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Cushing Hastalığında Nüksü Öngören Faktörler

Predicting Factors of Recurrence in Patients with Cushing's Disease

Alev Selek
Kocaeli Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Endokrinoloji Bilim Dalı, Kocaeli, Türkiye

ÖZ

GİRİŞ ve AMAÇ: *Cushing Hastalığının nüks oranı yüksektir; bu nedenle, nüksü öngören klinik özellikler, yüksek riskli hastaları belirlemek için tanımlanmalıdır. Bu faktörler hastalığın yönetimini ve izlem sıklığını etkileyebilir. Nüks etmiş CH (RD) ve uzun sürekli remisyon (SR) sağlanmış hastaların klinik özelliklerini karşılaştırarak hastalık nüksünü öngören klinik faktörleri belirlemeyi amaçladık.*

YÖNTEM ve GEREÇLER: *Cerrahi tedavi uygulanan 85 CH olan hasta retrospektif olarak değerlendirildi. Preoperatif tanı testleri ve postoperatif hastalık aktivitesi kaydedildi. Hipofiz tümör boyutu, invazyonu, p53 ve Ki-67 immünhistokimyasal boyama verileri ile postoperatif kortizol aksı geridönüş zamanı değerlendirildi.*

BULGULAR: *Çalışmaya 16 RD ve 54 SR hastası alındı. Preoperatif ACTH düzeyleri RD grubunda daha yüksekti. RD hastalarında preoperatif adenom boyutu ve kavernöz sinüs invazyonu ile Ki-67 indeksi SR grubuna göre daha yüksekti. RD'li 11 hastada (% 69) hızlı kortizol aksı geridönüşü görülürken SR grubunda sadece 6 hastada (% 11) vardı.*

TARTIŞMA ve SONUÇ: *Preoperatif ACTH yüksekliği, atmış tümör boyutu, kavernöz sinüs invazyonu ve yüksek Ki-67 indeksi, Cushing hastalığında nüksü öngörebilir faktörlerdir. Bununla birlikte, hızlı kortizol aksı geridönüşü de nüks ile ilişkili bulunmuştur.*

Anahtar Kelimeler: *Cushing Hastalığı; Nüks Cushing Hastalığı; HPA aks geri gönüş zamanı*

ABSTRACT

INTRODUCTION: *Cushing's Disease (CD) has high recurrence rate therefore clinical features predicting recurrence should be defined to discriminate patients with high risk. These factors can effect management and follow-up frequency. We aimed to compare the clinical features of the patients with recurrent CD (RD) and sustained remission (SR) in order to determine clinical factors that might predict disease recurrence.*

METHODS: *Surgically treated 85 patients with CD were evaluated retrospectively. Preoperative diagnostic tests and postoperative disease activity were noted. Pituitary tumor size, invasiveness and features such as p53 and Ki-67 immunohistochemical staining data also postoperative cortisol axis recovery time were evaluated.*

RESULTS: *16 RD and 54 SR patients were enrolled to the study. Preoperative ACTH but not cortisol levels were higher in RD group. RD patients had higher preoperative adenoma size and cavernous sinus invasion rate and Ki-67 index than SR group. Eleven (69%) patients with RD had early recovery time while 6 (11%) patients in SR group.*

DISCUSSION and CONCLUSION: *Higher preoperative ACTH levels, tumor size, cavernous sinus invasion and Ki-67 immunostaining would predict recurrence in CD. Additionally, rapid recovery of cortisol axis was found to be related with recurrence.*

Keywords: *Cushing's Disease; recurrent Cushing's Disease; HPA axis recovery time*

İletişim / Correspondence:

Dr. Alev Selek
Kocaeli Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Endokrinoloji Bilim Dalı, Kocaeli, Türkiye
E-mail: alevselek@gmail.com
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INTRODUCTION

Cushing disease (CD) is caused by prolonged exposure to elevated levels of endogenous glucocorticoids secondary to inappropriately high levels of Adrenocorticotropic Hormone (ACTH)-secreting pituitary adenoma and is associated with significant morbidity and mortality if untreated (1,2). Surgery is the first-line treatment which is the best in long-term control of hypercortisolism (3). If remission is not achieved or recurrence occurs, medical treatment, repeating surgery, or considering radiation therapy are recommended (4). Remission was achieved in about 65 to 90% of patients with a pituitary microadenoma and 15 to 65% with macroadenoma (5,6).

Postoperatively recurrence was reported approximately in 25 to 50% of patients who were followed for more than 5 years (7,8). The remission and recurrence rates are variable in literature. The reason of this is variations in defining remission and recurrence criteria, the length of follow-up of different studies and center's experience (9). Diagnosis of suspected recurrence can be challenging because there isn't any well defined criteria to diagnose recurrence. 24-hour urine free cortisol (UFC) and 1-mg Dexametasone suppression test (DST) were the most frequently used biochemical tests to evaluate recurrence in most of the studies. However, measuring late night salivary cortisol (LNSC) has been shown to be more sensitive and is being used more commonly in recent studies (10,11). Preoperative and postoperative clinical features predicting recurrence should be defined to discriminate patients with high risk of recurrence. These factors can effect clinical managment, follow-up frequency and modality.

This retrospective study was conducted to evaluate the preoperative and postoperative clinical features of the patients with recurrent CD and compare with the patients in sustained remission. We aimed to determine clinical factors that might predict disease recurrence.

METHODS

This retrospective evaluation included 138 patients with the diagnosis of CD between 2007 and 2016 in a university hospital. Patients with missing confirmatory clinical, laboratory and radiologic data for CD and patients with <6 months of follow up were excluded. Finally this study included 85 CD patients with complete clinical, laboratory, radiologic and follow up data.

Data collection

The clinical, laboratory, imaging and postsurgical pathologic records and also clinical follow up data of all patients were obtained from our outpatient clinic. Preoperative diagnostic tests were reevaluated in all patients and postoperative disease activity, remission and recurrence status were also noted.

ACTH, p53 and Ki-67 immunohistochemical staining data of the pituitary tumor tissues were obtained from postoperative pathology reports which have been evaluated by a single endocrine pathologist.

All patients with CD underwent magnetic resonance imaging (MRI) preoperatively and postoperatively also whenever needed on follow up. Tumor features including size, cavernous sinus invasion and optic chiasm compression were evaluated on pituitary MRI. Visible lesions with a diameter of ≥10 mm were defined as macroadenoma (MAC) and microadenoma (MIC) was defined as visible lesions <10 mm of diameter or in cases with MRI negative/doubtful but postoperative remission was achieved.

Hormonal evaluation for diagnosis, remission and recurrence

Preoperative basal ACTH and cortisol levels were recorded by calculating the average of the two morning values closest to the operation. Hypercortisolism was confirmed by at least two positive screening tests; increased free cortisol excretion (fold increase from upper limit of normal (×ULN) was calculated) or failure to suppress plasma cortisol after low dose of dexamethasone or increased midnight cortisol levels. The pituitary origin of the hypercortisolism was established on the basis of ACTH concentrations above 10 pg/mL, adequate suppression of cortisol during high dose dexamethasone administration (>50% suppression from baseline levels) or a high petrosal sinus to peripheral plasma ACTH gradient (if test was available). In some cases CRH stimulation test was also available.

Postsurgical remission was defined as a low (<5 pg/mL) or undetectable serum cortisol level at first 48 hours after pituitary surgery. CD cases were operated without surgical steroid coverage and monitorised closely for adrenal insufficiency symptoms and signs postoperatively. In case of adrenal insufficiency, blood samples were taken for cortisol levels and steroid treatment was started immediately. Otherwise replacement was decided according to postoperative morning cortisol levels. Pituitary adrenal axis recovery time was calculated in cases on steroid replacement. The recovery time point was determined as the time when steroid could be safely withdrawn and calculated as mounts. Early recovery was defined as if steroid treatment could be withdrawn within one month or there was no need for steroid replacement.

Sustained remission in CD was decided in case of; clinical adrenal insufficiency, disappearance of clinical hypercortisolism; and normal UC levels and successful suppression of cortisol levels after low-dose dexamethasone (after glucocorticoid withdrawn) for a minimum of 6 months after pituitary surgery. Patients who failed to meet these criteria were classified as having persistent CD. Recurrence was defined as the reappearance of clinical symptoms and signs of hypercortisolism and at least two screening tests pointing to CD activity more than 6 months after surgery.

Ki 67 percentage and p53 positivity were also assessed. An adenoma with Ki 67 index ≥ 3% and p53 positivity was defined as atypical adenoma.

Statistical analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). Kolmogorov-Smirnov tests were used to test the normality of data distribution. Continuous variables were expressed as mean± standard deviation, median (25.th-75.th percentiles), and categorical variables were expressed as counts (percentages). Differences between the groups were analyzed by Student t test and one-way ANOVA for numerical variables with normal distribution and Mann Whitney U test, for numerical variables with nonnormal distribution and Pearson chi-square test for categorical variables. The relationship between numerical variables was evaluated by Spearman Correlation Analysis. $p<0.05$ was considered statistically significant for significance.

The study protocol was approved by the local ethics committee. Informed consent had been taken from all study subjects and controls. There is no conflict of interest for any authors.

RESULTS

Clinical characteristics

The demographic characteristics of surgically treated 85 patients with CD were shown in table 1. The mean age at the diagnosis was 39 (±12) in entire group and there was no gender difference for age (p=0.3). There were 69 (81%) female and 16 (19%) male patients. The mean follow up period was 39 (range 9-145) months.

Patients

85 surgically treated CD patients were evaluated and 70 (82%) of them had postoperative remission. Among them 54 (77%) patients had sustained remission and 16 (23%) had recurrent disease. Finally 16 recurrent and 54 sustained remitted CD patients were enrolled to the study. The flow chart of patient enrollment according to clinical outcome was shown in the figure below.

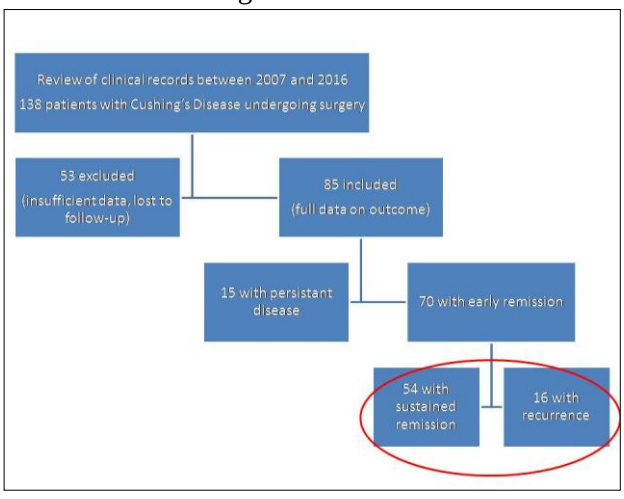

Figure 1. Patient enrollment flow chart

Clinical findings

The disease recurrence was seen an average of 21±17 months and patients with recurrent disease (RD) had shorter mean follow up period than patients with sustained remission (SR) (33±32 vs 62±29 months). The mean age and gender distribution were similar in two groups (Table 1).

Table 1. Demographic characteristics of patients

	Recurrent disease (n=16)	Sustained remission (n=54)	Entire Cohort (n=85)	P value
Age (y) mean ± SD	37 (±11)	37,6 (±12)	39,1 (±12)	0,3
Sex (M/F)	2/14	11/43	16/69	0,47
Follow-up time (mo) Mean (± SD)	62 (±29)	33 (±32)	39 (±32)	**<0.001**
Bold written values were statistically significant				

RD patients had higher preoperative adenoma size (p=0.01) (Table 2), 11 (69%) patients in RD group had macroadenoma while only 15 (28%) in SR group (p=0.004) (Table 3). Also patients in RD group had higher preoperative cavernous sinus invasion rate but optic chiasm compression was not different from SR group (p=0.006 and p=0.32 respectively). Pathologic examination revealed that atypical adenoma was seen more frequently in patients with RD than SD group (p<0,001) (Table 3). RD patients had higher mean Ki-67 index than SR group, 5,4 (±9,7) and 1,5 (±1,4) respectively (p<0,001) (Table 2).

In patients with RD preoperative ACTH levels were higher than SD patients but preoperative cortisol levels were similar (p=0,046 and p=0,1 respectively) (Table 2).

Table 2. Preoperative laboratory, imaging and recovery time data of patients with CD according to recurrence

	Recurrent disease (n=16)	Sustained remission (n=54)	P value
Tumor size (mm) Median (25-75%)	11,5 (7-18)	7,1 (5-10)	**0.01**
Preop ACTH (pg/mL) Median (25-75%)	72 (55-128)	57 (39-81)	**0.046**
Preop cortisol (pg/mL) Median (25-75%)	22 (15-29)	18,6 (15-23)	0.1
Recovery time (mo) Mean (± SD)	5,5(±4,8)	11(±7,5)	**0,036**
Ki-67 (%) Mean (± SD)	5,4 (±9,7)	1,5 (±1,4)	**p<0,001**
Bold written values were statistically significant			

Table 3. Pituitary tumor characteristics of patients with CD according to recurrence

		Recurrent disease (n=16)	Sustained remission (n=54)	P value
Adenoma size				**0,004**
	Micro	5 (31%)	39 (72%)	
	Macro	10 (69%)	15 (28%)	
Cavenous sinus invasion				**0,006**
	Yes	6 (38%)	5 (9%)	
	No	10 (62%)	49 (91%)	
Atypical pathology				**0,001**
	Yes	8 (50%)	6 (11%)	
	No	8 (50%)	48 (89%)	
Bold written values were statistically significant				

There weren't any difference between RD and SR groups for confirmation and discrimination test of CD. Urinary free cortisol excretion, low and high dose of dexamethasone suppression tests and midnight cortisol levels were similar between groups. Also these parameters were not correlated with recovery or recurrence time. Recurrence was seen minimum 7 and maximum 56 months after first operation, The mean recurrence time was 21±17 months. All 16 recurrent patients had second surgery, 8 of them had sustained remission afterwards. One patient was also remitted after additional radiosurgery. Remaining 7 patients had active disease and 4 of them also undergone radiosurgery. 2 patients has stable metabolic parameters therefore they are still followed-up without treatment but 5 patients are on gabergoline and pasireotide treatment.

Recovery time from relative adrenal deficiency was also assessed, 11 (69%) patients with RD had early recovery time while 6 (11%) patients in SR group (p<0,001). The mean recovery time was 5,5 (±7,8) month in RD group and 11 (±7,5) months in SR group (Table 2). Four patients had permanent adrenal insufficiency, the pituitary adrenal axis of these patients had not recovered in a time period over 36 months. All these patients were remitted after first operation therefore 5% of the patients with early postoperative remission had permanent adrenal insufficiency.

DISCUSSION

In the current study, we evaluated the clinical findings of patients with CD and compared the patients with sustained remission and recurrent

disease in order to determine clinical factors that might predict disease recurrence. According to our results patients with RD had higher tumor size, more invasive and atypical tumors then SR patients. Also RD patients had higher preoperative ACTH levels and lower recovery time from relative adrenal insufficiency.

CD is a serious condition with an excess mortality and unfortunately, the risk of recurrence after initial surgical cure is high and necessitates lifelong monitoring (12-14). The clinical and biochemical findings to diagnose recurrent disease remains challenging, especially in early and/or mild phases (15). The diagnostic criteria used to define RD is widely variable in the literature therefore reported recurrence rates are different. In current study, the recurrence rate was 23% among postoperative remitted patients which is consistent with recent literature (16,17). In most of studies postoperative ACTH and cortisol levels and tumor size were found to be related with remission but there is only limiting data to predict which patients will have recurrence. Higher preoperative ACTH levels have been shown to predict disease recurrence (16) and mortality (17) during follow-up. Patients with recurrence had higher preoperative ACTH but similar cortisol levels then patients with sustained remission.

Macroadenomas have been thought to have higher recurrence rates than microadenomas (18,19), but no statistical difference was found based on tumor size in a meta-analysis (10). However, tumor invasiveness, especially cavernous sinus invasion, was found to be more significant than size in predicting recurrence (20). In our study higher tumor size and cavernous sinus invasion were found more frequently in patients with RD therefore an invasive macroadenoma might be a predictive factor for recurrence.

The recent studies showed that, the clinically aggressive adenoma phenotype was predicted by the higher Ki-67 labeling index and these tumors have high probability for recurrence (21). Atypical adenoma were seen more frequently in RD patients in current study with a significantly higher Ki-67 index than SR patients. Another parameter assessed for pathologic aggressiveness was p53, p53 immunostaining was seen similarly in patients with RD and SR. The 2017 World Health Organization classification of tumors of the pituitary gland stated that, there is no evidence for the utility for p53 immunostaining and suggested against using it on a regular basis (21).

Recovery time of the endogenous hypothalamo-pituitary–adrenal axis (HPA) was calculated in all patients with early remission. Most patients with RD had recovery time less than one month. SR patients had significantly longer recovery time which might predict long term remission. Alexandraki et al. (22) also speculated that the recurrence rates appear to relate with the recovery of the endogenous HPA axis, and they have not seen recurrence in any patient with recovery time more than three years. In our cohort there wasn't any RD patients with recovery time over two years, according to these results shorter recovery time might predict recurrence.

The current study was a retrospective study which limits the accuracy. But all preoperative biochemical analysis of the patients were done according to our routine protocol that would reduce of possibility mistakes. Although mean clinical follow-up was 39 months there were some patients with shorter follow-up in cohort. But most of the patients with SR had more than five years follow-up which increases the strength of the study.

In conclusion, higher preoperative ACTH levels, tumor size, cavernous sinus invasion and Ki-67 immunostaining would predict recurrence in CD. Beside these factors, rapid recovery of HPA axis was found to be related with recurrence and it would be an additional predictive factor. There are a few studies assessing this factor in recurrent disease therefore studies with higher number of patients and longer follow-up are needed to strength this finding.

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