Thirty-Four Patients with Cushing's Syndrome: Our Clinical Experience in the Past 20 Years

Otuz Dört Cushing's Sendromu Olgusu: 20 Yıllık Klinik Deneyimlerimiz

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Abstract

Objective: Cushing's syndrome is a relatively rare disorder caused by chronic endogenous hypercortisolemia. We aimed to present patients with Cushing's syndrome who were diagnosed and followed at our endocrinology clinic.

Materials and Methods: 34 patients (26 female, 8 male) with Cushing's syndrome were enrolled in this retrospective study.

Results: Of 34 patients, 20 had Cushing's disease and 14 had Cushing's syndrome. Regarding the clinical signs of Cushing's syndrome, purple striae were present in 31 subjects (91.2%), hirsutismus in 21 (72.4 %), buffalo hump in 33 (97.1%), moon face in 33 (%97.1), plethora in 33 (%97.1), and menstrual irregularities in 21 (84%) subjects. Diabetes mellitus (DM), hypertension and osteoporosis were found to be 13/34 (39.4%), 23/34 (69.7%) and 18/34 (66.7%), respectively. Following the treatment, primary adrenal failure, secondary adrenal failure, central hypothyroidism, central hypogonadism and central diabetes insipidus were found to be 3 (8.8%), 3 (8.8%), 4 (11.7%), 4 (11.7%) and 4 (11.7%), respectively.

Conclusions: As reported in the literature, Cushing's disease is the most common form of Cushing's syndrome and various complications such as adrenal failure, hypogonadism, diabetes insipidus can develop following the treatment. *Turk Jem 2009; 13: 75-9*

Key words: Cushing's syndrome, Cushing's disease, hypercortisolemia

Özet

Amaç: Cushing's sendromu nadir görülen, kronik endojen hiperkortizoleminin yol açtığı morbid bir hastalıktır. Biz kliniğimizde tanı konulan ve takip edilen 34 Cushing 's sendromlu hastayı sunmayı amaçladık.

Gereç ve Yöntemler: Bu retrospektif çalışmaya 34 (26 kadın, 8 erkek) Cushing 's sendromlu hasta dahil edildi.

Bulgular: Otuz dört hastanın 20'si Cushing's hastalığı, 14'ü Cushing's sendromu tanısı aldı. Cushing's sendromunun klinik bulgularından, mor strialar 31 (%91,2), hirsutismus 21 (%72,4), buffalo hump 33 (%97,1), aydede yüzü 33 (%97,1), pletore 33 (%97,1) ve adet düzensizliği 21 (%84) hastada görüldü. Diyabetes mellitus (DM), hipertansiyon ve osteoporoz sırasıyla 13/34 (%39,4), 23/34 (%69,7) ve 18/34 (%66,7) hastada bulundu. Tedavi sonrasında takiplerde primer adrenal yetmezlik, sekonder adrenal yetmezlik, santral hipotroidizm, santral hipogonadizm ve santral diyabetes insipidus oranları sırasıyla 3 (%8,8), 3 (%8,8), 4 (%11,7), 4 (%11,7) ve 4 (%11,7) olarak saptandı.

Sonuç: Literatürle uyumlu olarak, Cushing's hastalığı Cushing's sendromunun en çok görülen şeklidir ve tedavi sonrası farklı komplikasyonlar, örneğin; adrenal yetmezlik, hipogonadizm, diyabetes insipidus gelişebilir. *Türk Jem 2009; 13: 75-9*

Anahtar kelimeler: Cushig's sendromu, Cushing's hastalığı, hiperkortizolemi

Introduction

In Cushing's syndrome the most frequent signs are gaining excess weight and central obesity. Also, hypertension, plethorea, hirsutismus, glucose intolerance, DM, menstrual irregularities, osteoporosis and hepatosteatosis are the other frequent findings (1,2). 85% of endogenous Cushing's syndrome is ACTH-dependent. Of these, 68% is pituitary adenoma, whereas 15% is ectopic ACTH syndrome. Adrenal causes account for approximately 15% of Cushing's syndrome (3,4,5). Low-dose dexamethasone suppression test (DST), 24-h urinary free cortisol (UFC) levels, high-dose DST, corticotropin-releasing hormone (CRH) test and imaging modalities are among the current diagnostic approaches (4). In treatment, unilateral adrenalectomy is method of choice in adrenal adenomas, while transsphenoidal hypophyseal surgery is such in hypophyseal microadenomas.

In this study, we report our clinical experience in 34 patients with Cushing's syndrome.

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Materials and Methods

Population and Study Design

34 patients diagnosed and treated as Cushing's syndrome, as general term, at our university endocrinology clinic between 1989 and 2008 years, were included in this retrospective study. Iatrogenic Cushing's cases were excluded from the study. Data consisting of age, sex, height, weight, body-mass index (BMI), systolic and diastolic blood pressure (BP) and pulse rate were recorded. The typical clinical findings were determined.Osteoporosis, DM and gonadal dysfunction were assessed from a metabolic point of view. Screening for osteoporosis was performed with bone mineral density (BMD) measurement by DEXA at lumbar spine (L1-L4) and femural neck.

Laboratory Examination

Plasma basal cortisol and ACTH levels, low-dose (1 mg) and high-dose (8 or 16 mg) of dexamethasone suppression tests and 24-h UFC levels were measured. 24-hour UFC levels which were >2-fold above the normal levels were considered as consistent with Cushing's syndrome. Following 1-mg DST, cortisol level below 3 µg/dl was accepted to be a positive response. For 8-mg or 16-mg DST, 50% or more decrease in the basal cortisol level was accepted to be a positive response for Cushing's disease. Radyological screening with CT or MRI were obtained focusing on the suspected site (pituitary or abdominal). The treatment modalities and the outcomes were also studied. Plasma cortisol levels were measured by ELISA or RIA methods, serum ACTH levels - by HPLC. Normal limits of ACTH and cortisol levels are 10-50 pg/ml and 3-25 µg/dl at the central laboratory of our hospital. Remission was assessed at one and six months with performed basal cortisol level and 1mg DST.

Statistics

Data obtained from patients were analysed by using SPSS 10.0 program. The results were presented as mean ± SEM. The frequencies of all parameters were calculated. The differences between pre- and post-treatment measures were assessed by using paired-samples t-test and $p< 0.05$ was accepted as significant in 95% confidence interval.

Results

Clinical Findings

Mean age, BMI, systolic and diastolic blood P, cortisol and ACTH levels of the patients are shown in Table 1, and clinical and metabolic findings of patients with Cushing's syndrome are shown in Table 2. MRI/BT showed microadenoma in most of the patients with Cushing's disease (CD) (n=15, 75%), (See Table 3). Visual field defects were detected in 2 patients (10%). Inferior petrosal sinus sampling (IPSS) was performed only in one patient and confirmed the diagnosis of CD. Adrenal CT/MRI revealed adrenal hyperplasia in 5 (36%) and adrenal adenoma in 9 (64%) patients with diagnosed Cushing's syndrome (CS) (See Table 4).

Abdominal ultrasound was performed in 26 patients and the findings were as follows: completely normal in 8 (30.8%) subjects, hepatosteatosis in 8 patients, hepatosteatosis with hepatomegaly in 5 patients, adrenal hyperplasia in 2, nephrolithiasis in 2, and hepatomegaly alone in 1 patient.

Metabolic Abnormalities

The mean basal serum cortisol level of all patients was 71.49±27.7 µg/dl (range: 9-744 µg/dl). Among the patients considered to have CS, serum ACTH levels were found to be 11.1±6 pg/ml. In patients with CS, the mean 24-h UFC level was 195.6±35 µg/24 h (n=5, range: 35.4-685 µg/24h).

In patients with CD, the mean ACTH level was 197±57 (range 43.6-886 pg/ml) and the mean 24-h UFC level was 483±163 µg/24h (n=6, range: 37-1015 µg/24h).

1-mg DST was applied to 30 patients and the mean cortisol level was 32.02±8.6 (range: 3.4-275 µg/dl). Out of 20 patients with CD, 12 (60%) showed suppression (>50% vs. basal level) during the 8 mg DST. 16-mg DST was performed in 8 patients who had no supression with 8-mg dexamethasone, and 6 of them showed suppression.

The mean white blood cell (WBC) and eosinophil counts were 9417±389 and 169±14.5, respectively. There was no significant difference between pre- and post-treatment WBC and eosinophil levels (p=0.22, p=0.28, respectively).

The diagnosis was confirmed with IPSS in the patient considered to have CD, but with normal pituitary imaging (presented in Table 3 as number 15). Metabolic investigations of 34 patients with Cushing's syndrome showed DM in 13 (39.4%) patients. Of 27 patients who had BMD measurements, 17 (63%) had osteoporosis at left femoral neck and 18 (66.7%) at anteroposterior lumbar vertebrae (mean T-score was -2.7±0.4 and -2.9±0.2, respectively).

Managements of the Patients

The management and the outcomes of the patients are shown briefly in Table 3 and 4. Surgery was performed focusing on the targets which were disclosed by CT or MRI scans. Among surgical methods performed in the study: Transsphenoidal pituitary

Table 1. The certain characteristics of the patients with Cushing's disease and Cushing' syndrome

	Cushing disease (n=20)	Cushing syndrome (n=14)
Mean Age(years)	30±2.2	31.8±1.2
Mean BMI(kg/m^2)	33.4±2.1	31.13±1.06
Mean SBP(mmHg)	145±7.2	148.3±6.02
Mean DBP(mmHg)	95±3.8	96±3.2
Mean serum basal cortisol levels (µg/dl)	97.5±25	26.8±9
Mean serum ACTH levels (µg/ml)	197±57	11.1±6
Urine free cortisol levels (µg/24 h)	483±163	195.6±35
1 mg DST (cortisol levels)	31±8.2	16.4±3.4
8/16 mg DST (cortisol levels)	14.4±0.78	15±8.5

Table 2. Clinical and metabolic findings of patients with CS

	Patients (n)	Frequency (n/(%)
Obesity	28	23/82
Plethorea	34	33/97.1
Hypertension	33	23/69.7
Hirsutismus	29	21/72.4
Menstruel irregularities	25	21/84
Strias	34	31/91.2
Moon face	34	33/97.1
Buffalo Hump	34	33/97.1
Acne	34	21/61.8
Osteoporosis (AP vertebrae)	27	18/66.7
Diabetes Melllitus	33	13/39.4
Hepatosteatosis	26	8/30.8
Nepfrolitiasis	26	2/7.7

surgery was in 11 (55%), and transcranial pituitary surgery was in 6 (30%) subjects. Macroadenoma was detected in 3 patients who underwent transcranial pituitary surgery. The patients with CD were assessed by neurosurgery department to make the decission about transcranial pituitary surgery. For patients with CS, unilateral adrenalectomy and bilateral adrenalectomy were performed in 6 (42.8%) and 4 (28.5%), respectively. Data on medical treatments of 28 patients were obtained. 53.6% of them did not take any medication. 7 (25%) and 6 (21.4%) patients were administered aminoglutethimide and ketoconazole, respectively. As mentioned above, surgical treatment was performed along with medical treatment in some patients.

The efficacy of all treatment modalities was assessed based on the data from 26 patiens (the patients were assesed at one and 6 months after surgery): cure rate was 76%, on the other hand, failure of treatment was seen in the remaining 16%. The complications related to the treatment of 26 patients included secondary adrenal insufficiency in 3 patients (8.8%), primary adrenal insuffi-

Table 3. Caracteristics of the 20 patients with Cushing's disease

Subject	Typical Cushingoid Features*	Low-dose (1mg) dex-sup test	High-dose (8/16mg) dex-sup test	Pituitary MRI/CT	Type of Surgery	Cure
1	yes	NS	S	8 mm	TS	yes
2	yes	NS	S	4 mm	TS	yes
3	yes	NS	S	6 mm	TS	yes
4	yes	NS	S	8 mm	TS	yes
5	yes	NS	S	3 mm	TS	yes
6	yes	NS	NS	4 mm	TS	yes
7	yes	NS	S	8 mm	TS	yes
8	yes	NS	-	4 mm	TC	yes
9	yes	NS	-	16 mm	TC	yes
10	yes	NS	-	20 mm	TC	yes
11	yes	NS	-	hyperplasia	TS	yes
12	yes	NS	NS	8 mm	ketaconasole	?
13	yes	NS	NS	4 mm	TS	yes
14	yes	NS	S	5 mm	TC	yes
15	yes	NS	S	normal	TC	yes
16	yes	NS	S	3-4 mm	ketaconasole/TS	yes
17	yes	NS	S	normal	aminoglutetimid	following
18	yes	NS	S	9 mm	following	following
19	yes	NS	-	1 0mm	TC	yes
20	yes	NS	S	7 mm	TS	yes

(*)Truncal obesity, buffalo hump, plethorea, violesance stria (>1cm widht), easy bruisability…

S: supression; NS: no supression; TS: Transsphenoidal pituitary surgery; TC: transcranial surgery

Table 4. Caracteristics of the 14 patients with Cushing's syndrome

Subject	Typical Cushingoid Features (*)	Low-dose (1mg) dex-sup test	High-dose (8/16mg) dex-sup test	Abdominal MRI/CT	Surgery	Cure
1	yes	NS	NS	Adrenal adenoma (5x3cm)	R.adrenalectomy	yes
2	yes	NS	S	B. adrenal hyperplasia	ketaconasole	yes
3	yes	NS	-	Adrenal adenoma (2.5cm)	R.adrenalectomy	yes
4	yes	NS	-	Adrenal adenoma	B.adrenalectomy	yes
5	yes	NS	S	Normal	?	?
6	yes	NS	NS	Adrenal adenoma (4.5cm)	R.adrenalectomy	yes
7	yes	NS	NS	Adrenal adenoma	B.adrenalectomy	Nelson
8	yes	NS	S	B.Adrenal hyperplasia	B.adrenalectomy	yes
9	yes	NS	S	B.adrenal hyperplasia	B.adrenalectomy	Nelson
10	yes	NS	-	Adrenal hyperplasia	Following	
11	yes	NS	-	Adrenal adenoma (2cm)	L.adrenalectomy	yes
12	yes	NS	-	Adrenal adenoma	L.adrenalectomy	yes
13	yes	NS	S	Adrenal adenoma (3.5x2cm)	Following	
14	yes	NS	S	Adrenal adenoma (4x3cm)	R.adrenalectomy	Yes

(*)Truncal obesity, buffalo hump, plethorea, violesance stria (>1cm widht), easy bruisability…

S: supression; NS: no supression; R: Right; L: Left; B: Bilateral

ciency 3 in patients (8.8%) and central hypothyroidism in 4 patients (11.7%). Central hypogonadism and central diabetes insipidus were seen in 4 (11.7%) and 4 patients (11.7%), respectively. Transient diabetes insipidus, neurological complications and recurrence were not observed.

Discussion

Cushing's syndrome is usually seen between the third and fifth decades of life, and causes morbidity and mortality associated with chronic hypercortisolemia. Women are affected more than men (5,6). In this study, the mean age of the patients was 31.8±2.2 years, and the frequency of female patients (26/34) was consistent with the reported studies (7).

Regarding the etio-pathogenesis, of 34 patients, 20 had CD (58.8%) and 14 had CS (41.2%). CD was found to be more frequent among our patients (3,4). In a study by Erem C et al. from Turkey, CD was reported in 39 patients (71%), adrenal adenoma in 13 patients (23.6%) and adrenal carsinoma in 3 patients (5.5%) (8).

Among the morbidities due to Cushing's syndrome, impaired glucose tolerance, DM and fasting hyperglycemia have been reported to be 35%, from 15 to 20%, and from 10 to 15% respectively (1,2). In the present study, DM was found in 13 patients (39.4%), which was a higher rate than that in the reported studies. We can speculate that this high rate of DM is due to delay in the diagnosis of CS. In addition, obesity (n=23, 82%) and the relatively advanced age of the patients might also be involved. There was a positive correlation between the age of our patients and DM (p=0.004). The rate of nephrolithiasis associated with Cushing's syndrome was found to be lower than that of the reported studies (7.7% vs 15%, respectively) (7,9). Hypertension rate and skin findings were observed to be similar to the reported studies (2,10). The rate of osteoporosis was relatively higher in our study than in the reported studies (59% and 66.7 %, respectively) (6). However, this difference could be related to many factors including ethnicity, gender, age, nutrition.

Currently, in the differential diagnosis of CD and CS, HDDST (8/16 mg) has not routinely been recommended in the clinical practice due to its low sensitivity and specifity (65-100%) (11,12). Among the patients with CD in whom HDDST was performed, of 20 subjectssuppression (>50% vs. basal serum cortisol) was observed in 18 (90%). Only 6 of the patients with CS showed supression during HDDST (HDDST was not performed in all patients with CS).

Plasma ACTH measurement is also an important step in the differential diagnosis of Cushing's syndrome (2). In CS of adrenal origin, plasma ACTH level is expected to be below <5pg/ml. When ACTH level is found to be >20 pg/ml, ACTH-dependent CS should be considered (5,13). In our 20 patients with CD, serum ACTH level was 197±57 pg/ml, which was consistent with other studies (7,8).

Recently, midnight plasma cortisol measurements have been performed for establishing the diagnosis of Cushing's syndrome. We had only 4 patients with midnight cortisol measurements and their results were found to be higher than those in Cushing's syndrome. Regarding the sensitivity and specifity, these measurements were reported to be comparable to the 24-h urine cortisol measurement and low-dose DST (5,14). Likewise, salivary cortisol measurement is also a sensitive method used in the diagnosis of Cushing's syndrome (15,16). But, we had no patient whose salivary cortisol level was measured. In the subjects who have findings of Cushing's syndrome, if 24-h urine cortisol level is 2-fold higher than the normal range, Cushing's syndrome is confirmed (17). Out of 34 patients, 11 had results of 24-h urine cortisol measurements, as variable, which were similar to that in the study by Bos Kuil MJ, et al (18).

IPSS was performed in 1 patient who had normal pituitary MRI scan, central to peripheral venous ACTH ratio was found to be >2/1. In a study on ACTH-dependent CS, Wiggam et al. confirmed the diagnosis of CS in 82% of total of 53 patients by using IPSS (19).

As general, following the pituitary surgery, complication rate is nearly 5%, and the mortality is low, and transient diabetes insipidus can be seen in 10% of patients. Haemorrhagia, rhinorrhea, vision loss and persistent diabetes insipidus are rare (2,20). In the present study, the high complication rates (in 10 patients, 29.4%; with more than one complication in some patients) may be due to delay in diagnosis and admittance for surgery, and due to absence of experienced pituitary surgeons.

One of the two patients, who developed Nelson syndrome following the bilateral surrenalectomy, underwent transsphenoidal adenomectomy, and the other was treated with conventional radyotherapy (5000 Rad). In a study including 53 patients, by Assie et al., Nelson syndrome was reported in half of the patients who had bilateral surrenalectomy (21).

Medical treatment with ketoconazole or aminoglutethimide was administered in a short period (a few months) in certain patients, but their results and data were not enough to be discussed here. When we reviewed all our treatment modalities, we assessed the cure rate as 76% (26 patients), which was relativelly good.

In conclusion, in this retrospecitive study consisting of 34 patients with Cushing's syndrome, we found that the general findings of Cushing's syndrome were similar to those reported in the literature, with a little variation in the rate of frequency. However, the rates of Cushing's syndrome and DM were higher than in the literature, and the complication rates following the surgery were found to be also high.

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