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Trans-Sphenoidal Surgery for "Growth Hormone-secreting adenoma; Revisiting Surgical Outcome

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Abstract

Objective: The purpose of this research is to review our clinical experience in transsphenoidal surgery for pituitary adenomas performed by Recep Tayyip Erdogan University Faculty of Medicine, Department of Neurosurgery and contribute to the literature in this way.

Methods: This is a case review of Growth Hormone secreting pituitary adenoma operated in the Recep Tayyip Erdogan University Faculty of Medicine Department of Neurosurgery from January 2014 to May 2021. All patients underwent a microscopic transnasal approach. It was aimed gross total excision of adenoma. For functioning adenomas, hormonal assessment was done on follow-up (8 weeks) and remission was said to be achieved if normal hormonal levels were achieved along with gross total tumor removal. Surgical complications were evaluated, and postoperative follow-up with laboratory and imaging studies were performed.

Results: 78 patients were operated by trans nasal route in our hospital between January 2014-June 2021. Of these 78 pituitary tumors, 22 were growth hormone secreting adenoma. The study population consisted of 22 people, 11 men and 11 women, and the average age of the population was calculated as 60.45 years ± 18.4. Statistical analysis showed that the difference between the pre-operative and post-operative somamedine and growth hormone level was statistically significant

Conclusions: Microscopic Trans-Sphenoidal Surgery for Acromegalic patients is a minimally invasive, safe, and efficacious choice

Key words: Adenoma, Surgery, Trans-sphenoidal, Pituitary.

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Introduction

Pituitary gland locates in an area of complex anatomical structures, but it holds a very important physiological role to maintain all body function (1). The most common type of pituitary tumor is a benign pituitary adenoma, which occurs in the sellar and suprasellar regions (2). These tumors are referred to as those atypical tumors, which are not only benign slowly developing, but also show development of the pituitary gland (3). 12% of all cerebral tumors are pituitary adenoma (PA)(4). It is the third primary brain tumor to be common. (5). While most of them are not symptomatic, they may cause a wide range of signs which depend on their hormone function (3). PA's primary clinical signs include endocrinologic syndrome characteristic, whether because of hormone hypersecretion or deficiencies, compressive symptoms or unusually acute or subacute pituitary apoplexy (6). PA can be of various subtypes depending on the source cell or the corresponding hormones (non-functioning PA, prolactinoma, somatotropinoma, corticotropinoma, thyrotropinoma, and gonadotropinoma) (7). Functioning PA is relatively more morbid and mortal due to the associated hormone hypersecretion syndromes (7). Functional PA diagnosis is determined using biochemical hormone hypersecretion confirmation and imaging pituitary lesion (7). The treatment of functioning pituitary tumors consists of one or more of the following 3 modalities: surgery, radiation therapy (RT) and medical therapy (7). In the late 1960s, pituitary surgery evolved from a craniotomy approach toward less invasive approaches, in particular microscopic and endoscopic (8,9). All tumor tissue (i.e. gross total resection) should be removed, pressures should be alleviated and the risk of relapse reduced (10). Currently, surgical procedure can be carried out by two different techniques: microscopic or endoscopic (7). The trans-sphenoidal route (both the sublabials and cross-nasals)– with the advent of the operative microscope in the 1960s – became the gold standard for approaching the sellar area lesions (11). The first-line treatment of most types of tumors is transsphenoidal surgical resections, except for prolactinomas, in which the treatment is preferred with dopamine agonists (7), because these adenomas' surgical approaches have higher risk of complications (4). Other options for managing PA are RT and medical therapy (7). Growth hormone (GH)-secreting PA is an insidious disease with an estimated incidence of 30 to 50 cases/1 million population annually (12). Acromegaly is caused by an excess of GH, most commonly caused by a somatotroph PA, and is associated with significant metabolic changes that have a negative impact on quality of life (13). Uncontrolled acromegaly patients experience a lower life expectancy of 10-15 years and suffer from multimorbidity (14).

Methods

Recep Tayyip Erdogan University Non-Invasive Clinical Research Ethical Committee approved the study. Preoperative and postoperative medical records of the patients were evaluated. Data collection involved examination of the clinical and surgical notes, including indications for surgery, histopathology, pituitary magnetic resonance imaging (MRI) findings, cerebrospinal fluid (CSF) leak grade, complications. Hormonal and visual status were also evaluated. According to pre-operative hormonal and clinical features, tumors were classified into clinically ‘functioning’ and ‘non-functioning’. Pre- and post-operative somatomedin and GH levels were compared. The postoperative results were evaluated in terms of the control of hormone hypersecretion and safety of surgical procedure.

Neuroimaging evaluation

Traditional MRI sequences, such as contrast-enhanced (CE), T1 weighted image (WI), and T2WI, are commonly used to assess adenoma characteristics such as invasion and size (15). All patients in this study were evaluated with a 1.5 T magnetic resonance imaging (MRI) unit before surgery, using T1- and T2-weighted spin echo before and after the addition of gadolinium-based contrast. This radiological model was used to assess the configuration and size of tumors, as well as their extensions into the suprasellar, infrasellar, or parasellar region. Preoperative MRI are presented in Figure 1.

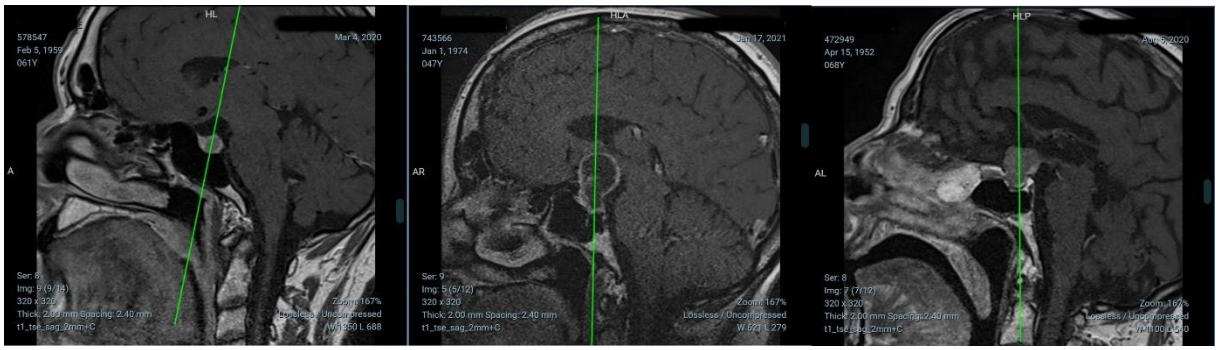

Figure 1. Preoperative MRI of patients

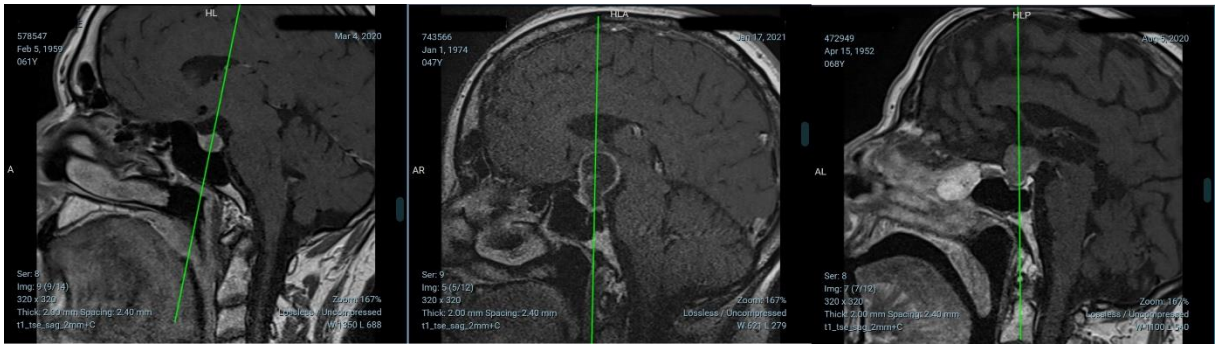

Figure 2. Postoperative MRI of patients

Surgical Procedure

The transsphenoidal approach was performed using an endonasal transseptal microsurgical technique. The patient was positioned semi-sitting, with the head rotated 15° to the right and tilted to the left. The sphenoid sinus is about 20 mm deep, 70 – 90 mm deep to the nasal spine, and has a 30° angle to the nasal cavity floor (9). Irrigation was used to control venous bleeding after removing the sphenoid sinus mucosa. The sellar floor was removed sufficiently, and the dura was opened. The tumor was resected. The arachnoid layer has been closely watched. Hemostasis was meticulously maintained in the tumor cavity, and hemostatic agents such as a gelatin sponge (Spongostan; Ferrosan, Seborg, Denmark) were used, when necessary, in the cavity. The dura was opened in a cruciate fashion from laterally to medially to prevent inadvertent injury to the sinuses. The nasal bony septum, sphenoidal rostral bone fragments, cellulose, and an autologous abdominal adipose graft were used to reconstruct the sella turcica floor. As in Villar-Taibo et al's study, surgical complications were classified as intraoperative (during surgery), immediate postoperative (within the first week after surgery), and late postoperative (within the first month after surgery) (6).

Follow-up

Follow-up monitoring included postoperative MRI, endocrinological and neurological evaluations, performed at 3 months after surgery as in the study of Asioli et al. (16). The patients were followed for a period of 61 months. MRI scans were obtained 3 and 6 months after surgery. Postoperative MRI are presented in Figure 2.

Statistical analysis

SPSS 20.0 for Windows (SPSS, Inc, Chicago, Illinois, USA) was used to perform statistical calculations. When describing sociodemographic variables, frequencies, means, standard deviations and median were used. Normality for continuous variables was tested by using Shapiro–Wilk test. Wilcoxon sign rank test was performed because preoperative and postoperative somatomedin and GH level were not normally distributed. Significance was set at $p < 0.05$.

Results

78 patients were operated by trans nasal route in our hospital between January 2014-June 2021 in the Neurosurgery Department of Recep Tayyip Erdogan University University Faculty of Medicine. All operations have been conducted in collaboration with 2 neurosurgeons. Of these 78 PA, 22 were GH secreting adenoma. The tumors were classified as microadenomas (0–10 mm; n:2), macroadenomas (10–29 mmn:15), large adenomas (≥30 mmn:4), and giant adenomas (≥40 mmn:1) based on their diameter. Acromegaly was present in 22 cases. There were 11

women and 11 men in this group, with a mean age of 60,45 years ± 18.4. All 22 patients underwent a single surgical procedure. The surgical goal was gross total resection and hormonal cure, which have been achieved in the majority of patients. Median hospitalization duration was 4 days. Demographic and operative data are given in table 1. Early period CSF fistulas were observed in 3 patients. Diabetes insipidus occurred in 3 patients. Reoperation for recurrent adenoma was required only in 3 patients.

Table 1. Demographic and Operative Data

Age (year, mean±SD)	60.45±18.4
Gender (female/male) N	11/11
BMI (kg/m2, mean±SD)	26.49 ± 4.75
Tumor classification	**N**
Microadenoma	2
Macroadenoma	15
Large Adenoma	4
Giant Adenoma	1
Operation duration (minute, mean±SD)	98.12±22.35
Hospitalization duration (day, median)	4±1,37

BMI: Body Mass Index

Postoperative assessments

Every single patient was closely followed up for the development of complications. At the 8th week and 3rd month, after surgery, routine follow-up was performed in the outpatient clinic. A full hormonal test was performed to assess pituitary function in depth. An MRI was routinely performed at 6 months to assess a tumor remnant as well as to establish a baseline measurement for future recurrence assessments. There was no death in this series. The mean pre- and post-operative 8th week somatomedin levels were 342,19 ng/mL and 144,77 ng/mL respectively. The difference of pre-operative and post-operative level of somatomedin was statistically significant (P=0.002, <0.01). Mean pre-operative growth hormone level was decreased from 2,6 ng/mL to 0.7 ng/mL. The difference was also statistically significant (p=0.003, <0.01) (Table 2).

Table 2. Pre and postoperative somatomedine and growth hormone levels

Hormonal parameters	Preoperative (mean±SD)	Postoperative (mean±SD)	p
Somatomedin, ng/mL	342.19±303.96	144.77±93.37	0.002**
Growth hormon, ng/mL	2.6±3.99	0.75±1.23	0.003**

Wilcoxon sign rank test,**p<0.01

Discussion

Acromegaly is the result of unrestricted GH secretion, which is a serious medical disorder. (17). Although typically benign under a histological point of view, PAs can exhibit an aggressive clinical and radiological behavior, characterized by quick growth, along with resistance or early recurrence, with the gross invasion of the surrounding tissues after treatment. (16). As the pituitary adenoma is the most common cause of acromegaly pituitary MRI may be helpful in the diagnosis of acromegaly. Enlarged pituitary gland with gadolinium uptake and extend of adenoma to the suprasellar region are observed on MRI. Findings on MRI for spine are hypertrophy of spinal ligaments and cartilaginous structures and osteoarthritis. In addition to these findings, joints MRI shows ligamentous and cartilaginous hypertrophy and crystal deposition (18). The long-term effects of chronic GH excess on metabolism and the cardiovascular system are negative, and include diabetes mellitus, arterial hypertension, heart disease, and an increased risk of cancer (17). In acromegaly, somatostatin receptor ligands (octreotide, lanreotide, pasireotide), dopamine agonists (cabergoline) and GH receptor antagonist (pegvisomant) are used for medical treatment (19). The surgical treatment of these adenoma is aimed at restoring GH levels as soon as possible (13), we noted a statistically significant decrease of GH levels in this study.

Pituitary adenomas are tumors of extra-arachnoidal origin, so usually grow outside the confines of CSF (20). As the tumor lies in close relationship to the diaphragm sellae and subarachnoid space, there is always a risk of iatrogenic arachnoid breach (20). As a result, CSF leak is a common complication of this surgery (20) among several transsphenoidal chirurgical complications. Apart from CSF leak, transient diabetes insipidus, permanent diabetes insipidus, minor nasal bleeding, and hyposmia can be seen after microsurgical surgery (21). The optimal treatment for GH secreting PA is trans-sphenoidal pituitary surgery (22). The first treatment option in acromegaly is surgical removal of the adenoma. Patients with severe mass effects, such as vision loss or double vision, require immediate surgical treatment. Medical treatment can be applied before surgical treatment in patients at risk of anesthesia such as cardiomyopathy, uncontrolled diabetes mellitus, severe hypertension and sleep apnea. Following the application of medical treatment for 3-6 months, surgical intervention can be performed for patients whose anesthesia and surgical risks are reduced. After successful adenoma resection, clinical improvement begins within days (19). The anatomy of the pituitary fossa's roof varies greatly (23). A "barrier" of three anatomical structures exists between the adenoma and the CSF (23). This tripartite structure progressing from the cephalad to the cauda consists of arachnoid, dura

mater (ie sellar diaphragm) and pituitary gland tissue. Of these three elements, only the arachnoid is found in every human (23). In the literature, CSF leaks have been reported varying from 0.5% to 10.3% (20). We had a total of 3 (13,6%) cases with postoperative CSF leak. Three cases needed re-exploration. Potential morbidities following CSF leaks include meningitis, prolonged hospitalization, tension pneumocephalus and additional operations (24).

Outcomes of Surgery

Surgical procedure outcomes are frequently reported in the literature in a clinician-centered manner (25). Traditional surgical outcome studies concentrate on efficacy measures like remission rates and gross total resection (25). An important aim of treatment of patient with PA is to improve or preserve health-related quality of life (26). The recovery of pituitary function is much less than that of vision (27). Re-emergence of symptoms of acromegaly with re-increased GH and IGF-1 levels is defined as recurrence after surgical control (28). According to the literature, the recurrence rate ranges from 0% to 31% (28). In this study, the patients were followed for 6±1 months. Recurrence was observed in 3 patients. Although we are aware that the postoperative timing of MRI following PA surgery is still controversial, MRI scans of patients were obtained at the third and sixth months after surgery (29). Follow-up of asymptomatic residual tumor should be following up (29). Early evaluation is frequently difficult in the setting of acute postoperative changes such as hemorrhage, packing, and, in some cases, undescended residual tumor (29). The rationale for early postoperative imaging is to give surgeons a chance to intervene earlier for residual tumor (29). Important predictors of surgical outcome of GH-secreting PA are tumor size, invasiveness, duration of acromegaly, and preoperative GH levels (13). GH-secreting PA, the predominant cause of acromegaly, is associated with a standardized mortality rate of 0.72–1.13(28). No mortality was seen in this series.

Conclusion

This study indicates that patients undergoing surgery for acromegaly can have excellent outcomes. Low complication rates and high resection rates were noted in the present study. The length of stay in hospital was not long. Although it is considered a relatively safe procedure in transsphenoidal pituitary surgery, postoperative complications should be expected. Knowing about these complications is the first step in preventing them (1). Timely diagnosis and effective treatment to control hormone hypersecretion and relieve mass effects along with replacement of deficient hormones are crucial to reduce these associated health risks (7), because PA invasion of local structures on MRI is associated with postoperative outcomes following surgical resection (15). We recommend the transsphenoidal surgery for GH secreting PA as a safe and effective approach.

Ethics Committee Approval: This study was conducted with the approval of the ethics committee of Recep Tayyip Erdogan University Faculty of Medicine, Non-Invasive Clinical Research Ethics Committee. (Ethics Committee date and Decision no: 26.04.2021 2021/75)
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