

CUSHING'S DISEASE, TRANSSPHEOIDAL SURGICAL RESULTS OF 11 CASES

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INTRODUCTION

Harvey Cushing first described pituitary dependent hypercortisolemia in 1932.¹ The diagnosis and treatment of Cushing's disease have remained as the major challenge to endocrinologists and surgeons. The disease which accounts for up to 60% of endogenous Cushing's syndrome, is a serious endocrinopathy characterized by hyper secretion of adrenocorticotrophic hormone (ACTH) (which is secreted by the pituitary gland) resulting in bilateral adrenocortical hyperplasia and chronic hypercortisolism.²⁻⁴ The clinical manifestations of hypercortisolemia are: obesity, moon faces, dorsal fat pad, purple striae, hirsutism, muscle weakness, osteoporosis, hypertension, and mental disorders.^{3,5}

These ACTH producing tumors exhibit increased secretion of ACTH and cortisol. In addition, the feedback relationship between the pituitary and the adrenal glands is abnormal. Cushing's patients demonstrate high base line urinary 17-hydroxycorticoids and free cortisol as well as high-plasma ACTH and cortisol levels. Lack of response is also demonstrated in low dose suppression test (L-DST), although cortisol secretion is documented to a value below 50% of the base line,⁶ after administration of high-dose suppression test (H-DST) of dexamethasone.

In the past several therapeutic procedures such as radical subtotal or bilateral total adrenalectomy, transfrontal hypophysectomy, pituitary stalk section pituitary irradiation of various types, and administration of mitotane or related drugs have all proven disappointing.⁷⁻⁹ Most patients with Cushing's disease have ACTH producing pituitary adenoma. Since Hardy¹⁰ reported the successful selective removal of such adenomas in 1969, transsphenoidal adenomectomy has gradually replaced bilateral adrenalectomy as the primary treatment for Cushing's disease in many institutions.^{2,4,8,11,12} The goal of this report was to

BACKGROUND—Cushing's disease is the most common cause of endogenous Cushing's syndrome (up to 60%) and is usually due to pituitary hyperplasia or basophilic adenoma.

MATERIALS AND METHODS—Eleven cases of Cushing's disease that have been admitted to Shariati Hospital since June 1992 up to September 2000, had been reviewed. These included three male, and eight female patients with an age range between (9 - 34) years with a mean of 21 - 5 years.

The most common symptoms were headache, weight gain, and menstrual/libido disturbances. Obesity, moon face, hypertension, depression were the most common signs in our series.

These patients were diagnosed on the basis of high serum and urinary free cortisol, abnormal 2-mg dexamethasone and normal 8-mg dexamethasone suppression test.

RESULTS—The neuroimaging investigation revealed normal sella turcica in 7 cases, double floor and enlarged sella turcica in 4.

Computerized tomography was the most valuable tool which showed the adenoma in 9 cases, MRI with gadolinium injection were helpful in better delineation of the lesion in the last three cases. All patients were treated surgically via transsphenoidal approach.

The mean duration of follow-up was 5 yrs (range, 0.5 - 8 yrs). There were regression of the clinical symptoms in 9 cases (82%), and recurrence of these symptoms in one patient six month after the operation (9%). One patient died because of uncontrolled sepsis two months after operation (9%).

CONCLUSION—In conclusion the transsphenoidal approach is a safe and effective procedure for treatment of patients with diagnosis of Cushing's disease of pituitary origin.

Keywords: Cushing's disease; pituitary adenoma; transsphenoidal surgery.

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Table 1. Size of tumor, duration of signs and symptoms, level of cortisol and ACTH in Cushing's patients.

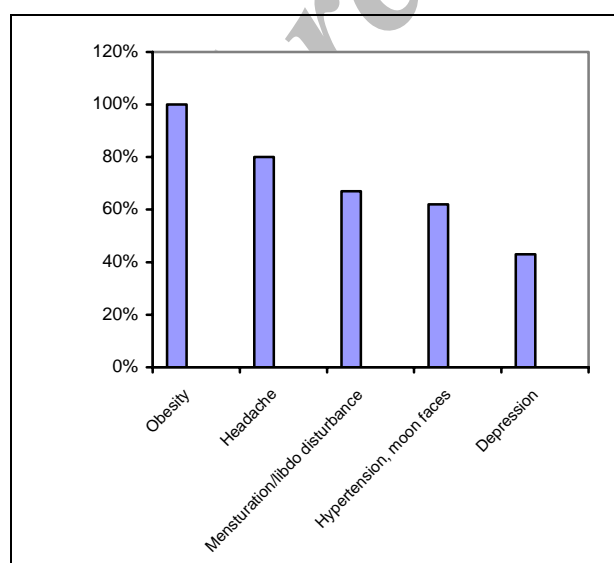
Patient	Sex	Size of the tumor	Duration of signs and symptoms	Urinary and serum cortisol	Serum ACTH level
1	Female	Microadenoma	2 years	High	High
2	Female	Microadenoma	3 years	High	High
3	Female	Microadenoma	8 years	High	High
5	Female	Microadenoma	1 year	High	High
6	Male	Microadenoma	1 year	High	High
7	Male	Microadenoma	5 years	High	High
8	Female	Microadenoma	3 years	High	High
9	Female	Microadenoma	1 year	High	High
4	Female	Microadenoma	6 years	High	Normal
10	Female	Microadenoma	2 years	High	Normal
11	Male	Microadenoma	1 1/2 years	High	Normal

show the surgical results of 11 cases of Cushing's disease that were treated surgically via transsphenoidal approach in the neurosurgical department.

MATERIALS AND METHODS

Between June 1992 and September 2000, there were 11 patients (8 females and 3 males) out of 130 pituitary adenomas, with Cushing's disease who had transsphenoidal microsurgical exploration of the sella turcica at Shariati Hospital. The average age of the patients was 21.5 years (range, 9 to 34). The average duration of the disease at the time of surgery was 3 years (range, 10 months to 8 years). Clinical features of these patients are summarized in Figure 1.

Obesity (100%), headache (81%), hirsutism, menstrual/libido disturbance (72%), hypertension, moon faces (63%), and depression (45%) were the most common signs and symptoms. In addition to the usual clinical features of hypercortisolism, all of these patients had: (1) elevated serum and urinary

**Figure 1.** Clinical features of patients with Cushing's diseases.

free cortisol; (2) elevated plasma cortisol level at 4.00 p.m.; (3) abnormal 2-mg dexamethasone suppression test; (4) normal 8-mg dexamethasone suppression test; and (5) normal or elevated levels of ACTH in plasma, as determined by immunoassay techniques (Table 1).

The preoperative radiological evaluation included standard anteroposterior and lateral roentgenograms of the skull, localization of sella turcica, and thin-section computerized tomography (CT), with sagittal and coronal reformations of the sellar region in all patients. Abdominal ultrasonography and CT of the adrenal glands were used selectively. MRI (magnetic resonance imaging), with gadolinium injection, was used in the last three cases.

RESULTS

In 7 patients the plain skull X-ray and localized sella turcica were normal, and double floor and enlarged sella turcica were noted in four patients. Brain CT revealed microadenoma in five patients, was suspicious in two cases, and identified macroadenoma in four. Patients were operated via transsphenoidal approach, ACTH producing adenomas (micro in 7 and macro in 4) were identified and removed, and later the pathology was confirmed by histopathological studies. Five of the micro adenomas were detected on the left side and two of them were present on the right side of the gland.

CSF leakage was noted intraoperatively in 3 cases and continued postoperatively in 2 cases. Postoperative diabetes insipidus (DI) developed in seven patients, were transient in six patients and permanent in one. Meningitis was the consequence of uncontrolled CSF rhinorrhea in two cases, which was controlled by antibiotic therapy in one and led to death in the second one who was suffering from diabetes mellitus, preoperatively. Postoperative endocrine evaluation was carried out three weeks after surgery, and the patient was regarded to be in

remission if the cortisol levels returned to the normal range. Nine patients remained in remission after surgery with mean duration of follow-up of 5 years (range, 0.5 – 8). The signs and symptoms of Cushing's disease reappeared in one patient with microadenoma six month postoperatively and the patient was referred, by medical colleagues, for bilateral adrenalectomy to a general surgeon.

DISCUSSION

In a series of 12 patients reported by Cushing, who had clinical manifestation of hypercortisolism, basophilic adenoma were found in six of the eight postmortem studies indicative of a pituitary etiology of the disease.¹ Although the role of hypothalamic releasing hormones in the proliferation of pituitary cells is still unresolved, recent findings suggest that prolonged stimulation by hypothalamic hormones may play an important role in pituitary hyperplasia and/or adenoma.

Different therapeutic procedures such as radical subtotal or bilateral total adrenalectomy, transfrontal hypophysectomy, pituitary stalk section, pituitary irradiation of various types, and administration of drugs such as mitotane or related drugs have all been disappointing in one way or another.^{7-9,13} Although primary irradiation of the pituitary gland can eventually produce remission in 50% to 80% of patients with Cushing's disease, the hypercortisolism may not be resolved for many months after pituitary irradiation and some of the patients develop panhypopituitarism.^{7,9} Selective adenomectomy can correct the condition immediately.^{2,5,8,11,14-16}

Pituitary adenomectomy via transsphenoidal approach is the treatment of choice. This ideal treatment would not only correct the hypercortisolism, but it would also leave the patient with normal pituitary and adrenocortical functions with no need for life-long endocrine replacement therapy.^{8,17} When the clinical presentation, biochemical, and radiological data suggest the diagnosis of Cushing's disease, surgical pituitary exploration is the treatment of choice. Several factors are important in achieving the best possible postoperative results. These include the completeness and accuracy of the preoperative endocrine work-up, meticulous neuroimaging investigations, and the skill and experience of the surgeon.³

This report examines the surgical results of 11 patients diagnosed as having Cushing's disease preoperatively. The clinical signs and symptoms, preponderance of females (73%), average age (21.5

years), and the length of time between onset of symptoms and diagnosis (3 years) were as expected for Cushing's disease.^{2,11} The number of abnormal skull X-ray (37%) was more than those reported by the others (10% to 20%).^{8,17} This may be due to the larger number of macroadenomas in this group. The incidence of specifically abnormal CT scans (81%), five microadenomas and four macroadenomas, was somewhat higher than those in the previously reported series,^{2,8,11,15} and may reflect the improved resolution of the newer scanners. Positive brain MRI, with gadolinium injection, has been helpful in better delineation of the lesion, which is in keeping with Vest-Courtalon's report.¹⁸

Although preoperative lateralization of ACTH-secreting pituitary micro adenoma by bilateral and simultaneous inferior petrosal venous sinus sampling was not possible,¹⁹ transsphenoidal surgical approach revealed micro adenoma in seven cases (five in the left side and two in the right side of the gland in two cases). Macroadenoma was present in four patients with a short history of signs and symptoms which led to early diagnosis (Table 1). These eccentrically placed tumors were also reported by Boggan et al² and Kuwayama.¹⁵ The proportion of macroadenoma to micro-adenoma was higher compared with other reports,^{2,5,8,11} which may be due to the small number of patients. Complications such as CSF leakage, meningitis, diabetes insipidus, and death were more than those reported by others.^{5,13,20}

With a mean follow-up of 5 years, there was recurrence of clinical symptoms in one patient 6 months postoperation, while 9 patients (82%) remained in remission. This remission rate is consistent with the results reported by Boggan et al² and Salassa et al,⁸ and is less than the result reported by Hardy¹⁰ and Kuwayama et al.^{15,21} The question of whether the correction of clinical and biochemical abnormalities in the short term after surgery assures the long term remission or permanent "cure" of the disease is still unanswered. However, because Cushing's disease can recur up to 8 years after surgery, patients in clinical remission should have periodic endocrinologic reevaluation.⁵

In conclusion: (1) brain MRI with gadolinium injection can better delineate the microadenomas in Cushing's patients; (2) transsphenoid surgical approach is the treatment of choice in patients with Cushing's disease, and is a safe procedure in experienced hands; and (3) for better evaluation of patients in clinical remission, long follow up-eight years or more-and periodic endocrinologic reevaluation is recommended.

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