

Results of Transsphenoidal Surgery in 35 Cases of Cushing's Disease

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This study aims at analyzing the outcomes of transsphenoidal surgery in 35 patients of Cushing's disease (CD), the highest number of patients seen during 11 years from one center in Iran.

Materials and Methods: Retrospective data from case records of all patients were retrieved. The diagnosis of CD was based on clinical presentation, hormone studies, adrenal and pituitary imaging, and thoracic imaging as and when considered appropriate. Age, sex, clinical parameters, laboratory investigations, intra-operative findings, post-operative complications, duration of hospital stay and follow up observations were evaluated using appropriate statistical methods.

Results: Of 35 patients, 26 were female and 9 male with a mean age of 28 ± 10 years. The most frequent presenting symptom had been obesity (57%) which was present for 30 ± 29 months. Four patients had macroadenoma and the other 31 (86%) had microadenoma. All patients were operated by transsphenoidal route; there were no intra-operative complications. Two patients had temporary CSF rhinorrhea and 9 had temporary diabetes insipidus in the post-operative period without any need for surgical intervention. Eight patients were lost to follow up and the remaining 27 were followed for 22 ± 23 months (minimum 3 months and maximum 8.5 years). Remission was achieved in 32 patients (88%), while the

remaining 3 did not benefit from surgery. Recurrence occurred in 3 cases (14%), requiring repetition transsphenoidal surgery with success in two.

Conclusion: Transsphenoidal adenomectomy is an effective modality of treatment for patients with Cushing's disease with near zero mortality and acceptable morbidity.

Key Words: Cushing's disease, Transsphenoidal surgery

Introduction

Cushing's syndrome is considered to be one of the more difficult medical problems for diagnosis, determination its etiology, and formulation of the treatment. Adrenal hyperplasia due to excess ACTH secretion from a pituitary adenoma is the most common cause (65-70%) and this is arbitrarily called Cushing's disease.¹ Others are either due to secretion of ACTH or CRH from an ectopic source or by an adrenal neoplasm, benign or malignant.²

This study analyzes the results of transsphenoidal surgery in 35 patients with Cushing's disease over an 11-year period (starting from 1993); this is so far perhaps the largest number of patients reported in Iran.

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Materials and Methods

This is a sequential case series study of Cushing's disease, operated by transsphenoidal route in our hospital. Most of the patients were admitted to the endocrine ward of the Taleghani Hospital for clinical and appropriate investigation. All had detailed history and clinical examination, and evaluation of serum cortisol levels from samples taken morning, afternoon and following overnight dexamethason. Twenty-four hour urinary free cortisol was estimated before and following standard low dose and high dose dexamethason suppression. Serum ACTH and other pituitary hormones were also determined. Imaging procedures including abdominal computed tomography, coronal dynamic computed tomography or magnetic resonance imaging of the pituitary gland or both after contrast injection, and thoracic computed tomography in selected cases were carried out in the Taleghani hospital or in our institution. Patients were selected for surgical intervention when findings of their evaluations corresponded to one of the following three groups: 1) typical hormonal findings for Cushing's disease i.e. high basal serum and 24hour urine cortisol, no cortisol suppressibility to low dose dexamethason suppression test (LDDST) but good suppression after high dose dexamethason suppression test (HDDST) and normal or, high serum ACTH; normal or bilateral adrenal hyperplasia on abdominal computed tomography; micro or macroadenoma in pituitary imaging. 2) endocrine evaluation typical for Cushing's disease, as above; adrenal computed tomography normal or bilateral adrenal hyperplasia; no positive finding in pituitary neuro imaging. 3) patients whose endocrine evaluations were not definitive for Cushing's disease but had findings of a micro or macroadenoma in their pituitary neuro imaging. After selection for operation, the patients were interviewed and their consent was documented. One day before operation, the nasal mucosa was washed every hour by normal saline containing 1% of gentamycin. On the day of opera-

tion, the patients received intravenous infusion of 100mg hydrocortisone every 4-hour and 2000 mg cefazolin at the beginning of anesthesia induction. Patients were operated in supine position with extension of the head. Using operating microscope and through transseptal - transsphenoidal approach, the anterior wall and part of the floor of sella turcica was removed and the dura was opened by a cruciate incision. Sometimes tumors were found easily as dura was opened with no problems faced in their excision, but at other times, pituitary exploration was necessary to locate the adenoma. When the adenoma was distinctly seen at preoperative imaging, the corresponding location was explored for it, but with no adenoma in CT/MRI, a transverse incision was made on the pituitary gland and it was divided to four quadrants, each one being examined for location of the tumor. Well-defined tumors were resected completely, while with no definite tumor total hypophysectomy was performed. After tumor removal, a thin margin of normal gland was removed for assurance of complete resection. In cases with intact arachnoid, a cottonoid soaked with absolute alcohol was inserted into the empty space of resected tumor for 3 minutes. After hemostasis with sur-gicele, sellar wall was reconstructed with bone from vomer and the sphenoid sinus was packed with muscle. Nasal cavity pack was removed after 48 hours. Patients received hydrocortisone during their hospital stay and were referred to the endocrinologist for re-evaluation of their disease activity and continuation of appropriate medical treatment. Variables including age, sex, duration of hospital stay, clinical presentation of the disease and its duration, findings in clinical examination, results of endocrinological evaluations, findings of imaging procedures, intra-operative findings, follow up duration, result of the treatment and recurrence after remission were retrieved from patient files for analysis.

Results

Age and sex: Of the 35 patients operated, 26 (74%) were female and 9 (26%) male, with ratio of 3 to 1. Their mean age was 28 ± 10 , with the youngest being a 7 year-old boy and the oldest, a 56 year-old lady. The distribution was highest in women between the ages of 31 to 45 years (Fig.1). Twenty-one patients (60%) were housewives, 8 (23%) were students, 3 were teachers and 3 laborers.

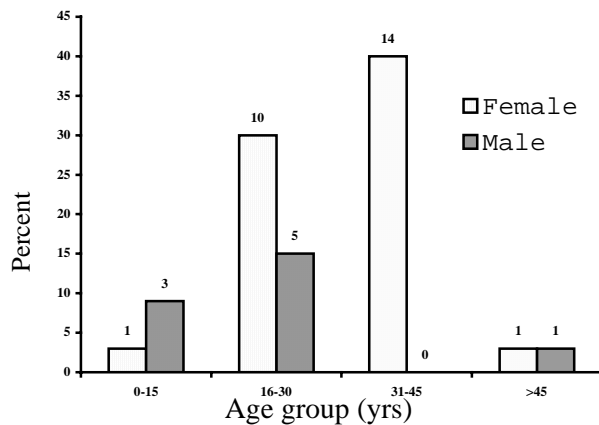


Fig.1. Age and sex distribution in 35 patients with Cushing's disease

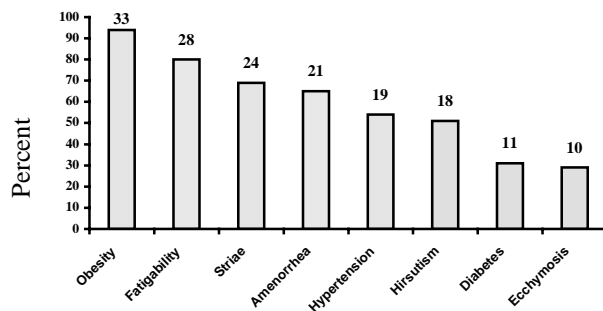


Fig.2. Clinical findings in 35 patients with Cushing's disease

Hospital status: 26 patients were referred from the endocrinology ward of Taleghani Hospital and 9 from other centers. Their hos-

pital stay was 14 ± 8 days, the shortest duration being 5 and the longest 40 days.

Clinical findings: Obesity was the most frequent presenting symptom seen in 20 patients (57%), followed by other symptoms such as amenorrhea in 3, hirsutism in 3 and headache in 4 patients. Duration of presenting symptom was 30 ± 29 months with 1 month as the shortest and 12 years for the longest duration.

Distribution of clinical findings is shown in Fig.2, with fatigability, cutaneous striae and hirsutism as the most common findings after obesity.

Endocrine investigations: One case presented with Nelson's syndrome. Of the other 34 patients, 26(76%) had typical suppression tests i.e. no suppression after LDDST and good suppression with HDDST, and only in 8 cases, endocrine evaluation was not definitive for Cushing's disease (no suppression with either tests) but their pituitary imaging was positive.

Neuroimaging (plain X-ray) Sellar X-ray was present in 31 patients; this was normal in 26 (84%) enlarged in 4, and double floor in one case only.

Thoracic CT scan: Was performed in only 5 patients and was normal in all of them.

Abdominal CT scan: Was obtained in 24 (68%), showing bilateral adrenal hyperplasia in 7, and being normal in the other 17 cases.

Pituitary gland imaging: 27 patients (77%) had dynamic coronal CT scan of sella turcica and 25 (71%) had MRI (in 18 patients both MRI and CT scan were performed). Pituitary gland imaging findings are shown in Fig.3.

Among 4 cases with macroadenoma, cavernous sinus invasion was evident in one case, extension in 3, sphenoid sinus invasion in 2 and hydrocephalus with no relation to adenoma in one. In 22 patients results were positive for microadenoma and 9 patients had normal imaging of the pituitary gland.

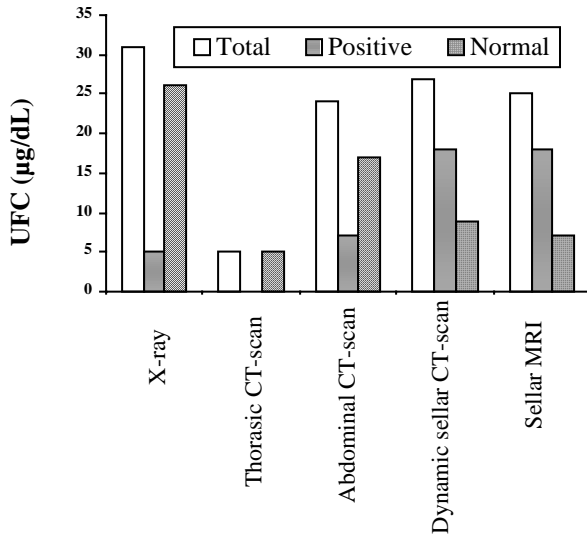


Fig. 3. Imaging procedures in 35 patients: 17 cases had MRI and CT-scan both; 10 cases had CT-scan only 8 cases had MRI only

Surgical findings: All patients were treated by transsphenoidal approach. In 4 cases with macroadenoma, total tumor removal was accomplished with successful preservation of normal glands in 2 of them. In the other 31 patients, microadenoma could be found in 30 and in only one total hypophysectomy was performed. Except for one patient, in the other cases tumor was soft and suctionable and could easily be differentiated from normal gland tissue. Microadenoma was located on the left side in 10, right side in 10 and midline in 11 cases. Overall in 32 patients

(91%) normal pituitary gland was preserved at the end of operation. In 7 cases, condition was suitable for using absolute alcohol. In 9 patients (20%), tearing of arachnoid occurred at the time of surgery.

Two patients had postoperative cerebrospinal fluid rhinorrhea, which led to bacterial meningitis in one; both were treated successfully with conservative measures. Postoperative diabetes insipidus occurred in 11 patients (31%), being temporary in all. There was no mortality.

Follow up results: Eight patients were lost from follow up and could not be contacted by any means. Follow up duration was 22 ± 23 months in the remaining 27 cases, ranging from 3 months to 8.5 years. Results of surgical outcome in 3 different groups of patients are shown in Table 1. Of 27 cases, 23 patients (85%) achieved full remission according to their follow up clinical examination; endocrinological evaluations are shown in Figures 4 and 5. Three patients (14%) had recurrence of their problem 1.5 year after operation in 2 cases and after 8 years in one. All 3 were again operated by transsphenoidal route, with successful results in 2. The other one had bilateral adrenalectomy 5 months later.

Table 1. Surgical outcome according to patient group

Groups	Remission		
	Positive	Negative	Total
1: Positive endocrine results\ positive neuroimaging	15	1	16
2: Positive endocrine results\ negative neuroimaging	5	1	6
3:Negative endocrine results\ positive neuroimaging	3	1	4
Total	23	3	26

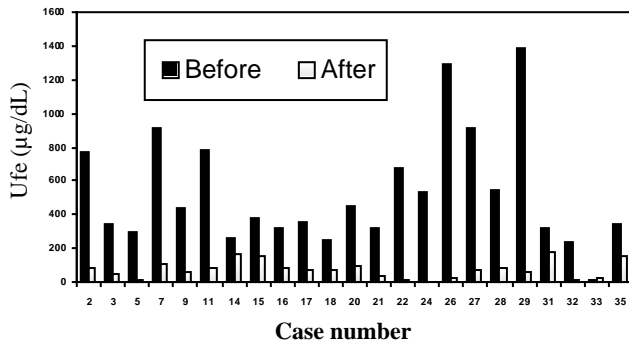


Fig.4. 24 hour urine free cortisol levels before and after operation

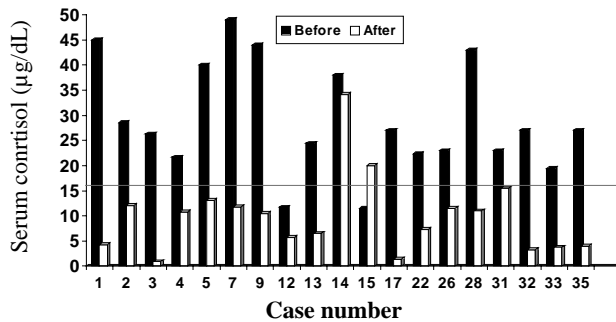


Fig. 5. Serum cortisol levels before and after operation

Discussion

Treatment of Cushing's disease has been difficult and usually unsuccessful before the advent of modern diagnostic tools and use of the operating microscope in neurosurgical procedures.¹⁻⁴ This study showed 88 per cent remission in our patients with Cushing's disease. This success rate with transsphenoidal resection of the ACTH secreting pituitary

adenomas is similar to results of other studies; present literature documents a 70 to 90 per cent remission rate after surgery.⁵⁻⁹ Such successful results are achievable by careful and proper selection of patients for surgery after thorough clinical, endocrinological and imaging studies.

In 6 patients although the endocrine evaluation was typical for Cushing's disease, there was no positive finding in pituitary imaging, which may be seen in 25 to 50 per cent of all patients⁹⁻¹²; microadenoma was found in 5 (83%) at operation and only one patient underwent total hypophysectomy. With petrosal sinus sampling for this group of patients, the positive results may be higher than this,^{7,13} but with our limitations in its performance, transsphenoidal exploration seems to be a good approach for such patients. Zero mortality and low risk of complications (6% CSF rhinorrhea, 31% DI) in transsphenoidal surgery, makes it a very good treatment modality in Cushing's disease and even with recurrence, a problem in 14% of our cases, the results of the second surgical approach were encouraging.

Transsphenoidal adenomectomy seems to be the preferred modality of treatment for patients with Cushing's disease, with no mortality and acceptable morbidity; it is recommended for all patients with proven or highly suspected pituitary etiology.

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