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FOCUS SESSION

Neurosurgical treatment of Cushing disease in pediatric patients: case series and review of literature

Nurperi Gazioglu[1] · Huseyin Canaz[1] · Mahmut Camlar[2] · Necmettin Tanrıöver[3] · Naci Kocer[4] · Civan Islak[4] · Olcay Evliyaoglu[5] · Oya Ercan[5]

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Abstract

Aim Pituitary adenomas are rare in childhood in contrast with adults. Adrenocorticotropic hormone (ACTH)-secreting adenomas account for Cushing's disease (CD) which is the most common form of ACTH-dependent Cushing's syndrome (CS). Treatment strategies are generally based on data of adult CD patients, although some difficulties and differences exist in pediatric patients. The aim of this study is to share our experience of 10 children and adolescents with CD.

Patients and method Medical records, images, and operative notes of 10 consecutive children and adolescents who underwent transsphenoidal surgery for CD between 1999 and 2014 in Cerrahpasa Faculty of Medicine were retrospectively reviewed. Mean age at operation was 14.8 ± 4.2 years (range 5–18). The mean length of symptoms was 24.2 months. The mean follow-up period was 11 years (range 4 to 19 years).

Results Mean preoperative cortisol level was 23.435 μg/dl (range 8.81–59.8 μg/dl). Mean preoperative ACTH level was 57.358 μg/dl (range 28.9–139.9 μg/dl). MR images localized microadenoma in three patients (30%), macroadenoma in four patients (40%) in our series. Transsphenoidal microsurgery and endoscopic transsphenoidal surgery were performed in 8 and 2 patients respectively. Remission was provided in 8 patients (80%). Five patients (50%) met remission criteria after initial operations. Three patients (30%) underwent additional operations to meet remission criteria.

Conclusion Transsphenoidal surgery remains the mainstay therapy for CD in pediatric patients as well as adults. It is an effective treatment option with low rate of complications. Both endoscopic and microscopic approaches provide safe access to sella and satisfactory surgical results.

Keywords Cushing's disease · Endoscopic pituitary surgery · Pediatric · Transsphenoidal microsurgery

Introduction

Cushing's disease (CD) is the most common form of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome (CS) and is rare in pediatric and adolescent patients. CD is caused by an ACTH-secreting pituitary corticotroph adenoma and is associated with significant morbidity in children [1]. Main clinical features of pediatric patients with CD include growth impairment, weight gain, hypertension, and pubertal delay or arrest. Transsphenoidal pituitary surgery is still a main treatment option. Although remission rates vary, it provides removal of adenoma without requirement of long-term replacement therapy [2]. Treatment strategies are generally based on data of adult CD patients, although some difficulties and differences exist [3]. Results of surgical technical difficulties and postoperative hypopituitarism may cause negative effect on growth and puberty [2]. Transsphenoidal

✉ Huseyin Canaz
huseyin.canaz@istanbulbilim.edu.tr

[1] Department of Neurosurgery, Istanbul Bilim University, Istanbul, Turkey

[2] Department of Neurosurgery, Tepecik Research and Training Hospital, University of Health Sciences, Izmir, Turkey

[3] Department of Neurosurgery, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey

[4] Department of Radiology, Division of Neuroradiology, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey

[5] Pediatric Endocrinology and Adolescent Divisions, Department of Pediatrics, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey

pituitary surgery includes two approaches, which are microsurgery and endoscopic surgery.

The aims of this study are to share our experience of 10 children and adolescents with CD and review the literature about transsphenoidal surgery of pediatric patients with CD.

Patients and methods

One hundred seventy-six consecutive patients underwent transsphenoidal surgery for CD by a single surgeon between 1999 and 2017 in Cerrahpasa Faculty. Seventeen patients who were 18 years old or younger were classified as pediatric patients. Medical records, images, and operative notes of 10 pediatric patients (3 males and 7 females) who underwent neurosurgical treatment for CD were retrospectively reviewed. Transsphenoidal microscopic pituitary surgery (TSMS) and endoscopic transsphenoidal pituitary surgery (ETSS) were performed for neurosurgical treatment of CD.

Mean age at operation was 14.8 ± 4.2 years (range 5–18). The mean length of symptoms was 24.2 months. Weight gain was present in all but one patient: mean BMI was 29.97 (range 24.2–40.4). Presenting symptoms were hirsutism (6/10), headache (3/10), acne (1/10), hypertension (4/10), stria (4/10), moon face (5/10), and amenorhea (2/10) (Table 1).

All patients were evaluated by a multidisciplinary team, in which a neuroradiologist, a pediatric endocrinologist, and a pediatric neurosurgeon were included.

Diagnosis of CD was proven by clinical findings, loss of plasma cortisol circadian rhythm and no suppression of cortisol levels after low-dose suppression test. The etiology of hypercortisolism was determined by measurement of plasma ACTH levels, high-dose and very high-dose dexamethasone suppression tests in all patients, and the corticotrophin releasing hormone (CRH) test.

Magnetic resonance imaging (MRI) was performed at 1.5 T preoperatively in all patients. T1-weighted spin echo sequences were constructed in the sagittal and coronal planes with a 2-mm slice thickness before and after gadolinium administration, in the coronal plane a dynamic sequence was also constructed within the first 60 s of contrast injection. Sinus anatomy was evaluated with preoperative paranasal CT scan. One-millimeter axial slices were acquired through the pituitary fossa, and images were reconstructed in the sagittal and coronal planes.

Cavernous sinus sampling (CSS) for ACTH was performed in 5 patients without evidence of pituitary adenoma or with suspected lesion below 5 mm. Diagnosis of CD was confirmed by surgery and positive pituitary tissue pathology.

TSMS was started with a sublabial mucosal incision and followed by submucosal dissection of the anterior hard palate and the nasal septum unilaterally. A nasal speculum was inserted to displace the nasal septum laterally and to keep the mucosal tunnel open and an operating microscope was introduced. Kerrisson rongeur and punch was used to remove the anterior wall and septations of sphenoid sinus. A micro dissector and Kerrison rongeur were used to open the sellar floor.

The first step of ETSS was introducing a 0° rigid endoscope, 4 mm in diameter and 18 cm in length, into the right nostril. The middle turbinate was located and pushed laterally, and the sphenoid ostium (a key anatomical landmark) was defined. Posterior part of nasal septum and mucosa was resected in order to perform binostril approach to allow two surgeons to work together. A wide opening was made in the anterior wall of the sphenoid sinus and sphenoid sinus septations were removed with a high-speed microdrill. The sellar floor was opened with Rhoton curette if it was thin enough. Otherwise, Kerrisson rongeur or microdrill was used to open the sellar floor.

Sellar floor was reconstructed by autologous bone grafts. Surgical cavity was filled with fibrin glue to prevent cerebrospinal fluid (CSF) leakage after both TSMS and ETSS if arachnoid membrane was teared.

Table 1 Presenting symptoms and findings of patients

Pt. No.	Gender	Age	Length of history	BMI	Presenting symptoms	ACTH	Cortisol	Radiology
1	Male	18	10 months	24.2	Hypertension, headache, acne	48.4	26	Microadenoma
2	Female	18	6 years	38.7	Hypertension, hirsutism, weight gaining, stria	28.9	14.1	R-macroadenoma
3	Female	18	12 months	28.5	Hirsutism, moon face, amenorrhea	51,9	8,81	L-macroadenoma
4	Female	17	4.5 years	32.4	Hirsutism, amenorrhea, short stature	477	22.4	Rathke cyst + microadenoma
5	Male	15	1 month	25.3	Hypertension, headache, stria	31.1	8.89	Normal
6	Female	18	8 months	40.4	Moon face, overweight, hirsutism, stria	50.4	24.3	L-microadenoma
7	Female	12	6 months	26.9	Hirsutism, headache	37.7	22.6	L-macroadenoma
8	Female	16	5 years	27.7	Moon face, stria, hirsutism	88.3	18.4	R-macroadenoma
9	Male	5	7 months	25,5	Hypertension, moon face	139.9	59.8	Normal
10	Female	11	1 year	30.1	Moon face, overweight	49.28	29.05	Normal

Pt. no, patient number; *BMI*, body mass index; ACTH, adrenocorticotropic hormone; *R*, right; *L*, left ACTH and cortisol levels are mentioned in μg/dl

Patients were considered in remission when there was clinical adrenal insufficiency and serum cortisol levels were < 2.5 μg/dl at postoperative 48th hour or < 1.8 μg/dl with low-dose dexamethasone suppression test in the postoperative 3rd month, reformation of circadian rhythm, amelioration of symptoms, and no clue of adenoma in MR imagings.

All patients returned to neuroendocrine outpatient clinic at regular intervals for endocrinological evaluations. The mean follow-up period was 11 years (range 4 to 19 years).

Results

Mean preoperative cortisol level was 23.435 μg/dl (range 8.81–59.8 μg/dl). Mean preoperative ACTH level was 57.358 μg/dl (range 28.9–139.9 μg/dl).

MR imagings localized the adenoma in seven patients (70%) in our series. Three patients (30%) had a microadenoma, four patients (40%) had macroadenoma. CSS was performed in three patients (30%) whose MR imagings showed no clue for adenoma. In patient 4, a Rathke's cleft cyst (RCC) and suspected microadenoma were defined in imagings. A cystic adenoma was diagnosed in the imagings of patient 7. CSS was also performed for patients 4 and 7 in order to confirm the diagnosis of central etiology. Lateralization of ACTH secretion was evident in all patients who underwent CSS. ACTH-staining adenoma was confirmed with histopathological evaluation in all patients.

TSMS and ETSS were performed in 8 and 2 patients respectively. Remission was provided in 8 patients (80%) in our series. Four patients (40%) met the remission criteria after TSMS. In two patients (20%), additional TSMS was performed for remission. ETSS was performed two times after TSMS to gain remission in one patient (10%). One patient (10%) met the remission criteria after initial ETSS. Clinical recovery and biochemical cure were achieved after initial operation in 5 patients (50%). Three patients (30%) were accepted as cured after additional operations. Cure was achieved after CSS in 4 patients (80%) (Table 2). Two patients had persistent hypocortisolism (20%). One of the patients with hypocortisolism, also had diabetes insipidus (DI) (10%). Bilateral adrenalectomy was suggested for patient 2, but she did not accept the procedure. Radiotherapy was not considered for any patients. Mean postoperative cortisol level was 8.71 μg/dl (range 1.1–30.38 μg/dl). It is not reported any surgical complication in any patients. Pituitary insufficiency occurred in two patients (20%).

Discussion

CD may lead to remarkable morbidity in pediatric patients. The way of treatment has changed in the past decades. Bilateral adrenalectomy was considered as initial therapy and widely performed in the past. Although it was effective in lowering cortisol levels, pituitary adenoma remained with the risk of post-adrenalectomy Nelson's syndrome [1]. In our series, we suggested adrenalectomy for only one patient, but she did not accept the procedure because of potential risks. Medical therapy to lower cortisol levels is a short-term treatment option, but it is not recommended as mainstay therapy for CD [1]. Transsphenoidal pituitary surgery, which provides selective removal of the microadenoma, is considered treatment of choice in pediatric patients with CD [4]. Although the small size of adenoma and the pituitary fossa and absent or incomplete pneumatization of the sphenoid bone constitute technical difficulties, the success of transsphenoidal surgery which depends on the definition of postoperative remission is reported 70 to 98% in different articles [5–7]. Remission rate was 50% after first operations and 80% after additional operations in our series. Both TSMS and ETSS provide access to sellar fossa with a low rate of complications and morbidity. Transsphenoidal surgery has recently evolved with the introduction of endoscope. Today, ETSS is considered method of choice for pituitary surgery and we switched to ETSS after 2006, because it is less invasive than TSMS with equivalent rates of complete tumor resection and shorter hospital stays in adults and children [7]. It is reported in the recent studies that patients experience significantly fewer nasal symptoms after ETSS and ETSS improves quality of postoperative course in children regardless of type of lesions [8, 9].

Some aspects of CD show difference in pediatric age. Frequency is higher in males compared to females. Radiological evidence of pituitary adenoma is frequently absent [10]. In contrast with literature, females were dominant (7 to 3) in our series. MR imagings of pituitary were normal in three patients and there was remarkable suspicion in two cases; therefore, venous sampling was necessary in 50% of our cases. We limited our study with the age of 18. Definition of pediatric age is important for this group of patients for comparing the results. American Academy of Pediatrics defines pediatric age under 21 years whereas WHO (World Health Organization) defines it 19 years or younger. Most of the studies about pediatric CD include patients at the age of 18 or younger [2, 3, 6, 7]. Pediatric age is defined as 18 years or younger in Turkey.

The clinical features of CD are generally the consequence of increased levels of cortisol production. Presentation is highly variable. The diagnosis is usually delayed because growth failure may be the only symptom for a long time [11]. On the other hand, signs and symptoms may be underestimated or not accepted as pathologic by the family. Although weight gain was present in nine patients, only two patients were complaining of it in our series.

The remission rate was 80% (8/10) in our series. It was 50% (5/10) after initial surgery. Remission rate after

Table 2 Details of treatment and outcomes

Pt. No.	CSS	Initial operation	Additional operations	Histopathology	Postop cortisol levels	Remission	Follow-up
1	−	TSMS	None	Adenoma ACTH+	1.1	+	19 years
2	−	TSMS	TSMS	Adenoma ACTH+	15.5	−	18 years
3	−	TSMS	TSMS	Adenoma ACTH+	1.76	+	14 years
4	+	TSMS	None	Adenoma ACTH+	7.56	+	13 years
5	+	TSMS	None	Adenoma ACTH+	8.23	+	11 years
6	−	TSMS	TSMS	Adenoma ACTH+	4.7	+	9 years
7	+	TSMS	None	Adenoma ACTH+	1.5	+	8 years
8	−	TSMS	ETSS+ETSS	Adenoma ACTH+	13.4	+	7 years
9	+	ETSS	None	Adenoma ACTH+	3	+	7 years
10	+	ETSS	None	Adenoma ACTH+	30.38	−	4 years

Postoperative cortisol levels are mentioned in μg/dl

Pt. No., patient number; *CSS*, avernous sinus sampling

transsphenoidal surgery is reported 70–90% in the literature. However, it is not possible to compare different series because remission criteria shows significant differences among the studies [12–18]. Our remission criteria was one of the most strict criteria in the literature.

Postoperative DI occurs due to neurogenic injury of magnocellular neurons in the hypothalamus, where arginine vasopressin is produced and transported to the posterior pituitary gland with hypothalamo-hypophyseal tract. DI may appear because of many factors, like tumor size, adherence to surrounding structures, histopathology, and surgical technique. It is important to preserve neurovascular structures and to prevent the injury of vital structures including hypothalamus, infundibulum, and neurohypophysis during the operation [6]. The risk of iatrogenic injury is higher when pituitary adenoma occurs in mucoid wedge in front of the neurohypophysis in patients with CD. Persistent DI occurred in one patient (10%) in our series. She was treated by hormone replacement.

Preoperative localization of ACTH-secreting adenomas is important for differential diagnosis. MRI is the gold standard technique of preoperative imaging for pituitary adenomas. When MRI is insufficient for localizing the microadenomas of pituitary or laboratory tests are not clear, preoperative central venous sampling may be necessary to recognize CD or to correctly localize the microadenoma [19]. Central venous sampling can minimize damage to normal pituitary gland and improve the remission rates of transsphenoidal surgery for CD. Central venous sampling can be performed within the petrosal sinus or the cavernous sinus [20, 21]. Inferior petrosal sinus sampling was defined to distinguish CS and CD in 1985. Success of the method about localization of adenoma was denounced high in the initial reports. However, these results could not be maintained in the following reports with larger patient groups. Asymmetrical venous drainage of the cavernous sinus may be a reason of lower success rates [22]. In 1993, CSS was defined to preoperatively predict the lateralization of adenoma. The difference between ACTH levels of two sides was considered to be ≥ 1.4 pg/ml for lateralization [23]. It is reported that correct lateralization of adenomas is about 57–80% with CSS. It is also useful for diagnose of CD. Central levels of ACTH were considered to be three times greater than peripheral levels to define central etiology [22–24]. We preferred to perform CSS for confirmation and lateralization of adenoma because of false positive rates of inferior petrosal sinus sampling may reach 60% [25]. We performed CSS in five patients and confirmed the results with intraoperative histopathological findings in all patients. No additional surgery was performed after initial operations. We achieved remission in 4 of 5 patients (80%). CSS is an invasive technique which requires general anesthesia and heparinization. CSS may be technically more difficult in pediatric patients. That is why a well experienced interventional neuroradiology team has a vital role. In our series, we did not perform venography; therefore, thromboembolic complications did not occur in any patient.

RCC and pituitary adenomas have a common embryologic origin. Cells of anterior pituitary, where pituitary adenomas arise, are formed by anterior wall of Rathke's pouch and RCCs are the remnants of Rathke's pouch. However, pituitary adenomas may very rarely occur concurrently with RCC [26]. Incidence of RCC is 11–33% in general population. The rate of concomitant RCC and pituitary adenoma is 0.51–1.7% [27–29]. Within this group of patients, most of the adenomas are growth hormone or prolactin releasing ones [26, 29]. It is extremely rare to be seen RCC in a pediatric patient with CD. Although it is difficult to diagnose preoperatively because of variable signal intensity and position of RCC, the presence of a non-enhancing cyst with a pituitary adenoma may suggest an accompanying RCC. Treatment of these patients requires surgical excision to reduce mass effect and medication for hormonal irregularities. Microadenoma was located in the

right side of the pituitary gland according to CSS results in patient 4. We performed resection of right side of pituitary and RCC. Patient met remission criteria in the 3rd month after TSMS.

Transsphenoidal surgery is the mainstay treatment which provides remission in 70–90% of patients with CD [30, 31]. However, hypercortisolism may persist or may recur in up to 25% of patients achieving remission after surgery. Second-line treatments include second transsphenoidal surgery, Gama Knife radiosurgery (GK), medical therapy, and bilateral adrenalectomy [32]. Repeat pituitary surgery may be successful in achieving remission in approximately 55% of patients [33]. GK is an important option for patients who are not candidate for second operation. Although conventional radiotherapy (RT) was used for decades, stereotactic RT has recently become available and taken its place. Risks of RT include anterior hypopituitarism (35–60% of patients at 5 years after RT), optic neuropathy (1–2%) and other cranial neuropathies, secondary tumor formation, and temporal lobe necrosis [34]. As stereotactic RT causes less damage in normal brain tissue, it is possible that these risks will decrease in patients who received stereotactic RT. However, in CD, available information has not been rigorously proven. At a median time about 4 years after GK, rate of new onset hypopituitarism is 11–22% [35, 36]. Nevertheless in the series with the longest median follow-up (17 years), risk of new onset hypopituitarism was 66% [37]. One of the problems experienced in stereotactic RT of ACTH-secreting adenomas, which are frequently very small and invisible even with magnetic resonance imaging, is the correct identification of residual tumor. In this situation, usual practice is to cover the entire sella to be sure to include the residual adenoma and obtain amelioration of CD. This problem is not usually encountered in other types of pituitary tumors, such as growth hormone-secreting or nonfunctioning adenomas [38]. In our series, we preferred additional surgery as second-line therapy in order to avoid long-term sequelae of GK in pediatric patients.

Conclusion

Medical treatment for CD is not efficient enough yet. Transsphenoidal surgery remains the mainstay therapy for CD in pediatric patients as well as adults. It is an effective treatment option with low rate of complications. Both endoscopic and microscopic approaches provide safe access to sella and satisfactory surgical results in experienced hands. Although recent studies shows that ETSS tends to replace TSMS in the future, determining factor for surgical technique is still experience of surgeon. In this point, acquaintance of surgical team to both approaches allows better decision.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

References

1. Savage MO, Dias RP, Chan LF, Afshar F, Plowman NP, Matson M, Grossman AB, Storr HL (2010) Diagnosis and treatment of Cushing's disease in children. Endocr Dev 17:134–145. https://doi.org/10.1159/000262535
2. Oliveira RS, Castro M, Antonini SR, Martinelli CE Jr, Moreira AC, Machado HR (2010) Surgical management of pediatric Cushing's disease: an analysis of 15 consecutive cases at a specialized neurosurgical center. Arquivos brasileiros de endocrinologia e metabologia 54(1):17–23
3. Yordanova G, Martin L, Afshar F, Sabin I, Alusi G, Plowman NP, Riddoch F, Evanson J, Matson M, Grossman AB, Akker SA, Monson JP, Drake WM, Savage MO, Storr HL (2016) Long-term outcomes of children treated for Cushing's disease: a single center experience. Pituitary 19(6):612–624. https://doi.org/10.1007/s11102-016-0756-8
4. Guaraldi F, Storr HL, Ghizzoni L, Ghigo E, Savage MO (2014) Paediatric pituitary adenomas: a decade of change. Horm Res Paediatr 81(3):145–155. https://doi.org/10.1159/000357673
5. Lonser RR, Wind JJ, Nieman LK, Weil RJ, DeVroom HL, Oldfield EH (2013) Outcome of surgical treatment of 200 children with Cushing's disease. J Clin Endocrinol Metab 98(3):892–901. https://doi.org/10.1210/jc.2012-3604
6. Zhan R, Xu G, Wiebe TM, Li X (2015) Surgical outcomes of the endoscopic transsphenoidal route to pituitary tumours in paediatric patients >10 years of age: 5 years of experience at a single institute. Arch Dis Child 100(8):774–778. https://doi.org/10.1136/archdischild-2015-308365
7. Storr HL, Drake WM, Evanson J, Matson M, Berney DM, Grossman AB, Akker SA, Monson JP, Alusi G, Savage MO, Sabin I (2014) Endonasal endoscopic transsphenoidal pituitary surgery: early experience and outcome in paediatric Cushing's disease. Clin Endocrinol 80(2):270–276. https://doi.org/10.1111/cen.12275
8. Pledger CL, Elzoghby MA, Oldfield EH, Payne SC, Jane JA Jr (2016) Prospective comparison of sinonasal outcomes after microscopic sublabial or endoscopic endonasal transsphenoidal surgery for nonfunctioning pituitary adenomas. J Neurosurg 125(2):323–333. https://doi.org/10.3171/2015.6.JNS142695
9. Massimi L, Rigante M, D'Angelo L, Paternoster G, Leonardi P, Paludetti G, Di Rocco C (2011) Quality of postoperative course in children: endoscopic endonasal surgery versus sublabial microsurgery. Acta Neurochir 153(4):843–849. https://doi.org/10.1007/s00701-010-0929-6
10. Savage MO, Storr HL (2012) Pediatric Cushing's disease: management issues. Indian J Endocrinol Metab 16(Suppl 2):S171–S175. https://doi.org/10.4103/2230-8210.104032
11. Jagannathan J, Dumont AS, Jane JA Jr, Laws ER Jr (2005) Pediatric sellar tumors: diagnostic procedures and management. Neurosurg Focus 18(6A):E6
12. Valassi E, Feelders R, Maiter D, Chanson P, Yaneva M, Reincke M, Krsek M, Toth M, Webb SM, Santos A, Paiva I, Komerdus I, Droste M, Tabarin A, Strasburger CJ, Franz H, Trainer PJ, Newell-Price J, Wass JA, Papakokkinou E, Ragnarsson O, Group ES (2018) Worse health-related quality of life at long-term follow-up in patients with Cushing's disease than patients with cortisol producing adenoma. Data from the ERCUSYN. Clin Endocrinol 88(6):787–798. https://doi.org/10.1111/cen.13600

13. Evang JA, Carlsen SM, Svartberg J, Aanderud S, Johannesen O, Schreiner T, Ramm-Pettersen J, Bakke SJ, Lund-Johansen M, Bollerslev J (2006) Endogenous Cushing's syndrome. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke 126(5):599–602
14. Shirvani M, Motiei-Langroudi R, Sadeghian H (2016) Outcome of microscopic transsphenoidal surgery in Cushing disease: a case series of 96 patients. World Neurosurgery 87:170–175. https://doi.org/10.1016/j.wneu.2015.11.046
15. Kuo CH, Yen YS, Wu JC, Chen YC, Huang WC, Cheng H (2015) Primary endoscopic transnasal transsphenoidal surgery for magnetic resonance image-positive Cushing disease: outcomes of a series over 14 years. World Neurosurg 84(3):772–779. https://doi.org/10.1016/j.wneu.2015.04.059
16. Osswald A, Plomer E, Dimopoulou C, Milian M, Blaser R, Ritzel K, Mickisch A, Knerr F, Stanojevic M, Hallfeldt K, Schopohl J, Kuhn KA, Stalla G, Beuschlein F, Reincke M (2014) Favorable long-term outcomes of bilateral adrenalectomy in Cushing's disease. Eur J Endocrinol 171(2):209–215. https://doi.org/10.1530/EJE-14-0214
17. Kakade HR, Kasaliwal R, Khadilkar KS, Jadhav S, Bukan A, Khare S, Budyal SR, Goel A, Lila AR, Bandgar T, Shah NS (2014) Clinical, biochemical and imaging characteristics of Cushing's macroadenomas and their long-term treatment outcome. Clin Endocrinol 81(3):336–342. https://doi.org/10.1111/cen.12442
18. Clayton RN, Jones PW, Reulen RC, Stewart PM, Hassan-Smith ZK, Ntali G, Karavitaki N, Dekkers OM, Pereira AM, Bolland M, Holdaway I, Lindholm J (2016) Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study. Lancet Diabetes Endocrinol 4(7):569–576. https://doi.org/10.1016/S2213-8587(16)30005-5
19. Graham KE, Samuels MH, Nesbit GM, Cook DM, O'Neill OR, Barnwell SL, Loriaux DL (1999) Cavernous sinus sampling is highly accurate in distinguishing Cushing's disease from the ectopic adrenocorticotropin syndrome and in predicting intrapituitary tumor location. J Clin Endocrinol Metab 84(5):1602–1610. https://doi.org/10.1210/jcem.84.5.5654
20. Bonelli FS, Huston J 3rd, Carpenter PC, Erickson D, Young WF Jr, Meyer FB (2000) Adrenocorticotropic hormone-dependent Cushing's syndrome: sensitivity and specificity of inferior petrosal sinus sampling. AJNR Am J Neuroradiol 21(4):690–696
21. Flitsch J, Ludecke DK, Knappe UJ, Grzyska U (2002) Cavernous sinus sampling in selected cases of Cushing's disease. Exp Clin Endocrinol Diabetes 110(7):329–335. https://doi.org/10.1055/s-2002-34989
22. Burkhardt T, Flitsch J, van Leyen P, Sauer N, Aberle J, Grzyska U, Ludecke DK (2015) Cavernous sinus sampling in patients with Cushing's disease. Neurosurg Focus 38(2):E6. https://doi.org/10.3171/2014.10.FOCUS14687
23. Teramoto A, Nemoto S, Takakura K, Sasaki Y, Machida T (1993) Selective venous sampling directly from cavernous sinus in Cushing's syndrome. J Clin Endocrinol Metab 76(3):637–641. https://doi.org/10.1210/jcem.76.3.8383143
24. Teramoto A, Yoshida Y, Sanno N, Nemoto S (1998) Cavernous sinus sampling in patients with adrenocorticotrophic hormone-dependent Cushing's syndrome with emphasis on inter- and intracavernous adrenocorticotrophic hormone gradients. J Neurosurg 89(5):762–768. https://doi.org/10.3171/jns.1998.89.5.0762
25. Ludecke DK (1989) Intraoperative measurement of adrenocorticotropic hormone in peripituitary blood in Cushing's disease. Neurosurgery 24(2):201–205
26. Babu R, Back AG, Komisarow JM, Owens TR, Cummings TJ, Britz GW (2013) Symptomatic Rathke's cleft cyst with a coexisting pituitary tumor; brief review of the literature. Asian J Neurosurg 8(4):183–187. https://doi.org/10.4103/1793-5482.125662
27. Nishio S, Mizuno J, Barrow DL, Takei Y, Tindall GT (1987) Pituitary tumors composed of adenohypophysial adenoma and Rathke's cleft cyst elements: a clinicopathological study. Neurosurgery 21(3):371–377
28. Sumida M, Migita K, Tominaga A, Iida K, Kurisu K (2001) Concomitant pituitary adenoma and Rathke's cleft cyst. Neuroradiology 43(9):755–759
29. Wu W, Jia G, Jia W, Li G, Zhang J, Zhang L (2018) Pituitary adenoma associated with Rathke's cleft cyst: report of 15 cases. J Can Sci Neurol 45(1):68–75. https://doi.org/10.1017/cjn.2017.252
30. Biller BM, Grossman AB, Stewart PM, Melmed S, Bertagna X, Bertherat J, Buchfelder M, Colao A, Hermus AR, Hofland LJ, Klibanski A, Lacroix A, Lindsay JR, Newell-Price J, Nieman LK, Petersenn S, Sonino N, Stalla GK, Swearingen B, Vance ML, Wass JA, Boscaro M (2008) Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 93(7):2454–2462. https://doi.org/10.1210/jc.2007-2734
31. Hofmann BM, Hlavac M, Martinez R, Buchfelder M, Muller OA, Fahlbusch R (2008) Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years. J Neurosurg 108(1):9–18. https://doi.org/10.3171/JNS/2008/108/01/0009
32. Vance ML (2009) Cushing's disease: radiation therapy. Pituitary 12(1):11–14. https://doi.org/10.1007/s11102-008-0117-3
33. Tritos NA, Biller BM (2015) Update on radiation therapy in patients with Cushing's disease. Pituitary 18(2):263–268. https://doi.org/10.1007/s11102-014-0615-4
34. Loeffler JS, Shih HA (2011) Radiation therapy in the management of pituitary adenomas. J Clin Endocrinol Metab 96(7):1992–2003. https://doi.org/10.1210/jc.2011-0251
35. Castinetti F, Nagai M, Dufour H, Kuhn JM, Morange I, Jaquet P, Conte-Devolx B, Regis J, Brue T (2007) Gamma knife radiosurgery is a successful adjunctive treatment in Cushing's disease. Eur J Endocrinol 156(1):91–98. https://doi.org/10.1530/eje.1.02323
36. Jagannathan J, Sheehan JP, Pouratian N, Laws ER, Steiner L, Vance ML (2007) Gamma Knife surgery for Cushing's disease. J Neurosurg 106(6):980–987. https://doi.org/10.3171/jns.2007.106.6.980
37. Hoybye C, Grenback E, Rahn T, Degerblad M, Thoren M, Hulting AL (2001) Adrenocorticotropic hormone-producing pituitary tumors: 12- to 22-year follow-up after treatment with stereotactic radiosurgery. Neurosurgery 49(2):284–291 discussion 291-282
38. Losa M, Picozzi P, Redaelli MG, Laurenzi A, Mortini P (2010) Pituitary radiotherapy for Cushing's disease. Neuroendocrinology 92(Suppl 1):107–110. https://doi.org/10.1159/000314299