Clinical Case Report

Medicine®

OPEN

Invasive ACTH-secreting pituitary macroadenoma in remission after transsphenoidal resection

A case report and literature review

Zhe Zhuang, MD[a,b], Xiaohai Liu, MD[a], Xinjie Bao, MD[a], Boju Pan, MD[c], Kan Deng, MD[a], Yong Yao, MD[a], Wei Lian, MD[a], Bing Xing, MD[a], Huijuan Zhu, MD[d], Lin Lu, MD[d], Renzhi Wang, MD[a], Ming Feng, MD[a,*]

Abstract

Rationale: Knosp grade 4 adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma is a rare cause of Cushing disease. After the 1st surgery, the remission rate among these patients is extremely low.

Patient concerns: We presented a case of a 33-year-old female with classical Cushingoid symptoms. Further investigations revealed ATCH-dependent hypercortisolemia, as well as a Knosp grade 4 pituitary macroadenoma.

Diagnosis: Cushing disease, caused by a Knosp grade 4 pituitary macroadenoma.

Interventions: The patient underwent endoscopic endonasal transsphenoidal surgery with the assistance of intraoperative transsphenoidal Doppler and image-guidance devices.

Outcomes: Pathologic examinations confirmed that the lesion was an ACTH-secreting pituitary adenoma. The patient was in biochemical remission after surgery. Her postoperative magnetic resonance imaging showed gross-total tumor resection. There was no evidence of recurrence during the 1-year follow-up.

Lessons: With intraoperative Doppler and image-guidance, gross-total resection and biochemical remission can be achieved in Cushing disease when the internal carotid artery is completely encased by the pituitary adenoma.

Abbreviations: ACTH = adrenocorticotropic hormone, CD = Cushing disease, GH = growth hormone, HDDST = high-dose dexamethasone suppression test, 24h UFC = 24-hour urinary-free cortisol, ICA = internal carotid artery, LDDST = low-dose dexamethasone suppression test, LH = luteinizing hormone, MRI = magnetic resonance imaging, PRL = prolactin, TSS = transsphenoidal surgery.

Keywords: Cushing disease, invasive, pituitary adenoma, remission, transsphenoidal surgery

1. Introduction

Cushing disease (CD) is a condition of pathologic hypercortisolism caused by adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas. This ACTH-dependent hypercortisolemia would lead to devastating comorbidities including but not limited to cardiovascular disease, infections, and venous thrombosis, all of which make the overall mortality among patients with Cushing disease 1.7 to 4.8 times higher than that among healthy population.[1–4] Currently, the 1st line therapy for Cushing disease is surgical excision of the pituitary adenomas.[5] Based on results from long-term follow-up researches, patients who achieved remission criteria with 1 operation had better quality of life than the rest who needed 2nd-line therapies.[4,6] Furthermore, the size of adenoma, the extent of parasellar involvement, as well as the surgeon's technique, are key features in determining the clinical outcomes.[7,8] With transsphenoidal surgery, the reported remission rates among ACTH-secreting pituitary microadenomas range from 65% to 95%.[3,8–12] While macroadenomas have relatively lower remission rates of 12.5% to 71.1%, with more operative complications and higher recurrence rates.[8,9,13–19] Cavernous sinus invasion is another unfavorable prognostic factor for transsphenoidal surgery.[3] Specifically, the reported remission rates among ACTH-secreting pituitary adenomas with cavernous sinus invasion range from 0% to 60%.[9,12,13,19,20] The surgical remission rates of Knosp grades 3 and 4 adenomas are lower, based on our comprehensive search of PubMed database.[13,19,21–23]

Here, we reported a case of Cushing disease caused by Knosp grade 4 ACTH-secreting pituitary adenoma. After thorough evaluation and transsphenoidal surgery, the patient was in remission. Subsequently, a systematic literature review of Knosp grades 3 and 4 ACTH-secreting pituitary adenomas was conducted. The clinical manifestations, surgical details, and postoperative recovery of these patients were discussed.

2. Case report

A 33-year-old Asian woman had developed typical Cushingoid appearance, as well as amenorrhea and insomnia for 2 years. She had no visual loss or headache and denied history of

Editor: N/A.

The authors have no funding and conflicts of interest to disclose.

[a] Department of Neurosurgery, Chinese Academy of Medical Sciences and Peking Union Medical College, Peking Union Medical College Hospital, [b] School of Medicine, Tsinghua University, [c] Department of Pathology, [d] Department of Endocrinology, Chinese Academy of Medical Sciences and Peking Union Medical College, Peking Union Medical College Hospital, Beijing, China.

[*] Correspondence: Ming Feng, Department of Neurosurgery, Chinese Academy of Medical Sciences and Peking Union Medical College, Peking Union Medical College Hospital, Beijing 100730, China (e-mail: Jackietz@163.com.

Medicine (2018) 97:46(e13148)

Received: 24 June 2018 / Accepted: 15 October 2018

http://dx.doi.org/10.1097/MD.0000000000013148

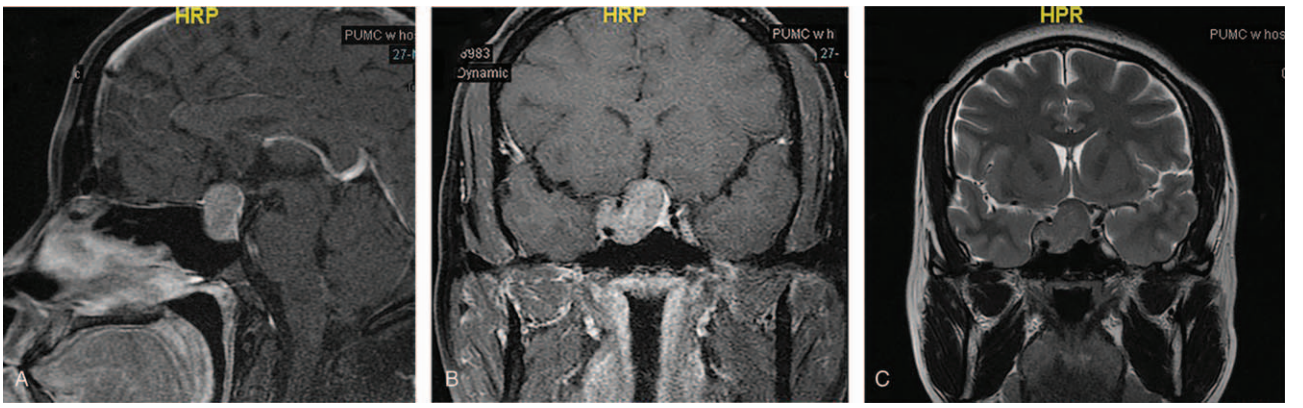

Figure 1. Preoperative magnetic resonance imaging. (A) Saggital postcontrast T1-weighted, (B) coronal postcontrast T1-weighted, and (C) coronal T2-weighted MRI show a Knosp grade 4 pituitary macroadenoma which extends from the sella turcica into the suprasellar space.

glucocorticoid intake. On examination, her blood pressure was 159/107 mm Hg. She had a moon face with acne and hyperpigmentation, supraclavicular and dorsal fat pads, as well as central obesity (body mass index 23.9 kg/m^2, waistline 82 cm). Systemic physical examination was otherwise unremarkable. Laboratory test results revealed a serum cortisol (8 AM) level of 23.01 μg/dL (reference range 4–22.3 μg/dL), and a 24-hour urinary-free cortisol (24-hour UFC) value of 409.50 μg/24 h (reference range 12.3–103.5 μg). In addition, her serum ACTH level (8 AM) was 100.60 pg/mL (reference range 0–46 pg/mL). She also had a slightly elevated serum prolactin (PRL) level of 34.31 ng/mL (reference range <30 ng/mL). Her 24-hour UFC values were 101.25 μg/24 h after low-dose dexamethasone suppression test (LDDST) (reference range <10 μg) and 264.81 μg/24 h after high-dose dexamethasone suppression test (HDDST) (reference range <50% of baseline level). All other anterior pituitary hormones were within the normal range. Magnetic resonance imaging (MRI) with gadolinium enhancement (Fig. 1) showed a heterogeneously enhanced mass ($2.0 \times 2.5 \times 1.8\ cm^3$ in size) in the sella turcica and suprasellar space. The mass had invaded the right cavernous sinus and encased the right internal carotid artery (ICA) completely (Knosp grade 4). We also arranged computed tomography scans of chest and abdomen, as well as somastatin receptor scintigraphy, none of which had abnormal findings. The patient was diagnosed with Cushing disease despite her impaired response to HDDST, due to the reported observations that high-dose dexamethasone induced ACTH suppressibility was lost in some ACTH-secreting macroadenomas.[15,17,24] Besides, all the comorbidities including hypertension, diabetes mellitus, and hyperlipemia were treated accordingly before her surgery.

Endoscopic endonasal transsphenoidal surgery was conducted, with intraoperative endonasal transsphenoidal Doppler and image-guidance devices to locate the tumor precisely and avoid damaging the ICA. The tumor tissue was grayish white in appearance, and abundant in blood supply. The texture was soft and fragile, with no pseudocapsule. The intrasellar and suprasellar part of the lesion was the 1st to be removed, then was the compressed pituitary tissue with abnormal appearance. Finally, the tumor tissue around right ICA was resected through the defect on the medial wall of cavernous sinus, with the location of ICA confirmed by transsphenoidal Doppler and image guidance. The total size of resected tumor tissue added up to around $20 \times 25 \times 15\ mm^3$. Subsequent saline irrigation confirmed no residual tumor tissue in the surgical field. The diaphragm descended into the pituitary fossa after tumor removal, and no cerebrospinal fluid leakage was noted during the procedure.

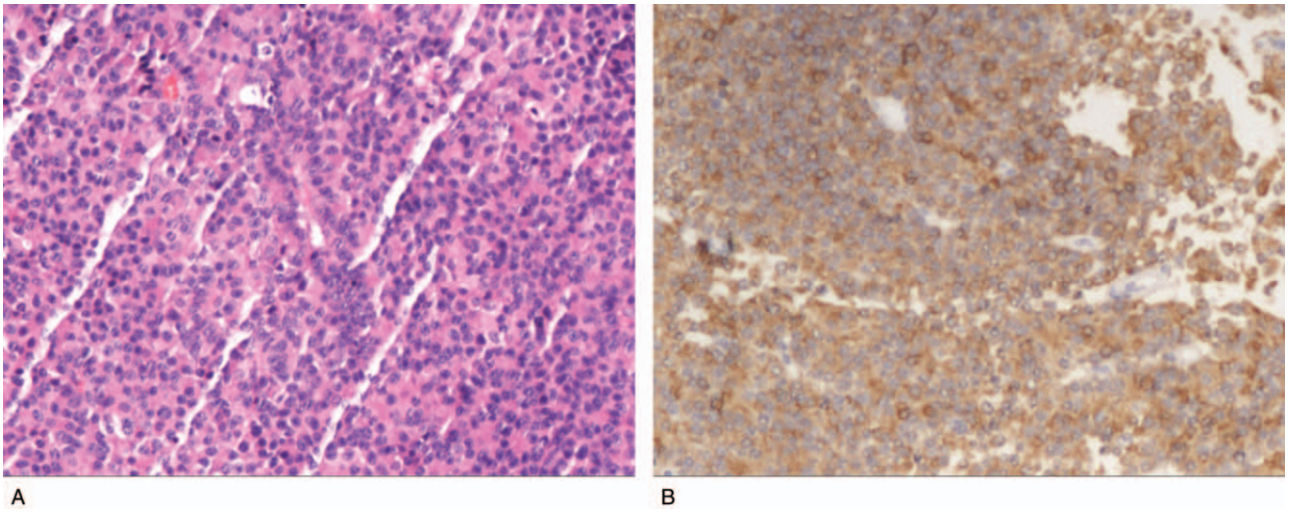

Figure 2. Postoperative pathologic stainings of the resected pituitary tumor, with (A) hematoxylin eosin, (B) anti-adrenocorticotropic hormone antibody. The original magnification of these pictures was 200 times.

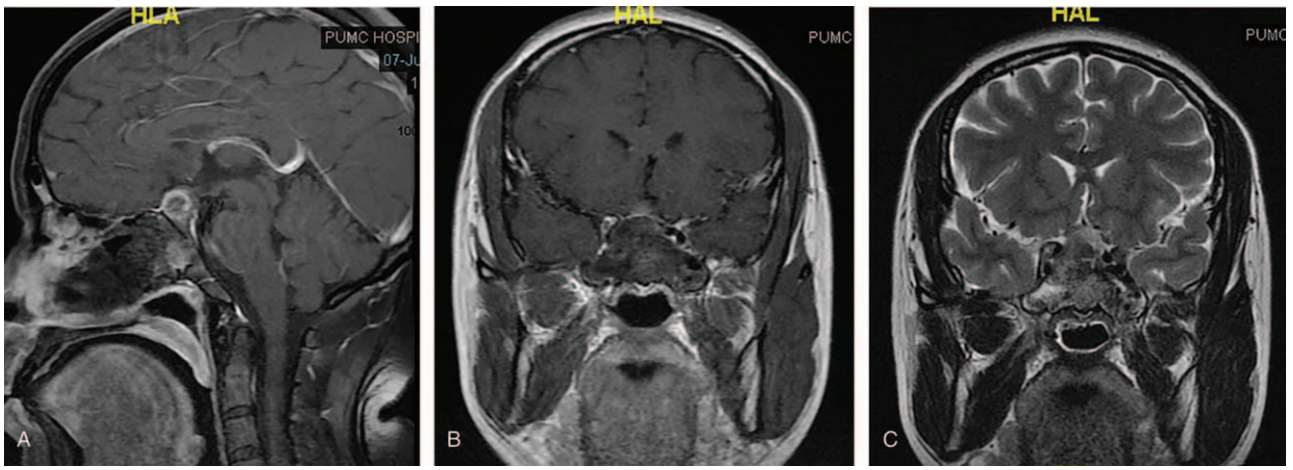

Figure 3. Postoperative magnetic resonance imaging (MRI). No residul tumor is found on the (A) saggital postcontrast T1-weighted, as well as the coronal (B) postcontrast T1-weighted and (C) T2-weighted MRI.

After surgery, the resected tumor specimen was processed for hematoxylin and eosin staining and immunohistochemistry staining (Fig. 2) in the pathology department of our institution. Results of histopathologic examination confirmed our preoperative diagnosis of ACTH-secreting pituitary adenoma. And the immunohistochemistry staining results were as follows: ACTH (+), growth hormone (GH) (+), follicle-stimulating hormone (±), PRL (−), luteinizing hormone (LH) (−), thyroid-stimulating hormone (−), P53 (−), and Ki-67 (index 1%).

The patient's postoperative course was rather smooth, despite transient diabetes insipidus in the 1st 12 hours. Lab results confirmed that she was in remission.[5] Her postoperative morning serum cortisol level was 4.97 μg/dL on day 1 (8 AM), then dropped to 1.60 μg/dL on day 2 (8 AM). She experienced symptoms of secondary adrenal insufficiency including mild headache and nausea on postoperative day 2, and temporary hydrocortisone replacement was prescribed. In addition, her daily ACTH levels (8 AM) were 17.4, 13.3, and 7.7 pg/mL on the first 3 days after surgery. On postoperative day 3, her blood pressure maintained in the range of 110 to 120/70 to 80 mm Hg without medication. Postoperative MRI (Fig. 3) revealed gross-total resection of the Knosp grade 4 macroadenoma. She was discharged 3 days after the surgery. As of this report, the patient was 1 year into her recovery. During her last follow-up, she had a serum cortisol (8 AM) level of 5.49 μg/dL and ACTH level of 16.1 pg/mL. Informed written consent was obtained from the patient for publication of this case report and accompanying images.

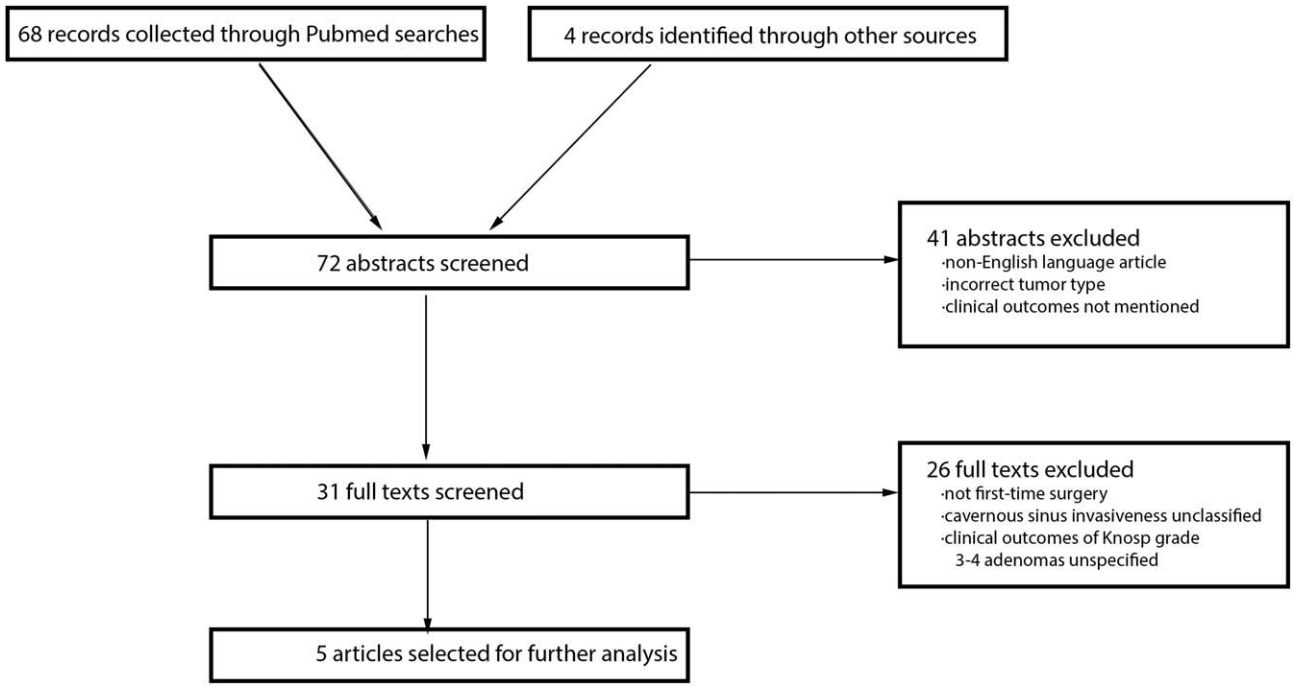

Figure 4. This PRISMA diagram shows the method we used in the PubMed literature search.

Table 1

Literature review: clinical outcomes after initial surgery for Knosp grades 3 and 4 adrenocorticotropic hormone-secreting pituitary adenomas.

Authors, year	Patient characteristics		Surgery approach	Remission rate	Initial remission criteria (cited from the original articles)
Shin et al. (2017)[23]	CD Knosp 3–4	N = 50 N = 6	Endoscopic endonasal approach	3/6 for Knosp 3–4	Symptoms of adrenal insufficiency requiring HRT, 36-h PO fasting nadir cortisol level $\leq$5 μg/dL, and/or 8 AM cortisol level $\leq$5 μg/dL within 2 wk PO
Witek et al, (2016)[19]	CD Knosp 3 Knosp 4	N = 59 N = 4 N = 6	Transsphenoidal approach	0/4 for Knosp 3 0/6 for Knosp 4	6 AM nadir serum cortisol level $\leq$2.5 μg/dL within 2 d PO
Wagenmakers et al, (2013)[17]	CD Knosp 3 Knosp 4	N = 86 N = 8 N = 3	Transsphenoidal approach with endoscope	3/8 for Knosp 3 1/3 for Knosp 4	Disappearance of clinical symptoms of hypercortisolism, and cortisol levels <1.8 μg/dL (50 nmol/L) within 2 d PO, and/or normal suppressive response to LDDST (<1.8 μg/dL) within 3 mo PO
Kuo et al, (2015)[22]	CD Knosp 3 Knosp 3	N = 40 N = 0 N = 5	Endoscopic transsphenoidal approach	2/5 for Knosp 4	Morning serum cortisol <5 mg/dL, or 24-h UFC <20 mg/24 h, or normal 24-h UFC PO.
Ceylan et al, (2010)[21]	CD Knosp 3 Knosp 4	N = 20 N = 2 N = 2	Endoscopic endonasal transsphenoidal approach	3/4 for Knosp 3–4	Normal 24-h UFC and circadian rhythm of plasma cortisol levels, and serum cortisol level of 2 μg/dL after 2-mg dexamethasone-suppression overnight

CD = Cushing disease, d = day, h = hour, HRT = hydrocortisone replacement therapy, LDDST = low-dose dexamethasone suppression test, mo = month, N = number, PO = postoperation, UFC = urinary-free cortisol, wk = week.

3. Discussion

In Cushing disease, patients with cavernous sinus invasion had lower biochemical remission rates after transsphenoidal surgery, comparing to those with noninvasive pituitary adenomas.[7,8]

To evaluate the surgical outcomes of ACTH-secreting pituitary adenomas, especially those with Knosp grades 3 and 4 cavernous sinus invasion, we conducted a systematic literature search.

As shown in Figure 4, PubMed database was searched for relevant literature, with strings including ((“Cushing disease”) AND (“cavernous sinus invasion”)), ((“Cushing disease”) AND (“knosp”)), ((“pituitary ACTH adenoma”) AND (“cavernous sinus invasion”)) and ((“pituitary ACTH adenoma”) AND (“knosp”)). A total of 68 articles were generated from the PubMed search, and 4 outside of the search. Then the abstracts were used to determine whether the surgical outcomes of Cushing disease were the focus. Forty-one articles were excluded, and full texts of the rest were used to determine inclusion or exclusion. The inclusion criteria for analysis were functional ACTH-secreting adenoma, Knosp grades 3 and 4, surgery for the 1st time, surgical outcomes reported in the article. While the exclusion criteria were non-English language articles, incorrect tumor type, Knosp grades 0 to 2 adenoma, clinical outcomes not mentioned or incomplete. Full text screening generated 5 articles that fit the criteria, and all of them are listed in Table 1.[13,19,21–23]

In these studies, surgeries were performed with the universal endonasal transsphenoidal approach. In the cohort reported by Shin et al,[23] 6 patients suffered from Knosp grades 3 and 4 ACTH-secreting pituitary adenoma, and 3 achieved the biochemical remission criteria adopted by the authors. Wagenmakers et al[19] reported biochemical remission of 1 patient with Knosp grade 4 adenoma, and 3 with Knosp grade 3 adenoma. Kuo et al[22] also reported a total of 5 patients with Knosp grade 4 adenoma, and postsurgery 2 patients were in remission. However, none of the patients with Knosp grades 3 and 4 adenoma were in remission after surgery, according to the case series from Witek et al.[13]. In the meantime, Ceylan et al[21] provided 2 patients with Knosp grade 4 adenoma and 2 with Knosp grade 3 adenoma. 3 of Ceylan’s patients were in remission.

To conclude, 36 patients with Knosp grades 3 and 4 ACTH-secreting pituitary adenoma had been reported, and 12 achieved the remission criteria adopted by the original articles after their 1st surgery. However, those remission criteria were different. Specifically, Witek et al[13] and Wagenmakers et al[19] adopted stricter criteria, in comparison to the current Cushing disease guideline recommended criteria, that is, morning serum cortisol levels <5 μg/dL or 24-hour UFC value of 10 to 20 μg/24 h in the first 7 days postoperation.[5] Whereas the criteria used by Ceylan et al[21] were less strict. While in our case, the patient’s surgical outcome was evaluated with the criteria recommended by the current guideline.[5] The difference in adopted remission criteria might affect the conclusions of some patients’ clinical outcomes. However, these articles did not include the original postoperative lab results, which made the re-evaluation of each patient’s postoperative endocrinal state with the current guideline recommended criteria unfeasible.

Our case, along with the results from the systematic literature review, suggested that Cushing disease caused by Knosp grade 4 pituitary adenoma can be successfully controlled with 1 operation. Furthermore, a multidisciplinary team would advance the clinical management of Cushing disease. Clinicians should continue to investigate and report new cases, for better understanding of this condition.

Author contributions

Conceptualization: Xinjie Bao, Boju Pan, Kan Deng, Yong Yao, Wei Lian, Bing Xing, Huijuan Zhu, Lin Lu, Renzhi Wang.
Data curation: Zhe Zhuang.
Formal analysis: Zhe Zhuang.
Investigation: Zhe Zhuang, Boju Pan, Kan Deng, Yong Yao, Wei Lian, Bing Xing, Huijuan Zhu, Renzhi Wang.
Methodology: Zhe Zhuang, Xinjie Bao, Boju Pan, Wei Lian, Huijuan Zhu, Renzhi Wang, Ming Feng.
Resources: Xiaohai Liu, Boju Pan, Kan Deng, Yong Yao, Bing Xing, Huijuan Zhu, Lin Lu, Ming Feng.
Supervision: Ming Feng.
Validation: Zhe Zhuang.

Writing – original draft: Zhe Zhuang.
Writing – review & editing: Zhe Zhuang, Xiaohai Liu, Xinjie Bao, Renzhi Wang, Ming Feng.
Zhe Zhuang orcid: 0000-0002-8049-1166.

References

[1] Dekkers OM, Horvath-Puho E, Jorgensen JO, et al. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. J Clin Endocrinol Metab 2013;98:2277–84.
[2] Bolland MJ, Holdaway IM, Berkeley JE, et al. Mortality and morbidity in Cushing's syndrome in New Zealand. Clin Endocrinol 2011;75:436–42.
[3] Hammer GD, Tyrrell JB, Lamborn KR, et al. Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. J Clin Endocrinol Metab 2004;89:6348–57.
[4] Lindholm J, Juul S, Jorgensen JO, et al. Incidence and late prognosis of cushing's syndrome: a population-based study. J Clin Endocrinol Metab 2001;86:117–23.
[5] Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2015;100:2807–31.
[6] Sautner D, Saeger W. Invasiveness of pituitary adenomas. Pathol Res Practice 1991;187:632–6.
[7] Santoro A, Minniti G, Ruggeri A, et al. Biochemical remission and recurrence rate of secreting pituitary adenomas after transsphenoidal adenomectomy: long-term endocrinologic follow-up results. Surg Neurol 2007;68:513–8.
[8] Blevins LSJr, Christy JH, Khajavi M, et al. Outcomes of therapy for Cushing's disease due to adrenocorticotropin-secreting pituitary macroadenomas. J Clin Endocrinol Metab 1998;83:63–7.
[9] Yamada S, Inoshita N, Fukuhara N, et al. Therapeutic outcomes in patients undergoing surgery after diagnosis of Cushing's disease: A single-center study. Endocr J 2015;62:1115–25.
[10] Juszczak A, Ertorer ME, Grossman A. The therapy of Cushing's disease in adults and children: an update. Horm Metab Res 2013;45:109–17.
[11] Kelly DF. Transsphenoidal surgery for Cushing's disease: a review of success rates, remission predictors, management of failed surgery, and Nelson's Syndrome. Neurosurg Focus 2007;23:E5.
[12] Honegger J, Schmalisch K, Beuschlein F, et al. Contemporary microsurgical concept for the treatment of Cushing's disease: endocrine outcome in 83 consecutive patients. Clin Endocrinol 2012;76:560–7.
[13] Witek P, Zielinski G, Szamotulska K, et al. Clinicopathological predictive factors in the early remission of corticotroph pituitary macroadenomas in a tertiary referral centre. Eur J Endocrinol 2016;174:539–49.
[14] Woo YS, Isidori AM, Wat WZ, et al. Clinical and biochemical characteristics of adrenocorticotropin-secreting macroadenomas. J Clin Endocrinol Metab 2005;90:4963–9.
[15] Cannavo S, Almoto B, Dall'Asta C, et al. Long-term results of treatment in patients with ACTH-secreting pituitary macroadenomas. Eur J Endocrinol 2003;149:195–200.
[16] Kakade HR, Kasaliwal R, Khadilkar KS, et al. Clinical, biochemical and imaging characteristics of Cushing's macroadenomas and their long-term treatment outcome. Clin Endocrinol 2014;81:336–42.
[17] Katznelson L, Bogan JS, Trob JR, et al. Biochemical assessment of Cushing's disease in patients with corticotroph macroadenomas. J Clin Endocrinol Metab 1998;83:1619–23.
[18] Trouillas J, Roy P, Sturm N, et al. A new prognostic clinicopathological classification of pituitary adenomas: a multicentric case-control study of 410 patients with 8 years post-operative follow-up. Acta Neuropathol 2013;126:123–35.
[19] Wagenmakers MA, Boogaarts HD, Roerink SH, et al. Endoscopic transsphenoidal pituitary surgery: a good and safe primary treatment option for Cushing's disease, even in case of macroadenomas or invasive adenomas. Eur J Endocrinol 2013;169:329–37.
[20] Dehdashti AR, Gentili F. Current state of the art in the diagnosis and surgical treatment of Cushing disease: early experience with a purely endoscopic endonasal technique. Neurosurg Focus 2007;23:E9.
[21] Ceylan S, Koc K, Anik I. Endoscopic endonasal transsphenoidal approach for pituitary adenomas invading the cavernous sinus. J Neurosurg 2010;112:99–107.
[22] Kuo CH, Yen YS, Wu JC, et al. Primary endoscopic transnasal transsphenoidal surgery for magnetic resonance image-positive Cushing disease: outcomes of a series over 14 years. World Neurosurg 2015; 84:772–9.
[23] Shin SS, Gardner PA, Ng J, et al. Endoscopic endonasal approach for adrenocorticotropic hormone-secreting pituitary adenomas: outcomes and analysis of remission rates and tumor biochemical activity with respect to tumor invasiveness. World Neurosurg 2017;102: 651.e1–8.e1.
[24] Klibanski A, Zervas NT. Diagnosis and management of hormone-secreting pituitary adenomas. N Engl J Med 1991;324:822–31.