Outcome of Microscopic Transsphenoidal Surgery in Cushing Disease: A Case Series of 96 Patients

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OBJECTIVE: **To analyze the results of transsphenoidal surgery in patients with Cushing disease and outcome.**

METHOD: **Retrospective analysis of the records of 96 patients with Cushing disease from 1997 to 2012.**

RESULTS: **There were 73 females and 23 males, with a mean follow-up of 44 months (range, 3–13 years). The sex ratio was significantly different in children and teenagers versus adults. Magnetic resonance imaging showed microadenoma, macroadenoma, and no adenoma in 66, 18, and 12 patients, respectively. There was no surgical mortality. Early remission (normal 24-hour urinary free cortisol and basal serum cortisol <5 μg/dL) was achieved in 94.8%. Regression analysis showed that only tumor size, cavernous sinus extension, and tumor consistency influenced remission. Recurrence was seen in 21.9%. Regression analysis showed that age, preoperative basal cortisol levels, and follow-up duration influenced recurrence. Correlation analysis showed that there was a significant negative correlation between patient age and the follow-up period. After detection of recurrence, 17 patients underwent repeat transsphenoidal surgery that resulted in remission in 12 patients (70.6%). The other 5 patients were referred for gamma knife radiosurgery or bilateral adrenalectomy.**

CONCLUSIONS: **Transsphenoidal surgery is a safe and highly efficient procedure in the treatment of Cushing disease. Macroadenomas, cavernous sinus invasion, and harder tumor consistencies, however, are associated with lower remission rates (higher disease persistence) and younger age, higher preoperative cortisol levels, and longer follow-up periods are associated with higher recurrence.**

INTRODUCTION

Cushing syndrome is one of the most difficult medical conditions for diagnosis, determination of its cause, and formulation of its treatment. Cushing disease (CD) is caused by increased pituitary secretion of adrenocorticotropic hormone (ACTH), most commonly (65%–70% of cases) by an adenoma (or rarely, carcinoma), which results in increased production of cortisol. The disease is associated with multiple adverse cardiovascular, metabolic, musculoskeletal, and mental consequences that decrease the patients' quality of life.[1,2] CD has a 4-fold increase in mortality, reported to be as high as 50% within 5 years.[2] This excess mortality rate may persist even after successful treatment.[3,4] Moreover, it has a trend to recur even after remission. Therefore, patients with CD require early and aggressive intervention to prevent this excess mortality.

Transsphenoidal surgery (TSS) is the treatment of choice for CD and can be repeated if the disease persists or recurs.[5,6] Although different remission criteria have been used in different studies,

Key words
- Cushing disease
- Outcome
- Recurrence
- Remission
- Transsphenoidal surgery

Abbreviations and Acronyms
ACTH: Adrenocorticotropic hormone
CD: Cushing disease
CSF: Cerebrospinal fluid
CT: Computed tomography
GKRS: Gamma knife radiosurgery
HDDST: High-dose dexamethasone suppression test
LDDST: Low-dose dexamethasone suppression test
MRI: Magnetic resonance imaging
TSS: Transsphenoidal surgery
UFC: Urinary free cortisol

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remission is usually defined as normalization of urinary free cortisol (UFC) levels,[7-9] cortisol <3 μg/dL or <50 nmol/L after a 1-mg overnight dexamethasone suppression test,[8,9] morning cortisol <5–7 μg/dL,[10] and/or ACTH <5 pg/mL[11] plus clinical signs and symptoms of adrenal insufficiency or hypocortisolism (being dependent on steroid replacement).[7,9] The postoperative morning serum cortisol level <50 nmol/L is considered by some as an apparent immediate cure.[12] Failure to achieve this criterion is considered persistence, and loss of remission at least 1 year after TSS is considered recurrence or relapse.[8]

Remission and recurrence rates after TSS vary and are dependent on tumor size, intrasellar versus extrasellar extension, visibility of tumor on preoperative imaging, and neurosurgical expertise.[5] Generally, remission and recurrence rates in the range of 65%–95%[13] and 8%–35%,[5,8,12] respectively, have been reported after TSS for microadenomas responsible for CD. The results have been reported to be inferior for macroadenomas[12] and repeat surgery.[7]

There have been a few reports on the long-term outcome of pituitary surgery in the management of pituitary adenoma causing CD. In the current study, we investigate the results and outcome of TSS in 96 patients with CD who were treated in our institute by a single neurosurgeon with a mean follow-up of approximately 4 years and in some cases exceeding 10 years. This is the first report to include long-term results of TSS for CD from Iran.

METHODS

Patients

Patients who underwent TSS for an ACTH-secreting pituitary adenoma from 1997 to 2012 took part in this study. The patients were recruited in a consecutive manner. All patients were operated on in Shohada Tajrish Hospital, a tertiary care academic facility, and Tehran Clinic Hospital. The study design was approved by the ethical committee of Shahid Beheshti Medical University and was performed with adherence to the statements of the Declaration of Helsinki and regulations of the institutional review board.

CD was diagnosed on the basis of relevant clinical features, a basal (8 AM) ACTH level >5 pg/dL, basal cortisol after a 1-mg dexamethasone suppression test >5 μg/dL, or 24-hour UFC >300 μg/day. All patients were referred after evaluation in endocrine departments by pituitary hormone analysis, including ACTH, cortisol, and low- (LDDSTs) and high-dose dexamethasone suppression tests (HDDSTs). Then, the presence of a pituitary adenoma was investigated by magnetic resonance imaging (MRI), which included axial, coronal, and sagittal views in both T1- and T2-weighted images, and T1-weighted images after gadolinium, and dynamic sella region MRI in cases with microadenomas. Tumors were classified as microadenomas (largest tumor diameter <10 mm) and macroadenomas (largest tumor diameter >10 mm). Computed perimetry was obtained in patients with macroadenoma, those with evidence of chiasmal compression by tumor on MRI, or those with subjective or objective visual complaints. Computed tomography (CT) scans were performed in both axial and coronal sellar views. Imaging of adrenal glands was performed whenever deemed necessary.

TSS was performed via a transnasal approach under a surgical microscope view. Selective adenectomy was the preferred procedure. Postoperative complications were kept to a minimum by performing complete removal of the adenoma, preservation of normal gland, keeping the arachnoid layer intact to prevent leakage of cerebrospinal fluid (CSF), and reconstruction of the sellar wall. If no adenoma was found during surgery, the sella turcica was explored, followed by subtotal hypophysectomy if exploration yielded negative results. After tumor removal, routine histopathologic analysis was performed to establish the diagnosis. All surgical procedures were performed by 1 neurosurgeon (M.S., the senior author of this study). Surgical endoscopy was not used in any patients.

On the first day after surgery, morning (basal) serum cortisol and 24-hour UFC levels were measured. Three outcome groups were identified according to remission status after first TSS: remission, persistence, and recurrence.[5] Disease remission was defined according to recently established radiologic and hormonal consensus criteria.

Follow-up information was obtained from periodic visits to our clinic or through contacts by telephone with the patient's referring physician or with the patient and the patient's family. Patients were followed after surgery on a regular basis. On follow-up visits, a complete pituitary hormone profile (including morning serum cortisol and 24-hour UFC) was obtained on months 6 and 12 and annually thereafter. MRI was obtained whenever deemed necessary. Failure to maintain remission was suspected by uncontrolled or recurrent clinical signs or relevant laboratory data and investigated by MRI. Decisions on the necessary management (medical therapy, reoperation, gamma knife radiosurgery [GKRS], radiation therapy, or bilateral adrenalectomy) were taken accordingly.

All data were recorded in a computerized database. The database included information on the clinical symptoms and signs, the preoperative and postoperative laboratory and imaging results, operative findings, results of surgery, complications, clinical outcome, and postoperative management.

All analyses were performed with the PASW Statistics (version 18) package (Predictive Analytics Software [SPSS Inc., Chicago, Illinois, USA]). For all analysis, P values less than 0.05 were considered statistically significant.

RESULTS

In the study period, 96 patients underwent TSS for ACTH-secreting pituitary adenoma. Seventy-three patients (76%) were female and 23 were male (24%; female/male ratio, 3.2). However, subgroup analysis showed that the sex ratio was significantly different in children and teenagers versus adults (64% males in the group of patients <20 years vs. 19% for those >20 years; t test analysis, $P < 0.001$). The age of the patients ranged from 7 to 65 years (mean 31.4 ± 12 years). **Figure 1** shows the age and sex distribution of the patients. The most common presenting symptom was obesity. **Figure 2** shows the clinical findings in these patients.

All patients had hormonal evaluation as basal serum cortisol, UFC, ACTH and their changes after LDDST and HDDST. Table 1 shows these hormonal assessment.

Preoperative Imaging

Imaging results are presented in **Tables 1** and **2**. Pituitary MRI showed microadenoma in 66 patients (68.8%) and macroadenoma in 18 (18.8%), and in 12 patients imaging failed