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Evaluation of clinical, laboratory and treatment modalities of pituitary adenomas: Single center experience

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Abstract

Pituitary adenomas are a group of disease with broad different clinical characteristics and complications. We aimed to present the data of patients being followed in a single center and discuss the pituitary adenomas based on the literature. Two hundred and twenty patients followed at Department of Endocrinology and Metabolism, Medical School of Ondokuz Mayis University, were included into study. Clinical characteristics, laboratory findings and treatment modalities were examined retrospectively. 59% of patients were female and 41% were male. Mean age during the diagnosis was 43.7 years. Pituitary macroadenomas were 62% of all adenomas and 73% of pituitary adenomas were functional. Among the functional adenomas, the most frequently seen types were prolactin-secreting adenoma and growth-hormone secreting adenoma. Treatment options were surgical treatment (67%), medical treatment (20%) and radiotherapy (7%). Post-operative complications were developed in 27 (13.2%) of patients. In patients with non-functional adenoma, the cure after surgery was detected as 19.6% and the remission after the surgery was detected as 8.9%. In this study, the characteristics of the pituitary adenomas were found similar to the literature in general. The early diagnosis of the disease has a significant importance in terms of treatment and the response to the treatment.

Keywords: acromegaly, Cushing disease, nonfunctional adenomas, pituitary adenoma, prolactinoma, TSHoma

1. Introduction

Pituitary adenomas are the benign tumors of the anterior pituitary gland and the most common cause of sellar masses up to 10 percent of all intracranial neoplasms (1). Autopsy and radiological studies revealed that the expected prevalence may be as high as 20% (2). Population studies from different countries have estimated that the prevalence of pituitary adenomas is 75.7–115.5 cases per 100,000 of population (3-5). Adenomas can originate from any type of cell of the pituitary and may produce hypersecretion of the hormones. Decreased secretion of hormones due to compression of pituitary cells may also occur. Sellar masses can present with abnormalities related to hypo or hypersecretion of pituitary hormones, or as an incidental finding on radiological examination performed for different indications. Most of these tumors are incidentalomas without clinical significance.

Pituitary adenomas have an important role in endocrinological practice. The aim of this study is to collect the data of the pituitary adenoma cases to reveal our own results based on the literature and discuss them.

2. Materials and methods

This single-centered retrospective study was carried out in patients with pituitary adenomas followed at Department of Endocrinology and Metabolism, Medical School of Ondokuz Mayis University. Two hundred and twenty patients followed between June 2004 – October 2014 were enrolled in the study. The study protocol was approved by the Local Ethics Committee. Sociodemographic data of all participants regarding age, sex, marital status and level of education were recorded. Age at diagnosis, adenoma type, adenoma size, application complaints, levels of preliminary pituitary hormones, radiological examination method used in diagnosis, types of treatment, mode of operation, postoperative complications, medical treatment, radiotherapy, remission, cure and recurrence rates, follow-up frequency were examined. For prolactinoma, measurement of serum prolactin; a level above the upper limit of normal was used for the diagnosis after excluding medication use, renal failure, hypothyroidism, and parasellar tumors. Acromegaly was diagnosed with the measurement of serum insulin like growth factor-1 (IGF-1) and nadir growth hormone (GH) after 75 gr oral glucose tolerance test (OGTT). GH equal to or greater than 1 µg/L after an OGTT, in conjunction with clinical suspicion and high IGF-I levels adjusted for age and sex matched references were the criteria for the diagnosis of acromegaly. The diagnosis of Cushing disease was

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established based on clinical features of hypercortisolism coupled with the failure to suppress plasma cortisol at 8 a.m. to a level below 1.8 μg per deciliter after the administration of 1 mg of dexamethasone at 11 p.m. or elevated 24-hour urinary free cortisol levels. Inferior petrosal sinus sampling was done if the adenoma size was < 6 mm. A central-to-peripheral plasma ACTH gradient of ≥2.0 before CRH administration, or ≥3.0 after CRH, verified the diagnosis of a pituitary source of ACTH. TSH secreting adenoma was diagnosed with elevated or inappropriately suppressed thyrotropin levels with normal or elevated thyroid hormone levels. Differential diagnosis was made with high molar ratio of serum alpha subunit to TSH. Adenomas with no hormonal production was accepted as nonfunctional adenoma. Symptoms were evaluated separately in each group of adenomas. They were not classified as symptoms related with mass effect or hormonal hyperfunction. Panhypopituitarism, central diabetes insipidus, rhinorrhea, meningitis, central, hypothyroidism, deep vein thrombosis was evaluated as postoperative complications.

2.1. Statistical analysis

SPSS 15.0 statistical package program was used for statistical evaluation of the data. Categorical variables were defined as % ratio. The findings were evaluated with the student T test. Chi-square test was used to compare categorical variables. $p<0.05$ was regarded as significant.

3. Results

Of the 220 cases included in the study, 129 (59%) were female and 91 (41%) were male. The age at the time of diagnosis varied from 18 to 75 years, with an average age of 43.7 years. The average age was 40.9 years in female and 47.7 years in men ($p<0.05$). Pituitary microadenoma was detected in 38% of the patients and pituitary macroadenoma in 62% of the patients. When evaluated clinically, 73% of pituitary adenomas were functional and 27% were found nonfunctional. The average age was 41.9 years for functional adenomas and 48.8 years for nonfunctional adenomas ($p<0.05$) (Table 1). In functional adenomas, microadenoma rate was 45% and macroadenoma rate was 55%, these rates were 18.6% and 81.4%, respectively for nonfunctional adenomas ($p <0.05$).

Among functional adenomas, 29.5% were prolactin-secreting adenoma, 29% of GH-secreting adenoma, 12.7% of ACTH producing adenoma and 1.8% TSH-secreting adenoma. When adenoma type and adenoma size were compared; 28.6% were ACTH-secreting adenomas, 81.2% of GH-secreting adenomas, 40% of PRL-secreting adenomas and 81.4% of non-functional adenomas were macroadenoma (Table 2).

The patients were evaluated according to the symptoms at the time of admission. Symptoms were present in 90% of patients. The most common symptom was headache (21%). Enlargement in hands-foots and visual impairment were the following complaints. When the cases were evaluated in terms of radiological diagnosis, the first used diagnostic imaging was pituitary MRI in 196 cases (89%). It was followed by brain MR (7.3%).

Table 1. Basic characteristics of pituitary adenomas

	N	*%*	p
Male	91	41.4	< 0.05
Female	129	58.6	
	Mean	**SD**	**p**
Age (total)	43.7	10.9	
Male	47.7	12.7	< 0.05
Female	40.9	9.1	
	N	*%*	p
Microadenoma	84	38	< 0.05
Macroadenoma	136	62	
Functional	160	73	< 0.05
Nonfunctional	60	27	

The results were examined in terms of treatment. Surgical treatment was applied to 64.7% of the patients. Forty-two of the patients who did not undergo surgery received medical treatment, only one patient received gam knife after medical treatment and one patient received gam knife treatment alone because of surgery risk. Eighteen patients were followed without any treatment. Treatment information of sixteen patients could not be reached. It has been determined that 92.3% of surgically operated cases were operated transsphenoidally and 7.6% were operated transcranially.

It was determined that postoperative complications were developed in 27 cases (13.2%). Mortality due to postoperative complication was not detected in any of the cases. The average age of those who developed postoperative complications was 46 years and 43 years for those who did not develop complications ($p>0.05$). In terms of postoperative complications; panhypopituitarism in eight cases (29.7%), partial diabetes insipidus in five cases (18.5%), rhinorrhea and meningitis in three cases (11.1%), hypothyroidism in three cases (11.1%), rhinorrhea only in two cases (7.4%), ophthalmoplegia and meningitis in one case (3.7%), acute renal failure in one case (3.7%), hypothyroidism and diabetes insipidus in one case (3.7%), rhinorrhea and pneumocephalus in 1 case (3.7%), deep vein thrombosis in one case (3.7%) and epistaxis in one case (3.7%) were detected. The postoperative complication rates were 15.4%, 12%, 9.5% and 18.9% for ACTH secreting adenomas, GH secreting adenomas, PRL secreting adenomas and non-functional adenomas, respectively. There was no statistically significant difference between adenoma types and complication rates ($p> 0.05$). In term of compliance for patients for postoperative follow-up, 58 (26.3%) patients came to control once a year, 42 (19%) twice a year, 24 (10%) four times a year and one patient came every month. While it was observed that 125 cases followed up regularly, it was determined that others did not come controls regularly.

3.1. Non-functioning adenoma

Nonfunctioning adenomas were account for 27% of all cases.

47.5% were female and 52.5% were male. The average age of diagnosis was 48 years. In 89.8% of cases with nonfunctional adenomas, symptoms were detected at the time of diagnosis. The most common symptom was headache (35.1%). Other symptoms were impaired vision (22.5%), loss of libido (4.8%) and nonspecific symptoms (27.4%). Pituitary insufficiency was detected in laboratory examination in 32% of patients. Surgical treatment was applied to 39 of 59 (69.6%) patients. Hormone replacement therapy was applied in 13 (33.3%) patients due to pituitary insufficiency developed after surgery.

Table 2. Characteristics of subtypes of pituitary adenomas

		Results (n/%)				
		PRL-secreting adenoma	GH-secreting adenoma	ACTH secreting adenoma	TSH-secreting adenoma	Non-functional adenoma
Adenoma type	**n/%**	65 (29.5)	65 (29)	28 (12.7)	3 (1.8)	59 (27)
Sex	**Female**	40 (61.5)	37 (57)	23 (82.1)	1 (33.3)	28 (47.5)
	Male	25 (38.5)	28 (43)	5 (17.9)	2 (66.7)	31 (52.5)
Average age of diagnosis	**Year**	40	45	37	52	48
Adenoma size	**Microadenoma**	39 (60)	12 (18.8)	20 (71.4)	1 (33.3)	11 (18.6)
	Macroadenoma	26 (40)	53 (81.2)	8 (28.6)	2 (66.7)	48 (81.4)
Symptoms	**Present**	54 (83)	60 (92.2)	28 (100)	2 (66.7)	53 (89.8)
	Non present	11 (17)	5 (7.8)	0 (0)	1 (33.3)	6 (10.2)
Surgery	**n/%**	7 (1)	60 (92.3)	21 (84)	2 (66.6)	39 (66.1)
Postoperative complication	**%**	9.5	12	15.4	0	18.9

3.2. Prolactin secreting adenomas

Prolactin-secreting adenomas were account for 29.5% of all cases. 61.5% of the cases were female. The average age of diagnosis was 40 years. 60% of adenomas were microadenoma. Prolactin levels were detected >200 ng/ml in 67.8% of macroprolactinoma cases, <200 ng / in 73% of microprolactinoma cases. At the time of diagnosis, symptoms were detected in 83% of cases with prolactinoma. The most common symptom was galactorrhea (36%). Other symptoms were menstrual irregularity (16.4%), loss of libido (13.9%), headache (11.3%), visual impairment (7.3%) and nonspecific symptoms (15.1%). Surgical treatment was applied to 24 (36.9%) of the 65 cases. Postoperative medical treatment was continued in 17 of 24 patients who underwent surgical treatment. Of the 65 cases followed for prolactinoma, 47 were treated with cabergoline. Remission was achieved in 76% cases with only bromocriptine therapy, in 3% cases with only cabergoline therapy, in 6% cases with surgical therapy alone and in 9% cases with surgery + medical treatment in microprolactinomas. 4% of microprolactinomas were found to be unstable despite all treatment modalities. In macroprolactinoma cases remission rates were 24% with cabergoline alone, 36% with surgery and cabergoline, 8% with surgical treatment alone. Remainders were not in remission despite any surgical and/or medical treatment.

3.3. Growth hormone secreting adenomas

Growth hormone secreting adenomas were found to be 29% of all cases. 57% of the cases were female. The average age of diagnosis was 45 years. 79% of GH secreting adenomas were macroadenomas. At the time of diagnosis, 92.2% of the cases were symptomatic. While the most common symptom was enlargement of hands and feet (68.7%), other symptoms were headache (18.7%), impaired vision (7.8%), enlargement of tongue and snoring (1.8%), hoarseness (1.5%) and loss of libido (1.5%), respectively. Surgical treatment was applied 55 (90%) patients. Five patients did not receive surgical treatment. One patient was followed up without treatment. Treatment information was not available for four patients. 61.4% of patients who underwent surgical treatment were treated with medical treatment in the postoperative period. In addition to medical treatment, gam knife was applied to six and radiotherapy was applied to two of these patients. In medical treatment, octreotide was applied to 33 patients. Pegvisomant, cabergoline or pegvisomant + cabergoline were added plus to octreotide in eight patients.

3.4. ACTH secreting adenomas

ACTH secreting adenomas account for 12.7% of all cases. 82.1% of the cases were female. The average age at the time of diagnosis was 37 years. 71.4% of adenomas were microadenoma. 100% cases had symptoms at the time of diagnosis. The most seen symptom was weight gain (26%). Other common symptoms were easy bruising (18%), edema in the body (18%), hirsutism (12%), galactorrhea (6%), headache (6%), infertility (4%), visual impairment (2%) and unregulated diabetes mellitus (2%). There were nonspecific symptoms in 6% of cases. Surgery was applied for 21 (84%) patients. Recurrence was developed in 20% of cases after surgery. Post-surgical cure was detected in 60% of cases. In 20% of cases remission could not be achieved after surgery due to residual tumor. Of these patients metirapon treatment was applied to 1 patient.

3.5. TSH secreting adenoma

Only three (1.8%) patients had TSH secreting adenoma. Two patients were male and had macroadenomas. Female patient

had microadenoma and followed without treatment. Surgery was applied to two patients with macroadenomas. Octreotide treatment was given both of two patients after surgery due to un remission.

4. Discussion

In our case series, prolactin-releasing adenomas, GH secreting adenomas and non-functional adenomas (NFPAs) were the most seen adenomas. ACTH secreting adenoma and TSH secreting adenoma were the following adenomas. In a report from England, the distribution of each pituitary adenoma subtype was 57% for prolactinoma, 28% for nonfunctioning adenoma, 11% for acromegaly, 2% for corticotrophin adenoma and 2% for unknown functional status (6). Prolactinomas are the most common functional adenomas, accounting for up to 60% of all pituitary adenomas. Microadenomas are more frequent than macroadenomas and a net predominance is observed in women aged 25–44 years compared to men, while this difference disappears after menopause (7). In accordance with the literature, 61.5% of the cases of our prolactinoma series was female, the average age of diagnosis was 40 years and 60% of adenomas were microadenoma. For prolactinomas, serum prolactin levels generally parallel with tumor size and prolactin level of more than 250 ng/mL is usually diagnostic for a macroprolactinoma (8). Our findings support these basic characteristics of prolactinoma. We measured prolactin levels >200 ng/mL in 67.8% of macroprolactinoma cases, <200 ng/mL in 73% of microprolactinoma cases. In treatment dopamine agonist therapy is recommended to lower prolactin levels, to decrease tumor size and to restore gonadal function for symptomatic prolactin-secreting microadenomas or macroadenomas (9). Cabergoline is the first option among dopamine agonists because it has higher efficacy in normalizing prolactin levels and higher frequency of pituitary tumor shrinkage. In the medically treated patients, normalization of prolactin level was achieved in 71% of the patients and total or partial degree of tumour shrinkage in 80% of the patients (10). In our study, remission was achieved in 76% of microprolactinoma and 24% of macroprolactinoma after dopamin agonist therapy.

Non-functioning pituitary adenomas do not cause a hormonal hypersecretion. The prevalence of NFPAs is 7–41.3 per 100,000 of population and they account for 14–54% of pituitary adenomas (11). They usually found incidentally on brain imaging performed for any unrelated indication. Clinically nonfunctioning macroadenomas account for about 80% of all pituitary macroadenomas (12). This can be explained with that clinically nonfunctioning adenomas are silent at the stage of microadenomas and only become clinically evident at the stage of macroadenomas. We also found 81.4% of nonfunctional adenomas as macroadenoma in our study. Most symptoms are related with mass effect, such as headaches, visual field defects and hypopituitarism. Laboratory evaluation for hypopituitarism should be performed for all NFPAs. The overall prevalence of partial hypopituitarism in patients with NFPAs ranges from 37% to 85% (13, 14). In our study, pituitary insufficiency was detected in 32% of patients in laboratory examination. Therefore, it should be kept in mind that approximately 1/3 patients may have insufficiency to require hormone replacement therapy among NFPAs.

Growth hormone secreting adenomas cause acromegaly due to increased growth hormone and insulin-like growth factor-1 (IGF-1) secretion. Prevalence of pituitary adenomas is 8.6/100.000 for somatotroph adenomas (6). Approximately 70% of patients with acromegaly have an invasive macroadenoma at diagnosis. We also found macroadenomas in 79% of GH secreting adenomas in our cases. Excess of GH and IGF-1 leads to multiple characteristic changes in the patient's appearance, skeletal deformities, and metabolic disorders. These changes include altered facial appearance, frontal-skull bossing, prognathism, enlarged extremities, increased shoe or ring size, carpal tunnel syndrome, hyperhidrosis, and coarse oily skin. Symptoms were present at the time of diagnosis in 92.2% of our cases and the most common symptom was enlargement in extremities (68.7%). The main treatment goals for acromegaly are resecting the pituitary adenoma and suppressing growth hormone and IGF-1 hypersecretion. The usual first-line treatment is surgery, if remission cannot be achieved, medical treatment with somatostatin analogues, dopamin agonists and pegvisomat and radiotherapy are available for second line treatments. Control of growth hormone secretion and IGF-1 levels was achieved in 73% of patients with microadenomas and 61% of patients with macroadenomas who underwent surgical resection (15, 16). Surgical treatment was applied 90% of our GH secreting adenomas. 61.4% of patients who underwent surgical treatment were treated with medical treatment in the postoperative period. In the literature, it is seen that hyperprolactinemia is present in 30% of patients with pituitary acromegaly due to pituitary stalk compression or cosecretion of prolactin from somatotroph adenomas with growth hormone (17). In our study, prolactin elevation was also detected in 20% of cases with GH secreting adenoma.

Corticotropin-secreting adenomas cause Cushing disease. They account for up to 15% of pituitary tumors (18). Adenomas are typically microadenoma and female to male ratio is 5-10/1. Compatible with the literature, ACTH secreting adenomas in our study was account for 12.7% of all cases, 82.1% of the cases were female and 71.4% of adenomas were microadenoma. Selective transsphenoidal adenomectomy is recommended as initial therapy. Remission achieved in approximately 75% of patients and recurrence seen in approximately 10% of patients (19). The second line treatment options are radical pituitary surgery, radiotherapy, stereotactic radiosurgery, medical therapy, and bilateral adrenalectomy. Medical therapy may improve clinical and biochemical outcomes but results of the studies about medical

therapy of Cushing disease are often inconsistent (20). In our study, post-surgical cure was detected in 60% of ACTH-secreting adenoma cases and medical treatment was given as metirapon only one patient.

Thyrotropin-secreting tumors are the least frequent type of pituitary adenomas compromising for approximately 1% of adenomas (21). Goiter, thyroid nodules, and hyperthyroidism are the manifestations in patients with TSH-secreting adenomas. Treatment of thyrotropinoma generally involves a transsphenoidal operation. Sanno et al. reported remission rate as 62.5% with surgery and 87.5% with combination therapy in 16 thyrotropin pituitary adenoma cases (22). We had only three TSHoma cases and surgery applied to two of them with macroadenoma. No remission was revealed and medical therapy with octreotide was given two of them.

The biological and morphological features of pituitary adenomas show variability. It is important to evaluate pituitary adenomas with clear biochemical imaging, and clinical phenotypes and define tumor characteristics and endocrine syndromes for individualized treatment or follow-up procedures.

Conflict of interest

There is no conflict of interest to declare.

Acknowledgments

None to declare.

Ethical Approval

The study was approved by the Ethics Committee of Ondokuz Mayıs University (date: 22.08.2013, No. 2013/392). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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