ORIGINAL ARTICLE

Pituitary apoplexy: An emergent and potential life-threatening complication of pituitary adenomas

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ABSTRACT

BACKGROUND: Pituitary apoplexy is an emergent and potential life-threatening complication of pituitary adenomas if not managed properly. The aim of our study is to present our series of pituitary adenomas and to focus on the clinical, radiological, and surgical characteristics of this rare complication.

METHODS: In this study, a total of 143 patients with pituitary adenoma underwent surgical treatment between 2016 and 2018. All patients were operated using endoscopic endonasal transsphenoidal (EET) technique. The data of pituitary apoplexy cases were recorded. Resection rates, hormonal results, and visual outcomes of patients with pituitary apoplexy were evaluated.

RESULTS: Of the 143 patients, 8 (5.59%) were presented with the symptoms and radiological findings of pituitary apoplexy. The mean age was 26.75 years, and 4 (50%) of them were male and 4 were female. Pre-operative mean Knosp grading score was 2.1 All of eight patients underwent emergent surgical intervention and total resection was achieved in 75% of patients with apoplexy. Hormone levels were significantly decreased after surgery ($p<0.05$), except prolactin ($p>0.05$). Cerebrospinal fluid leakage occurred in one patient. None of the patient with pituitary apoplexy died in our series.

CONCLUSION: Pituitary apoplexy is an important complication of pituitary adenomas. Early diagnosis and surgical intervention provide excellent ophthalmological and hormonal outcomes. Emergent EET approach is crucial for patients with ophthalmological findings and macroadenomas.

Keywords: Endoscope; outcome; pituitary adenoma; pituitary apoplexy.

INTRODUCTION

Pituitary apoplexy is a clinical syndrome presented with sudden onset of headache and associated with ophthalmological or endocrinological deterioration due to a quick expansion of a mass lesion within the sella turcica as a result of hemorrhage, infarction, or necrosis within a pituitary tumor and adjacent pituitary gland.[1–3]

Classical presentation of pituitary apoplexy is characterized by severe headache with or without visual and hormonal disturbances.[4,5] Magnetic resonance imaging (MRI) is the gold standard for the diagnosis of pituitary apoplexy as well as pituitary adenoma.[6,7] Some patients may have hormonal and/or electrolyte disturbances at the time of presentation.[2,3]

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Conservative and surgical methods can be preferred for the treatment of pituitary apoplexy.[2,8] Each treatment should be individualized for the patient. Sudden onset with ophthalmoplegia and visual disturbances usually require emergent surgical intervention.[3,5,9] Today, endoscopic techniques are state-of-art options for surgical treatment. Endoscopic endonasal transsphenoidal (EET) technique provides quick and safe clinical and radiological improvement.[1] However, there is no enough information about the hormonal outcomes of emergent surgical intervention to the pituitary apoplexy.

In this study, we presented our series with pituitary adenomas and focused on the hormonal and ophthalmological outcomes of patients admitted with pituitary apoplexy. We discussed our results with the current literature.

MATERIALS AND METHODS

This is a retrospective observational study. We examined 143 patients who were admitted to the Department of Neurosurgery, our clinic between January 2016 and December 2018 and were operated endoscopically for pituitary adenoma. Ethics committee approval was obtained for the study. Patients who had the diagnosis of pituitary apoplexy at admission and patients with pre- and post-operative clinical, hormonal, radiological, and ophthalmological data were included in the study. All patients were followed for at least 1 year after surgery. Age, gender, hormonal activity, pathological diagnosis, and Knosp grading of the patients were analyzed.

Serum growth hormone (GH), prolactin (PRL), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels were measured pre- and postoperatively.

All patients were evaluated with MRI pre- and postoperatively early (in first 24 h after surgery) and 3 months after surgery. Lesions were classified into macroadenomas (>1 cm) and microadenomas (<1 cm) according to their sizes. Knosp grading system was used to categorize tumor extension and degree of cavernous sinus invasion.[10,11] Resection rates were defined as: Total resection (when no remaining tumor is observed on early MRI scans), subtotal resection (more than 80% of tumor resection compared with preoperative imaging), and partial resection (< 80%).[7]

Visual acuity and visual field defects were evaluated in patients with visual disturbances, using computerized visual field testing preoperatively and 3 months after surgery.

All cases were operated using EET approach. Depending on the suitability of the nasal passage in all cases, a nasal septal flap was prepared from the right or left side and used during the reconstruction phase. In patients with active cerebrospinal fluid (CSF) leak preoperatively, fat and fascia grafts were harvested from the left thigh lateral and used to repair the defect. Synthetic dura material and synthetic tissue adhesive were also used in all cases to repair the defect.

All statistical analysis was performed using Statistical Package for the Social Sciences v.25.0 (IBM Corp, Armonk, NY, USA). Wilcoxon test was used for the comparison of hormonal changes after surgery. P<0.05 was accepted as statistically significant.

RESULTS

All 143 patients with pituitary adenoma were operated by EET approach. 83 (58.04%) of them had macroadenoma. Pituitary apoplexy was observed only in 8 (5.59%) patients. Four (50%) of them were male and four were female. The mean age was 26.75±10.44 years, ranged between 16 and 40 years. Seven (87.5%) patients had severe headache, 4 (50%) patients had visual disturbances, four patients had amenorrhea and galactorrhea. Histopathological diagnosis of all patients presented with pituitary apoplexy was pituitary adenoma. Five (62.5%) patients had prolactinoma and three patients had non-functional pituitary adenoma. Hormonal abnormalities at the clinical presentation were correlated with histopathological results. Mean operation time was 2.3 h. The average length of stay was 5 days.

When 83 patients with macroadenoma were evaluated using Knosp grading scale, 18 (21.6%) patients were grade 0, 10 (12%) patients were grade 1, 12 (14.4%) patients were grade 2, 20 (24%) patients were grade 3, and 23 (27.7%) patients were grade 4. Resection rates of pituitary macroadenomas based on MRI studies within the first 24 hours after surgery; partial resection in 4 (4.8%) cases, subtotal resection in 16 (19.3%) cases, and total resection in 63 (75.9%) cases (Figs. 1 and 2). Total resection was achieved in 6 (75%) of eight patients with pituitary apoplexy.

Hormonal changes in eight patients with pituitary apoplexy are:

- The mean pre-operative TSH level was 1.90±1.49 mIU/ml, and post-operative TSH level was 0.72±0.41 mIU/ml. The TSH level was decreased after surgery and the change was statistically significant (p=0.017, Z=–2.38)
- The mean pre-operative ACTH level was 29.11±18.58 pg/ml, and post-operative ACTH level was 18.78±8.30 pg/ml. The ACTH level was decreased after surgery and the change was statistically significant (p=0.012, Z=–2.52)
- The mean pre-operative GH level was 2.67±4.50 ng/ml, and post-operative GH level 0.43±0.36 ng/ml. The GH was decreased after surgery and the change was statistically significant (p=0.012, Z=–2.52)
- The mean pre-operative PRL level was 116.16±241.03 ng/ml, and post-operative PRL level was 69.05±82.51 ng/ml. PRL level was decreased after surgery but this change was not statistically significant (p=0.161, Z=–1.40)
- The mean pre-operative FSH level was 4.47±2.29 mIU/ml,

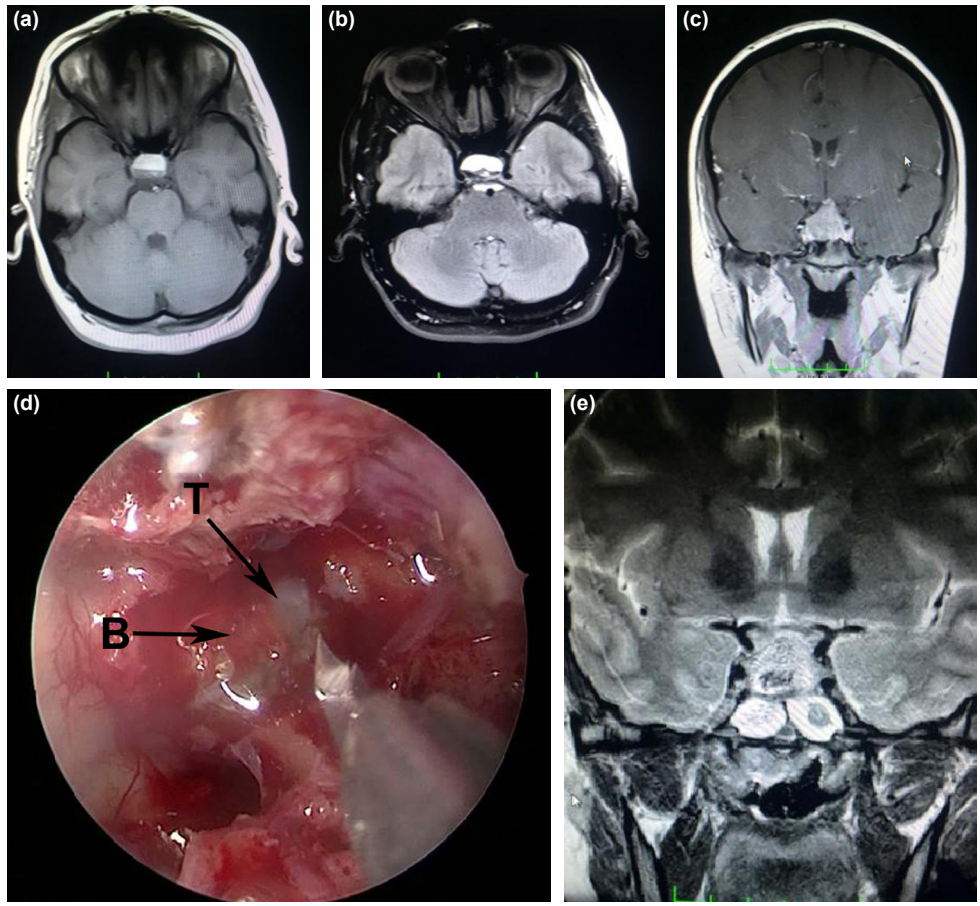

Figure 1. A 17-year-old female patient presented with pituitary apoplexy. Pre-operative T1-axial magnetic resonance imaging (MRI) slices **(a and b)** show hyperintense blood in the sellar region, T1-coronal MRI slice **(c)** shows compression of optic chiasm. She underwent tumor removal using endoscopic endonasal transsphenoidal approach. Tumor was removed with intrasellar blood products **(d)**. Post-operative T2-coronal MRI **(e)** confirmed total resection of pituitary adenoma. T: Tumor, B: Blood products.

and post-operative FSH level was 4.10±2.22 mIU/ml. The FSH level was decreased after surgery and the change was statistically significant (p=0.018, Z=–2.36).

- The mean pre-operative LH level was 2.64±2.11 mIU/ml, and post-operative LH level was 1.96±1.71 mIU/ml. The LH level was decreased after surgery and the change was statistically significant (p=0.018, Z=–2.36).

Thirteen patients (9.1% of all pituitary adenoma cases) had visual field defects before the surgery. In the computerized visual field test performed at the 3rd month after surgery, the visual field defect of 10 (76.9%) patients was improved. Also visual complaints of these cases were disappeared. In three patients, visual field defect continued despite the decrease in size.

DISCUSSION

Pituitary adenomas constitute 10% of all intracranial neoplasms.[12,13] They are located in the sellar and parasellar region. Pituitary macroadenomas are larger than 1 cm in diameter and usually cause sellar enlargement.[14] They presented with headache, visual impairment, cranial nerve dysfunctions or hormonal abnormalities according to their mass effect.[9,15] Pituitary apoplexy is a clinical condition secondary to expansion of the intrasellar contents because of an infarction and/or hemorrhage in the tumor. In 25% of cases, pituitary apoplexy develops secondary to a pituitary adenoma.[2,3]

The incidence of pituitary apoplexy is not exactly determined. It may vary between 0.6% and 22% based on different diagnostic criteria of pituitary apoplexy.[5] In our series, the incidence of pituitary apoplexy was 5.59% among the cases with pituitary adenoma and this rate was similar with the literature.

As mentioned before, the diagnosis is usually made by MRI during the follow-up of a previously diagnosed pituitary adenoma or after the onset of symptoms related to pituitary apoplexy.[6] The presence of hemorrhage or necrosis within the pituitary adenoma or gland confirms the diagnosis of pituitary apoplexy.[3] We also diagnosed pituitary apoplexy in all cases using MRI after the patient's admission to the hospital.

The pathophysiology of pituitary apoplexy is not well known, but some intrinsic characteristics of pituitary tumors make

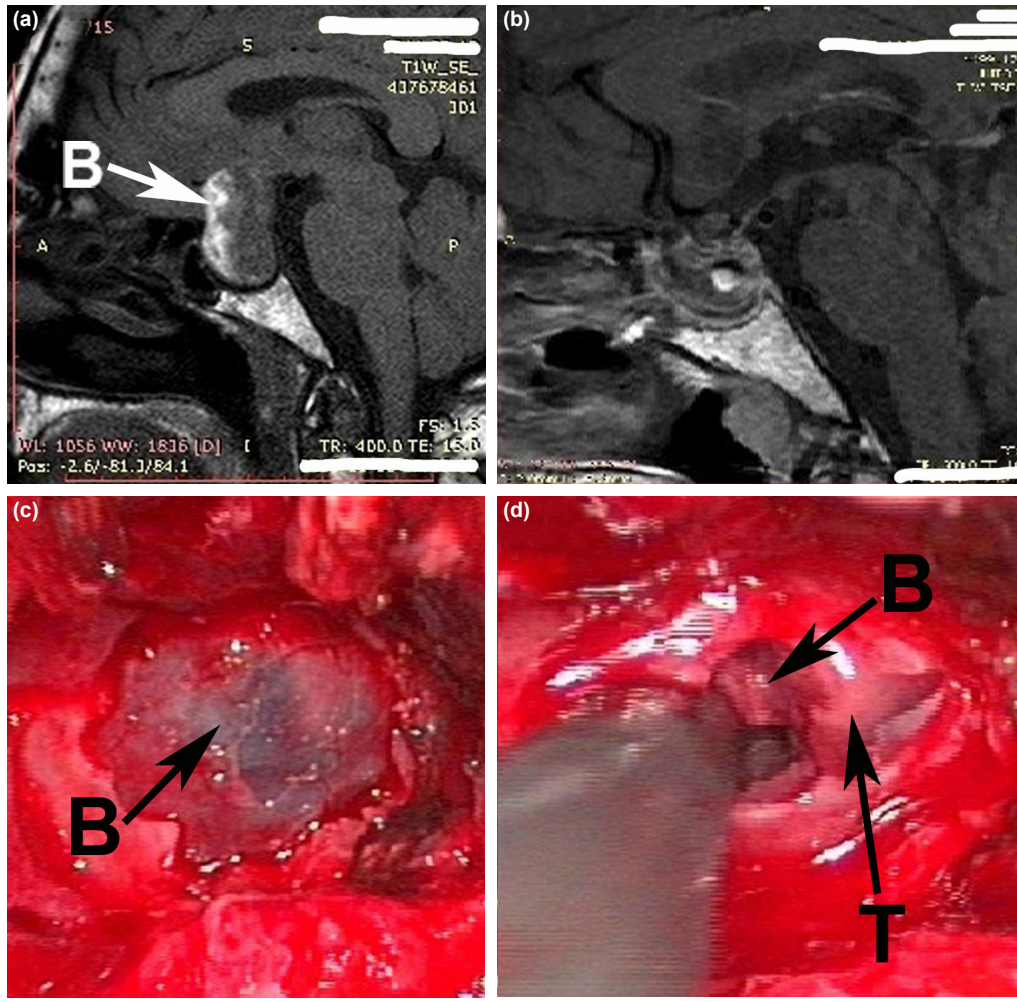

Figure 2. A 40-years old female patient presented with pituitary apoplexy. Pre-operative T1-sagittal non-contrast magnetic resonance imaging (MRI) slice shows blood within the tumor **(a)**. Post-operative T1-sagittal MRI slice shows total resection of pituitary adenoma **(b)**. Intraoperative endoscopic view before the dural opening shows the black shadow of blood products in the sellar region **(c)**. After the dural opening tumor tissues with blood products are visible in black color **(d)**. B: Blood; T: Tumor.

it prone to bleed and develop necrosis or infarction in the tumor. There are some risk factors for pituitary apoplexy.[16] These risk factors can be divided into 4 categories: (1) Large tumor size (macroadenoma) and less blood flow for the tumor; (2) acute increase of blood flow into the pituitary gland or adenoma due to hypertension, diabetes, trauma, or increased intracranial pressure; (3) hormonal stimulation of the pituitary gland or tumor, such as endocrine stimulation tests, pregnancy, and exogenous estrogen therapy; and (4) use of anticoagulation drugs such as thrombolytic, and antiplatelet therapy. In our series, all of eight patients had pituitary macroadenoma when the symptoms begun and none of them had the history of the use of anticoagulation drugs at the time of diagnosis.

Once the diagnosis is made, there are two options for the treatment of pituitary apoplexy. Both conservative and surgical treatment modalities have been advised for the management of this emergent clinical condition.[2,3,8] Patients without severe or progressive neuro-ophthalmological deficits can be managed conservatively.[17] On the other hand, there are two major principles of pituitary apoplexy management; emergent decompression surgery; and immediate high-dose corticosteroid replacement. However, the treatment should be individualized for each patient based on the previous reports.[2,3,8] If conservative management was chosen, close clinical and radiological follow-up is required. Transsphenoidal approach is usually preferred for the surgical treatment.[6,7] However, transcranial trans-sylvian approach is also an option.[6] Most patients have a good recovery in visual function and extraocular palsy after the transsphenoidal surgery. Rapid decompression of optic pathway usually associates with satisfactory visual outcome in patients with pre-operative visual disturbances. At present, EET approach is the safest and rapid way to manage a patient with pituitary macroadenoma associated with apoplexy.[7,11,14] In addition, surgical intervention, when necessary, should be performed as soon as possible as it is associated with better visual outcome.

Although emergent EET approach is the gold standard for the surgical treatment of pituitary apoplexy, the surgical technique is not different than the classical pituitary adenoma.[6] EET approach provides a wider panoramic view with better resection rates and decreased complication rates compared to the microscopic technique.[7] Also being a minimally invasive procedure, this technique preserve the nasal architecture maximally.[18–22] Meanwhile, intratumoral hemorrhage and necrosis are the main difference of pituitary apoplexy from the classical pituitary tumor surgery. Removal of blood products and necrotic pituitary tissues is crucial for adequate decompression of optic chiasm and nerves in patients with apoplexy.[1,6] Rutkowski et al.[23] reported their series of pituitary apoplexy in 32 patients and they concluded that neurological deficits are improved moderately after the surgical treatment. The timing of surgery did not significantly affect the improvement of endocrinological or neurological disturbances.[23] Giritharan et al.[4] reported a series of 31 patients with pituitary apoplexy. They treated 11 patients conservatively, 11 with emergent surgery within 7 days of presentation, and nine with surgery more than 7 days from presentation. The authors did not find any statistically significant differences in the rates of visual or endocrine recovery among the groups, despite the fact that the emergent surgery cohort possessed higher rates of baseline visual and endocrine dysfunction. Although the number of our cases was less than these series, we obtained similar neurological and endocrinological results.

Li et al.[5] performed a study among 843 patients with pituitary adenoma and the incidence of pituitary apoplexy was 14.4% in this series. They found that the risk factors for pituitary apoplexy are tumor size, pathologic type, and the blood pressure of patients. In our series, the incidence of pituitary apoplexy was 5.59% and there was no correlation between the development of pituitary apoplexy and the tumor's size and histological properties.

Rajasekaran et al.[24] described a pituitary apoplexy score (PAS), which may be calculated at patient's admission. It is formulated based on three neuro-ophthalmic parameters (visual acuity: 0, 1, and 2; visual field defect: 0, 1, and 2; and ocular paresis: 0, 1, and 2) and on Glasgow Coma Scale (GCS: 0, 2, and 4). Marx et al.[17] recommended surgery only for pituitary apoplexy patients with a PAS ≥4.

Goshtasbi et al.[25] performed a meta-analysis on the conservative and surgical management of pituitary apoplexy and they found that both methods can improve the visual and endocrinological symptoms and the treatment should be multifaceted and tailored to the individual case and clinical judgment.

Endoscopic technique is always compared with microscopic technique in the literature. Cappabianca et al.[19] reported that the percentage of patients with complete tumor resection was higher in the endoscopically treated group (46.8% vs. 35%) in a study with invasive macroadenoma patients. This can be explained by the fact that the endoscope is a tool that can be used in the sella turcica to observe lateral or non-visional areas that cannot be seen by microscope to find residual tumors.[26] Duz et al.,[27] Higgins et al.,[28] and Neal et al.[29] reported better results with the endoscopic approach, whereas O'Malley et al.[30] and Casler et al.[20] showed higher rates of resection with the microscopic technique.

In cases with macroadenomas compressing the optic chiasm, one of the main purpose of surgery is decompression of the chiasm rather than the complete tumor resection.[6,7,14] There is no significant difference between groups regarding the improvement of visual field defects, but longer follow-up period may be required for long-term evaluation.[31–34] Visual complaints improved after surgery in 10 of 13 patients who had pituitary adenoma with preoperative visual field defects. It was observed that visual field defects did not improve despite adequate decompression in the other three patients. This may be secondary to the long-term presence of optic nerve and chiasm compressions.

Hormonal changes after surgery are very important for patients with pituitary adenoma as well as for pituitary apoplexy. Ekberov et al.[6] performed a study in 85 patients with pituitary adenoma and they found that the hormonal outcomes are not related to the gender of patients, preoperative tumor size and type of surgery. In our study, we found that all pituitary gland hormone levels were significantly decreased after surgery except PRL. However, this result may be due to low number of patients with pituitary apoplexy.

The complication rates of the previous endoscopic studies range from 10% to 26.3% and mortality rates of 0% to 0.68%.[19,26,35–37] The complications and mortality rate of microscopic transsphenoidal approach are 8.2–47% and 0–0.9%, respectively.[38,39] In our study, one patient with pituitary adenoma died in the postoperative period due to respiratory complications (mortality rate 0.69%), and none of the patients who were presented with pituitary apoplexy died after surgery. Our mortality rate is similar to the literature. The possible reason of low mortality rate in our endoscopic technique is better visualization, less bone and mucosal dissection, and good teamwork.

Intra- or post-operative CSF leak is the most common complication of EET approach. The incidence of diabetes insipidus (DI) (temporary or permanent) ranges from 2.5% to 20%.[36,40] Temporary DI is possibly caused by temporary dysfunction of the vasopressin due to surgical trauma.[39] In our series, during the endoscopic pituitary macroadenoma resection, active CSF leak occurred in 8 (5.59%) patients. These cases were followed up with lumbar drainage system placed intraoperatively. Endoscopic endonasal repair was performed in three of these patients which rhinorrhea did not improve with treatment. Our CSF leak rate was similar to previously reported endoscopic series.[19,36,37]

There are two limitations of our study including its retrospective nature and low patient population.

Conclusion

Emergent EET approach is a safe and minimally invasive procedure for the treatment of pituitary adenomas presenting with pituitary apoplexy. Serum hormone levels are dramatically reduced after surgery and ophthalmological signs are mostly improved. This technique can be rapidly and safely performed by well-trained neurosurgeons.

Ethics Committee Approval: This study was approved by the Health Sciences University Gülhane Scientific Research Ethics Committee (Date: 30.11.2020, Decision No: 220/436).

Peer-review: Internally peer-reviewed.

Authorship Contributions: Concept: A.M.G., A.D., B.K.U.; Design: A.M.G., A.D., B.K.U.; Supervision: A.M.G., A.D., B.K.U.; Resource: M.G., M.O.D., B.K.U., S.G., İ.E.; Materials: M.G., M.O.D., B.K.U., S.G., İ.E.; Data: M.G., M.O.D., B.K.U., S.G., İ.E.; Analysis: M.O.D., S.Y., A.K., G.K., A.N.; Literature search: M.O.D., S.Y., A.K., G.K., A.N.; Writing: M.G., S.Y., A.K.; Critical revision: A.N.

Conflict of Interest: None declared.

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ORİJİNAL ÇALIŞMA - *ÖZ*

Hipofizer apopleksi: Hipofiz adenomalarının acil ve potansiyel olarak hayatı tehdit eden komplikasyonu

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AMAÇ: Hipofizer apopleksi, uygun şekilde tedavi edilmezse, hipofiz adenomalarının acil ve potansiyel olarak yaşamı tehdit eden bir komplikasyonudur. Çalışmamızın amacı, hipofiz adenomaları çalışmamızı sunmak ve bu nadir komplikasyonun klinik, radyolojik ve cerrahi özelliklerine odaklanmaktır.
GEREÇ VE YÖNTEM: Bu çalışmada 2016–2018 yılları arasında toplam 143 hipofiz adenomalı hastaya cerrahi tedavi uygulandı. Tüm hastalar endoskopik endonazal transsfenoidal (EET) teknik ile ameliyat edildi. Hipofizer apopleksi olgularının verileri kaydedildi. Hipofizer apopleksi hastalarının rezeksiyon oranları, hormonal sonuçları ve vizüel sonuçları değerlendirildi.
BULGULAR: Yüz kırk üç hastanın sekizinde (%5.59) hipofizer apopleksi semptomları ve radyolojik bulguları vardı. Ortalama yaş 26.75 olup dördü (%50) erkek, dördü ise kadındı. Ameliyat öncesi ortalama Knosp derecelendirme skoru 2.1 idi. Sekiz hastanın hepsine acil cerrahi girişim uygulandı ve apopleksi hastalarının %75'inde total rezeksiyon sağlandı. Hormon düzeyleri ameliyat sonrası prolaktin dışında anlamlı olarak azaldı ($p<0.05$). Bir hastada beyin omurilik sıvısı sızıntısı meydana geldi. Hipofizer apopleksi hastalarının hiçbirisi ölmedi.
TARTIŞMA: Hipofizer apopleksi, hipofiz adenomalarının önemli bir komplikasyonudur. Erken tanı ve cerrahi müdahale mükemmel oftalmolojik ve hormonal sonuçlar sağlar. Acil EET yaklaşım, oftalmolojik bulguları ve makroadenomları olan hastalar için çok önemlidir.
Anahtar sözcükler: Endoskop; hipofiz adenoması; hipofizer apopleksi; sonuç.

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