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Silent Adenomas of Pituitary Gland : It's Immunohistochemical Features and Clinical Characteristics

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Objective : The aim of the study was to review the clinical and radiological findings of those non-functioning adenomas(NFAs) with positive immnoreactivity for anterior pituitary hormones.

Methods : Sixty patients with pituitary adenoma were treated at the author's institution between January 2000 and July 2005. All consecutive patients were underwent transsphenoidal surgery by same operator. In addition to the routine histopathological examination, surgical specimen was examined by immunohistochemical staining against adenohypophyseal cells. And clinical analysis was performed by retrospective review of medical records, neuroimaging examinations and immunohistochemical technique. We classified these pituitary adenomas into functioning adenomas (group F), immuno-positive NFAs (group S, so-called silent adenoma) and immuno-negative NFAs (group N), and compared clinical and radiological differences between group F, N, and S.

Results : Of the 60 cases, group F was 25, group S was 25, and group N was 10. Among the group S, 5 cases showed reactivity against PRL, 1 against GH, 1 against both PRL and GH, 1 against TSH and GH, 2 against ACTH, 11 against FSH and 4 against both LH and FSH. Radiologically, invasiveness was noted in 8 in group S, compared to 3 in group N and 1 in group F ($p = 0.02$). Intratumoral bleeding was noted in 7 of group S, 2 of group N and 2 of group F ($p > 0.05$).

Conclusion : Silent adenomas were thought to behave more aggressive than other subgroups of pituitary adenomas. And so we suggest the immunohistochemical study against adenohypophyseal cells may be helpful for evaluating clinical course of pituitary adenoma, expecially for, NFAs.

KEY WORDS : Silent adenoma · Immunohistochemistry · Invasiveness · Intratumoral hemorrhage.

Introduction

Pituitary tumors are defined by the characteristic clinical syndromes that accompanied with hormone overproduction. But approximately 25 to 30 percent of patients with pituitary tumors have no clinical evidence of hormone hypersecretion[9,10]. Such tumors are classified as nonfunctioning adenomas(NFAs). These NFAs can be separated into two main categories based on immunohistochemical and electron microscopic appearances[5]. One group, known as null cell adenomas and oncocytomas, includes tumors showing no characteristics of normal adenohypophyseal cell and possessing neither morphological nor immunohistochemical markers indicating their cytogenesis or direction of differentiation[5]. The second group includes tumor exhibiting immunohistochemical or ultrastructual features of recognizable adenohypophyseal cells, but no signs of hormone excess[5,16]. This subgroup has been called silent adenomas.

The term of silent adenomas was coined in 1978, and was defined as evidence of immunoreactive hormone in tumor cells of a pituitary adenoma that is not associated with endocrine symptomatology[6]. This subgroup showed different biological behaviors. It has been assumed that null-cell adenomas and oncocytomas are slowly growing tumors, whereas some silent adenomas, particularly silent corticotroph adenomas or somatotroph adenomas have a more rapid growth rate and more

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prone to be associated with apoplexy or invasiveness and exhibit a more frequent rate of recurrence[6,7,10,16,19].

And so we examined the immunohistochemical reactivity against each hormone from the NFAs. Also we reviewed the clinical characteristics of silent adenomas and whether this subgroup behave more aggressively than other subgroups of pituitary adenomas by means of comparison with existing data.

Materials and Methods

Patients and data collection

Of the 96 sellar and suprasellar tumor cases were treated with surgery by same operator from January 2000 to July 2005, 60 patients revealed pituitary adenoma were selected. Among these, female patients outnumbered males (M:F=29:31), and the age distribution was 19 to 73 years (median, 47.1). Transsphenoidal approach(TSA) was chosen as primary method of surgery in all pituitary adenomas. Their medical records were reviewed for initial manifestations, endocrinological studies, neuroradiological and histopathological findings. The clinical follow-up period ranged from 5 to 67 months (mean, 26). Regular radiological follow-up was possible in 49 patients and the mean interval was 9.6 months.

Endocrinological evaluation

Measurements of serum prolactin(PRL), growth hormone (GH), thyroid-stimulating hormone(TSH), adrenocorticotrophic hormone(ACTH), luteinizing hormone(LH), and follicle stimulating hormone(FSH) were performed.

Neuroradiologic evaluation

Magnetic resonance imaging(MRI), revealed pituitary adenoma, was reviewed with tumor bleeding, invasiveness and extrasellar extension by neuroradiologist. The extent of tumor growth and invasiveness were classified according to the Hardy's criteria. The Grade III and IV were classified to invasive adenoma. Radiological evaluation after operation was classified in two categories : local mass control (no evidence of recurrence after gross total removal, and no evidence of growth of residual mass) and no local mass control (increased size of the residual mass).

Immunohistochemical evaluation

The tumors were removed by transsphenoidal approach. Surgically obtained tumor tissue was fixed in formalin and embedded in paraffin, followed by tissue staining with hematoxylin and eosin (H&E). And the immunostaining was performed with the avidin-viotin-peroxidase complex technique, detected by DACO EnVision Kit(Dako, Denmark). Immunoperoxidase studies were performed on sections prepared from formalin-fixed and paraffin-embedded specimens that were dewaxed and rehydrated at graded alcohols. Endogenous peroxidase was blocked by dipping sections in 3% aqueous hydrogen peroxide for 10 min, and antigen retrieval was performed with 10 min microwave treatment in 10mmol/L citrate buffer, pH 6.00. Diluted primary antibodies for anti-Gonadotropin (1:100; Novocastra, UK), anti-GH (1:100; DAKO, Denmark), anti-PRL (1:100; Novocastra, UK), anti-ACTH (1:200; Novocastra, UK), anti-TSH (1:100; Novocastra, UK) were treated at room temperature for 1 hour. After the primary antibody incubation, the sections were incubated with secondary antibody and avidin-viotin-peroxidase complex. The sections were lightly counterstained with hematoxylin.

Classification of pituitary adenoma

First in our study, the adenomas were classified into functioning or nonfunctioning adenomas(NFAs) according to the symptoms and blood hormone levels. Second, immunohistochemical study against adenohypophyseal cells were done. And then the NFAs were subclassified according to immunohistochemical reactivity. Of the 60 cases, silent adenoma was named as group S, functioning adenoma as group F. Immuno-negative NFA was named as group N. We examined the surgical specimen of the patients with pituitary adenomas with the immunohistochemical technique and compared clinical and radiological differences between group S, F, and N.

Statistical analysis

The Fisher's exact test was used to assess the significance of the invasiveness and intratumoral bleeding between group S, F, and N. A probability value of less than 0.05 was considered to be statistically significant.

Results

Clinical presentation

Of the 60 cases, group S was 25 (41.7%), group N was 10 (16.7%), and group F was 25 (41.7%). Among clinically NFAs (35 cases), group S was 25 (71.4%), and group N was 10 (28.6%). The average age of the group S, N, and F were 51.0, 55.8, and 38.1 years-old, respectively (Table 1). Because the symptoms of hormonal hypersecretion in endocrinolo-

Table 1. Age and sex distribution of subgroups in pituitary adenomas

	Group N	Group F	Group S	Total
	10(17%)	25(42%)	25(42%)	60
M/F	5/5	6/19	18/7	29/31
Age	46~72yr	19~59yr	35~73yr	19~73yr
(mean age)	(55.8yr)	(38.1yr)	(51.0yr)	(47.1yr)

Group N : immuno-negative nonfunctioning adenoma, Group F : functioning adenoma, Group S : silent adenoma

gically active tumors will obviously present before evidence of suprasellar or parasellar extension, the patients' average age of group F was younger than those of the group S and N. But significant difference of average age between the group S and N was not recognized.

The common symptoms of the group S and N were headache (58%) and visual field defect (39%) due to mass effect, and none of these groups exhibited clinical signs of hormone hypersecretion. But those of the group F were 12 with amenorrhea and/or galactorrhea, 11 with acromegaly and 2 with Cushing's syndrome. On the other hand, the endocrine abnormality (minimally elevated serum prolactin level) was only seen in 7 patients among NFAs. Visual field defects were documented in 15 patients with the group S and 6 with the group N. Similarly, headache were documented in 18 patients with the group S and 7 with the group N. Accordingly, significant differences of symptoms and signs were not recognized between the group S and N.

Neuroradiologic evaluation

Neuroradiologic characters of each subgroups in pituitary adenomas are summarized in Table 2 and 3. In group S, the average size of the tumor was 2.9cm. It was 2.4 cm in group N, and 1.2cm in group F. Suprasellar extensions (Stage B, C, D) were 19 in group S, 6 in group N, and 4 in group F. And the invasions to cavernous sinus (Stage E) were 5, 3, and 1 in the same order. Grade III and IV were 8 in group S, 3 in group N, and 1 in group F. There were 12 invasive and 42 non-invasive pituitary adenomas. In summary, invasiveness was noted in 8 (32%) in group S, compared to 3 (30%) in group N, 1 (4%) in group F ($p=0.02$). Intratumoral bleeding occurred in 11 patients (group S; 7/25, group N; 2/10, and group F; 2/25) ($p>0.05$).

Immunohistochemical evaluation of NFAs

After confirmed cellular monomorphism and lack of acinar organization in surgically obtained tumor tissue by staining with hematoxylin and eosin(H&E), tissue examination of immunohistochemical reactivity against PRL, GH, TSH, ACTH, LH and FSH was done. On the basis of the immunohistochemical study, 35 patients of clinically NFAs were examined and 25 were found to be silent adenoma : 5 cases showed reactivity against prolactin, 1 against GH, 1 against both prolactin and GH, 1 against TSH and GH, 2 against ACTH, 11 against FSH and 4 against both LH and FSH (Table 4).

Treatment results

TSA was performed in all pituitary adenomas, and the number of gross total/near total removal group was 48 (group S; 17, group N; 7, and group F; 24), and the number of subtotal removal group was 12 (group S; 8, group N; 3, and group F; 1). In our clinical study, postoperative radiotherapy (RTx) was not performed routinely on residual mass. Among subtotal removal group, postoperative radiotherapy was performed in only 7 patients (group S; 5 and group N; 2), mostly within 1 month of operation. In group F, endocrinological

Table 2. Neuroradiologic characters of subgroups in pituitary adenomas

	Group N	Group F	Group S	Total
Average size(cm)	2.4	1.2	2.9	2.1
Invasiveness	3	1	8	12
Hemorrhge	2	2	7	11

Group N : immuno-negative nonfunctioning adenoma, Group F : functioning adenoma, Group S : silent adenoma

Table 3. Hardy's criteria of subgroups in pituitary adenomas

	Grade					Stage						
	I	II	III	IV	Total	0	A	B	C	D	E	Total
Group N	0	7	2	1	10	0	1	3	3	0	3	10
Group F	12	12	0	1	25	12	8	3	1	0	1	25
Group S	1	16	4	4	25	0	1	10	6	3	5	25
Total	13	35	6	6	60	12	10	16	10	3	9	60

Group N : immuno-negative nonfunctioning adenoma, Group F : functioning adenoma, Group S : silent adenoma

Table 4. Clinical and immunohistochemical findings in patient with silent adenoma

Patient	Sex/Age	C.C	IHC	Inv.	He.	Stage	resection	Local mass control
1	M/39	VD	PRL	-	+	C	T	+
2	M/65	HA	PRL	+	-	E	ST	+
3	M/34	VD	PRL	+	-	E	ST	+
4	M/44	VD	PRL	+	-	E	ST	+
5	F/43	VD	PRL	+	-	D	ST	+
6	F/62	VD	GH	-	+	C	T	+
7	M/38	VD	PRL, GH	+	-	E	ST	+
8	F/38	HA	GH, TSH	-	-	B	T	+
9	F/53	VD	ACTH	+	+	C	ST	+
10	F/45	HA	ACTH	-	+	B	T	+
11	M/72	HA	FSH	-	-	B	T	+
12	M/43	HA	FSH	-	+	B	T	+
13	M/60	HA	FSH	-	-	B	T	+
14	M/73	HA	FSH	-	+	B	T	+
15	F/59	HA	FSH	-	-	C	T	+
16	M/61	-	FSH	-	-	A	T	+
17	M/50	VD	FSH	-	+	C	T	+
18	M/44	VD	FSH	+	-	D	ST	+
19	M/49	HA	FSH	-	-	B	T	+
20	M/38	VD	FSH	-	-	C	T	+
21	M/65	VD	FSH	+	-	E	ST	+
22	M/63	VD	FSH, LH	-	-	B	T	+
23	M/54	HA	FSH, LH	-	-	B	T	+
24	F/35	VD	FSH, LH	-	-	D	T	+
25	M/48	HA	FSH, LH	-	-	E	T	+

C.C., chief complaint; IHC, immunohistochemistry; Inv., invasiveness; He., hemorrhage; VD, visual disturbance; HA, headache; PRL, prolactin; GH, growth hormone; ACTH, adrenocorticotrophic hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone; T, total; ST, subtotal

normalization was seen 20 patients (PRL 10, GH 8, and ACTH 2) and improvement in 5 patients (PRL 2 and GH 3) and the serum PRL level was also normalized in 7 patients among clinically NFAs. Local mass control was obtained in all patients, irrespective of removal extent and postoperative RTx. Postoperative complications occurred in 17 of 60 of the our cases. In operating invasive adenomas, differentiation of normal gland was impossible and most of normal gland was removed with removal of tumor. Therefore, panhypopituitarism was the most common complications and diabetes insipitus(DI) was observed in 10 patients. Permanent DI was showed in 4 patients. Intraoperative cerebrospinal fluid(CSF) leakage was seen in 7 patients and transient lumbar drain (within 2 weeks) was applied in 3 patients of these. There was no reoperation due to CSF leakage. There was not any postoperative meningitis nor wound infection.

Discussion

Pituitary tumors are defined by the charateristic clinical syndromes that accompany tumor hormone overproduction. Approximately 25 to 30 percent of patients who present with pituitary adenomas have no clinical evidence of hormone hypersecretion; such tumors are classified as NFAs[9,10]. Because patients with NFAs lack a characteristic clinical syndrome or serum hormone markers, they present with symptoms related to tumor mass effect such as headache, visual loss, or symptoms of hypopituitarism.

Clinically, NFAs are morphologically heterogeneous and can be separated into two main categories based on immunohistochemical and electron microscopic appearances[5]. One group, known as null cell adenomas and oncocytomas, includes tumors showing no characteristics of normal adenohypophyseal cells and possessing neither morphological nor immunmohistochemical markers indicating their cytogenesis or direction of differentiation[5]. The second group includes tumors exhibiting immunohistochemical and ultrastructural features of recognizable adenohypophyseal cells, but no signs of hormone excess[5,16]. These silent adenomas are composed of adenohypophyseal cell types, including silent gonadotroph, thyrotroph, corticotroph, and somatotroph adenomas. As demonstrated by immunocytochemistry and in situ hybridization, silent adenomas contain and produce one or more adenohypophyseal hormones and also express the messenger ribonucleic acid of the related hormone indicating gene expression[8,13,15,17].

In the study by Kovacs and colleagues, 99 of 343 surgically removed pituitary adenomas were unassociated with clinical or laboratory evidence of hormone hypersecretion[12]. Fifty-three cases of these NFAs showed staining for one or more anterior pituitary hormones, including FSH-β, LH-β, TSH-β, and /or α-subunit, GH, and ACTH[12]. Black et al.[3] also examined 160 surgically resected pituitary tumor specimens for hormone production. They found a twenty-three percent of the all patients showed the immunocytochemical staining for adenohypophysial cells. Fifty-eight percent of these silent adenomas showed immunostaining for FSH-β. Among them, fifty-two percent was stained for multiple glycoprotein hormones, and mixed glycoprotein hormone-prolactin cell types were also found in 16 percent. Similar findings were observed by Jameson et al., they analyzed pituitary hormone gene expression in clinically NFAs using specific oligonucleotide probes for the messenger RNAs(mRNAs) encoding the α-subunits, LH-β, FSH-β, TSH-β, GH, PRL, and ACTH[8]. Expression of one or more of the anterior pituitary hormone genes was found in 12/14 (86%) of the patients with clinically classified NFAs. In this study, the expression of one or more of the glycoprotein hormone genes (α-subunits, LH β, FSH β, TSH β) was also identified most commonly (79%) with expression of multiple β-subunit genes in many cases. In our study, twenty-five cases (71.4%) of the clinically NFAs showed the immunohistochemical staining for adenohypophysial cells. The immunohistochemical staining for FSH was 15 cases (60%) and anomg them, 4 cases (26.7%) showed the staining for LH and FSH, both. The results was similar to previous reports[3,8,10,12]. In addition, 6 cases showed immunoreactivity against prolactin, 3 against GH, 1 against TSH, and 2 against ACTH. Among them, there were immunohistochemical stainings which matched for multiple adenohypophyseal cells (Table 4).

The question why these tumors are clinically or biochemically silent has not been resolved[20]. Some authors have insisted that silent adenomas may produce biologically inactive hormones, precursor proteins, or hormone fragments[8,14]. Others have suggested that the abnormalities may occur in exocytosis of hormone from the cell membrane, so that, despite normal biosynthesis, active secretion does not take place[6,10,11]. On the other hand, Yamada et al.[21] and Klibanski[10] insisted that the amount of hormones discharged from the individual cell was lower than the normal range to produce any clinical findings, because only few cells in tumor can secrete hormones no matter what their size is. But conclusive evidence is lacking and the mechanism of silence is still elusive[4,6,13,16].

From the clinical standpoint, the fundamental question is whether these various immunohistochemically distinct tumor types differ in relation to biological behavior, pace of growth, invasiveness, recurrence, and therapeutic responsiveness[20]. Although further studies on a large number of cases are required to clarify immunohistochemical stainings-clinical correlations, some authors have insisted that silent adenomas, particularly silent corticotroph adenomas and silent somatotroph adenomas, are more prone to be associated with apoplexy or invasive-

ness, and exhibit a more frequent rate of recurrence[1,2,6,7,16,18,19]. Bradley et al.[2] concluded that postoperative radiotherapy should be considered carefully in silent ACTH adenomas owing to being a more aggressive course in the case of recurrence. And also, Yamada et al.[20] suggested that clinically NFAs, especially in young women with macroadenoma, should be examined by immunohistochemistry to achieve a correct diagnosis, since some silent adenomas should be treated as hormone secreating adenomas, which may respond to bromocriptine or octreotide medication[21]. On the other hand, the several reports have shown that the majority of silent gonadotrophin adenomas usually do not infiltrate surrounding structures in spite of large size and the clinical course of these tumors is generally good[10,16]. But in our study, 3 cases of only FSH staining presented with intratumoral bleeding, and 2 of only FSH staining showed the infiltration on both cavernous sinus. This findings were not consisted with previous reports[10,16]. In addition, intratumoral bleeding occurred in 2 cases with silent ACTH adenomas, 1 with silent GH adenoma and 1 with silent PRL adenoma. And invasiveness occured in 4 cases with silent PRL adenoma, 1 with silent ACTH adenomas and 1 with mixed silent adenoma (GH-PRL). In summary, it was shown that invasiveness and intratumoral bleeding all have a tendency to increase in the group S(8(32%), 7(28%)), compared to the group N(3(30%), 2(20.0%)) and the group F(1(4%), 2(8%)). However, statistical significance was noted in invasiveness ($p=0.02$), not in intratumoral bleeding ($p>0.05$).

Conclusion

In our study, immunoreactivity against gonadotrophin, TSH, PRL, GH, and ACTH was found in 25 of 35 clinically NFAs, which took a considerable part. And these silent adenomas showed more aggressiveness than other subgroups of pituitary adenomas. The limitation of this study is that clinical follow-up period is too short to estimate the recurrence rate, however, this immunohistochemical study against adenohypophyseal cells can be useful method in predicting clinical course of the patients with NFA. And so we think that further research to find out characters of these silent adenoma is needed.

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References

1. Asa SL, Ezzat S : The cytogenesis and pathogenesis of pituitary adenomas. **Endocr Rev 19** : 798-827, 1998
2. Bradley KJ, Wass JA, Turner HE : Non-functioning pituitary adenomas with positive immunoreactivity for ACTH behave more aggressively than ACTH immuno-negative tumors but do not recur more frequently. **Clin Endocrinol 58** : 59-64, 2003
3. Black PM, Hsu DW, Klibanski A, Kliman B, Jameson JL, Ridgway EC, et al : Hormone Production in clinically nonfunctioning pituitary adenomas. **J Neurosurg 66** : 244-250, 1987
4. Horvath E, Kovacs K : Pathology of the hypothalamus and pituitary gland in Mendelsohn G(ed) : **Diagnosis and Pathology of Endocrine Diseases**. Philadelphia : JB Lippincott, 1988, pp379-412
5. Horvath E, Kovacs K : The adenohypophysis. In Kovacs K, Asa SL(eds) : **Functional endocrine pathology**. Boston : Blackwell, 1990, Vol 1, pp245-281
6. Horvath E, Kovacs K, Killinger DW, Smyth HS, Platts ME, Singer W : Silent corticotropic adenomas of the human pituitary gland. a histologic, immunocytologic, and ultrastructural study. **Am J Pathol 98** : 617-638, 1980
7. Horvath E, Kovacs K, Smyth HS, Killinger DW, Scheithauer BW, Randall R, et al : A novel type of pituitary adenoma : morphological features and clinical correlations. **J Clin Endocrinol Metab 66** : 1111-1118, 1988
8. Jameson JL, Klibanski A, Black PM, Zervas NT, Lindell CM, Hsu DW, et al : Glycoprotein hormone genes are expressed in clinically nonfunctioning pituitary adenomas. **J Clin Invest 80** : 1472-1478, 1987
9. Jeon WY, Kim OL, Kim SH, Bae JH, Choi BY, Cho SH : The sugcical result of pituitary adenoma by transsphenoidal approach. **J Korean Neurosurg Soc 30** : 1278-1283, 2001
10. Klibanski A : Nonsecreting pituitary tumors. **Endocrinol Metab Clinic North Am 16** : 793-804, 1987
11. Kovacs K, Horvath E, Bayley TA, Hassaram ST, Ezrin C : Silent corticotroph cell adenoma with lysosomal accumulation and crinophagy; A distinct clinicopathologic entity. **Am J Med 64** : 492-499, 1978
12. Kovacs K, Horvath E, Ryan N, Ezrin C : Null cell adenoma of the pituitary. **Virchows Arch A Pathol Anat Histol 387** : 165-174, 1980
13. Kovacs K, Lloyd R, Horvath E, Asa SL, Stefaneanu L, Killinger DW, et al : Silent somatotroph adenomasof the human pituitary. A morphological study of three cases including immunocytochemistry, electron microscopy, in vitro examination and in situ hybridization. **Am J Med 134** : 345-353, 1989
14. McComb DJ, Ryan N, Horvath E, Kovacs K : Subclinical adenomas of the human pituitary. **Arch Pathol Lab Med 107** : 488-491, 1983
15. Nagaya T, Seo H, Kuwayama A, Sakurai T, Tsukamoto N, Nakane T, et al : Pro-opiomelanocortin gene expression in silent corticotroph cell adenoma and Cushing's disease. **J Neurosurg 72** : 262-267, 1990
16. Randall RV, Scheithauer BW, Laws ER Jr : Hormone containing nonsecreting pituitary tumors : clinically silent monohormonal pituitary adenomas. **Trans Am Clin Climatol Assoc 96** : 98-103, 1984
17. Sakurai T, Seo H, Yamamoto N, Nagaya T, Nakane T, Kuwayama A, et al : Detection of mRNA of prolactin and ACTH in clinically nonfunctioning pituitary adenomas. **J Neurosurg 69** : 653-659, 1988
18. Scheithauer BW, Jaap AJ, Horvath E, Kovacs K, Lloyd RV, Meyer FB, et al : Clinically silent corticotroph tumors of the pituitary gland. **Neurosurgery 47** : 723-729, 2000
19. Scheithauer BW, Kovacs KT, Laws ER Jr, Randall RV : Pathology of invasive pituitary tumors with special reference to functional classification. **J Neurosurg 65** : 733-744, 1986
20. Yamada S, Kovacs K, Horvath E, Aiba T : Morphological study of clinically nonsecreting pituitary adenomas in patients under 40 years of age. **J Neurosurg 75** : 902-905, 1991
21. Yamada S, Sano T, Stefaneanu L, Kovacs K, Aiba T, Sawano S, et al : Endocrine and morphological study of a clinically silent somatotroph adenoma of the human pituitary. **J Clin Endocrinol Metab 76** : 352-356, 1993

Commentary

This article was designed to address the very interesting issue regarding relationship between clinico-radiological findings the non-functioning pituitary adenoma with positive immunoreactivity for anterior pituitary hormones.

Even though the authors concluded that silent adenomas might behaved more aggressively compared with other sub-

groups of pituitary adenomas, the answer need to be confirmed after evaluating more large series of clinical data. The morphological appraisal of pituitary adenomas has its limitations. Whether considered from the stand-points of routine histology, hormone immunophenotype, or ultrastructural morphology, none of these techniques permits reliable inferences about tumor behavior or prognosis[1]. Accordingly, pituitary adenomas are not amendable to any form of histopathologic grading that could reliably distinguish between aggressive variants from indolent ones. A variety of approaches can be used to classify pituitary tumors, ranging from simple to sophiscated and with each its own individual merits and limitations. The management of pituitary tumors is a multidisciplinary endeavor, and nosolocial preferences vary between specialits. A five-tiered classification of adenohypophyseal tumors has been proposed to the World Health Organization. In this scheme five descriptive levels are applied to each adenoma : clinical presentation and secretory activity, size and invasiveness, histological features, immunohistochemical profile and ultrastuructural type. Approximately one fourth of all pituitary adenomas are unassociated with clinical or biochemical evidence of hormone hypersecretion. Known as clinically nonfunctioning pituitary tumors, this morphologically diverse class of lesions included null cell adenomas, oncocytomas, silent corticotroph adenoma type 1 and 2, silent subtype 3, and the rare silent somatotroph adenoma. It has been customary and convenient to also include gonadotroph adenomas in this class because hypersecretion is unassociated with a clinically evident hypersecretory state. Concealed clinically by their endocrinological silence, non-functioning pituitary adenomas manifest only after they have grown to sufficient size to produce mass effects. Contrary to authors's description, the nonfunctioning pituitary adenoma's longterm biological behavior is not so aggressive. Because of the relatively slow growth of these tumors and their usual occurrence in elderly patients, symptomatic recurrence is generally less a less serious and a less frequent threat than it is for most functioning adenomas. Symptomatic recurrence develops in relatively few patients. Law's et all reported recurrence in 16 among 100 patients, and only 6 of whom were symptomatic and in need of subsequent therapy. They also descriebed that during 10-year follow-up period, the overall outcome was quiet favorable, with 76% of patients enjoying symptom-free or progression-free survial, or both. Comparable results were reported by Bradley and coworkers, who documented a 90% recurrence free survival over a 5-year period. A somewhat higher symptomatic recurrence rate was reported by Comtois and asssociates. In a cohort of 71 patients, all of whom had gross total tumor resection and were followed for mean period of more than 6 years, 15(21%) had symptomatic recurrences. Radiotherapy is generally employed in a far more selected fashion and is usually reserved for those patients in whom rapid progression can be documented. For the more indolent and slow-growing lesions for which years may pass before symptomatic recurrence, repeat resection is generally preferable to radiotherapy. As stated above, we need more clinical data to conclude that the biological behavior is more aggressive in case of non-functioning pituitary adenoma.

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Reference

1. Thapar K, Kovacs K : **Tumors of the sellar region**. In Bigner DD, McLendon RE, Bruner JM(eds) : Russel and Rubinstein's Pathology of Tumors of the Nervous System. Baltimore, Williams & Wilkins, 1998, pp 561-677