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ORIGINAL ARTICLE - BRAIN TUMORS

Surgical treatment and outcome of TSH-producing pituitary adenomas

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Abstract
Background Thyrotropin-producing adenomas (TSHomas) account for approximately 1–2% of all pituitary tumors. Recently, there has been debate on primary treatment as some studies suggest a high rate of hypopituitarism after transsphenoidal surgery and therefore suggest primary use of somatostatin analogs (SSA) instead. We would like to challenge this assumption by presenting our single-center experience with transsphenoidal surgery for TSHoma.
Methods Fifteen patients treated consecutively between May 2010 and December 2016 were analyzed for long-term postoperative remission and pituitary function.
Results Data on the development of TSH, fT3 and fT4 were available for 12 of 15 patients (mean follow-up was 18 months, 8 patients >12 months), showing mean TSH levels of 1.289 mU/l (0.02–2.04, SD 0.66), mean fT3 levels of 3.76 pmol/l (0.5–6.16, SD 1.8) and mean fT4 levels of 16.5 pmol/l (11.7–21.9, SD 3.66). Six of those patients were substituted with a mean of 85.4 μg L-thyroxine after a median follow-up of 20.7 months. The other six patients did not receive L-thyroxine at a median follow-up of 15.5 months. One patient with a known tumor remnant on MRI stayed euthyreotic with cabergoline at the timepoint of follow-up 22 months after the operation.
Control of the corticotrop axis was also available in 12 of 15 with no patient showing a corticotroph insufficiency in the long term.
Conclusions We argue that transsphenoidal surgery for TSHoma should be considered as the treatment of choice as remission following surgery is highly probable and postoperative hypopituitarism is very unlikely if patients are referred to centers with high pituitary surgery case loads.

Keywords TSHoma · Pituitary · Transsphenoidal surgery · Hypopituitarism

Introduction

Thyrotropin-producing adenomas of the pituitary gland (TSHomas) account for approximately 1–2% of all pituitary tumors [13] and have a prevalence of 2.8 cases per 1 million [12]. In the past their diagnosis was often delayed [1], and patients were commonly misdiagnosed and treated for Graves' disease [13]. Therefore, most patients presented to the neurosurgeon after a significant delay with invasive macro-adenomas [1] often generating visual impairment and other symptoms of mass effect [13].

In times of ultra-sensitive immunometric assays and detection of circulating free thyroid hormones by direct immunoassays, diagnosis of TSHoma has become less difficult. Nevertheless, clinical symptoms and the laboratory constellation of TSHoma might resemble the very rare syndrome of resistance to thyroid hormone action (RTH) [11] and therefore still lead to improper treatment [7].

The diagnosis of TSHoma is established by measurable, non-suppressed TSH levels with elevated levels of fT4 and

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fT3, followed by MRI of the pituitary and in uncertain cases by TRH-stimulation and T3-suppression tests [2] or detection of the α-subunit [1].

Transsphenoidal removal of the pituitary adenoma is considered the first-line treatment for TSHoma [9]. If complete surgical removal of the pathology is not successful or not possible, radiotherapy and/or medical treatment with somatostatin analogs (SSAs) has to be considered in cases of persistent disease [2].

SSAs are considered safe and have only a few side effects [8], but they warrant life-long therapy in almost all cases and do not represent a curative approach.

Radiotherapy is an established second-line therapy in case of unsuccessful surgery. In 2014, Malchiodi et al. presented the largest retrospective, multicenter study on TSH-secreting adenomas so far, including 19 patients who underwent radiotherapy, leading to "good hormone control" in 37% of patients within 12–24 months. From their results, radiosurgery and fractionated radiotherapy seem to be equally effective regarding hormonal control; however, significant tumor shrinkage was only observed in radiosurgery. Both fractionated radiotherapy and radiosurgery of the sellar region harbor a significant risk of hypopituitarism. Hypopituitarism of up to 55% following external beam radiotherapy (EBRT) and up to 40% after radiosurgery and cranial nerve deficit in approximately 5% following EBRT and 14% after radiosurgery have been observed. Radiation-induced malignancy and cerebrovascular events have also been described [9].

Recently, there has been debate on primary treatment as some studies suggest a high rate of hypopituitarism after transsphenoidal surgery for TSHoma, and therefore some authors advocate the primary use of SSA [7] instead of surgery as the first-line treatment.

We would like to challenge this assumption by presenting our single-center experience with a reasonably large series of 15 consecutively treated patients undergoing transsphenoidal surgery for TSHoma between 2010 and 2016 with an emphasis on long-term postoperative remission and long-term pituitary function.

Methods and materials

Patients

Fifteen patients treated consecutively between May 2010 and December 2016 were retrospectivly analyzed on long-term postoperative remission and pituitary function. They were identified and then analyzed using the electronic patient file regarding initial symptoms and development of symptoms as well as parameters of pituitary function before and after the surgical intervention and if possible long-term follow-up. All patients were transferred to us with the proven diagnosis of TSHoma for surgical treatment. One patient presented after thyroidectomy and one patient after radioiodine therapy. Six patients received carbimazol/thiamazol before a correct diagnosis.

Laboratory testing and diagnostic criteria

During the hospital stay, levels of TSH, fT3 and fT4 as well as corticotropin function were measured by means of ACTH and cortisol levels. All blood draws were performed 1 day prior to surgery, 1 day after surgery and then 2 to 5 days after surgery again.

According to the recommendations of the European Thyroid Association, TSHoma was suspected if high concentrations of fT3 and/or fT4 were found in combination with non-suppressed levels of TSH. The diagnosis was then established through MRI of the pituitary region as described below. The criteria were either applicable at our hospital or before initiation of treatment if patients were referred from external experts.

Imaging

In all patients, 1.5-T, T1-weighted magnetic resonance imaging (MRI) of the sellar region was performed before and after contrast enhancement with transversal, coronal and sagittal planes prior to admission.

Remission criteria

Decreases of TSH levels to subnormal levels with fT3 and fT4 also decreasing to subnormal levels were deemed positive criteria for chemical remission as indicated by Beck-Peccoz et al. in 2013 [2].

Surgical technique

Procedures were conducted by specialized surgeons via a microscopic transnasal-transsphenoidal approach. All procedures were retrospectively analyzed for complications, CSF leakage and the general appearance of the lesion. Specimens were sent for neuropathological analysis to identify and classify the underlying pathology of the lesion.

All patients gave written informed consent to the use of all patient- and treatment-related data. This study is in accordance with the local, institutional and general ethical guidelines.

Results

Demographics and history (Table 1)

Fifteen patients were retrospectively enrolled; five patients (33%) were male and ten female (66%). The mean age was 43 years (range 16–61 years, SD 16.2); mean time from first onset of symptoms to operation was 36 months (range 2–180 months, SD 53.5). Thirteen patients (87%) suffered from symptoms indicating hyperthyroidism (tachycardia, palpitations, fatigue, sweating and involuntary weight loss); impaired visual field and/or acuity were reported by three patients (20%), another three patients had headaches (20%), four patients were infertile (27%), and two patients had palpable goiters (13%). All patients had been previously treated for hyperthyroidism with methimazole (n = 6), radioiodine therapy (n = 1) or thyroid surgery (n = 3). Four patients received thyroid hormones: one of them after tyroidectomy, another after radioiodine therapy and the other two suspected falsly because of high levels of TSH indicating hypothyroidism. One patient was treated with SSA; bromocriptine treatment was used in one patient.

Table 1 Demographic and clinical characteristics of all patients of all patients

Characteristics	
Age (years)	
Median	46
Range	16–61
Sex, no. (%)	
Male	5 (33)
Female	10 (66)
Recurrent disease, no. (%)	
Yes	3 (20)
No	12 (80)
History	
Time from first symptoms to surgery (months)	
Median	18
Range	2–180
Symptoms	Patient no.
Tachycardia/palpitations	6
Fatigue	4
Sweating	5
H/A	3
Infertility	4
Diplopia/visual	3
Goiter	2
MRI	
Median size (mm)	11 × 9 × 10
Range (mm)	4–39

Imaging (Table 1)

Preoperative MRI showed definitive results in all cases with a mean tumor size of 9.3 mm (coronal diameter in standard T1-weighted contrast-enhanced MRI; range 4–36 mm, SD 8.1).

Laboratory testing (Tables 2 and 3)

Preoperative blood draws revealed mean TSH levels of 11.4 mU/l (range 0.95–54.2, SD 15.8), mean fT3 of 7.8 pmol/l (range 3.1–17.3, SD 3.65) and mean levels of fT4 of 23.7pmol/l (range 4.1–35.1, SD 8). One of these patients (no. 1) had suppressed TSH levels undergoing therapy with octreotide with elevated fT3 and high-normal fT4 levels and underwent surgery because of intolerance of her medication. One patient (no. 8) had elevated TSH levels and normal fT3 and fT4 levels and had undergone radioiodine therapy 7 years before the pituitary tumor was diagnosed. Two patients with thyreostatic therapy had elevated TSH levels in combination with low or normal fT3 and fT4 (patient nos. 11 + 14). One patient with complete thyroidectomy in the history presented with high TSH and normal fT3 and fT4 (patient no. 15). The other ten patients showed elevated fT3 and fT4 levels with non-suppressed (n = 4) or elevated (n = 6) TSH levels.

Fourteen patients had normal corticotroph function with mean cortisol levels of 419 nmol/l (range 146–648, SD 198.75). One patient with a giant adenoma (no. 10) had suppressed ACTH and cortisol levels prior to surgery.

Three patients had elevated prolactin levels between 1286.94 pmol/l and 3286.93 pmol/l (patient nos. 3, 5 and 7), two of those were macroadenomas (more than 2 and more than 3 cm in diameter), and the tumor size of the third patient was not known.

Surgical treatment

All patients underwent microscopic, monoportal, transsphenoidal surgery; three patients had already undergone the procedure in other neurosurgical departments. One of those patients went into remission after her first surgery and suffered from recurrent disease 6 years later. We treated the other patient after she had undergone failed surgery elsewhere, and another patient had been operated on three times previously (1, 3 and 5 years before). In the stretch between the operation and time of follow-up, there had been no CSF leakages and no mortalities.

Histology

The intraoperative specimens were fixed in buffered formalin for at least 2 h followed by paraffin embedding of all tissue in every case; 4-μm paraffin sections were stained for hematoxilin and eosin (H&E) and periodic-acid Schiff reaction (PAS) following

Table 2 Laboratory testing of all patients

Patient no.		Preoperative			Postoperative (day 1)			Postoperative (days 2–5)			Follow-up			
		TSH	fT3	fT4	TSH	fT3	fT4	TSH	fT3	fT4	TSH	fT3	fT4	Time of FU
1		0.95	8.6	19.6	0.069	5.7	19.6	0.02	5.3	13.9	1.98	4.05	20.2	36
2		4.58	7	25.9	0.332	2.7	23.4	0.385	3.2	18.2	1.9	3.75	13.7	33
3		1.83	6.7	23.4	0.119	3.1	23.4	0.07	2.2	16.1	1.6	0.53	15.05	24
4		2.64	9.4	33.1	0.102	4.6	28.5	0.024	2.4	13.4	0.5	4.4	15.7	24
5		4.28	9.6	27.9	0.03		17.1	0.01	2	12.3	1.24	0.5	13.77	20
6		5.48	7	29.1	0.115	3.1	25.2	0.01		19.2	1.54	3.71	15.8	11
7		43.65	17.3	30.6	3.018	3	23.4	3.5	3.4	14.6	1.56	5.16	20.51	22
8		5.14	4.2	19.8	0.568	2.8	18.8	0.598	2.5	17.1	0.39	0.32	14.57	7
9		14.059	12.5	35.1	0.379	5	35.2	0.041	2.7	20.4	1.24	3.3	12.7	7
10		2.63	6.5	26.4	0.342	4.3	29.5	0.046	2.9	21.5	0.02	4.48	21.88	13
11		12.1	5	14	0.751	3.7	12.8	3.34	4.6	11.8	1.46	6.16	21.84	12
12		7.711	9.1	28.2	0.246	3.4	21	0.287	3.5	17.1	2.04	5.29	11.7	8
13		5.82	7.3	20.8	0.26	3.6	24.2	0.03	3.2	19.9				
14		54.2	3.1	4.1	3.3	1.5	4	0.66	0.4	4.2				
15		6.06	3.5	18	1.08	2	15.9	3.56	2.3	15.6				
	Median	5.48	7	25.9	0.332	3.25	23.4	0.07	2.8	16.1	1.5	3.9	15.38	18.08
	Min	0.95	3.1	4.1	0.03	1.5	4	0.01	0.4	4.2	0.02	0.32	11.7	7
	Max	54.2	17.3	35.1	3.3	5.7	35.2	3.56	5.3	21.5	2.04	6.16	22.9	36

TSH values are mU/l

fT3 and fT4 are pmol/l

Time of FU: follow-up after surgery in months

standard laboratory procedures. Immunohistochemistry for pituitary hormones (ACTH, STH, prolactin, FSH, LH, TSH), glial fibrillary acidic protein (GFAP), pan-cytokeratin (KL1), mitotic marker phosphohistone-3 (PH3), proliferation marker Ki67 (MIB-1) and accumulation of tumor suppressor protein p53 was performed on an automated Ventana HX IHC system (Ventana-Roche Medical systems, Tucson, AZ, USA) following the manufacturer's instructions. In general, the microscopic appearance of adenoma in all 15 patients was fairly similar with mostly chromophobic elongated tumor cells in solid arrangements (Fig. 1a). Occasionally, perivascular fibrosis was present (Fig. 1b). TSH immunoreactivity varied between strong and weak (Fig. 1c). Proliferative and mitotic activity varied between tumors from cases with low Ki67-labeling indices between 1–2% and only occasional one mitotic figure per high power field; on the other hand, there were two atypical adenomas with a Ki67 labeling index of 7% or 14%, respectively, and up to seven mitotic figures/HPF, accompanied by accumulation of p53 in more than 5% of tumor cells (Fig. 1d).

Postoperative laboratory tests (Tables 2 and 3)

TSH levels decreased to a mean of 0.71 mU/l (range 0.03–3.3, SD 1) on postoperative day 1 and to 0.84 mU/l (range 0.01–3.56, SD 1.2) between postoperative days 2 and 5 (Fig. 2). Postoperative day 1 levels of fT3 and fT4 were measured at a mean of 3.46 pmol/l (range 1.5–5.7, SD 1.1) and 21.5 pmol/l (range 4–35.2, SD 7.4) (Figs. 3 and 4). A further decrease in fT3 and fT4 levels was observed on days 2 and 5 with fT3 reducing to a mean of 2.9 pmol/l (range 0.4–5.3, SD 1.2) and fT4 levels of 15.7 pmol/l (range 4.2–21.5, SD 4.3).

Postoperative pituitary function was assessed with ACTH levels at a mean of 3.43 pmol/l (range 1.32–24, SD 5.9) on day 1 and at a mean of 11.4 pmol/l (range 2.5–28, SD 8.5) between days 2 and 5 (Fig. 5). Cortisol was measured with a mean of 612.9 nmol/l (range 88.2–1412, SD 358.5) at day 1 and with a mean of 416.8 nmol/l (range 13.8–797.2, SD 219.8) between days 2 and 5 (Fig. 6). One patient showed levels of cortisol that were below the threshold for pituitary insufficiency (patient no. 5, cortisol of 22.5 nmol/l) but recovered to normal levels on long-term follow-up. For another patient who postoperatively showed a low cortisol level (patient no. 13), follow-up is pending.

In two patients an AIP-gen mutation was verified, and in another one it was highly suspected and further diagnostics were recommended.

Follow-up (Tables 2 and 3)

Data on the long-term development of TSH, fT3 and fT4 were available for 12 of 15 patients, since the last three cases dated

Table 3 ACTH and cortisol levels of all patients

Patient no.		Preoperative		Postoperative (day 1)		Postoperative (days 2–5)		Follow-up		
		ACTH	Cortisol	ACTH	Cortisol	ACTH	Cortisol	ACTH	Cortisol	Time of FU
1		7.93	648.37	6.82	700.7	6.6	502.1	7.8	430	36
2		4.4	527	3.08	623.5	3.08	389	11.2	234	33
3		7.7	513.2	5.28	1412.6	4.18		4.62	226	24
4		5.73	640.1	9.41	88.2	12.76	645.6	5.28	250	24
5			146.227	9.46	767	14.52	22.5	7.3	212.4	20
6		1	151.745	1.32	427.6	5.5	571.1	3.76	893	11
7		2.2	121.396	3.8	1296.7	2.64	427.6	2.53	269.44	22
8		4.62	397.296	3.3	491.1	5.06	400	10.12	380.7	7
9		20	201.407	13.0	550	16.0	444	4.4	283.3	7
10		7	82.77	14.0	555.6	15.0	472.2	1.8	278.8	13
11		10	413.85	13.0	355.5	20.0	475		317.4	12
12		14	132.432	9.0	741.6			4.18	277.8	8
13		9	74.493	14.0	275	2.5	13.8			
14		10	366.947	12.0	655.5	28.0	797.2			
15		23	369.7	24.0	252.7	24.0	258.3			
	Median	7.82	366.947	9.41	555.6	6.6	458.1	4.62	278.3	18.08
	Min	1.1	74.493	1.32	88.2	2.64	22.5	1.8	212.4	7
	Max	23	648.365	24	1412.6	20	645.6	11.2	893	36

ACTH values are pmol/l

Cortisol values are are nmol/l

Time of FU: follow-up in months

back no more than 6 months, and the patients had not entered the follow-up phase yet. Those registered follow-ups show mean levels of TSH of 1.289 mU/l (0.02–2.04, SD 0.66), mean levels of fT3 of 3.76 pmol/l (0.5–6.16, SD 1.8) and mean levels of fT4 of 16.5 pmol/l (11.7–21.9, SD 3.66). Six of those patients were substituted with a mean of 85.4 μg L-thyroxine after a median follow-up of 20.7 months. The other six patients did not receive L-thyroxine at the median follow-up of 15.5 months. No patients were found hyperthyroidal or needed further thyreostatic treatment. One patient with a known tumor remnant in MRI stayed euthyreotic with cabergoline at the timepoint of follow-up 22 months after the operation.

ACTH levels were available in 11 of 15 and cortisol levels in 12 of 15 patients showing no insufficiency with mean ACTH levels of 5.73 pmol/l (1.8–11.2, SD 3.02) and mean cortisol levels of 337.7 nmol/l (212.4–893, SD 186).

Discussion

TSHomas are considered rare diseases [13]; they usually present as large and often invasive macroadenomas [1], which may explain the relatively low cure rates by surgery alone [3]. SSA treatment of TSHomas has proven to significantly reduce TSH levels and lead to an euthyroitic state in many patients [14], but it is considered a long-term if not lifelong treatment [14].

This study was conducted to analyze the short- and long-term results of surgical treatment of TSHoma at the authors' institution. Our results show no cases of hypopituitarism and a satisfying rate of disease remission after transsphenoidal surgery of TSH-producing pituitary adenomas. Long-term follow-up regarding tumor remission was available in 12 of 15 patients, with a remission rate of 91.7%. The one patient with a known tumor remnant in MRI stayed euthyreotic with cabergoline at the time point of follow-up 22 months after the operation. Of 15 patients who were operated on at our center between 2010 and 2016, a long-term follow-up of corticotroph pituitary function could be investigated in 12 cases with no pituitary deficiency in any of the cases. In three other cases of patients who had undergone surgery recently, no laboratory results could be retrieved as the patients did not yet report back to our department.

These results are in line with those of other centers of pituitary surgery with reported rates of 9% of pituitary deficiency following transsphenoidal surgery for TSHoma [9], but is in contrast to the relatively low remission and cure rates of other studies, which range from 0 to 72% [3].

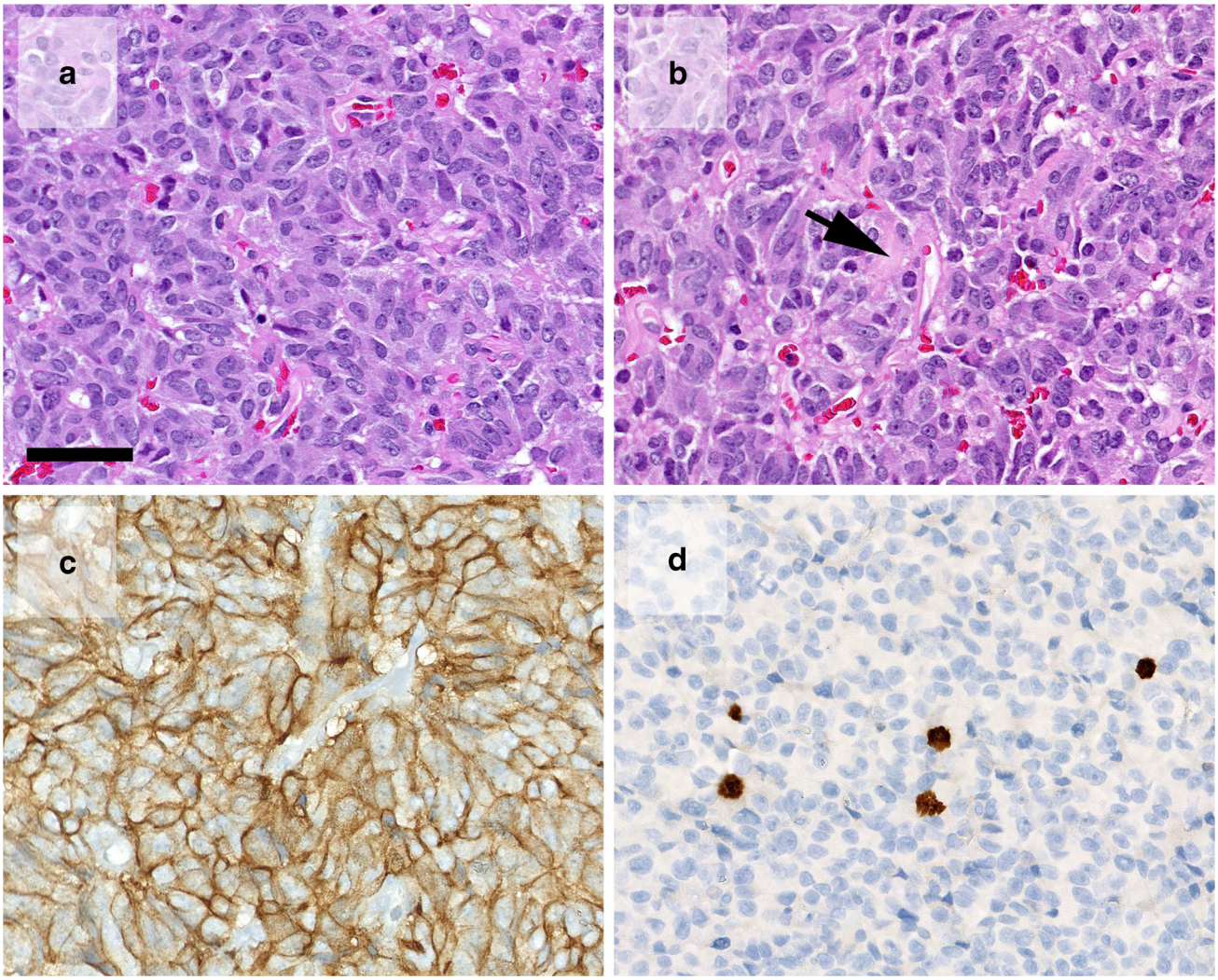

Fig. 1 Microscopic appearance of the adenoma in all 15 patients was fairly similar with mostly chromophobic elongated tumor cells in solid arrangements (**a**). Occasionally, perivascular fibrosis was present (**b**). TSH immunoreactivity varied between strong and weak (**c**). Usually, proliferative and mitotic activity varied between tumors from cases with low Ki67-labeling indices between 1–2% and only occasionally one mitotic figure per high power field; on the other hand, there were two atypical adenomas with a Ki67-labeling index of 7% or 14%, respectively, and up to seven mitotic figures/HPF, accompanied by accumulation of p53 in more than 5% of tumor cells **(d)**

Most published series describe a high rate of either invasive tumor growth [3], which may be explained by the diagnostic difficulties, and the prolonged history of disease in these patients. Other authors mention the often fibrous and firm aspect of the tumors, which is explained by either the comparatively high expression of fibroblast growth factor [6] in TSH-producing adenomas or by previous therapy guided toward decreasing the levels of thyroid hormones, which may facilitate pituitary tumor growth and autonomy, analogous to Nelsons syndrome in Cushing's disease after adrenalectomy [13]. We found a considerably small number of tumors with invasive growth into the cavernous sinuses in our series, which may be a reason for the relatively high remission rate in our patients. We believe that this low rate is mostly due to the modern diagnostic methods to detect TSH and thyroid hormones, which makes diagnosing TSHoma much easier, and therefore patients may be referred to the pituitary surgeon earlier.

The fibrous and firm character of the lesions and the difficulty of surgical preparation may be the cause of the high rate of postoperative pituitary dysfunction that some authors describe [7].

In our patients, a fibrous aspect of the tumor was not described by the surgeon in any of the cases, which was confirmed by the histopathological analysis in all cases. Eight of our patients received some kind of treatment directed at lowering thyroid hormone levels, which was either with antithyroid drugs such as methimazole or thyroid surgery or radioiodine therapy. None of our patients showed signs of corticotroph dysfunction or other pituitary deficiencies after surgery.

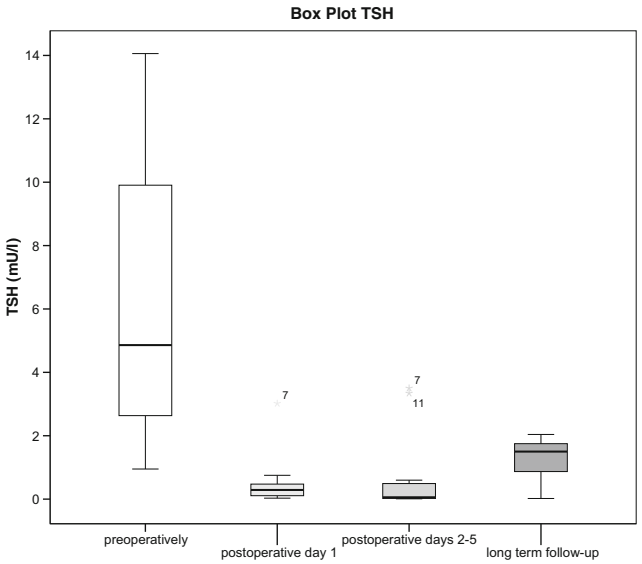

Fig. 2 Box plot for TSH

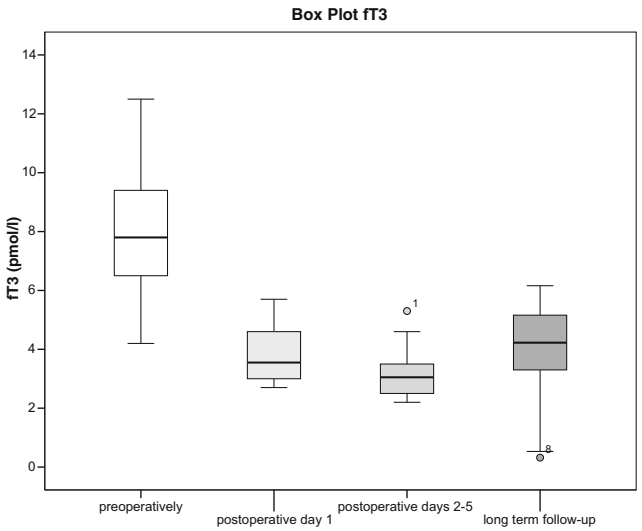

Fig. 3 Box plotfor fT3

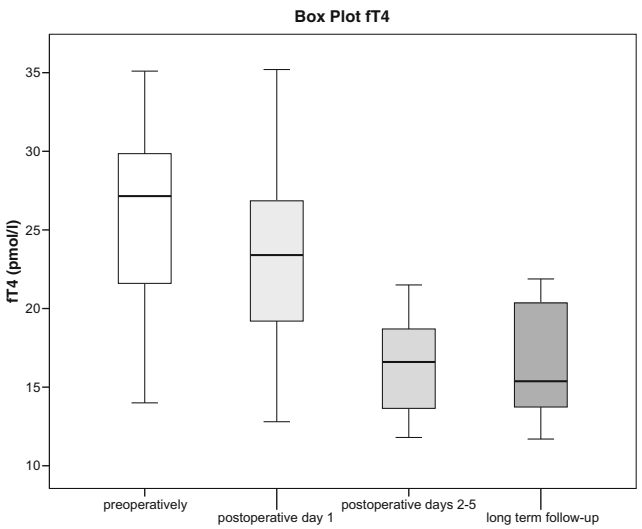

Fig. 4 Box plot for fT4

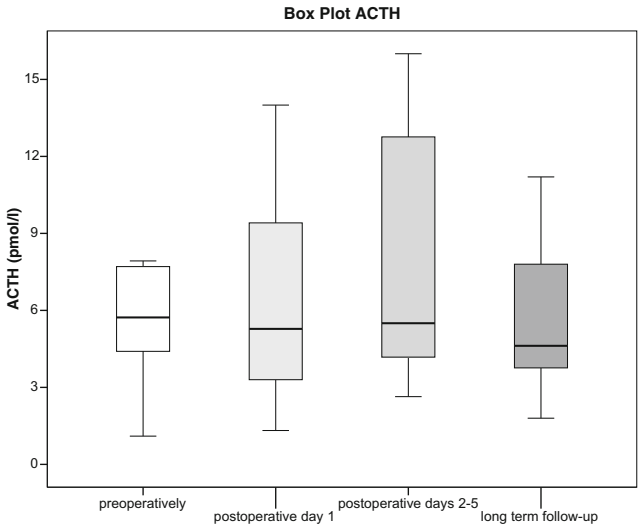

Fig. 5 Box plot for ACTH

In our series 6 of 15 patients (33%) had normal or subnormal fT4 levels prior to surgery. This is congruent with the finding of Mindermann and Wilson who reported a series of 19 patients diagnosed with TSH-producing adenoma: Even though fT4 was not measured in all patients, only seven had elevated levels, four had normal, and two even had fT4 levels below normal prior to surgery [10]. However, in the series reported by Mindermann and Wilson, 42% had at least one form of preoperative thyroid ablation (surgical thyroidectomy, radiothyroidectomy and autoimmune ablation combined).

Comparable to the results in our cohort, many patients received treatment for hyperthyroidism. In both series this might explain the major part of the normal or even low preoperative fT4 levels and may even be the cause of the development of TSH-producing adenomas as was previously shown experimentally [5].

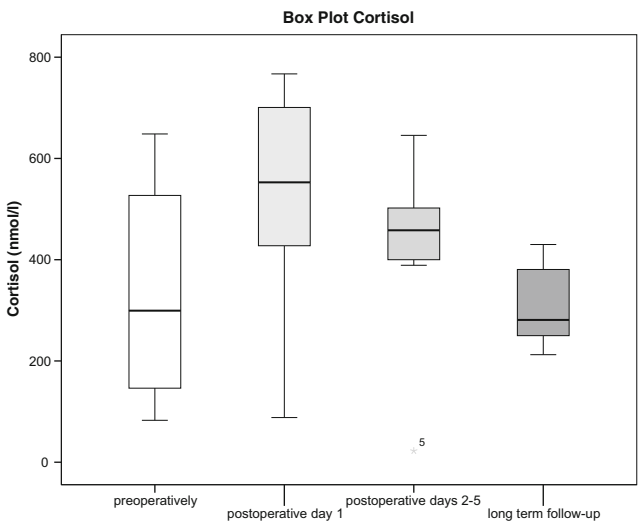

Fig. 6 Box plot for cortisol

Postoperative complications after transsphenoidal surgery—e.g., hypopituitarism—become less frequent with higher experience of the performing neurosurgeon [4]. As described by Ciric et al. [4], the learning curve was relatively shallow with a statistically significantly decreased incidence of morbidity and death after performing 200 and 500 transsphenoidal operations, respectively. However, as experience grows with higher case loads, we suggest referring patients to pituitary centers with experienced pituitary surgeons.

In our cohort, 10 of 15 patients were female. The higher female-to-male ratio for TSH-producing adenomas is confirmed by most investigations, but strongly varies in its extent in the literature [10]. Mindermann and Wilson even reported that in their collective females even tended to develop their adenomas at a younger age, had a longer history of symptoms and had smaller tumors that were invasive less often than those seen in men.

We argue that transsphenoidal surgery for TSH-producing adenoma of the pituitary should always be considered as the treatment of choice. Even in patients harboring invasive tumors or giant adenomas, remission of hyperthyroidism following surgery is highly probable, even in case of debulking. Postoperative hypopituitarism is very unlikely if patients are referred to centers with high case loads of pituitary surgery.

Acknowledgements We thank the referring physicians and endocrinologists.

Compliance with ethical standards

Funding No funding was received for this research.

Conflict of Interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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