfunctional tumor 85 (22%) patients (Table 3, Figure 4).

Parallels among incidence, tumor type and regional distribution between pituitary tumors were also showed (Figure 5).

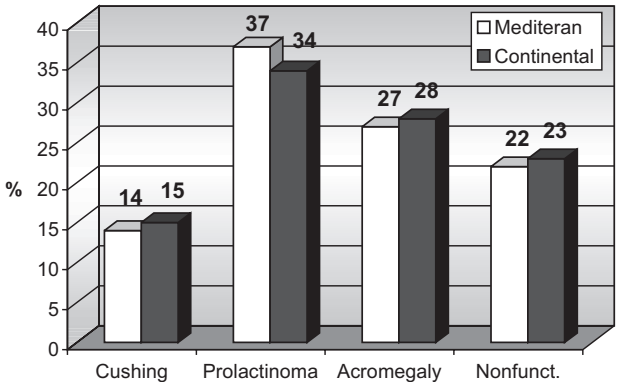

Fig. 5. Parallels between pituitary tumors based on tumor type, incidence and regional distribution. Nonfunct. – nonfunctional.

Conclusion

Our results show that there is no statistically significant difference among presentation of pituitary tumors between this two main regions: Continental and Mediterranean part of Croatia. The difference is almost usually 1%. Our results are very similar to incidence of pituitary tumors we found in literature. So, the natural and life conditions have no impact on appearance of some types of tumors. This is the largest center for evaluation of pituitary tumors in Republic of Croatia, but small number of patients is also evaluated in other hospitals.

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REGIONALNA RAŠIRENOST TUMORA HIPOFIZE U REPUBLICI HRVATSKOJ

S A Ž E T A K

Tumori hipofize su rijetki tumori središnjeg živčanog sustava (manje od 10%) koji su maligni zbog svoje lokalizacije, dok im je biološka priroda benigna. Obično su manji od 10 milimetara (mikroadenomi), ali nekada su veći od 1 cm (makroadenomi) pa i preko 5 centimetara i tada su obično funkcionalno nijemi (oko 20% svih hipofiznih tumora). Klinička slika ovisi o sijelu tumora i hormonskoj aktivnosti. U Centru za kliničku neuroendokrinologiju i bolesti hipofize Kliničke bolnice »Sestre milosrdnice« u zadnjih 10 godina obrađeno je i liječeno ukupno 504 bolesnika: 182 bolesnika s prolaktinskim tumorom, 137 s akromegalijom, 70 s Cushingovom bolešću te 115 bolesnika s funkcionalnim tumorom hipofize. Svi su bolesnici analizirani po regionalnoj pripadnosti (primorska i kontinentalna regija, 20 županija) i na razini cijele Republike Hrvatske. Obradom nismo utvrdili razlike u učestalosti pojave tumora hipofize između primorske i kontinentalne Hrvatske