



Transsphenoidal surgery for pituitary adenomas in pediatric patients: a multicentric retrospective study

Davide Locatelli¹ · Pierlorenzo Veiceschi¹ · Paolo Castelnovo² · Necmettin Tanriover³ · Olcay Evliyaoglu⁴ · Huseyin Canaz⁵ · Doga Ugurlar⁵ · Nurperi Gazioglu⁵

Received: 21 March 2019 / Accepted: 28 April 2019 / Published online: 11 May 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Introduction Pediatric pituitary adenomas are rare lesions. Incidence is reported between 1 and 10% of all childhood brain tumors and between 3 and 6% of all surgically treated adenomas. Although pituitary adenomas present with symptoms of hormone hypersecretion or neurological disruptions secondary to mass effect, they are almost constantly benign. Characteristics of patients may vary in different studies according to age, gender, size of adenoma, hormonal activity, and recurrence rates.

Methods Data on consecutive pediatric patients who were operated for pituitary adenoma with endoscopic endonasal transsphenoidal surgery (EETS) and transsphenoidal microsurgery (TMS) in the Department of Neurosurgery, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey, in the Neurosurgical Unit of the San Matteo Hospital, Pavia, Italy, and in the Division of Neurological Surgery Department of Biotechnology and Life Sciences, University of Insubria-Varese, ASST Sette Laghi, Ospedale di Circolo e Fondazione Macchi, Varese, Italy, between July 1997 and May 2018, were analyzed. Twenty-seven patients (11 males and 16 females), who were 18 years old or younger at the time of surgery, were included in the study. Medical records, images, and operative notes of patients were retrospectively reviewed.

Results There were 16 females (59.3%) and 11 males (40.7%). Mean age was 15.3 ± 3.3 (4–18). Thirty-two surgical procedures were performed for 27 patients (6 children required second operation). Thirteen patients (48.14%) had Cushing's disease (CD), 5 patients (18.5%) had growth hormone (GH)-secreting adenoma, 5 patients (18.5%) had prolactinoma, and 4 patients (14.8%) had non-functional adenoma. Twenty-two patients (81.4%) met remission criteria, and 5 patients (18.5%) did not meet remission criteria. Four patients met remission criteria after the second operation.

Conclusion Transsphenoidal approach affords effective release of mass effect and not only restoration but also perpetuation of normal endocrine functions in the majority of pediatric pituitary adenoma patients. Satisfactory results are reported with both EETS and TMS in the literature. Despite the technical difficulties in pediatric age, transsphenoidal resection of adenoma is still the mainstay treatment that provides cure in pediatric patients.

✉ Pierlorenzo Veiceschi
pierloveiceschi@gmail.com

Davide Locatelli
locatelli.dr.davide@gmail.com

Paolo Castelnovo
paolo.castelnovo@uninsubria.it

Necmettin Tanriover
nctan27@yahoo.com

Olcay Evliyaoglu
olcay.evliyaoglu@istanbul.edu.tr

Huseyin Canaz
huseyin.canaz@istanbulbilim.edu.tr

Doga Ugurlar
dogaugurlar@gmail.com

Nurperi Gazioglu
nurperi.gazioglu@gmail.com

- ¹ Division of Neurosurgery, Department of Biotechnology and Life Sciences, University of Insubria, Ospedale di Circolo e Fondazione Macchi, Via Guicciardini 9, 21100 Varese, Italy
- ² Division of Otorhinolaryngology, Department of Biotechnology and Life Sciences, University of Insubria, Ospedale di Circolo e Fondazione Macchi, Varese, Italy
- ³ Department of Neurosurgery, Istanbul University Cerrahpasa, Istanbul, Turkey
- ⁴ Department of Pediatric Endocrinology, Istanbul University Cerrahpasa, Istanbul, Turkey
- ⁵ Department of Neurosurgery, Demiroğlu Bilim University, Istanbul, Turkey

Keywords Pediatric pituitary adenomas · Endoscopic endonasal transsphenoidal surgery · Transsphenoidal microsurgery · Remission · Outcome · Skull base

Introduction

The role of the pituitary gland is vital for the sustention of homeostasis and for reproductive functions. This gland is developed in the fourth week of embryonic life from an invagination of the stomodeum to Rathke's pouch [1]. Pediatric pituitary adenomas are rare lesions. Incidence is reported between 1 and 10% of all childhood brain tumors and between 3 and 6% of all surgically treated adenomas [2]. In spite of these tumors are rarely seen, alterations in hormone functions may cause a significant effect on the quality of life of the child. Although pituitary adenomas present with symptoms of hormone hypersecretion or neurological disruptions secondary to mass effect, they are almost constantly benign [1]. Important developments occurred in the diagnosis, medical and surgical treatment of pediatric pituitary adenomas in the last two decades [3].

Characteristics of patients may vary in different studies according to age, gender, size of adenoma, hormonal activity, and recurrence rates. In this study, we report three institutions' experience regarding the neurosurgical treatment of pediatric pituitary adenomas and review of the literature.

Methods

We conducted a multicentric retrospective cohort study of pediatric pituitary adenoma cases which underwent transsphenoidal surgery at three tertiary centers. Data on consecutive pediatric patients, who were operated for pituitary adenoma with endoscopic endonasal transsphenoidal surgery (EETS) and transsphenoidal microsurgery (TMS) in the Department of Neurosurgery, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey, in the Neurosurgical Unit of the San Matteo Hospital, Pavia, Italy, and in the Division of Neurological Surgery Department of Biotechnology and Life Sciences, University of Insubria-Varese, ASST Sette Laghi, Ospedale di Circolo e Fondazione Macchi, Varese, Italy between July 1997 and May 2018, were analyzed. Twenty-seven patients (11 males and 16 females), who were 18 years old or younger at the time of surgery, were included in the study.

Medical records, images, and operative notes of patients were retrospectively reviewed. Indications of surgery were persevering endocrine dysfunction despite medical therapy, intolerance to medical therapy (either because of side effects or patient's predilection), or mass effect and cranial neuropathy. All patients were evaluated by a multidisciplinary team, in which a neuroradiologist, a pediatric endocrinologist, and a pediatric neurosurgeon were included. Informed consent was

obtained from all individual participants included in the study. 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. TMS and EETS were previously described [4, 5].

All patients were followed up by both neuroendocrine and neurosurgery outpatient clinic at regular intervals. Follow-up MRI was performed within 3 months after surgery. Gross total resection was defined as a lack of residual tumor on postoperative imaging studies. Indicators of remission were prolactin levels < 20 ng/ml in females and < 15 ng/ml in males on the first postoperative day for patients with prolactinoma. For acromegaly patients, remission was determined as a normal IGF-1 level combined with a basal GH level of < 1 μ g/l or combined with a GH level of < 0.4 μ g/l after oral glucose tolerance test suppression. Cushing patients were considered in remission when there was clinical adrenal insufficiency and serum cortisol levels were < 2.5 μ g/dl at the postoperative 48th hour or < 1.8 μ g/dl with low-dose dexamethasone suppression test in the postoperative 3th month.

The results were analyzed with the Mann-Whitney *U* test and Fisher exact test. All statistical analyses were performed using SPSS, version 21.0 (IBM Company, USA). The statistical significance level was 0.05, and *p* values were considered significant when < 0.05 .

Results

There were 16 females (59.3%) and 11 males (40.7%). Mean age was 15.3 ± 3.3 (4–18). Thirty-two surgical procedures were performed for 27 patients (6 children required second operation). EETS was performed for 19 patients, and TMS was performed for 8 patients as the first choice of treatment.

Thirteen patients (48.14%) had CD, 5 patients (18.5%) had GH secreting adenoma, 5 patients (18.5%) had prolactinoma, and 4 patients (14.8%) had non-functional adenoma.

No adenoma was determined in 2 patients (7.4%) who had CD. Twelve patients (44.4%) had microadenoma, and 13 patients (48.2%) had macroadenoma.

Cavernous sinus invasion was determined in 6 patients (22.2%): in 1 patient, Knosp grade was I; in 3 patients,

Knosp grade was II; and in 2 patients, Knosp grade was III. There was no statistically significant relationship between cavernous sinus invasion and remission ($p = 0.07$). In this series, there was no statistically significant difference for remission between age groups ($p = 0.457$) nor between microscopic and endoscopic transsphenoidal surgery ($p = 0.628$).

Twenty-two patients (81.4%) met remission criteria, and 5 patients (18.5%) did not meet remission criteria. Four patients met remission criteria after the second operation.

Six patients, who required second operation, had CD. Four of them had microadenoma, and 2 of them had macroadenoma. Five patients, who previously underwent TMS, required second operation. TMS was performed for 3 of them as the second operation, and EETS was performed for one patient as second operation. One patient, who previously underwent EETS, required second operation, and EETS was performed as the second operation (Table 1).

Postoperative transient diabetes insipidus and adrenal insufficiency occurred in a patient with macroadenoma and Cushing's disease. Postoperative CSF leakage happened in a patient with microadenoma and Cushing's disease. A patient with a growth hormone-secreting macroadenoma had postoperative transient diabetes insipidus (DI), CSF leakage, and meningismus. Both patients with CSF leakage underwent surgical repair. Persistent DI and partial hypopituitarism were experienced 19 months after surgery in a patient with growth hormone-secreting adenoma (case illustrated in Fig. 1).

Discussion

Pediatric pituitary adenomas consist of uncommon but challenging pathologies for their endocrine and neurological qualities. Pituitary adenomas comprise < 3% of pediatric brain tumors in early childhood [3]. It is important to remember that many adenomas represented in young adults may be originated in childhood. Contrasting with adenomas in adults, pituitary adenomas are usually functioning (80–97%), with adrenocorticotropin (ACTH)-secreting adenomas being the most common in early childhood, followed by prolactin (PRL)- and growth hormone (GH)-secreting adenomas [6]. Prolactinomas are more frequently seen in older children and adolescents [7]. There were 13 patients (50%) with CD, 4 patients (15.4%) with GH secreting adenoma, 5 patients (19.2%) with prolactinoma, and 4 patients (15.4%) with non-functional adenoma in our series.

With the exception of ACTH-secreting adenomas, the majority of pituitary adenomas are macroadenomas (diameter > 1 cm) and are frequently invasive in pediatric age [3]. In our series, there were 11 patients (42.3%) with macroadenoma: 4 patients with GH-secreting adenoma, 3 patients with non-functional adenoma, 3 patients with prolactinoma, and 1 patient with CD. Five patients (19.2%), who showed cavernous

sinus invasion, had also macroadenoma: 3 patients with GH-secreting adenoma, 1 patient with prolactinoma, and 1 patient with CD.

TMS has been accepted as the mainstay treatment for pituitary adenomas in adults and children for the past 20 years. It is used for selective removal of adenomas and for the debulking of lesions invading the cavernous sinuses. TMS is particularly challenging because of anatomical and technical reasons in pediatric population. Additionally, surgeon's experience is also a predictor of success [8, 9].

In Cerrahpaşa, we used the operating microscope for transsphenoidal (TS) surgery until 2007, when we switched to endoscopic endonasal techniques. Eight cases operated by microscopic TS approach are included in our series (Table 1).

Looking at the details, 5 of them were microadenomas, 1 patient with Cushing's disease had normal MRI, only 2 cases were macroadenomas, and 1 of them with Cavernous sinus invasion (Knosp grade I). It may be the cause of no statistically significant difference for remission. Repeat surgery was performed in 4 CD cases operated microscopically because remission was not achieved at the first operation (one of this case is illustrated in Fig. 2).

Since 2007, we are only using the endoscopic approach and we do recommend it for every case including pediatric cases.

EETS is a less invasive technique, which has been used in many centers and has shown equivalent rates of complete tumors resection, shorter hospital stays, decreased patient discomfort, and reduced or equivalent surgical complications in adults. EETS may also be preferred as the first-line treatment and for recurrent lesions in children. EETS has advantages for efficacy and safety reasons with reduction of surgical trauma, pain perception, pediatric intensive care unit staying, blood transfusions, pituitary deficiencies, and incidence of diabetes insipidus [10, 11].

Prolactinomas are the most common functional pituitary adenomas which are generally seen in late childhood and adolescence with a mean age at onset of symptoms of 14.5 years. They comprise 48–68% of pituitary adenomas in pediatric age [12]. Prolactinomas are the second most common pituitary adenoma after corticotroph adenomas under the age of 12 years [7]. Prolactinomas may be seen in several inherited syndromes, including MEN 1, Carney complex, and familial isolated pituitary adenomas [12]. Prolactin-secreting adenomas are more frequently seen in girls, with a ratio varying from 1.9/1 to 4.5/1 depending on age [13]. In our series, the female/male proportion of patients with prolactinoma was 3/2 and mean age at the time of operation was 14.8 years. Clinical features can occur in two ways. Males with prolactinomas have a higher incidence of neuroophthalmological signs like headache and visual field defects which may appear due to the mass effect of an invasive macroadenoma [6]. Secondly, symptoms including oligo- or amenorrhea, galactorrhea,

Table 1 Characteristics of studied patients

Patient no.	Gender	Age	Functional type	Adenoma size (mm)	Knosp grade	Intra-op CS invasion	First op	Second op	Remission status	Complications
1	M	18	ACTH	Microadenoma 3 × 4 × 4	\	–	TMS	–	+	–
2	F	18	ACTH	Microadenoma 5 × 5 × 7	\	–	TMS	TMS	–	–
3	F	18	ACTH	Macroadenoma 12 × 10 × 11	\	–	TMS	TMS	+	TDI + AI
4	F	17	ACTH	Invisible	\	–	TMS	–	+	–
5	M	15	ACTH	Microadenoma 3 × 2 × 2	\	–	TMS	–	+	–
6	F	18	ACTH	Microadenoma 5 × 3 × 5	\	–	TMS	TMS	+	–
7	F	12	ACTH	Microadenoma 4 × 7 × 5	\	–	TMS	–	+	–
8	M	14	PRL	Macroadenoma 25 × 15 × 20	II	+	EETS	–	–	–
9	F	16	ACTH	Macroadenoma 7 × 15 × 10	I	+	TMS	EETS	+	–
10	M	4	ACTH	Invisible	\	–	EETS	–	+	–
11	F	11	ACTH	Microadenoma 4.5 × 3 × 4	\	–	EETS	–	–	–
12	M	16	GH	Macroadenoma 32 × 37 × 35	III	+	EETS	–	–	–
13	F	18	PRL	Macroadenoma 16 × 10 × 10	\	–	EETS	–	+	–
14	M	17	GH	Macroadenoma 24 × 17 × 21	II	+	EETS	–	–	–
15	F	11	PRL	Microadenoma 3 × 3 × 3	\	–	EETS	–	+	–
16	M	15	PRL	Microadenoma 7 × 8 × 8	\	–	EETS	–	+	–
17	F	18	NF	Macroadenoma 29 × 27 × 15	\	–	EETS	–	+	–
18	M	14	ACTH	Microadenoma 7 × 8 × 5	\	–	EETS	EETS	+	–
19	F	14	ACTH	Microadenoma 4 × 5 × 7.2	\	–	EETS	–	+	CSF-leakage
20	F	18	NF	Macroadenoma 23 × 12 × 15	\	–	EETS	–	+	–
21	F	18	ACTH	Microadenoma 8 × 5 × 7.5	\	–	EETS	–	+	–
22	F	12	NF	Microadenoma 5 × 4 × 8.3	\	–	EETS	–	+	–
23	F	16	PRL	Macroadenoma 13 × 15 × 16	\	–	EETS	–	+	–
24	M	18	GH	Macroadenoma 29 × 25 × 15	III	+	EETS	–	+	CSF-leakage + meningismus + TDI
25	M	12	GH	Macroadenoma 26 × 38 × 14	\	–	EETS	–	+	–
26	M	18	GH	Macroadenoma 28 × 18 × 13	II	+	EETS	–	+	PDI + PH
27	F	18	NF	Macroadenoma 15 × 12 × 13	\	–	EETS	–	+	–

ACTH adrenocorticotropic hormone, *AI* adrenal insufficiency, *CS* cavernous sinus, *CSF* cerebrospinal fluid, *EETS* endoscopic endonasal transsphenoidal surgery, *F* female, *GH* growth hormone, *M* male, *NF* non-functional, *Op* operation, *PDI* persistent diabetes insipidus, *PH* partial hypopituitarism, *PRL* prolactin, *TDI* transient diabetes insipidus, *TMS* transsphenoidal microsurgery

gynecomastia, delayed puberty, and hypogonadotropic hypogonadism are the effects of hyperprolactinemia [14]. Medical therapy with dopamine agonists is the first-line treatment for prolactinomas. The purpose of therapy is normalization of prolactin levels and pituitary function and reducing the tumor size. Dopamine agonists are effective in the reduction of tumor size and controlling prolactin levels in approximately 80–90% of patients with microadenomas and about 70% of macroadenomas [1]. Persistence of hyperprolactinemia after 3 months of maximal dose treatment and < 50% reducing of adenoma size is defined as resistance to medical therapy. Surgical treatment should be considered in patients with macroadenomas unresponsive to maximum tolerable dopamine agonist therapy or persistence of neurophthalmological symptoms.

ACTH-secreting adenomas causing CD account for 54.8% of pituitary adenomas under age 12 years and 29.4% between ages 12 and 18 years. CD has a male predominance in pediatric patients. Ninety-eight percent of pediatric CD cases occur due to microadenomas [15]. ACTH-secreting adenomas rarely grow into the subarachnoid space or invade cavernous sinus or wall [16]. In our series, 10 patients with CD had microadenoma and 1 patient had macroadenoma. There was no radiological finding of adenoma in two patients. Contrast with literature, there were 4 males and 9 females with CD. The most common clinical presentation of CD in children is significant weight gain concomitant with severe failure to gain in height. Other common symptoms are headaches, hypertension, glucose intolerance, delayed pubertal development, and amenorrhea despite often significant virilization and hirsutism

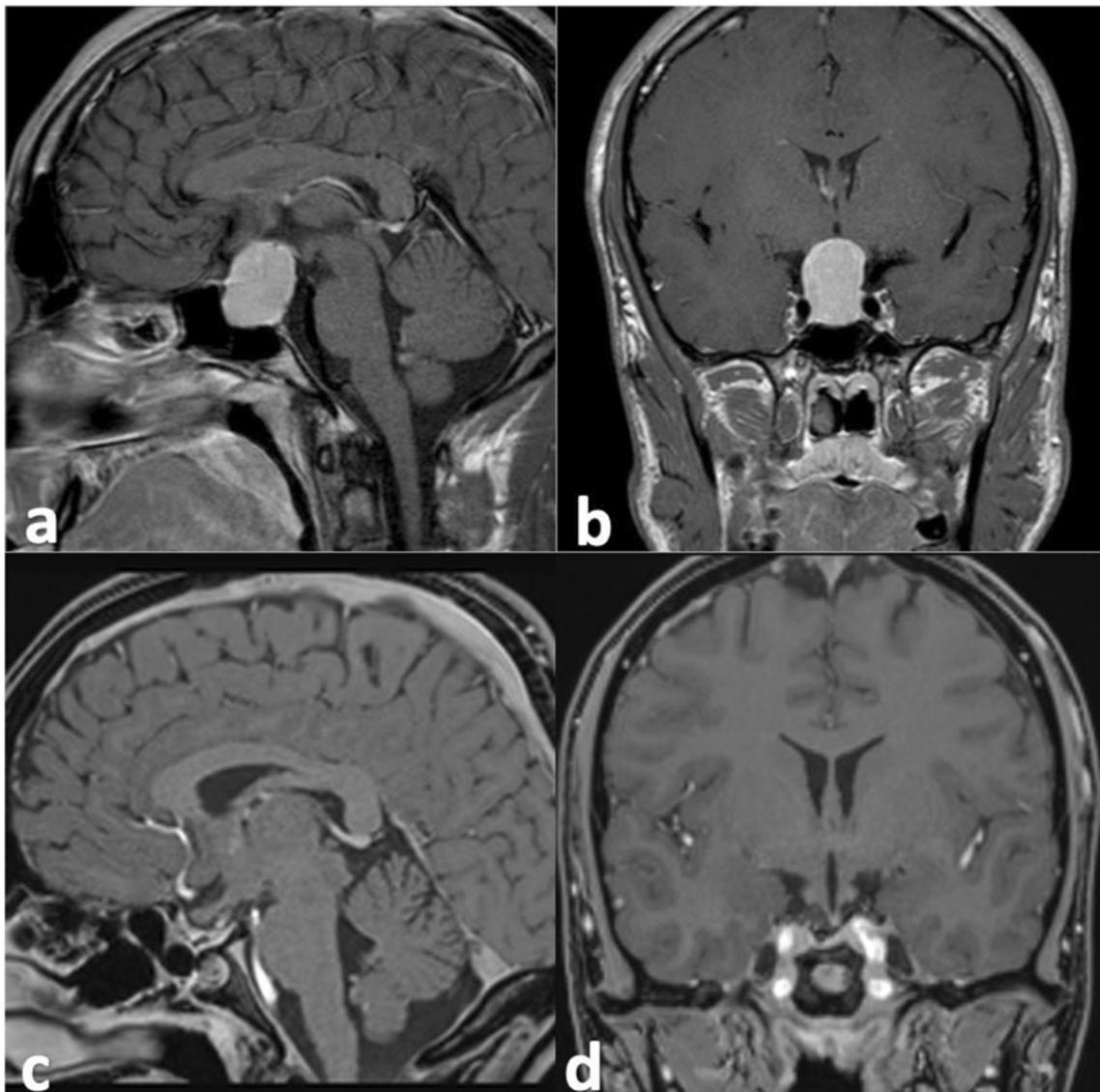


Fig. 1 Report of a 18-year-old boy affected by GH-secreting adenoma conditioning gynecomastia, prognathism, macroglossia, partial hypopituitarism, and severe visual impairment. **a** Sagittal and **b** coronal preoperative contrast-enhanced MRI showed a pituitary macroadenoma located in the sellar and suprasellar region. The patient underwent endoscopic endonasal removal of the lesion; skull base reconstruction

was performed with fat in the surgical cavity, fascia lata, and Hadad-Bassagasteguy flap. Nineteen months postoperative **c** sagittal and **d** coronal MRI demonstrated complete removal of the mass with no relapses. The patient experienced good health, with complete recovering of the visual deficit, persistent DI, and partial hypopituitarism

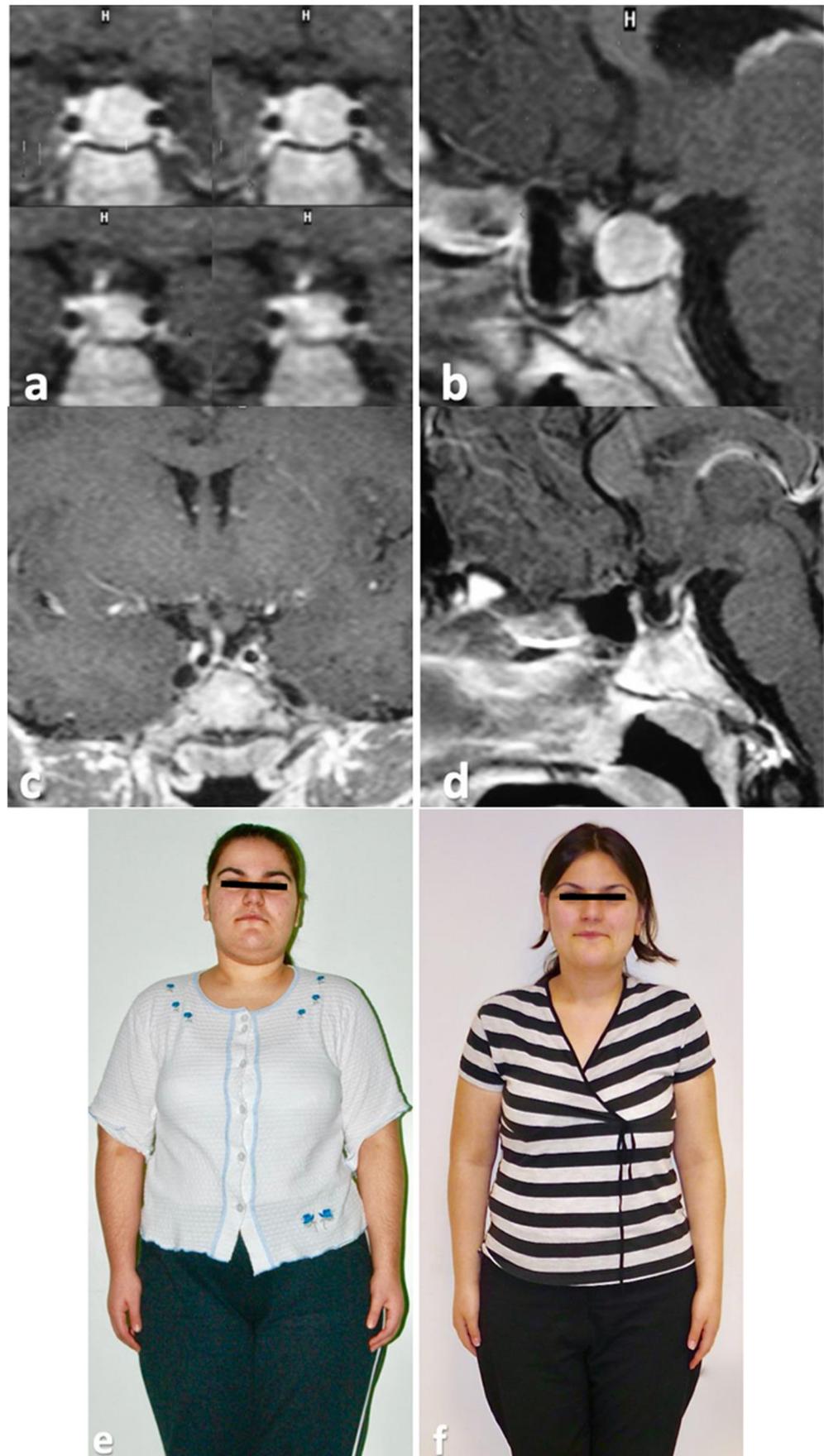
[1]. The mainstay treatment for CD in pediatric patients is always surgical. Hemihypophysectomy has been shown to be nearly 90% curative in situations where the surgical exploration is negative, or adenoma was not determined radiologically. Gamma-knife surgery is the treatment of choice when surgical intervention failed [17].

GH-secreting adenomas constitute 5–15% of pediatric pituitary adenomas with a higher prevalence in males. Approximately 90% of cases are macroadenomas, and 30–60% are invasive. Clinical features due to GH hypersecretion vary according to the degree of epiphyseal fusion. Children show a significant acceleration of growth especially before

epiphyseal fusion which leads to gigantism. After epiphyseal fusion occurs, clinical features of acromegaly become more distinct [18]. Treatment of choice in children with gigantism or acromegaly is transsphenoidal surgery. In our series, 4 patients had GH-secreting macroadenoma and cavernous sinus invasion was determined in 3 of them [19].

Non-functioning adenomas consist of 4–6% of pituitary adenomas in children. They are generally invasive macroadenomas. Presenting symptoms are usually visual defects or headache, or symptoms due to hyperprolactinemia or hypogonadism, typically in young females [20]. There were 2 female patients with non-functioning macroadenoma, and 1

Fig. 2 Report of a 18-year-old girl affected by ACTH-secreting macroadenoma. **a** Coronal and **b** sagittal preoperative enhanced sellar MRI showed a suspected macroadenoma. The patient underwent TMS removal of the lesion. Repeat surgery was performed after a week because remission was not achieved at the first operation. **c** Coronal and **d** sagittal 6 years post-operative MRI showed complete excision of the tumor. **e** Clinical photos showing pre-operative Cushingoid features and **f** 6 years after remission



female patient with non-functioning microadenoma in our series.

Pituitary apoplexy (PA) is a rare life-threatening clinical condition which is characterized by the sudden neuroendocrinological deterioration due to hemorrhage or infarction of the pituitary gland. PA is extremely rare in pediatric age and only seen in invasive adenomas [21]. Clinical manifestation of PA may be silent in pediatric age. In our series, an 18-year-old female presented with headache and blurred vision. A non-functioning macroadenoma with cavernous sinus invasion was diagnosed in radiological evaluation. She underwent EETS, and adenoma was totally removed.

Conclusion

Although pituitary adenomas are rarely seen in pediatric age and adolescence and are histologically benign lesions, their location, mass effect, and interference of normal hormone functions may cause significant morbidity. Transsphenoidal approach affords effective release of mass effect and not only restoration but also the perpetuation of normal endocrine functions in the majority of patients. The goal of the transsphenoidal approach is gross total tumor resection with the least harm, regarding anatomical variations and invasion to the surrounding structures. Satisfactory results are reported with both EETS and TMS in the literature. Experience of the surgeon designates the choice of treatment. Despite the technical difficulties in pediatric age, transsphenoidal resection of adenoma is still the mainstay treatment that provides cure in pediatric patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

- Keil MF, Stratakis CA (2008) Pituitary tumors in childhood: update of diagnosis, treatment and molecular genetics. *Expert Rev Neurother* 8(4):563–574. <https://doi.org/10.1586/14737175.8.4.563>
- Webb C, Prayson RA (2008) Pediatric pituitary adenomas. *Arch Pathol Lab Med* 132(1):77–80. [https://doi.org/10.1043/1543-2165\(2008\)132\[77:PPA\]2.0.CO;2](https://doi.org/10.1043/1543-2165(2008)132[77:PPA]2.0.CO;2)
- 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>
- Locatelli D, Massimi L, Rigante M, Custodi V, Paludetti G, Castelnuovo P, Di Rocco C (2010) Endoscopic endonasal transsphenoidal surgery for sellar tumors in children. *Int J Pediatr Otorhinolaryngol* 74(11):1298–1302. <https://doi.org/10.1016/j.ijporl.2010.08.009>
- Jiao W, Huang Y, Sun W, Lei T (2017) Microscopic transnasal transsphenoidal surgery for pediatric pituitary adenomas. *J Craniofac Surg* 28(4):1010–1012. <https://doi.org/10.1097/SCS.0000000000003632>
- Kunwar S, Wilson CB (1999) Pediatric pituitary adenomas. *J Clin Endocrinol Metab* 84(12):4385–4389. <https://doi.org/10.1210/jcem.84.12.6240>
- Jackman S, Diamond F (2013) Pituitary adenomas in childhood and adolescence. *Pediatr Endocrinol Revi: PER* 10(4):450–459
- 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>
- Personnier C, Cazabat L, Bertherat J, Gaillard S, Souberbielle JC, Habrand JL, Dufour C, Clauser E, SainteRose C, Polak M (2011) Clinical features and treatment of pediatric somatotropinoma: case study of an aggressive tumor due to a new AIP mutation and extensive literature review. *Horm Res Paediatr* 75(6):392–402. <https://doi.org/10.1159/000327831>
- Chivukula S, Koutourousiou M, Snyderman CH, Fernandez-Miranda JC, Gardner PA, Tyler-Kabara EC (2013) Endoscopic endonasal skull base surgery in the pediatric population. *J Neurosurg Pediatr* 11(3):227–241. <https://doi.org/10.3171/2012.10.PEDS12160>
- 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>
- Ciccarelli A, Daly AF, Beckers A (2005) The epidemiology of prolactinomas. *Pituitary* 8(1):3–6. <https://doi.org/10.1007/s11102-005-5079-0>
- Eren E, Yapici S, Cakir ED, Ceylan LA, Saglam H, Tarim O (2011) Clinical course of hyperprolactinemia in children and adolescents: a review of 21 cases. *J Clin Res Pediatr Endocrinol* 3(2):65–69. <https://doi.org/10.4274/jcrpe.v3i2.14>
- Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA, Endocrine S (2011) Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 96(2):273–288. <https://doi.org/10.1210/jc.2010-1692>
- Storr HL, Alexandraki KI, Martin L, Isidori AM, Kaltsas GA, Monson JP, Besser GM, Matson M, Evanson J, Afshar F, Sabin I, Savage MO, Grossman AB (2011) Comparisons in the epidemiology, diagnostic features and cure rate by transsphenoidal surgery between paediatric and adult-onset Cushing's disease. *Eur J Endocrinol* 164(5):667–674. <https://doi.org/10.1530/EJE-10-1120>
- Batista DL, Riar J, Keil M, Stratakis CA (2007) Diagnostic tests for children who are referred for the investigation of Cushing syndrome. *Pediatrics* 120(3):e575–e586. <https://doi.org/10.1542/peds.2006-2402>
- Magiakou MA, Mastorakos G, Oldfield EH, Gomez MT, Doppman JL, Cutler GB Jr, Nieman LK, Chrousos GP (1994) Cushing's syndrome in children and adolescents. Presentation, diagnosis, and therapy. *N Engl J Med* 331(10):629–636. <https://doi.org/10.1056/NEJM199409083311002>
- Pandey P, Ojha BK, Mahapatra AK (2005) Pediatric pituitary adenoma: a series of 42 patients. *J Clin Neurosci* 12(2):124–127. <https://doi.org/10.1016/j.jocn.2004.10.003>
- Growth Hormone Research S, Pituitary S (2004) Biochemical assessment and long-term monitoring in patients with acromegaly: statement from a joint consensus conference of the Growth Hormone Research Society and the Pituitary Society. *J Clin*

- Endocrinol Metab 89(7):3099–3102. <https://doi.org/10.1210/jc.2003-031138>
20. Yamaguchi-Okada M, Inoshita N, Nishioka H, Fukuhara N, Yamada S (2012) Clinicopathological analysis of nonfunctioning pituitary adenomas in patients younger than 25 years of age. *J Neurosurg Pediatr* 9(5):511–516. <https://doi.org/10.3171/2012.1.PEDS11330>
21. Chao CC, Lin CJ (2014) Pituitary apoplexy in a teenager—case report. *Pediatr Neurol* 50(6):648–651. <https://doi.org/10.1016/j.pediatrneurol.2014.02.004>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.