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Preoperative and Early/Late Postoperative Evaluation of Endocrine Functions of Patients who Underwent Pituitary Surgery

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ABSTRACT

Introduction and Aim: Pituitary masses may lead to hormonal insufficiencies due to compression or postoperatively. Endocrine functions in patients with postoperative pituitary insufficiency may eventually improve. Monitoring endocrine functions in these patients is crucial to avoid lifelong replacement therapy. In our study, we assessed preoperative and "early/late postoperative" endocrine functions of the patients in our clinic and aimed to emphasize the importance of endocrinologic evaluation.

Material and Method: In our study, a total of 103 patients aged 18 years and older who underwent transsphenoidal pituitary surgery and were followed up in our clinic were included. Patients' preoperative endocrine functions, as well as endocrine functions during early postoperative period (first 3 months), at the postoperative year 1 and at the final visit were recorded to be analyzed.

Results: Among the patients, 54 (52.4%) were male and 49 (47.6%) were female, with a mean age of 46.6±13.4 years. Of the patients included in the study, 85 (82.5%) were found to be diagnosed with pituitary adenoma. Of the patients, the mean tumor diameter was determined to be 2.21±1.07 cm and the mean duration of follow-up was determined to be 2.6±1.5 years. Median number of pituitary insufficiency in our patients was found to be 1 during the preoperative period, 3 within first 3 postoperative months, 2 at postoperative year 1, and 2 at the final visit. DI developed during preoperative period in 7 patients (6.8%), at postoperative week 2 in 80 (77.7%), and at postoperative month 3 in 56 (54.4%) patients. At final visits, 33 patients (32%) were found to have DI. Hypothyroidism was observed in 14.6% during preoperative period and in 59.2% at the 3rd month. Adrenal insufficiency was observed at a rate of 12.6% during preoperative period, whereas the rate was 56.3% at the 3rd month. Hypogonadism, however, was observed at a rate of 35.9% preoperatively, whereas the rate was 65% at the 3rd-month visit. No significant difference was determined when preoperative and postoperative rates of pituitary insufficiency in functional and nonfunctional pituitary adenomas were compared.

Conclusion: In our study, we observed that rates of particularly DI and adrenal insufficiency significantly increased at the postoperative month 3 compared with the preoperative period and tended to decrease at at the 12-month follow-up. Our rates of pituitary hormone insufficiency following pituitary surgery, which were higher than those reported in most previous studies, were the most important result of our study. Thus, considering a better understanding of the complications and eventual recovery of hormonal deficiencies, postoperative monitoring of endocrine functions is crucial for treatment management.

Keywords: Pituitary Adenoma, Pituitary Surgery, Pituitary Insufficiency, Diabetes insipidus,

Hipofiz Ameliyatı Olan Hastaların Preoperatif ve Postoperatif Erken/Geç Dönemde Endokrin Fonksiyonlarının Değerlendirilmesi

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ÖZ

Giriş ve Amaç: Hipofiz kitlelerinde bası bulgularına bağlı veya cerrahi sonrası hormonal yetmezlikler gelişebilir. Post-op hipofizer yetmezlik gelişen hastalarda endokrin fonksiyonlar zamanla düzelebilir. Bu hastaların endokrin fonksiyonları açısından takibi; hastanın ömür boyu replasman tedavisi almaması açısından önemlidir. Çalışmamızda kliniğimizde takip olan hastaların preoperatif ve postoperatif erken/geç dönem endokrin fonksiyonlarını değerlendirdik ve endokrinolojik değerlendirmenin önemini vurgulamayı amaçladık.

Materyal ve metod: Çalışmamıza hipofiz operasyonu geçirmiş olan ve kliniğimizde takipli 18 yaş ve üzeri 103 hasta dahil edildi. Hastaların preoperatif ve postoperatif erken dönem (ilk 3 ay), postoperatif 1. yıl ve hastanın son vizitindeki endokrin fonksiyonlar kaydedildi ve analizler gerçekleştirildi.

Bulgular: Hastalarımızın 54 (%52,4)'ü erkek, 49 (%47,6)'u kadındı ve yaş ortalamaları 46,6±13,4 yıl olarak belirlendi. Çalışmaya dahil edilen hastalardan 85 (%82,5)'inin hipofiz adenomu tanısı aldığı tespit edildi. Hastaların ortalama tümör çapları 2,21±1,07 cm ve takip süreleri 2,6±1,5 yıl olduğu saptandı. Hastalarda hipofiz yetmezlik sayısı medyan değerleri preoperatif dönemde 1, postoperatif ilk 3 ayda 3, postoperatif 1. yılda 2, son vizitte ise 2 olarak tespit edildi. Preoperatif dönemde 7 hastada (%6.8) DI mevcutken, postoperatif 2. haftada 80 (%77,7), postoperatif 3. ayda 56 hastada (%54.4) DI mevcuttu. Hastaların son takiplerinde ise 33 hastada (%32) DI tespit edildi. Preoperatif hastaların %14,6'sında 3. ayda %59,2'sinde hipotiroidi mevcuttu. Adrenal yetmezlik, preoperatif dönemde %12,6 olarak görülürken 3. ayda %56,3 düzeylerinde tespit edildi. Hipogonadizm ise

preoperatif dönemde %35,9 oranında görülürken 3. ay kontrollerinde %65 düzeylerindeydi. Fonksiyonel ve nonfonksiyel hipofiz adenomlarında cerrahi öncesi ve sonrasında gelişen hipofizer yetmezlik oranları karşılaştırıldığında aralarında anlamlılık bulunmadı.

Sonuç: Çalışmamızda özellikle DI ve adrenal yetmezliğin hastalarda görülme yüzdesinin postoperatif 3. ayda preoperatif döneme göre ciddi oranda arttığını, daha sonra ise 12. ay kontrollerinde de azalma eğiliminde olduğunu gözlemledik. Hipofiz cerrahi sonrası gelişen hipofiz hormon yetmezliği oranlarımız literatürdeki çoğu çalışmadan fazla olması çalışmamızın en önemli sonucuydu. Bu nedenle postoperatif dönemde endokrin fonksiyonların takibi, komplikasyonların daha iyi anlaşılması ve hormonal yetmezliklerde zamanla düzelme olacağı göz önüne alındığında tedavi yönetimi açısından önemlidir.

Anahtar Kelimeler: Hipofiz Adenomu, Hipofiz cerrahisi, Hipofizer yetmezlik, Diabetes insipidus,

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Introduction

Pituitary masses account for 15-20% of all intracranial tumors. The most common cause of pituitary masses is adenomas (%90), other, less common causes include it may result from less common causes including craniopharyngiomas (5-15%), carcinomas, meningiomas, metastases, abscesses, aneurysms, pituitary apoplexy, pituitary sarcoidosis, and Rathke pouch cysts[1]. Pituitary adenomas can be functional and/or cause compression due to mass effect. As a result of mass effect of adenomas, impaired vision and neurological deficits, as well as pituitary symptoms including secondary adrenal insufficiency, central hypothyroidism and hypogonadotropic hypogonadism may occur[2].

The first treatment option for functional pituitary adenomas other than prolactinoma and pituitary masses causing compression is transsphenoidal surgery. Following pituitary surgery, endocrine functions may improve due to hypersecretion after removal of functional adenomas or hormone levels may normalize in patients with pituitary insufficiency caused by compression. Furthermore, postoperative pituitary insufficiency may occur as a surgical compression in patients who have undergone pituitary surgery. Endocrine functions may recover in patients developing postoperative pituitary insufficiency as well. Monitoring of endocrine functions of these patients is crucial to avoid life-long replacement therapy[3].

Since there is limited number of studies on this issue in the literature, we evaluated preoperative and "early/late postoperative" endocrine functions of the patients in our clinic and aimed to emphasize the importance of endocrine evaluation.

Material and Method

In our study, patients who had underwent endoscopic endonasal transsphenoidal pituitary surgery at the University of Health Sciences Adana City Training and Research Hospital and were followed in Department of Endocrinology and Metabolic Diseases were included. The study was initiated after an ethics committee approval with decision number 1517 from our hospital's Ethics Committee on Clinical Research was obtained.

Medical records of 1078 patients with pituitary masses were examined retrospectively. Patients aged 18 years and older whose pituitary hormone levels during preoperative period, at postoperative month 3, at postoperative year 1 and at the final visit were available; preoperative and postoperative pituitary MRI results were available; immunohistochemical staining was performed; additionally those with other cellar lesions diagnosed by a pathologist were included in the study. A total of 103 patients with eligible records were included in the study. These patients' age, gender, date of diagnosis, age at diagnosis, date of surgery, postoperative treatments received, pituitary hormone levels, and MRI reports were recorded. Patients' preoperative endocrine functions, as well as endocrine functions during the early postoperative period (first 3 months), at the postoperative year 1, and at the final visit were evaluated. The total duration of follow-up was addressed as to cover the time from the date of operation to the present time. Whether improvement in endocrine functions was observed or not was determined.

For diagnosis of male hypogonadism, normal or low-normal gonadotropin levels in the presence of low-normal baseline testosterone levels were required. For diagnosis of gonadotropin deficiency in premenopausal women, normal or low-normal estradiol and gonadotropin levels in addition to menstrual irregularity in peripheral blood samples was required[4-5].

For diagnosis of central hypothyroidism, normal or below-normal TSH levels with below-normal free T4 levels were required[6].

For the diagnosis of adrenocorticotropic hormone insufficiency, patient files were examined; at the first step, baseline cortisol levels collected at 8 am were examined. A cortisol level ≥18 µg/dL was considered normal, but ≤3 µg/dL was considered adrenal insufficiency. When the cortisol level was 3-18 µg/dL, dynamic test results were examined. Those with a peak cortisol level below 18 µg/dl

in the ACTH stimulation test or insulin tolerance test were considered to have ACTH deficiency[6].

For diagnosis of GH deficiency, the presence of low IGF-1 levels together with more than 3 accompanying hormone insufficiencies was considered GH deficiency (6).

ADH deficiency was diagnosed from patient files based on serum and urine osmolarity results in patients with polydipsia and polyuria (≥3lt/24 hours)[7].

The number of pituitary hormone deficiencies per person was scored from 0 to 5.

Laboratory Data

Hormone levels from peripheral blood samples were studied using the chemiluminescence method (Beckman Coulter, DXI 800, Brea, CA, USA), complete blood count was performed on a Sysmex XN 9000 device, and measurements of other biochemical parameters were performed on a Cobas C 701 biochemistry autoanalyzer (Roche, Germany).

Specimens of 103 operated cases were kept within 10% formalin solution for 24 hours, and then 0.4-micron paraffin-embedded tissue slices were prepared, after which these slices were stained with H-E and then examined under an Olympus microscope.

Statistical Analysis

Statistical analysis of the data was performed by using SPSS (Statistical Package for the Social Sciences) 25.0 software program. Categorical variables were expressed as number and percentage, whereas continuous variables were summarized as mean and standard deviation (as median and minimum-maximum when necessary). Categorical variables were compared using Chi-squared test. Normality of distribution of the study parameters was determined using Shapiro-Wilk test. For paired group comparisons of non-normally distributed parameters, Mann Whitney U test was used. Wilcoxon test was used for examination of the differences between postoperative and preoperative findings. For all analyzes, level of statistical significance was considered 0.05.

Results

A total of 103 patients were included in the study. Of the patients, 54 (52.4%) were male and 49 (47.6%) were female. The mean age was determined to be 46.6±13.4 years (Table 1).

Of the patients included in the study, 85 (82.5%) were found to have pituitary adenoma (table 2).

Of the patients, mean tumor diameter was determined to be 2.21±1.07 cm and mean duration of follow-up was determined to be 2.6±1.5 years.

DI developed during preoperative period in 7 patients (6.8%), at postoperative week 2 in 80 (77.7%), at postoperative month 3 in 56 (54.4%) patients, 33 at final visits (32%). During preoperative period, 15 (14.6%) had hypothyroidism, while 61 (59.2%) had hypothyroidism at the postoperative month 3. Adrenal insufficiency was found in 13 (12.6%) patients during preoperative period and in 58 (56.3%) patients at the postoperative month 3.In the 3rd month posoperatively,in 40 patients evaluated , the cortisol level was below 3, and in20 patients, the basal cortisol level was above 18.Since the basal cortisol levels of 43 patients were between 3-18 , a 1mcg ACTH stimulasyon test was performed. In 25 of these patients who underwent the stimulation test , ınsufficiency was excluded because the cortisol level rose above 18 , while in 18 patients ,the stimulation test result was accepted as insufficiency .In the 3rd month postoperatively a total of 58 patients were diagnosed with secondary adrenal ınsufficiency , and all of these patients were started on treatment. Hypogonadism was observed in 37 (35.9%) during preoperative period, in 67 (65%) patients at the postoperative month 3, and in 63 (61.2%) patients at the postoperative month 12. GH deficiency was determined in 6 (5.8%) patients during preoperative period and in 10 (9.7%) patients at the postoperative month 3 (Table 3, Figure 1). Median number of pituitary hormone insufficiencies was determined to be 1 during preoperative period, 3 at the postoperative month 3, 2 at the postoperative year 1, and 2 at the final visit. Number of pituitary hormone insufficiencies was 0.81±0.9 during preoperative period, whereas it was 2.5±1.4 , 2.2±1.4 , and 2.1±1.4 at the postoperative month 3, at the postoperative year 1 and at the final visit, respectively (table 3).

Comparative analysis of preoperative and postoperative rates of pituitary insufficiency in functional and nonfunctional pituitary adenomas revealed no statistically significant difference (p>0.05) (Table 4).

Table 1. Patients' Demographic Characteristics and Baseline Laboratory Results

	Number (n)	Percentage (%)
Gender		
Male	54	52,4
Female	49	47,6
	Mean±sd	**Med (Min-Max)**
Age	46.6±13.4	47 (19-80)
Fasting blood glucose	120.3±60.7	100 (57-404)
BUN	25.5±12.3	23 (7-84)
Creatinine	0.68±0.24	0.62 (0.06-2.0)
ALT	22.9±15.8	18.1 (6.7-127.2)
AST	21.9±9.3	20 (11-61)
Na	139.8±4.4	140 (119-153)
K	4.52±2.9	4.2 (3.1-33)
Ca	9.1±0.6	9 (7.7-10.3)
Hgb	12.6±1.3	12.6 (10-16)

Table 2. Patients' Diagnosis

	Number (n)	Percentage (%)
Diagnosis		
Pituitary adenoma	85	82.5
Pineocytoma	2	1.9
Craniopharyngioma	8	7.8
Oligodendroglioma	1	1.0
Rathke cleft cyst	3	2.9
Spindle cell oncocytoma	1	1.0
Arachnoid cellar cyst	1	1.0
Meningothelial meningioma	2	1.9

Table 3. Hypothyroidism, adrenal insufficiency, hypogonadism, GH deficiency and diabetes insipidus findings during preoperative period, at the postoperative month 3, at the postoperative year 1 and at the final visit in patients with pituitary insufficiency

	Preop		Postop month 3		Postop year 1		Final visit	
	n	%	n	%	n	%	n	%
Hypothyroidism								
No	88	85.4	42	40.8	45	43.7	50	48.5
Yes	15	14.6	61	59.2	58	56.3	53	51.5
Adrenal insufficiency								
No	90	87.4	45	43.7	48	46.6	49	47.6
Yes	13	12.6	58	56.3	55	53.4	54	52.4
Hypogonadism								
No	66	64.1	36	35.0	40	38.8	40	38.8
Yes	37	35.9	67	65.0	63	61.2	63	61.2
GH deficiency								
No	97	94.2	93	90.3	94	91.3	93	90.3
Yes	6	5.8	10	9.7	9	8.7	10	9.7
Diabetes insipidus								
No	96	93.2	47	45.6	60	58.3	70	68.0
Yes	7	6.8	56	54.4	43	41.7	33	32.0
	Preop		**Postop month 3**		**Postop year 1**		**Final visit**	
	Mean±sd Med (Min-Max)		**Mean±sd Med (Min-Max)**		**Mean±sd Med (Min-Max)**		**Mean±sd Med (Min-Max)**	
The number of pituitary hormone deficiencies per person	0.81±0.9 1 (0-4)		2.5±1.4 3 (0-5)		2.2±1.4 2 (0-5)		2.1±1.4 2 (0-5)	

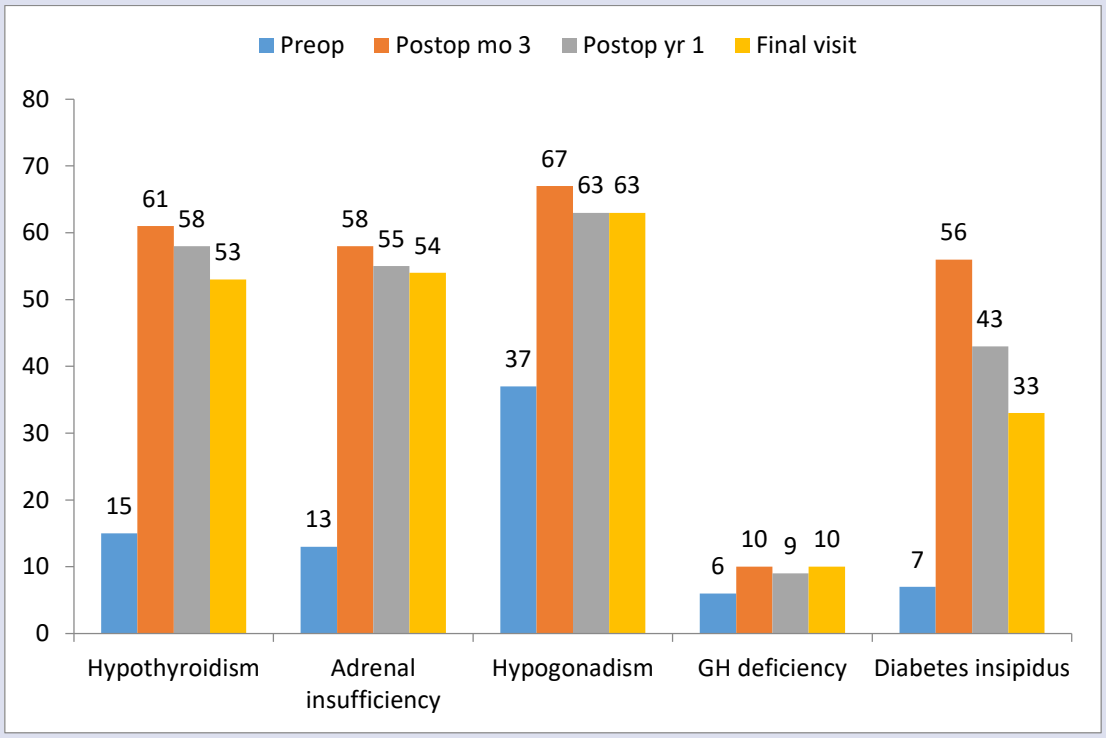

Figure 1. Number Of Patients with Pituitary Surgery Who Developed Pituitary Insufficiency During Preoperative Period, At the Postoperative Month 3, At the Postoperative Year 1 And at The Final Visit

Table 4. Differences between findings during preoperative period, at the postoperative month 3, at the postoperative year 1 and at the final visit between functional and nonfunctional adenoma groups

		Preop		Postop month 3		Postop year 1		Final visit	
		n	%	n	%	n	%	n	%
Hypothyroidism									
Functional		2	7.4	14	51.9	13	48.1	11	40.7
Nonfunctional		10	17.2	33	56.9	31	53.4	28	48.3
	p[c]		0.225		0.663		0.649		0.516
Adrenal insufficiency									
Functional		3	11.1	11	40.7	11	40.7	10	37.0
Nonfunctional		7	12.1	32	55.2	30	51.7	30	51.7
	p[c]		0.898		0.215		0.345		0.207
Hypogonadism									
Functional		8	29.6	18	66.7	17	63.0	18	66.7
Nonfunctional		21	36.2	37	63.8	34	58.6	34	58.6
	p[c]		0.552		0.796		0.704		0.479
Gh deficiency									
Functional		1	3.7	1	3.7	2	7.4	3	11.1
Nonfunctional		5	8.6	8	13.8	6	10.3	6	10.3
	p[c]		0.410		0.159		0.666		0.915
Diabetes insipidus									
Functional		1	3.7	16	59.3	13	48.1	9	33.3
Nonfunctional		5	8.6	29	50.0	21	36.2	16	27.6
	p[c]		0.410		0.426		0.295		0.588
			Preop Mean±sd		**Postop month 3 Mean±sd**		**Postop year 1 Mean±sd**		**Final visit Mean±sd**
Number of Pituitary Hormone insufficiencies									
Functional			0.77±0.9		2.29±1.5		2.14±1.6		2.00±1.5
Nonfunctional			0.82±0.9		2.39±1.4		2.10±1.4		1.96±1.4
	p[b]		0.745		0.791		0.897		0.977

p<0.05

Discussion

The most common cause of pituitary masses are pituitary adenomas. The primary goal of surgical treatment is to remove the tumor in nonfunctional tumors before hormonal insufficiency develops. In the case of functional tumors, the aim is to achieve hormonal control without causing insufficiency[8-9]. Preoperative hormonal deficiencies due to compression may resolve postoperatively, and endocrine function in patients who develop postoperative hormonal deficiencies may improve over time. In a previous study involving 150 patients, the patients were followed up for complications for 36 months. Pituitary insufficiencies were observed to begin within the first weeks after surgery and remitted in patients within a mean duration of 2-4 months[10]. In order to evaluate effect of surgery on endocrine functions, in our study we evaluated our patients during preoperative period, at the postoperative months 3-12 and at the final visit for development of hypothyroidism, adrenal insufficiency, hypogonadism, GH deficiency and diabetes insipidus. Moreover, we created a pituitary insufficiency score by scoring number of deficient hormones. As a result of the analyzes we performed by scoring each insufficiency from 0 to 5, number of pituitary hormone insufficiencies was 0.81±0.9 during preoperative period, whereas it was 2.5±1.4 , 2.2±1.4 , and 2.1±1.4 at the postoperative month 3, at the postoperative year 1 and at the final visit, respectively. In regard with median values, there was 1 hormonal insufficiency during preoperative period, whereas there were 3 hormonal insufficiencies during early postoperative period and 2 at the first year and at the final visit. In conclusion, we observed that pituitary insufficiencies of our cases began during early postoperative period and maintained similar at the long term, with minimal reductions after the 3rd month.

A study investigating hormonal remission following pituitary surgery reported that the most common hormonal insufficiency following transsphenoidal surgery was diabetes insipidus and that the risk of transient DI was 15-60%, particularly in suprasellar adenomas. They also reported that persistent DI was less common [11]. In a study by Viries et al., they reported that the most common complication following pituitary surgery was DI and suggested that postoperative DI should be treated with multiple factors taken into consideration[12]. In our study, when the patients were evaluated for diabetes insipidus, DI was found in 7 (6.8%) patients during preoperative period, 80 (77.7%) patients at the postoperative week 2, and 56 (54.4%) patients at the postoperative month 3. At the final visits of the patients, 33 (32%) were found to have DI. Regarding early-term development of hormonal insufficiencies, the most common increase was observed for frequency of DI. In the long-term, however, recovery rate for DI was determined to be higher compared with those of other hormonal axes. In terms of proportion, the greatest increase in DI among hormonal insufficiencies we determined in our study and the greatest recovery in DI in the long term were consistent with the literature, although our rates of persistent DI were higher.

The most common cause of secondary adrenal insufficiency is tumors of the hypothalamic-pituitary region. It may result from compression due to mass effect or accompanies panhypopituitarism developing after surgery. A previous study reported that, following pituitary surgery, 10% of the patients developed adrenal insufficiency, 34% of which required external cortisol treatment for 1-3 months and then recovered[13-14]. In our study, 56.3% of the patients developed adrenal insufficiency postoperatively. Furthermore, adrenal insufficiency persisted at the final visit in 52.4% of the patients. In our study, our rates of early- and late-term adrenal insufficiency were much greater than those reported in the literature.

Hypothyroidism was determined in 14.6% of the patients during the preoperative period and in 59.2% of the patients at the postoperative month 3, and this increase was statistically significant. At 12-month and final visits, hypothyroidism persisted at similar rates. In the previous studies, prevalence of thyroid insufficiency following surgery has been reported to be 10-50%[15]. Our findings, however, were higher than those in the literature.

Rate of hypogonadism, however, was 35.9% during preoperative period and 60% at 3- and 12-month visits. In the literature, it has been reported that hypogonadism develops in approximately 68-83% of the patients who undergo pituitary surgery due to any reason and persists at a rate of about 10%[14].

In our study, rate of patients with GH deficiency was approximately 9%, with minimal increase during postoperative period. The rate of patients developing hormonal insufficiencies other than GH deficiency was higher than those reported in the literature [13-14,16]. The lower rate of GH deficiency was attributed to not performing dynamic tests to evaluate and to the fact that insufficiency was defined as low IGF-1 values with accompanying 3 additional hormonal insufficiencies. Comparative analysis of preoperative and postoperative rates of pituitary insufficiency in functional and nonfunctional pituitary adenomas revealed no significant difference.

Our higher complication rates may be due to the fact that majority of our cases were macroadenomas. Another important factor for development of complications is surgical experience. Complication rates decrease with increased experience of the surgeon. Although our study was single-center and only operations performed by one surgeon were included in the study, we could not determined whether complication rates eventually decreased or not, since number of surgeries and complications was not separately described by years. This is a limitation of our study, which might also be the reason for our higher rates.

In conclusion, as multiple hormone deficiencies can be encountered after pituitary surgeries, we are in thought of that attention should be paid on pituitary insufficiencies which may develop following pituitary surgeries and that patients should be closely monitored due to potential recovery in time.

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