Primary Endoscopic Transnasal Transsphenoidal Surgery for Magnetic Resonance Image–Positive Cushing Disease: Outcomes of a Series over 14 Years

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■ BACKGROUND: **There are scant data of endoscopic transsphenoidal surgery (ETS) with adjuvant therapies of Cushing disease (CD).**

■ OBJECTIVE: **To report the remission rate, secondary management, and outcomes of a series of CD patients.**

■ METHODS: **Patients with CD with magnetic resonance imaging (MRI)-positive adenoma who underwent ETS as the first and primary treatment were included. The diagnostic criteria were a combination of 24-hour urine-free cortisol, elevated serum cortisol levels, or other tests (e.g., inferior petrosal sinus sampling). All clinical and laboratory evaluations and radiological examinations were reviewed.**

■ RESULTS: **Forty consecutive CD patients, with an average age of 41.0 years, were analyzed with a mean follow-up of 40.2 ± 29.6 months. These included 22 patients with microadenoma and 18 with macroadenoma, including 9 cavernous invasions. The overall remission rate of CD after ETS was 72.5% throughout the entire follow-up. Patients with microadenoma or noninvasive macroadenoma had a higher remission rate than those who had macroadenoma with cavernous sinus invasion (81.8% or 77.8% vs. 44.4%, $P = 0.02$). After ETS, the patients who had adrenocorticotropic hormone–positive adenoma had a higher remission rate than those who had not (76.5% vs. 50%, $P = 0.03$). In the 11 patients who had persistent/recurrent CD after the first ETS, 1 underwent secondary ETS, 8 received gamma-knife radiosurgery (GKRS), and 2 underwent both. At the study end point, two (5%) of these CD patients had persistent CD and were under the medication of ketoconazole.**

■ CONCLUSION: **For MRI-positive CD patients, primary (i.e., the first) ETS yielded an overall remission rate of 72.5%. Adjuvant therapies, including secondary ETS, GKRS, or both, yielded an ultimate remission rate of 95%.**

INTRODUCTION

Patients with Cushing disease (CD) are exposed to excessive glucocorticoids, which could cause various medical conditions and increase the risk of mortality (5, 17). Treatment is therefore warranted once the diagnosis of CD is established. Transsphenoidal surgery (TS) has long been the standard of care for patients with CD (3, 19, 20, 32, 33, 35, 36). Different reports have demonstrated variable remission rates after microscopic TS ranging from 50% to over 90% (2-4, 10, 14, 15, 29, 31). Multiple reasons could be attributed to the great variety of rates reported, such as diagnostic criteria, tumor size, assessment of remission, follow-up duration, adjuvant management, and even the nature of CD itself (25, 26).

In recent decades, application of endoscopes has gained great popularity in the approach to TS. Many reports have demonstrated that endoscopic transsphenoidal surgery (ETS) is a viable and effective approach for pituitary adenoma (6, 14, 39). It is generally accepted that ETS provides a more panoramic view than microscopic TS, allowing an increased surgical field and a close-up

Key words
- Cushing disease
- Endoscopic transsphenoidal surgery
- Macroadenoma

Abbreviations and Acronyms
CD: Cushing disease
CSF: Cerebrospinal fluid
ETS: Endoscopic transsphenoidal surgery
GKRS: Gamma knife radiosurgery
MRI: Magnetic resonance imaging
SD: Standard deviation
TS: Transsphenoidal surgery
UFC: Urine-free cortisol

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visual examination of the anatomic structures around the sella. However, there are scant data on the actual outcomes of ETS for CD. Whether the rates of remission, recurrence, and complications of ETS are comparable with microscopic TS remains elusive.

This study aimed to report a series of CD patients with magnetic resonance imaging (MRI)-proven microadenoma and macroadenoma managed by ETS. Not only the remission rates but also the management of relapses/nonremissions of CD are reported in detail. This is, to date, the first series to specifically examine MRI-positive CD patients managed primarily with ETS.

METHODS

Design of the Study

Consecutive patients with Cushing disease who underwent ETS as the first and primary treatment in the past 14 years were included. Their medical records, radiological evaluations, and pathological examinations were retrospectively reviewed until September 2014. All preoperation and postoperation endocrinology studies were also collected for investigation.

Inclusion Criteria

All patients were referred by endocrinologists in our institution for CD under the following criteria: a combination of 24-hour, urine-free cortisol (UFC); elevated serum cortisol levels; or other tests according to consensus guidelines (1). Defined pituitary mass lesion was reviewed under MRI examination before the operation. For every patient, ETS was applied as the primary treatment for the pituitary tumor. Adequate follow-up, including one or more clinical neuroimaging and endocrinologic evaluations, was necessary for inclusion in the current series. Exclusion criteria were patients who had received surgery elsewhere (e.g., craniotomy or transsphenoid surgery), radiosurgery, conventional radiation therapy, or any other prior forms of intervention.

Surgical Techniques for Endoscopic Transnasal Surgery

All operations were performed by the senior author (Yen Y.S.). Our standard approach refers to a 1-surgeon, 2-hand technique via single nostril, with the endoscope mounted on a pneumatic scope holder. A vertical linear mucosal incision was made with electric cautery near the root of the bony nasal septum. Without destruction of the middle turbinate, a nasal speculum was placed after dilatation of the space and fracture of the bony nasal septum. Subsequently, posterior septectomy was carried out, together with removal of the anterior portion of vomer bone, using high-speed drills and Kerrison rongeurs. The bony septum inside the sphenoid sinus and rostrum of sphenoid bone were further removed for exposure of the sella turcica. After confirmation with the navigation or fluoroscopy, the pituitary fossa was entered. Durotomy and subsequent lesionectomy were then performed. Angled endoscopes (e.g., 30- and 45-degree scopes) were usually used for macroadenoma and those tumors with cavernous sinus invasion. The similar TS technique of 1-surgeon, single-nostril, 2-hand technique with the use of an endoscope holder has been described elsewhere by the senior author (12, 38).

Complete resection of the adenoma with maximal preservation of the normal pituitary gland was always attempted. Dissection of the pseudo-membrane was sometimes achievable for microadenoma. The sellar floor was reconstructed using autologous bone grafts harvested during the approach. Fat graft from the abdominal wall, together with tissue glue, was applied in cases with intraoperative cerebrospinal fluid (CSF) leakage.

Follow-up and Further Management

Postoperation, all patients were routinely monitored for urine output, serum sodium, and specific gravity to evaluate for diabetes insipidus (DI) and/or syndromes of inappropriate antidiuretic hormone secretion. Furthermore, laboratory examinations included 24-hour urine-free cortisol (UFC), serum cortisol, and serum adrenocorticotropic hormone (ACTH) at an average of 72 hours postoperation. Oral cortisol supplement was dependent on clinical symptoms, signs of adrenal insufficiency, and biochemical evidence of hypocortisolemia. Clinical evaluation by the endocrinologist and neurosurgeon was arranged regularly at 4, 8, and 12 weeks postoperation. Radiographic evaluations (i.e., MRI) were arranged at 6 months postoperation and then annually thereafter.

Remission of CD was defined as postoperative hypocortisolism or eucortisolism. Hypocortisolism was defined as a 24-hour UFC level of $<$20 mg/24 hours or an early morning serum cortisol of $<$5 mg/dL in all, or the majority of, samples. Eucortisolism was defined as 24-hour UFC excretion within the normal range (1, 22, 35). Persistent CD was defined by persistent hypercortisolism without cortisol supplement or receiving further management within 12 months after the primary treatment. Recurrent CD was defined by relapse of hypercortisolism or clinical deterioration evaluated by the endocrinologist later than 12 months after the primary treatment.

For the patients with recurrent/persistent CD, which was proven by MRI or endocrinologic evaluations, a reoperation by ETS or gamma-knife radiosurgery (GKRS) was then arranged.

Surgical complications were defined as any adverse events, including CSF rhinorrhea, hematoma, visual disturbance, and other clinical deterioration, during the first 30 days after the ETS that needed further management.

Histological Analysis

All surgical specimens underwent histological analysis to confirm the diagnosis of corticotroph adenoma. Immunohistochemical stain with multiple pituitary hormones was performed with standard of care by specialized neuropathologists in our institute.

Statistical Analysis

Data are presented as the mean and standard deviation for continuous variables and as frequency and percentages for categorical variables. A Kaplan-Meier curve was performed for recurrence-free survival from the time of ETS to the last follow-up and further management of recurrence. A logistic regression model was used to analyze the prognostic factors of tumor control and to assess odds ratios. A P value of < 0.05 was considered statistically significant. All statistical analyses were performed using the software MedCalc (Ostend, Belgium).

RESULTS

Demographic Data

A total of 40 patients who received ETS as the first and primary treatment for CD were analyzed. The mean age at the time of ETS