Clinical laboratory findings and results of therapy in 55 patients with Cushing’s syndrome

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ABSTRACT. In this study, 55 patients with Cushing’s syndrome (CS) (50 female, 5 male; mean age 34±12.3 yr) who attended our clinics between the years 1983 and 2000 were retrospectively evaluated for clinical and laboratory features and modalities and results of therapy, due to a few similar studies over the last ten years. Cushing’s disease was diagnosed in 39 patients (71%), adrenal adenoma in 13 patients (23.6%) and adrenal carcinoma in 3 patients (5.5%). Centripedal obesity, moon face, hypertension, hirsutism and purplish striae were the most frequent findings. Loss of normal serum F circadian rhythm was found in all patients with CS. The overnight 1 mg oral dexamethasone suppression test and low-dose dexamethasone suppression test (LDDST) yielded 100% and 100% diagnostic sensitivity for CS, respectively. Sensitivity and specificity of the high-dose dexamethasone suppression test (HDDST) in distinguishing Cushing’s disease was found to be 82% and 100%, respectively. All of the patients with adrenal CS were not suppressed with HDDST. Sellar CT and/or MRI accurately identified the tumor in 58% of these patients. Recurrence was observed in 3 (11%) of the 28 patients with Cushing’s disease, treated by transsphenoidal adenomectomy. Recurrence was diagnosed 1.5, 3 and 6 yr after the operation in these 3 patients. One patient had residual tumor. In our case series, bilateral adrenalectomy plus pituitary irradiation achieved the highest remission rate (100%) in Cushing’s disease. In 2 out of 4 patients (50%) treated by left adrenalectomy associated with pituitary irradiation, recurrence was observed. Panhypopituitarism due to tumor apoplexy was observed in one of the patients with Cushing’s disease. All of the patients with adrenal CS, the tumor was accurately localized with imaging methods before the operation. The appropriate operative procedure resulted in complete remission in patients with adrenal adenoma. Consequently, Cushing’s disease was the most common form of CS. The overnight 1 mg oral DST and 24-h urine free F excretion (UFC) as screening tests, 2-day LDDST as diagnostic test and 2-day HDDST as differential diagnostic test were good studies. More successful outcomes have been achieved in treatment of Cushing’s disease with the development of pituitary surgery in the recent years, as well as in our case series. Surgery is also curative for adrenal adenoma patients.

Survival remains poor among carcinoma patients.


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INTRODUCTION

Cushing’s syndrome (CS) is characterized by excessive serum glucocorticoids that have escaped regulatory control (1, 2). Harvey Cushing first described the symptom complex composed of obesity, diabetes, hirsutism, and adrenal hyperplasia in 1912 and later observed basophilic pituitary adenomatous autopsies in 75% of the patients with this disorder (3, 4). CS can be separated into the categories of corti-
cotropin (ACTH)-dependent CS, in which inappropriately high plasma ACTH concentrations stimulate the adrenal cortex to produce excessive amounts of F, and ACTH-independent CS, in which excessive production of F by abnormal adrenocortical tissue causes the syndrome and suppresses the secretion of both CRH and ACTH (5). Recent developments in follow-up and treatment have affected prognosis in a positive way. Untreated CS has significant morbidity and mortality rates. Since almost all physical and psychological characteristics recover with curative surgery treatment, diagnosis of the disease is very important (5, 6).

The accurate differential diagnosis of CS is essential in order that appropriate and effective treatment can be recommended. The differential diagnosis of CS has been greatly improved over past 15 yr due to the introduction of several technological advances including a specific and a sensitive immunoradiometric assays for ACTH, CRH stimulating testing, inferior petrosal sinus sampling (IPSS) for ACTH, and CT, and MRI of the pituitary and adrenal glands. Appropriate use of these technologies provide a simple, cost effective, and accurate differential diagnosis (7).

In this study, 55 patients with CS were examined retrospectively in terms of clinical and laboratory characteristics and of treatment modalities.

MATERIALS AND METHODS

Between 1983-2000, 55 patients (50 women and 5 men, aged 34±12.2 yr) presented to our endocrine units (Istanbul University, Istanbul Medical Faculty and Karadeniz Technical University, Medical Faculty) with signs and symptoms of CS. Among them, 39 had Cushing’s disease, 16 had glucocorticoid-secreting adrenocortical tumors (13 adenomas and 3 carcinomas). Patients with suspected CS were evaluated with a series of biochemical tests (Fig. 1) (2, 7, 8).

CS was diagnosed by the presence of elevated serum F and 24-h urine free cortisol (24-h-UFC) concentrations that were nonsuppressible with the standard two-day, low-dose dexamethasone suppression test (9-11). Its etiology was determined according to the results of the following: standard two-day, high-dose dexamethasone suppression test, computed tomography (CT) or MRI scans with contrast enhancement of pituitary and/or adrenal glands, plasma ACTH levels, histopathological features, and therapeutic outcome.

In some cases of Cushing’s disease diagnosed with dynamic endocrine tests before 1988, it was not possible to find hypophyseal adenoma in sellar imaging, in this case radiotherapy and/or adrenalectomy was performed.

**Overnight 1 mg dexamethasone suppression test**

This test involved the administration of 1 mg of dexamethasone at bedtime (23:00 h) with determination of serum F early (08:00 h) the following morning. Normal subjects should suppress serum F to less than 3 μg/dl following the overnight 1 mg test (2, 8).

**24-hour UFC excretion as a screening and confirmatory test**

The determination of 24-h excretion of free F in urine was assayed by chemiluminescence method (Dpci Immulate) (N: 10-100 μg/24 h). In patients with clear clinical findings of CS, UFC of more than 250 to 300 μg/24 h was considered diagnostic (7).

**Circadian rhythm of serum F**

Blood was taken at 09:00, 18:00 and 24:00 h (asleep), not less than 48 h after admission to hospital. Loss of the normal circadian rhythm of serum F was defined as a sleeping midnight F greater than 1.8 μg/dl (11). Serum F assay was assayed by chemiluminescence method (Dpci Immulate).

**Standard two-day (low-dose) dexamethasone suppression test (LDDST)**

The LDDST involved the administration of 0.5 mg of dexamethasone at 6-h intervals from 08:00 h for eight doses with measurement of serum F at 08:00 h before and at 48 h. Twenty-four-hour UFC on the second day of the test were determined. In normal subjects the 48-h serum F level should be suppressed to <3 μg/dl, and 24-h-UFC level should be suppressed to <20-30 μg/d (8).

**Standard two-day, high dose dexamethasone suppression test (HDDST)**

This test was performed in the hospital by giving 2 mg dexamethasone orally every 6 h for two days. Serum F at 08:00 in the supine position after the last dexamethasone dose, and 24-h-UFC on the second day of the test were determined. Results were compared with baseline values before dexamethasone administration. A lowering of serum F concentration or 24-h-UFC to <50% of the basal value after dexamethasone administration was interpreted as suppressible, and suggestive of Cushing’s disease. A lack of suppression to <50% of the basal value was interpreted as non-suppressible, and suggestive of non-Cushing’s disease including glucocorticoid-secreting adrenocortical tumor and ectopic ACTH syndrome (12, 13).

**Nocturnal 8 mg dexamethasone suppression test**

In some cases, a nocturnal DST was performed one week after the standard DST had been completed, by comparing serum F concentrations of 08:00 am before and after the administration of a single dose of 8 mg dexamethasone at 23:00 h. A lowering of serum F concentration to <50% of the basal value after dexamethasone administration was interpreted as suppressible, and suggestive of Cushing’s disease (14, 15). A lack of suppression to <50% of the basal value was interpreted as non-suppressible, and suggestive of non-Cushing’s disease.

**Measurement of plasma ACTH level**

Blood samples were collected in plastic tubes at 08:00 h and before the standard LDDST and HDDST were performed. EDTA (7.2 mg/5 ml of whole blood) was used as an anticoagulant. Specimens were immediately transferred to the laboratory and centrifuged at 760xg for 10 minutes at 20° C. The plasma fraction was collected in a plastic tube containing 500kiu/ml of apro-