Outcome of Transphenoid Surgery for Corticotroph Pituitary Tumors

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Abstract

Background & Importance: The aim of this study was to demonstrate the result of transsphenoid microsurgery for Cushing disease in our center and comparing the results in details with other articles, to achieve the best decision for patients management in future.

Case Presentation: Between 1991 to 2015, 50 patients suffering from Cushing disease were operated. Before operation, endocrine tests and neuroimaging examinations were done for all patients and all of them were operated via transsphenoid approach. They were followed up in clinic with endocrine tests and imaging in regular intervals. During this study, 50 Cushing cases including 47 primary and three secondary tumors were operated. Thirty four (68%) tumors were microadenoma and 16 (32%) macroadenoma. A patient died due to post-operative fulminant meningitis (mortality=2%). Mean of follow-up was five years. Overall, 40 (80%) patients had remission after operation and 9 (18%) patients achieved no remission, three of them had macroadenoma and six microadenoma. During follow-up period, three (6%) patients had recurrence which needed second operation. In secondary tumor and in macroadenoma with cavernous sinus involvement, the result was not good (33% and 0% remission, respectively).

Conclusion: Transsphenoid surgery is a safe and effective first choice method to manage Cushing disease compared to other treatment modalities. In recurrent or resistant cases, other modalities could help to manage patients.

Keywords: Cushing Disease; Microadenoma; Cavernous Sinus; Transsphenoid Surgery

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Background & Importance

Management of corticotroph pituitary adenoma opens a challenging course which involves different specialties in diagnosis and treatment strategy. Cortricotroph adenomas represent nearly 8% to 10% of pituitary adenomas (1). They cause excessive production of adrenocorticotropin releasing hormone (ACTH) that can develop clinical well-known Cushing disease or less commonly nelson syndrome. (1,2). Most of the patients take medical care due to endocrine problem. Large tumor can also develop visual problem or intracranial pressure (ICP). Diagnosis of disease needs precise endocrine tests in basal and dynamic states. Brain MRI with gadolinium enhancement with dynamic sellar images can also be used as the most sensitive imaging to localized adenoma and anatomy of sellar region. In inconclusive cases, bilateral inferior petrosal sampling (IPS) could be helpful to identify Cushing disease (3). Surgery is the mainstay of treatment strategy for corticotroph adenoma, although other options such as radiation and medical therapy can be considered in recurrent or resistant cases. Transsphenoid approach was introduced to manage pituitary adenoma from early 20th century. This surgical technique was developed from sublabial to submucusal transeptal to endonasal and from macroscopic to microscopic and recent state-of-the-art endoscopic approach (4). In our series, we decided to evaluate results and endocrine outcomes of corticotroph adenoma which have been operated by the senior author during nearly 25 years.

Case Presentation

During the period of the study (1991 to 2015), 50 patients with Cushing disease were operated in our center. Among them, 47 patients had primary tumor and three patients had recurrent adenoma. Hormonal examination was carried out in all patients in endocrine clinic and the patients were precisely documented as Cushing disease based on endocrine tests. Brain imaging including dynamic MRI with and without contrast and CT scan were performed in all patients. We did not need to carry out petrosal sampling in any of our patients. After admission, informed consent was obtained from patients. First 40 patients were operated by submucosal transseptal method under microscope magnification, whereas last 10 patients were operated by endoscopic endonasal approach. One of our patient needed transcranial approach later due to tumor residual. All of patients were operated by senior author with collaboration of ENT surgeons, and tumor samples were evaluated by an experienced neuropathologist. Immunohistochemistry (IHC) was done in all cases. After operation, the patients were evaluated in neurosurgery and endocrine clinic during three month intervals. The patients considered to be in remission if they had the following criteria:

1) At the post-operative third day, serum cortisol level was less than five µg/dl and ACTH level undetectable;
2) Normalization of 24 hr free urine cortisol on follow-up examinaton.

This was a case series study. Statistical analysis was performed using SPSS software (version 16). During this study, 50 consecutive Cushing disease cases were operated. Mean age of patients was 34 years in range of 15 to 54 years. Thirty-four (71%) of patients were female and 16 (29%) were male. The most common symptoms of patients were centripetal obesity and hirsutism. Pre-operative studies demonstrated that 34 (68%) of tumors were microadenoma and 16 (32%) macroadenoma. After operation, 20 cases (40%) had transient diabetes insipidus managed with minirin spray and 10 cases (20%) had CSF leak which five of them (10%) showed

meningitis that all were managed conservatively. We lost one of our patients due to post-operative meningitis and its complications (mortality=2%). Mean of follow-up was five years. The patients follow-up data demonstrated that 40 (80%) of them had remission after operation and nine (18%) patients achieved no remission, three of them had macroadenoma and six tumors were microadenoma. During follow-up period, three (6%) of patients showed recurrence of Cushing disease after remission and all of them had microadenoma, which needed the second operation. One of these patients underwent bilateral adrenalectomy and in follow-up symptomatic nelson syndrome was found. In three patients with secondary tumor, one patient had macroadenoma without cavernous sinus involvement and two other patients had microadenoma. Only one of them (macroadenoma)achieved good results (33%). All of the patients with no remission were referred to radio oncologist for radiation therapy.

Discussion

Review of many articles about Cushing disease demonstrated that in experienced hand, surgery is the mainstay of treatment with overall acceptable results and low complication rates (5-12). Ranges of remission is different in series between 40% to 85% according to number of cases and remission criteria. Summary of some previous articles are demonstrated in table 2. In our study, we achieved hormonal remission in 80% of patients, which is nearly similar to results that reported by Fomekong and Dehdashti series (5,6). Some case series showed less remission in macroadenoma patients, as presented by Blevins, Shimon, Hammer and Fahlbusch (7-11). In our study, remission rate was relatively the same, in both micro- and macroadenoma like Fomekong and Wagenmaker series (5,12). In microadenoma cases, we could not achieve good result in six patients and review of data of these patients showed that we could not perfectly localize the site of adenoma during operation. We think that using neuronavigation and prep-localization of microadenoma location by good quality dynamic MRI could help the surgeon achieve better results. Fomekong and Wagenmaker also notified less success in MRI on invisible or poorly visible adenoma cases (5,12). In our macroadenoma cases, invasion to cavernous sinus was the cause of incomplete resection and poor results. In fact, as other series noted, invasion of cavernous sinus wall by tumor cells is the most important obstacle to achieve gross-total resection (GTR) in macroadenoma cases (10-14). Perhaps the reason for difference between our results in macroadenoma cases and other series is related to lower number of cavernous sinus involvement. We had two macroadenoma cases with cavernous sinus involvement, none of whom had remission after operation. In addition, we had poor results in secondary tumors (33% remission) which are comparable to other series (13,14). In these patients, poorly localized microadenoma resulted in poor outcome. We had relatively high rate of CSF leakage, and most of these complications occurred at the beginning of our trial which were related to aggressive tumor resection. With progression of our learning curve and using better techniques to repair skull base defects, the results will improve.

Conclusion

Transphenoid surgery is the first step of Cushing disease management with relatively safe and successful results in most cases. Pre-operative evaluation of patients with imaging and hormonal study is necessary to localize the lesion in sella to achieve the best results. Post-operative follow-up must be done in regular interval for proper management of recurrent or uncontrolled cases. Using new techniques such as navigation and endoscope-assisted approach will result in better outcomes.

Table 1. Summary of Contemporary Transsphenoidal Microsurgery Results in Cushing Disease

Author/Year	Number of Patients	Remission (%)	Recurrence (%)	Mortality (%)
Blevins et al./1998	106	91 (microadenoma) 67 (macroadenoma)	12 36	NA
Shimon et al./2002	82	78 (primary tumor) 62 (secondary tumor) 79 (microadenoma) 33 (macroadenoma)	5	0
Hammer et al./2004	289	82 (all primary tumor) 86 (microadenoma) 83 (macroadenoma)	9	1
Fahlbusch et al./2006	100	75	4.8	0
Dehdashti et al./2007	20	80	N.A	0
Fomekong et al./2009	40	84 (microadenoma) 94 (macroadenoma)	N.A	0
Wagenmaker et al./2013	71	83 (microadenoma) 94 (macroadenoma)	16	0
Dimopoulou et al./2013	120	70	34	NA
Kuo et al. /2015	40	72.5	NA	NA
Mehrazin et al. /2016 (Our Study)	50	84 (primary tumor) 33 (secondary tumor) 80 (macroadenoma & microadenoma)	6	2

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Conflicts of Interest
The authors have no conflicts of interest.

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