Results of surgical therapy of functioning pituitary adenomas

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Introduction. Functioning pituitary adenomas lead to substantial morbidity and increased mortality associated with typical endocrine syndromes. Surgical therapy is an integral part of the management of these tumours. The aim of this study was to evaluate the results of surgical transnasal procedures in patients with functioning pituitary adenomas who underwent the surgery at the Department of Neurosurgery, University Hospital Olomouc.
Methods. Patients with functioning pituitary adenoma (ACTH, GH, PRL) were indicated for surgery. All patients underwent preoperative and postoperative endocrinological examination and laboratory tests to assess excessive or deficient hormonal production and imaging examination.
Results. The cohort consisted of 58 patients, 33 of whom were women and 25 men. The age range was 12-77 years (mean age 47.6 years). Microadenoma was diagnosed in 58.6% of patients and macroadenoma in 41.4% of patients. The most common hypersecretory syndrome was excessive production of growth hormone (56.9%), followed by excessive production of adrenocorticotropic hormone (24.1%) and prolactin (12.1%). In the group with excessive production of ACTH, complete remission was achieved after the first surgery in 78.6% of cases (72.8% for microadenomas (8) and 100% (3) cases in macroadenomas); in the group with excessive GH production in 51.4% (63.2% (7) in microadenomas and 46.2% (12) cases in macroadenomas). In the group with excessive production of PRL, it was 57.1% (100% (2) in microadenomas and 40% (2) cases in macroadenomas).
Conclusion. Surgical therapy in the presented cohort led to the normalisation of hormonal excessive production in 58.6% of cases. A combination of drug therapy and radiotherapeutic methods was necessary in the remaining cases to achieve hormonal remission.

Key words: hormone-secreting pituitary adenomas, transsphenoidal surgery, Acromegaly, Cushing's disease

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INTRODUCTION

Pituitary adenomas are the most common tumour lesions in the region of the sella turcica and account for 10–15% of all intracranial tumours[1]. The incidence is approximately 4 cases per 100,000 persons per year[2]. Around a half of pituitary adenomas are associated with excessive secretion of pituitary hormones. The most common are prolactinomas, followed by somatotropic, corticotropic and, rarely, thyrotropic pituitary adenomas[3]. Functioning pituitary adenomas lead to substantial morbidity and increase mortality associated with typical endocrine syndromes. Macroadenomas can also lead to compression of the surrounding structures, which may result in impaired vision, oculomotor disorders or hypopituitarism due to the compression of healthy pituitary tissue. Therefore, prompt and effective treatment is essential to control the disease and reduce associated health risks[4].

The aim of this study was to evaluate the results of surgical transnasal procedures in patients with functioning pituitary adenomas.

MATERIAL AND METHODS

This retrospective study was performed from 1 January 2008 to 31 December 2018 at the Department of Neurosurgery of the University Hospital Olomouc and Faculty of Medicine of Palacký University in Olomouc. Patients who underwent surgery of a functioning pituitary adenoma were enrolled. The diagnosis of pituitary adenoma was always verified histologically. All patients underwent a clinical examination by a neurosurgeon and an endocrinological examination before surgery. The morphological diagnosis of pituitary adenoma was based on contrast-enhanced MRI of the pituitary gland, including dynamic scans.

The surgery was indicated in patients with a typical endocrine syndrome with excessive production of pituitary hormones (ACTH, GH, PRL). Surgery in prolactinoma cases, where drug therapy is primarily indicated, was performed in case of intolerance or insufficient effect of drug therapy, evaluated by prolactin level and/or tumour size reduction. A Computed Tomography (CT) scan of the base of the skull and paranasal sinuses was always performed before the surgery, complemented with

a rhinological examination of the nasal cavity by a cooperating otorhinolaryngologist.

Surgical therapy

A transnasal transsphenoidal approach was utilised in surgical therapy with either a microscopic or endoscopic technique. The microscopic method was combined with fluoroscopic control; a retractor was inserted into the nasal cavity to define the operative corridor to the sphenoid cavity. An endoscope with 30° optics (Storz®, Germany) was used for the endoscopic approach, inserted to the base of the sella turcica in cooperation with an otorhinolaryngologist. The adenoma was subsequently extirpated in the most radical way possible, both via microscopic or endoscopic optics, always using the same instruments and surgical procedure. Maximum effort was exerted to preserve the tissue of the normal pituitary gland. Muscle, fat, fascia, oxycellulose (Surgicel®) and tissue glue (Tisseel®) were used to reconstruct the sellar base.

Patients were followed at regular intervals post-surgery by an endocrinologist, a neurosurgeon and an ENT specialist. A follow-up contrast-enhanced MRI examination of the pituitary gland was performed at intervals of 3, 6 and 12 months after the surgery. The minimum follow-up period was 1 year.

Endocrinological examination

All patients underwent an endocrinological examination to assess excessive or deficient hormonal production. Standard examination included clinical examination, assessment of imaging studies and laboratory evaluation of hormonal profile (TSH, fT4, fT4, PRL, GH, IGF-1, ACTH, cortisol, LH, FSH, estradiol and testosterone).

Prolactinoma was diagnosed based on clinical symptoms, imaging studies and laboratory parameters with morning PRL levels above the reference limit level.

Table 1. Summarises the characteristics of the entire cohort and the results of therapy.

Sex	No.
Female	33 (56.9%)
Male	25 (43.1%)
Age	47.6 (12–77)
Size of Adenoma	
Macroadenoma	34 (58.6%)
Microadenoma	24 (41.4%)
Compression of surrounding structures	11 (19.0%)
Type of hormonal production	
ACTH	14 (24.1%)
GH	33 (56.9%)
PRL	7 (12.1%)
PRL + GH (synchronous)	4 (6.9%)
Type of surgical (transnasal) technique	
Microscopic	23 (39.7%)
Endoscopic	35 (60.3%)
Remission after treatment	
Partial	24 (41.4%)
Complete	34 (58.6%)
Hormonal deficit after surgery	27 (46.6%)
Hormonal substitution after surgery	27 (46.6%)
Adenoma residuum on MRI	18 (31.0%)
Surgical revision for continued hormonal overproduction	10 (17.2%)
Radiosurgery for continued hormonal overproduction	15 (26.3%)
Medicamentous therapy for continued hormonal overproduction	26 (44.8%)
Complete remission incuding adjuvant therapy	
Partial	10 (17.2%)
Complete	48 (82.8%)

Table 2. The results based on the type of excessive hormonal production.

Qualitative Variables		Type of secretion						*P*
		ACTH		GH		PRL		
		Count	%	Count	%	Count	%	
Sex	M	6	42.90	15	40.50	4	57.10	0.737
	F	8	57.10	22	59.50	3	42.90	
Size	Macroadenoma	3	21.40	26	70.30	5	71.40	0.005
	Microadenoma	11	78.60	11	29.70	2	28.60	
Deciti of different hormonal pathway befor the surgery	YES	0	0.00	2	5.40	2	28.60	0.108
	NO	14	100.00	35	94.60	5	71.40	
Remission after the first surgery	Complete	3	21.40	18	48.60	3	42.90	0.237
	Incomplete	11	78.60	19	51.40	4	57.10	
Hormonal deficit with the need for substitution	YES	9	64.30	14	37.80	4	57.10	0.223
	NO	5	35.70	23	62.20	3	42.90	
Compression of surrounding structures	YES	1	7.10	5	13.50	5	71.40	0.003
	NO	13	92.90	32	86.50	2	28.60	
Residual tumour on MRI	YES	1	7.10	14	37.80	3	42.90	0.079
	NO	13	92.90	23	62.20	4	57.10	
Final hormonal state – remission after adjuvant therapy	Partial	2	14.30	7	18.90	1	14.30	1
	Complete	12	85.70	30	81.10	6	85.70	

Table 3. The results of hormonal therapy depending on microscopic or endoscopic surgical technique.

Qualitative variables		Type of surgery				*P*
		microscopic		endoscopic		
		Count	%	Count	%	
Sex	M	9	39.10	16	45.70	0.787
	F	14	60.90	19	54.30	
Size	Macroadenoma	14	60.90	20	57.10	1
	Microadenoma	9	39.10	15	42.90	
Type of secretion	ACTH	2	8.70	12	34.30	0.056
	GH	16	69.60	17	48.60	
	PRL	2	8.70	5	14.30	
	PRL + GH synchronnous	3	13.00	1	2.90	
Remision after 1. surgery	Partial	7	30.40	17	48.60	0.188
	Complete	16	69.60	18	51.40	
Final hormonal state – remission after adjuvant therapy	Partial	4	17.40	6	17.10	1
	Complete	19	82.60	29	82.90	

Misdiagnosis of a non-functional adenoma, presenting with a high PRL level due to the compression of the pituitary stem, was also ruled out based on a positive response to the administration of dopamine agonists.

The level of IGF-1 was measured to screen for acromegaly or gigantism. Diagnosis was confirmed based on the following conditions: excessive production of IGF-1, evidence of a pituitary adenoma in imaging studies and corresponding clinical symptoms. Complete hormonal remission was confirmed as follows: the normalisation of postoperative IGF-1 and random GH levels <1.0 μg/L, as recommended by the "Acromegaly Consensus Group guidelines" from 2010 (ref.[5]). Patients with synchronous excessive production of GH and PRL were included in the statistical group with excessive production of GH.

Cushing's disease was confirmed based on ACTH levels and excess cortisol levels (morning cortisol, abnormality in the cortisol curve: measured at 6 a.m., 12 p.m., and 4 p.m., urinary cortisol and cortisol response to the low-dose dexamethasone test). A drop in morning cortisol levels of <138 nmol/L within seven days of surgery was required for the case to be considered a complete remission.

Normalisation of parameters was required for complete hormonal remission. Cases with monitored parameters remaining above normal limits were considered a partial remission.

Substitution according to valid guidelines was utilised in hormonal deficits discovered before the surgery (mass tumour effect) or after the surgery. Patients underwent regular endocrinological follow-up at intervals of 1, 3, 6 and 12 months and then annually.

All clinical chemistry tests were performed under standard conditions, and the clinical chemistry laboratory of the University Hospital Olomouc processed the samples immediately.

Statistical processing

Statistical processing of the cohort was performed using IBM SPSS Statistics 23 and all tests used the significance level P=0.05. Data was processed using descriptive statistics and comparisons were performed using Fisher's exact test and the method of adjusted residuals.

RESULTS

The cohort consisted of 58 patients, of which 33 were women and 25 were men. The age range was 12–77 years (mean age 47.6 years). Microadenoma was diagnosed in 58.6% of patients and macroadenoma in 41.4% of patients. The most common hypersecretory syndrome was excessive production of growth hormone (56.9%), followed by excessive production of adrenocorticotropic hormone (24.1%) and prolactin (12.1%). Synchronous excessive production of growth hormone and prolactin was noted in 6.9%. Table 1. summarises the characteristics of the entire cohort and the results of therapy. Complete remission of excessive hormonal production after the first surgery occurred in 58.6%; the reduction of excessive hormonal production was partial in the remaining cases and these patients required further therapy. In the full cohort, including patients after adjuvant therapy (surgical revision, radiosurgery or pharmacological suppressive therapy), complete remission was achieved in 82% of cases.

Table 2. shows the results based on the type of excessive hormonal production. The occurrence of microadenomas in the group with excessive ACTH production and macroadenomas in the group with excessive GH production was statistically more significant. Compression syndromes were more frequent in adenoma with excessive PRL production. In the group with excessive production of ACTH, complete remission was achieved after the first surgery in 78.6% of cases (72.8% for microadenomas (8) and 100% (3) cases in macroadenomas); in the group with excessive GH production in 51.4% (63.2% (7) in microadenomas and 46.2% (12) cases in macroadenomas). In the group with excessive production of PRL, it was 57.1% (100% (2) in microadenomas and 40% (2) cases in macroadenomas).

The microscopic transnasal technique was utilised in 23 patients and endoscopic transnasal technique in 35 patients. No statistically significant differences were detected in the monitored parameters between the two techniques (Table 3).

Table 4. lists the occurrence and types of complications after surgical therapy.

Table 4. The occurrence and types of complications after surgical therapy.

Type of complication	No.	%
Overall	17	29.3
Diabetes insipidus – permanent	5	8.9
Cerebrospinal fluid leak	7	12.5
Epistaxis	2	3.6
Palsy n. VI.	1	1.8
Meningitis	1	1.8
Stroke	1	1.8

DISCUSSION

Somatotropic adenoma was most the most common tumour in the presented cohort, specifically in 37 cases. The incidence of adenomas secreting growth hormone in the general population is 0.2–0.4/100,000/year, prevalence 6/100,000[6]. Acromegaly is a chronic, progressive and potentially fatal disease caused by a pituitary adenoma secreting growth hormone. This leads to excessive levels of circulating growth hormone (GH) and insulin-like growth factor 1 (IGF-1) (ref.[7]). Chronic untreated disease leads to the growth of peripheral body parts, supraorbital arches, thickening of the skin, hyperhidrosis or macroglossia. Systemic diseases primarily include cardiovascular disorders (arterial hypertension, cardiomyopathy), respiratory disorders (sleep apnoea), metabolic disorders (diabetes mellitus) and/or cancer[8]. Unfortunately, most patients already suffer from advanced disease due to diagnosis delays – the disease is often diagnosed only 8–10 years after the development of initial symptoms[9]. The goal of the therapy of acromegaly is to normalise biochemical parameters, alleviate clinical symptoms of the disease and reduce morbidity and mortality[10,11]. A combination of neurosurgery, pharmacotherapy and radiation therapy is sometimes necessary to achieve this goal[12]. In the presented cohort, complete remission was achieved after the first surgery in 51.4% (46.2% in macroadenomas and 63.6% of cases in microadenomas). Partial remission was achieved in 48.6% of cases. A problem in the comparison of results from other sites is the inconsistency of biochemical criteria for remission, which gradually develop depending on the progress of laboratory diagnostic methods. The presented study used stricter criteria of hormonal remission based on the "Acromegaly Consensus Group guidelines" from 2010 (ref.[5]). Agrawal et al. published a meta-analysis of the results of surgical therapy in patients with acromegaly based on the 2010 criteria. In microadenomas, full remission was achieved after the first surgery in the range of 56–100% of cases, in macroadenoma in 23–73% of cases[13]. Worse results are particularly achieved in tumour invasion into surrounding structures, especially into the cavernous sinus[14,15].

Excessive ACTH production by the pituitary gland was present in 14 cases in our cohort. If left untreated, Cushing's disease leads to a number of complications. These complications include osteoporosis, obesity, arterial hypertension, dyslipidemia, insulin resistance and/or hypercoagulation[16]. The risk of premature death is 4.8 times higher in Cushing's disease compared to the general population[17,18]. The primary therapeutic modality is surgery, almost exclusively via transsphenoidal approach. In the presented cohort, complete remission was achieved in 78.6% of cases (72.8% in macroadenomas and 100% of cases in microadenomas). Similarly to acromegaly, different criteria of hormonal normalisation used at different times and in different studies make the comparison of surgical results problematic. According to the literature, remission is achieved in 69–98% (on average in 79%) of cases. Better results are achieved in patients with microadenomas, with the success rate of 86–98%. In cases of macroadenomas, remission is achieved in the range of 31–83%. Long-term follow-up is necessary after the surgery due to the recurrence in 5–50% of cases after successful surgery. The median time from surgery to recurrence is 2.3 to 7.2 years[19,20].

There were 7 patients with prolactinoma in our cohort. Dopamine agonist therapy is indicated in most patients with prolactinoma. The reduction of prolactin levels is achieved in a matter of days and the size of the adenoma decreases within weeks to months. The treatment is ineffective in only 10–20% of patients with microprolactinoma and 20–30% of patients with macroprolactinoma. These patients are considered drug-resistant[21,22]. Surgery is only indicated in tumours refractory to pharmacological treatment, in pituitary apoplexy with visual impairment or in case of intolerance to the side effects of pharmacotherapy.

In our study there was no statistically significant difference in outcome as hormonal function between the endoscopic and microsurgical approach. However, the endoscopic approach has many advantages over the microscopic approach. Specifically, it leads to less traumatization of nasal cavity tissue and better visualisation of the pathology. This leads to higher radicality of resection and better postoperative outcomes in both secreting and non secreting adenomas[23].

The main limitation of the study is its retrospective nature and small number of patients.

CONCLUSION

Surgical therapy is an integral part of the therapy of functioning pituitary adenomas. In the presented cohort, surgical therapy led to the normalisation of excessive hormonal production in 58.6% of cases. A combination of drug therapy and radiotherapeutic methods was necessary in the remaining cases to achieve hormonal remission.

ABBREVIATIONS

ACTH, Adrenocorticotropic hormone; CT, Computed tomography; FSH, Follicle-stimulating hormone; fT3, Triiodothyronine; fT4, Thyroxine; GH, Growth hormone; IGF-1, Insulin-like growth factor 1; LH, *Luteinizing hormone;* PRL, Prolactin; TSH, *Thyroid Stimulating Hormone.*

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