İnönü Üniversitesi Tıp Fakültesi Dergisi
11(3) 135-141 (2004)

Retrospective Analyses of 25 Patients with Pituitary Macroadenomas+

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Aim: The aim of this study is to retrospectively evaluate the 25 patients (15 female, 10 male, mean age 43.24 ± 15.44 years) with pituitary macroadenomas; 12 clinically non-functioning tumors (CNFTs), 6 prolactinomas, 5 acromegalies, and 2 craniopharingiomas attempted to our Neurosurgery and Endocrinology Clinics.
Methods: The patients were evaluated demographically and endocrinologically with the nature of the tumor and operation modalities.
Results: Male dominancy was defined in CNFTs (58.3%), but in acromegalies (80%), and prolactinomas (66.6%) most of the patients were female. Both of the craniopharingiomas were women as well. Headache was the predominant (52%) complaint for all the cases, visual disturbances (36%) and hypogonadal symptoms (16%) were the others. Hypogonadotropic hypogonadism and hypopituitarism were the most frequent endocrinologic abnormalities at admission. Eighteen of the patients were operated. In 10 (40%) of them transsphenoidal surgery, and in 8 (32%) transcranial surgery was performed. The recurrence rate was 22.2%. Hypopituitarism was increased up to 50% (n=9) from 28%, and sustained diabetes insipidus from 4% to 27.8% (n=5) postoperatively.
Conclusion: Despite new treatment modalities in functioning adenomas promise expectations, pituitary macroadenomas seem to sustain as a dilemma especially for the endocrinologic dysfunctions in regards of tumor mass effect or operation sequels.

Key Words: Non-functioning pituitary adenomas, Prolactinomas, Acromegaly, Craniopharingiomas

Hipofiz Makroadenomu Olan 25 Hastanın Retrospektif Olarak Değerlendirilmesi

Amaç: Bu çalışmanın amacı, 2000-2004 yılları arasında Nöroşirurji ve Endokrinoloji Kliniklerimizde tedavi edilen hipofizer makroadenomlu 25 hastanın (15 kadın, 10 erkek, yaş ortalaması 43.24 ± 15.44 yıl) retrospektif olarak incelenmesidir.
Yöntem: Hastalar demografik ve endokrinolojik bulgulara, tümörün çapı, yayılımı ve operasyon şekline göre değerlendirilmiştir.
Bulgular: Olguların 12'si klinik olarak non-fonksiyone adenom (CNFT), 6'sı prolaktinoma, 5'i akromegali ve 2'si kranyofarinjiomadır. CNFT'lü vakalarda erkekler (%58.3), akromegali (%80) ve prolaktinomalarda (%66.6) ise kadınlar çoğunluktaydı. Kranyofarinjiomalı iki olgu da kadındı. Baş ağrısı (%52) görme bozuklukları (%36) and hipogonadal semptomlar (%16) başvuru anında belirtilen en sık şikayetlerdi. Hipogonadotropik hipogonadizm ve hipopitüitarizm tedavi öncesi tespit edilen en sık endokrinolojik bozukluklardı. Hastaların 18'i tümör özelliğine göre transsfenoidal (n=10, %40) yada transkranyal yoldan (n=8, %32) opere edildi. Nüks oranı %22.2 bulundu. Operasyonlardan sonra hipopitüitarizmin %28'den %50'ye (n=9), ve kalıcı diabetes insipidusun %4'ten %27.8'e (n=5) yükseldiği görülürken, vizyon bozukluklarının % 48'den %20'ye, oftalmopleji oranının ise %20'den %4'e düştüğü görüldü.
Sonuç: Her ne kadar hipofiz adenomlarında yeni tedavi yaklaşımları umut vaat ediyorsa da, makroadenomlar gerek kitle etkileri gerekse operasyona bağlı nedenlerle endokrinolojik ve cerrahi açıdan hala ciddi bir sorun olarak görünmektedir.

Anahtar Kelimeler: Non-fonksiyone hipofiz adenomu, Prolaktinoma, Akromegali, Kranyofarinjioma

+ Bu çalışma 13-15 Mayıs 2004' de, Kapadokya'da düzenlenen "ISPNE (International Society of Psychoneuroendocrinology), 3rd Regional Congress for Central and Eastern Europe' da poster olarak sunulmuştur. Turkish Journal of Endocrinology and Metabolism'de supplement olarak; 8(1):53-54, 2004 yayınlanmıştır.

With various signs and symptoms pituitary macroadenomas necessitate a collective labor of endocrinologists and neurosurgeons**.** The estimated incidence of pituitary tumors ranges 0.5-7.4 per 100,000 with the highest incidence occurring in women aged 15-44 years.1 They come to clinical attention due to mass effect or manifestations of pituitary hormone excess or insufficiency.2 These tumors are classified according to their cell type of origin. The hormone-secreting cells may give rise to functional pituitary tumors that hypersecrete one or more hormones including prolactin (PRL), growth hormone (GH), adrenocorticotropic hormone (ACTH), and rarely follicle-stimulating hormone (FSH), luteinizing hormone (LH) or thyroid-stimulating hormone (TSH). The tumors without any identifiable clinical hypersecretory syndrome are termed clinically nonfunctioning tumors (CNFTs).

Successful management aimed at normalization of hormonal excess or deficiency, decompression of local vital structures, and prevention of tumor recurrence often requires lifelong treatment and follow-up.

Not only the relatively low annual incidence of pituitary adenoma diagnosis and long natural history of these tumors have hampered to estimate clinical outcomes in significant numbers of patients, but the necessity to evaluate the various tumor types, a commonly accepted reliable tumor type-specific epidemiological information is nonexistent.[3]

Here we evaluated the patients with pituitary macroadenomas. We documented their endocrinologic and biochemical properties with treatment outcomes retrospectively.

METHODS

The aim of this study is to evaluate the patients with pituitary macroadenomas retrospectively who attempted to our Endocrinology and Neurosurgery Clinics, between 2000- 2004.

Twenty-five patients with pituitary macroadenomas were evaluated according to the hormonal activity, dimension, and invasiveness of the tumor. Tumor sizes were determined by radiographic analysis. Tumors greater than or equal to 10 mm dimension were considered macroadenomas. Tumor type is determined by hormonal biochemical profile and clinical presentation. Immunohistochemical confirmation was not available but pathological evaluation of the tumor tissue was performed to the patients who had undergone surgical excision of the tumor.

All laboratory values were interpreted based on the reporting laboratory's normal range. Concurrent hyperprolactinemia was defined as PRL elevation in a patient diagnosed CNFTs, acromegaly or craniopharingioma.

Hypogonadal symptoms included complaints of diminished libido, oligo-amenorrhea, infertility, or erectile dysfunction. Hypogonadotropic hypogonadism was diagnosed when estradiol or testosterone levels were low in the presence of inappropriately normal or low FSH and/or LH levels. Hypopituitarism included deficiency of the GH, gonadal (FSH, LH), thyroid (abnormal thyroid hormone levels with inappropriate THS levels), and adrenal axes.

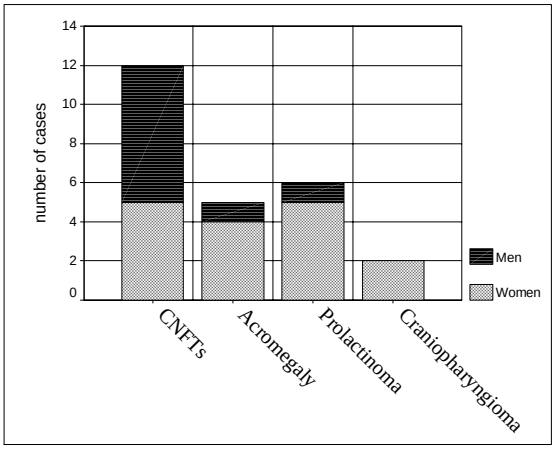
Radiological cure was defined as the absence of visualized tumor tissue on magnetic imaging (MRI), or computed tomography imaging (if MRI scans were not available). Biochemical control of prolactinoma was defined as normalized serum PRL levels. Biochemical remission of acromegaly was defined by both normalized insulin-like growth factor for age and sex and a glucose suppressed GH value less than or equal to 2 μg/L. Treatment modalities and rate of recurrences were documented.

RESULTS

The study group was consisted of 25 patients, 15 women (60%) and 10 men (40%) with mean age 43.24 ± 15.44 years (median 42, range 18-72 yrs.) Most of the tumors were clinically nonfunctioning tumors (CNFTs) (48%, n=12, mean age: 44.25±14.40 range:18-72yrs), prolactinomas were in the second line (24%, n=6, mean age: 36±11.73 range:25-55yrs), GH-secreting adenomas (20 %, n=5, mean age: 56.4±15.87 range:33-70 yrs), and craniopharingiomas (8%, n=2, mean age: 32±14.14 ages:22 and 44 yrs) were following lesions. There was not any significant difference for age

between the groups (p=0.095) (Gender distribution was shown on Figure 1).

Figure 1. Distribution of gender within the groups



Male dominancy was defined in CNFTs (58.3%), but in GH-secreting adenomas (80%), and prolactinomas (66.6%) most of the patients were women. Both of two patients with craniopharingiomas were female as well.

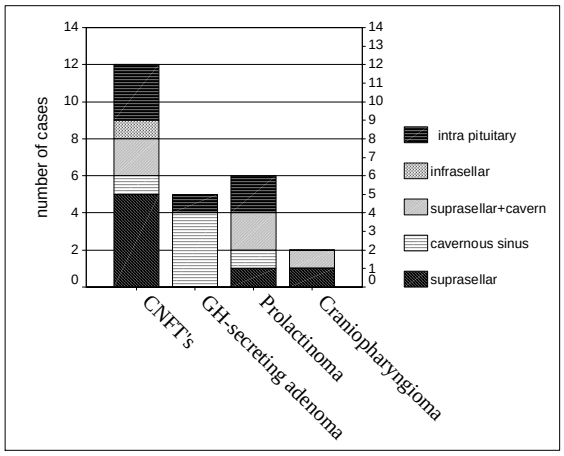
Concurrent hyperprolactinemia was not defined in any of the tumors (CNFTs, craniopharingiomas and acromegalies) before treatment. But two patients from CNFT and both of the craniopharyngiomas had concurrent hyperprolactinemia after treatment, so the concentration of the hormone within these groups was significantly different after treatment modalities (18.74 ± 5.3 vs. 23.35 ± 32.09, p= 0.001).

Headache was the predominant (n=17, 58%) complaint for all the cases, visual disturbances (n=12, 48%) and amenorrhea/ impotence (n=11, 44%) were the other most frequent symptoms, followed by ophtalmoplegia (n=5, 20%) and fatigue (n=4, 16%). The complaint of acral enlargement was present in all GH-secreting adenomas. Galactorrhea was present in 66.6 % of prolactinomas. One of the patients with craniopharingioma was presented with the symptoms of increased intracranial pressure, in means of a huge invasive tumor. She was the only patient (4%) with diabetes insipidus as a presenting feature within the group. The other patient with craniopharingioma was nearly asymptomatic except visual disturbances in means of chiasma opticum's compression (The tumor-specific presenting clinical features were documented in Table 1).

Hypogonadism (58.3%) was the most frequent endocrinologic abnormality in CNFTs, which was followed by hypopituitarism (16.6%), while 25% of patients had normal endocrinologic status at admission. Sixty percentages of acromegalic patients were hypogonad, and 40% was hypopituitary at first visit. Besides hyperprolactinemia, in 33.2% of prolactin-secreting adenomas hypopituitarism was present, while 16.8% of these patients had no more endocrinologic abnormality. One of the patients with craniopharyngioma had hypopituitarism at admission. (Preoperative and postoperative endocrinologic status of the patients were documented in Table 2).

In 5 patients tumors were localized in pituitary gland (20%), but all the others were extending to outer regions than pituitary gland (i.e. suprasellar extension 28%, n=7, cavernous sinus infiltration 48%, n=12, infrasellar extension 4%, n=1) (The invasiveness of the tumors were shown on Figure 2).

Figure 2. The invasiveness of the tumors



Different treatment modalities were preferred accordingly to the tumor mass and hormonal function. Eighteen of the patients were operated. In 10 (40%) of them transsphenoidal surgery, and in 8 (32%) transcranial surgery was performed. The recurrence rate was 22.2% (two of the CNFTs, one prolactinoma, and one craniopharingioma) in three of them transcranial surgery (75% of the recurrented adenomas) was performed.

Table 1. The tumor-specific presenting clinical features

	CNFTs (n=12)		Acromegaly (n=5)		Prolactinoma (n=6)		Craniopharyngioma (n=2)	
	Number	%	Number	%	Number	%	Number	%
Hypogonadal symptoms	3	25 %	3	60 %	4	66.6 %	1	50 %
Headache	8	66.6 %	3	60 %	4	66.6 %	2	100 %
Galactorrhea					4	66.6 %		
Visual disturbances	6	50 %	1	20 %	3	50 %	2	100 %
Ophtalmoplegia	1	8.3 %	1	20 %	2	21 %	1	50 %
Acral and maxillofacial changes			5	100 %				
Fatigue	3	25 %					1	50 %

Table 2. Preoperatively and postoperatively endocrinologic status of the patients

	CNFT' s		Acromegaly		Prolactinoma		Cranio.	
Number of cases	n=12		n=5		n=6		n=2	
Transcranial	n=4		n=2		n=1		n=1	
Transsphenoidal	n=7		n=1		n=1		n=1	
	Number	%	Number	%	Number	%	Number	%
Normal								
Preoperatively	3	25 %	-		-		-	
Postoperatively	1	9 %	1	33.3 %	-		-	
Hypogonadism								
Preoperatively	7	58.3 %	3	60 %	3	50 %	-	
Postoperatively	3	27.2 %	2	66.7 %	1	50 %	-	
Hypopituitarism								
Preoperatively	2	16.6 %	2	40 %	2	33.2 %	1	50 %
Postoperatively	6	54.5 %	-		1	50 %	2	100 %
Diabetes insipidus								
Preoperatively	-		-		-		1	50 %
Postoperatively	2	18.8 %	-		1	50 %	2	100 %
Hyperprolactinemia								
Preoperatively	-		-		*NA		-	
Postoperatively	2	18.8 %	-		*NA		2	100 %

* NA: Not applicable

Rate of endocrinologic deficiencies were noticeable in operated cases. Hypopituitarism was increased up to 50% from 28% (n=9 and 7 respectively), and diabetes insipidus up to 27.8% from 4% (n=5 and 1 respectively) postoperatively for the whole group. However visual disturbances were decreased to 20% (n=5) from 48% (n=12) and ophtalmoplegia to 4% (1) from 20% (n=5) after surgery. Two of the three patients with acromegaly, turned to normal endocrinological status, and the patient with preoperative hypopituitarism recovered in post-treatment period as well. For CNFTs despite 4 of the preoperatively hypogonad 7 patients recovered, hypopituitarism raised up to 54.5% (n=6) from 16.6% (n=2); additionally in two patients sustained diabetes insipidus and concurrent hyperprolactinemia developed. But the number of cases with visual disturbances decreased to 3 from 6, and the patient with ophtalmoplegia recovered. Hypogonadism and hypopituitarism established in each of the patients postoperatively in prolactinoma group, but the rates of these abnormalities were reduced compared to pretreatment period for the whole group. One patient with ophtalmoplegia and two patients with visual deficiencies were recovered after treatment modalities in prolactinoma group. Although both of the craniopharingiomas became hypopituitary after operation, visual deficiency and ophtalmoplegia were recovered in each of them. The rates of visual disturbances and ophtalmoplegia within the groups in pre and post-treatment periods are documented on Table 3.

DISCUSSION

In this paper we presented 25 patients with pituitary macroadenomas managed in our Endocrinology and Neurosurgery clinics retrospectively.

Table 3. The visual disturbances and ophtalmoplegia rates of the patients

	CNFTs		Acromegaly		Prolactinoma		Craniopharyngioma	
	Number	%	Number	%	Number	%	Number	%
Visual disturbances								
Pre-treatment	6	50 %	1	20 %	3	50 %	**2**	**100 %**
Post-treatment	3	25 %	-		1	16.6 %	**1**	**50 %**
Ophtalmoplegia								
Pre-treatment	1	8.3 %	1	20 %	2	21 %	**1**	**50 %**
Post-treatment	-		-		1	16.6 %	**-**	

Pituitary tumors are relatively common neoplasms, representing nearly 15% of all intracranial tumors.[4,5] The prevalence of clinically recognizable pituitary adenomas is 200 cases per million, and annual incidence is 15 cases per million.[6] Meanwhile asemptomatik adenomas of pituitary gland are found to be 6%-25% which was demonstrated by autopsy studies and/or systematic magnetic resonance imaging studies.[7-9] Endocrinologically active adenomas account for 75% of cases.[10] Thus pituitary adenomas –whether detected by clinical manifestations or incidentally – are becoming more frequently diagnosed. An accurate classification of a pituitary adenoma depends on immunucytochemical study performed on the surgically removed tissue, but for simplification of therapeutic decision a clinical classification is used, which is based on the presence or absence of a hypersecretion syndrome.[11] In this paper the patients were diagnosed by their histopathological and/or endocrinological features.

Despite pituitary adenomas generally tend to occur more frequently in younger women (15-44 yrs), macroadenomas tend to occur in men.[1,3] In this study there was not any statistical difference between the groups for age, and the mean ages of the groups were within the reported ranges. For CNFTs female predominance was reported.[3] However most of our patients with CNFTs were male. On the other hand -as it is respected- female dominancy was defined in prolactinomas. The unique male patient of this group had a huge tumor mass which was invaded to surrounding tissues. This finding is consistent with the previous reports.[12] Though gender has been reported to be equally distributed in GH-secreting adenomas, in our group female dominancy was defined.[3] These observations may reflect gender difference in patient inclination to seek medical attention for hypogonadal symptoms. The insufficient number of cases in our study is the other cause of these results as well.

Patients with pituitary macroadenomas generally present with mass-related effects such as headache and visual disturbances.[3,13,14] In our study group, headache was the predominant complaint for all the subgroups. The rates of the complaint were compatible with the literature as well. Acral enlargement and maxillofacial changes were reported to be about 75-85% of acromegalic patients.[3] All of our five patients were presenting these changing possibly due to delayed diagnose. Hypogonadal symptoms including amenorrhea/ impotence were the other common presenting future for all the groups, especially for prolactinomas. Galactorrhea, as a presenting feature, was reported to be 48% and 60% in previous studies while reported to be rare in males with macroadenomas.[3,15] Our unique male patient despite having a huge adenoma had not had such a symptom but the rate was 66.6% in the remainder. Pituitary insufficiency can be encountered in patients with any size or type of intrasellar mass and thus, serves as an important diagnostic indicator of a pituitary lesion. Hypogonadotropic hypogonadism was a relatively common pretherapeutic finding for all tumor types and corresponds to the frequency of hypogonadal symptoms at presentation. Except for the CNFTs, about half of our patients were suffering from hypogonadism (25% in former). Hypogonadism was reported to be about 32% in CNFTs generally concurrent with hyperprolactinemia. However concurrent prolactin secretion was found to be unrelated with the tumor size.[16] We could not establish these rates in our cases. But in remainders the rates of hypogonadism was consistent with the literature –in regards of 30-40% for various subgroups-.[3] Both higher hypopituitarism and hypogonadism were observed in acromegaly patients. This result probably not only depends on the tumor size but the duration of the lesion as well-as delayed diagnose of acromegaly compared to others-.[17]

The treatment modalities were chosen accordingly to the patients' choice, tumor size and invasion. One patient with acromegaly (70 years old, male) died preoperatively because of respiratory tract obstruction. Four of the patients with prolactinoma were treated with pharmacotherapy either with bromocriptine or cabergoline. The operation types were decided accordingly to the tumors' nature. Eighteen of the patients were operated. In 10 (40%) of them transsphenoidal surgery, and in 8 (32%) transcranial surgery was performed. The recurrence rate was 22.2% within the whole group.

Transcranial surgery was performed in 4 patients (33.2%) and transsphenoidal in 7 (58.3%) patients with CNFTs. In one each patient operated by either procedure the recurrence of the lesion was defined radiologically, in whom tumors were extending to suprasellary space. Recurrence rate was 18.2% (25% for transcranial, and 14.3% for transsphenoidal way) in operated group. In a 32 patient CNFTs (all macroadenomas) series recurrence rate was 25% in which transsphenoidal surgery was the only procedure for all the cases even in the presence of visual disturbances.[18] Probably as a result of big tumor mass postoperative hypopituitarism was raised in this group (from 16.6% to 54.5%).

Two of the patients were operated in prolactinoma group, one each patient operated by either procedure. The patient with the tumor extending to both suprasellary and cavernous sinuses operated by transcranial approach, in which tumor recurrence was defined, and visual deficiency sustained. The patient operated by transsphenoidal surgery was recovered not only for endocrinologic deficiencies but visual disturbances with ophtalmoplegia as well. Though transsphenoidal surgery seems to be safe and fairly curable (72%) for prolactin secreting microadenomas, the cure rate is about 35% for macroadenomas. These rates are nearly the same for endocrinologic cure as well.[19,20] As the small number of our operated prolactinomas it is difficult to estimate the accurate recurrence/cure rate for our patients.

Both of the patients with craniopharyngioma were operated, one each by either procedure. The patient with the tumor extending to both suprasellary and cavernous sinuses was operated by transcranial approach, in which tumor recurrence was defined with sustained visual deficiency. In the other patient, despite removal of the tumor, hypopituitarism with sustained diabetes insipidus and hyperprolactinemia established, but visual deficiency recovered. The recurrence rates for these tumors tend to increase within the first 2 years of the initial treatment, and rises up to 68% in ten years.[21,22] As we confessed for the prolactinomas, the minority of our patients hinders to obtain an accurate recurrence/cure rate for craniopharyngiomas as well.

Three of the acromegalies were operated; two of them by transcranial surgery and one by transsphenoidal. According to different series cure rate is less than 50% for invasive macroadenomas of acromegaly, and adjuvant pharmacotherapy is highly useful for residual disease.[23] Though isolated hypogonadism sustained in 2 of 3 patients, hypopituitarism recovered in 2 patients after surgery. Somatostatin can be used alone or additional to radiotherapy to avoid complications of excess GH secretion.[23] As a result of residual disease, sustained GH excess secretion was defined in two of our patients. So, they have been managed with long acting somatostatin.

To our knowledge the literature is limited in regard of functioning and non-functioning, micro and macroadenomas reported separately. So it is difficult to compare the results solely for each group. But in the lights of the literature given above our results are compatible with the previous reports.

With various signs and symptoms pituitary macroadenomas necessitate a collective labor of endocrinologists and neurosurgeons**.** Despite new treatment modalities in functioning adenomas promise expectations, pituitary macroadenomas seem to sustain as a dilemma especially for the endocrinologic dysfunctions in regards of tumor mass effect or operation sequels.

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