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Transsphenoidal adenomectomy for GH-, PRL- and ACTH-secreting pituitary tumours: outcome analysis in a series of 125 patients

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Abstract Transsphenoidal surgery (TSS) is a well recognised treatment for secreting pituitary adenomas, however a very wide variation of clinical outcomes and recurrence rates has been reported, depending on the different criteria used to define the cure. We reported the clinical outcome of a large series of patients operated on for a secreting pituitary adenoma according to the most recent stringent criteria of biochemical remission nowadays accepted. One hundred and twenty-five consecutive patients with a secreting pituitary adenoma (42 PRL-, 67 GH- and 16 ACTH-secreting adenomas) who were operated on by the two same neurosurgeons were considered for the study. Biochemical remission of disease was achieved in 56% of patients; 78% for patients with microadenoma and 47% for patients with macroadenomas, respectively. No cases of mortality or major immediate postoperative complications were observed. Tumour size, high hormone levels and dural invasion were significantly correlated to a poor surgical outcome. The recurrence rates ranged between 0 and 24%, being higher for PRL-secreting tumours. In conclusion, TSS is safe and effective in secreting pituitary tumours. It is still the first treatment for GH- and ACTH-secreting adenomas, whereas in patients with prolactinomas, surgery should be reserved for cases of resistance or intolerance to dopamine agonists.

Key words Pituitary adenoma • Acromegaly • Cushing's disease • Prolactinoma • Transsphenoidal surgery

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Introduction

Pituitary adenomas represent about 10%–15% of all brain tumours, usually presenting with neurological and endocrinological symptoms according to size and hormonal secreting features. Secreting adenomas are mainly represented by prolactinomas, followed by GH- and ACTH-secreting adenomas. Prolactinomas usually cause menstrual disturbances and/or galactorrhoea in women and impotence in men, whereas GH- and ACTH-secreting adenomas are characterised by serious cardiovascular and metabolic complications, responsible for an increased morbidity and mortality in such patients [1–3]. Moreover, macroadenoma (adenomas with a diameter more than 10 mm), growing in extrasellar space, may cause neurological deficits, especially visual disturbances.

Therapy for secreting adenomas is represented by medical therapy, surgery and radiotherapy. The dopamine agonists bromocriptine and more recently, cabergoline, are the treatment of choice for prolactinomas, achieving a normalisation of prolactin levels and tumour shrinkage in more than 80% of patients [4, 5]. Surgery is usually reserved for cases of drug resistance or intolerance, and patient's choice [6, 7]. Somatostatin analogues normalise GH/IGF-I hypersecretion in about 60% of acromegalic patients [8], however its high cost, the presence of side effects and the

need for life-long treatment, limit their use. Radiotherapy is effective in the long-term, however more than 50% of patients develop hypopituitarism [9, 10]. So far, transsphenoidal surgery (TSS) remains the treatment of choice for GH- and ATCH-secreting tumours [11]. However, a very wide variation of clinical outcomes and recurrence rates for all these secreting tumours has been reported, depending on the different criteria used to define cure, the difference in follow-up period, tumour characteristics and the surgeon's experience.

We reported the results and rate of recurrence for a series of patients operated on for a secreting pituitary adenoma according to the most recent stringent criteria of biochemical remission.

Patients and methods

Two hundred and sixty-eight consecutive patients with a pituitary adenoma were operated on by the same two neurosurgeons (V.E. and A.S.) between 1995 and 2004 at our institution. Of these patients, 127 presented with a secreting adenoma and were considered for this study, including 67 GH-, 42 PRL- and 16 ACTH-secreting pituitary adenomas. Only two cases of TSH-secreting adenomas were operated on in the same period and were not considered for the study. Macroprolactinomas were clinically diagnosed on the basis of high levels of prolactin more than 150 ng/ml [12] in the presence of a pituitary mass at magnetic resonance imaging (MRI) scan. High levels of PRL associated with a microadenoma at MRI imaging were considered diagnostic of a microprolactinoma. Biochemical remission of hyperprolactinaemia after TSS was defined as normalisation of PRL plasma concentration. Acromegaly was diagnosed on the basis of typical clinical features of patients and elevated fasting plasma GH levels, not suppressible <2 ng/ml during an oral glucose tolerance test with 75 g of glucose (OGTT), and high plasma insulin-like growth factor-I (IGF-I) levels. An MRI scan was performed in all patients to confirm the presence of a pituitary adenoma. Biochemical cure was strictly defined by glucose-suppressed plasma GH levels <1 ng/ml and normal age-corrected IGF-I values 3–6 months after TSS. The diagnosis of Cushing's syndrome was made on the basis of clinical features of patients, the absence of a circadian rhythm of plasma cortisol levels, and increased 24-h urinary cortisol levels. High levels of ACTH and characteristic response to high dose dexamethasone test [13] were considered diagnostic of pituitary-dependent syndrome, when associated with the presence of a pituitary mass at MRI. Biochemical remission of disease was evaluated 1–3 months after surgery by a normal circadian rhythm of plasma cortisol levels, normal 24-h urinary cortisol levels and morning cortisol <5 mg/dl after 1 mg dexamethasone the night before the blood sample. All patients underwent TSS and an immunohistochemical examination of the tumours was performed in all cases. Patients were followed yearly with a basal and dynamic testing evaluation of the pituitary function and a MRI scan, as appropriate. Recurrence was defined as a secondary failure to meet the criteria of biochemical remission illustrated above for each different secreting tumour.

Statistical analysis

Data are expressed as mean±SE. Statistical analysis was performed using the Statview 5.0 software. Fisher's Exact Test was used to examine the outcome of surgery in relation to preoperative bio-clinical parameters of patients. A p value less than 0.05 was considered significant.

Results

Patients' characteristics

Clinical characteristics of patients are shown in Table 1. Twenty-two patients had a macro- and 20 patients a microprolactinoma, respectively. Suprasellar extension and invasion of cavernous sinus was observed in 21 and 12 patients with macroadenomas, respectively. All but six patients were previously treated with dopamine agonist cabergoline for 6–72 months before surgery. Different degrees of hypopituitarism were present in 90% of patients. Indications for TSS were represented by resistance (54%) or intolerance (13%) to cabergoline, and patient's choice (26%). In two cases surgery was performed for the occurrence of a CSF leak during the medical treatment.

Among acromegalic patients, 20% had a microadenoma, whereas 80% had a macroadenoma. Among macroadenomas, 35 (52%) were intrasellar or with a slight suprasellar extension, whereas 19 (28%) had a large suprasellar extension up to optic chiasm. Invasion of cavernous sinus could be recognised in 26% of patients. Hypopituitarism was present in 45% of patients. Prolactin levels were high in 38% of patients. Fourteen patients had Cushing's syndrome, including 10 micro- and 6 macro- adenomas. In the group of macroadenomas, 4 patients had a suprasellar extension that was associated to cavernous sinus extension in 2 patients. Hypogonadism was present in 5 cases (35%). MRI scan confirmed the presence of a microadenoma in 10 cases. In two patients a surgical pituitary exploration was made in the presence of a negative scan.

Macroscopic evidence of dural infiltration at the time of surgery occurred in 46% of cases. Immunohistochemical studies confirmed the diagnosis in all cases of macroadenomas, whereas in 5 microadenomas the immunostaining resulted negative for PRL (3 cases) or ACTH (2 cases). Immunochemistry showed pure GH-secreting adenomas in 45 patients (67%), whereas mixed GH/PRL adenomas were present in 22 cases (33%).

Surgical outcome

No cases of mortality or major complications were observed, however some minor complications occurred (Table 2). Postoperative diabetes insipidus was observed in 11 patients,

Table 1 Preoperative clinical characteristics of 125 patients with secreting adenomas. Data are expressed as mean±SE where not otherwise specified

PRL-secreting adenomas, n (%)	42 (33)
Sex	14 M/26 F
Age (years)	33.2±2.5
Visual field defects, n (%)	6 (14)
Hypopituitarism, n (%)	39 (93)
MRI	22 M/20 m
PRL plasma levels (ng/ml)	571±170
Macroadenoma	1020±274
Microadenoma	73±15
GH-secreting adenomas, n (%)	67 (54)
Sex	32 M/35 F
Age (years)	43.2±2.2
Visual field defects, n (%)	9 (13)
Hypopituitarism, n (%)	30 (45)
MRI	54 M/13 m
GH plasma levels (ng/ml)	32.6±6.1
IGF-I plasma levels (ng/ml)	616±41.6
ACTH-secreting adenomas, n (%)	16 (13)
Sex	4 M/12 F
Age (years)	40.3±2.8
Visual field defects, n (%)	2 (12)
Hypopituitarism, n (%)	6 (37)
MRI	6 M/10 m
ACTH plasma levels (ng/ml)	119.8±28.0
Cortisol plasma levels (μg/dl)	39.3±11.2

M, macroadenomas; *m*, microadenomas; *MRI*, magnetic resonance imaging; *IGF-I*, insulin-like growth factor I

Table 2 Surgical outcome and postoperative follow-up in 125 patients with secreting pituitary adenomas

Characteristics	Median follow-up, months	No. of patients (%)
Clinical outcome		
PRL-secreting adenomas		21/42 (50)
GH-secreting adenomas		38/67 (57)
ACTH-secreting adenomas		11/16 (68)
Total		70/125 (56)
Improvement of visual function		10/17 (59)
Improvement of pituitary function		38/75 (51)
Surgical complications		
Worsening of pituitary function		8 (6)
Diabetes insipidus		11 (9)
Transient		7
Definitive		4
CSF leak		4 (3)
Others		2 (1.6)
Recurrence rate		
PRL-secreting adenomas	33	5/21 (24)
GH-secreting adenomas	31.4	0/38 (0)
ACTH-secreting adenomas	25.6	1/11 (9)
Total	31	6/70 (8.5)

requiring long-term medical therapy for definitive disease in 4 cases. A case of meningitis and a case of pulmonary embolism occurred in 2 patients with GH- and ATCH-secreting adenomas, respectively. Visual field defects improved in 10/17 patients and were unchanged in the remaining patients. Pituitary function worsened in 6% of patients, all of them with macroadenoma, requiring permanent postoperative hormone replacement therapy. On the contrary, it improved in 51% of patients with preoperative endocrinological deficits, especially gonadal function, whereas hypothyroidism and hypocortisolism recovered in 8% of patients.

Endocrinological outcome

Surgical success was 56% for the whole series of patients who underwent TSS (Table 2); 79% for patients with microadenoma, and 44% for patients with macroadenomas ($p<0.01$). Using univariate analysis, cavernous sinus invasion ($p<0.001$), tumour size ($p<0.01$) and dural invasion ($p<0.05$) were factors significantly correlated to a poor surgical outcome. GH levels >10 ng/ml ($p<0.01$) and PRL levels >500 ng/ml ($p<0.05$) were negative prognostic factors for GH- and PRL-secreting tumours, respectively.

Biochemical remission of acromegaly was achieved in 76% of patients with microadenoma and 51% of patients with macroadenomas ($p=0.09$). Normalisation of PRL levels occurred in 75% of microprolactinomas and 27% of macroprolactinomas ($p=0.01$). In patients with Cushing's disease, remission was achieved in 10 (80%) patients with micro- and 3 (50%) macroadenoma, respectively.

Follow-up

After a median follow-up of 31 months (range 7–78 months), all cured patients are still alive. The recurrence rate for the whole series was 8.5% (Table 2). No recurrences were observed in acromegalic patients during a median follow-up of approximately 31 months. In patients with prolactinomas, recurrence of hyperprolactinaemia occurred in 5 patients (24%) with microprolactinoma, within 4 years after TSS surgery. In patients with Cushing's disease, only one patient with macroadenoma had clinical and biochemical evidence of recurrent hypercortisolism. Five patients needed replacement therapy with hydrocortisone, whereas the others had a normal to low cortisol levels.

Discussion

Our study shows the surgical results in a series of patients with secreting pituitary adenomas. The overall remission rate was 56%; being 57%, 68%, and 50% for GH-, ACTH and PRL-secreting tumours, respectively.

Biochemical remission of acromegaly was achieved in 57% of patients, similar to that reported in the most recent series considering strict criteria of cure [14–16]. The concept of biochemical remission of acromegaly has in fact changed over the last few years, and these criteria are nowadays widely accepted as "cure" of disease [11, 17]. The biochemical remission of acromegaly according to these new criteria has an obviously favourable impact on mortality and morbidity related to disease [18, 19], mainly due to normalisation of cardiovascular and metabolic complications of disease [20, 21]. A similar outcome was observed for ACTH-secreting tumours. Our results, according to previous series [22–24], indicate that surgery is highly effective for Cushing's disease. So far, in both acromegaly and Cushing's syndrome, radiotherapy or medical therapy should be proposed for patients with postoperative persistence of hormone hypersecretion or those who are not suitable for surgery. On the other hand, the remission rate for PRL-secreting tumours was significantly lower than GH- and ACTH-secreting tumours and surgical cure was achieved in only 50% of patients, being only 27% for macroprolactinomas. The reported outcome for large macroprolactinomas is poor [25, 26] and dopamine agonists should always be considered the first line therapy, even in the presence of visual disturbances, whereas surgery should be reserved for patients resistant or intolerant to medical therapy. By contrast, the remission rate of microprolactinomas was satisfactory with a low incidence of complications, confirming that surgery may be an acceptable alternative to dopamine agonists [27, 28]. However, because of the high recurrence rate of hyperprolactinaemia after surgery, 24% in our series, and similar to others [25, 26, 29, 30], dopamine agonists represent the first line therapy also for patients with microadenoma and, especially in the last few years, indications for surgery are mainly represented by intolerance or resistance to dopamine agonists.

In our study we have investigated the prognostic significance of several factors to surgical outcome. According to previous reports [3, 23, 26, 31–34], statistical analysis showed that large adenomas with a suprasellar extension over the optic chiasm, or invasion of cavernous sinus, were related to a poor prognosis, as well as high GH and PRL levels.

Surgery was able to improve visual field defects in approximately 60% of patients, as well as the recovery of a normal pituitary function in approximately 50% of patients. The postoperative improvement of pituitary function has been well described for non-secreting pituitary adenomas [35, 36], whereas it has not been systematically considered for acromegaly and Cushing's. The chance to improve pituitary function exceeded the risk of worsening it, and the large majority of patients had normal postoperative pituitary function.

Our results confirm that TSS of pituitary adenomas is a safe and effective treatment and no deaths or major complications occurred. Minor complications occurred in 10% of patients, including CSF leak, diabetes insipidus and hypopituitarism, indicating that the current morbidity rate of TSS is low.

The overall recurrence rate ranged between 0% and 24% for the different types of secreting adenomas, the highest being amongst prolactinomas. No recurrences were observed amongst acromegalic patients after a follow-up of 31 months. Our results compare favourably with previous series, which reported recurrence rates ranging

from 5% to 10% [32–34], and are similar to those reported in recent series considering the same criteria of biochemical remission of acromegaly [14–16], finally indicating that successful TSS can be almost definitive for these patients. By contrast, recurrences for PRL-secreting tumours were higher than GH-secreting ones, and similar to previous reports [29, 30], finally supporting the choice of medical therapy for all patients with microprolactinoma, despite the high rate of early postoperative normalisation of prolactin levels. The recurrence rate of ACTH-secreting tumours was similar to recent reports [3, 22, 37] suggesting that either undetectable postoperative plasma cortisol requiring replacement therapy or normal cortisol circadian rhythm (associated to a normal overnight dexamethasone suppression test), as reported also in the present study, are associated to a favourable long-term remission.

In conclusion, TSS is a safe and effective treatment for secreting pituitary tumours. It represents our current approach to GH- and ACTH-secreting adenomas, whereas medical therapy with dopamine agonists is the first treatment for prolactinomas. Recurrence of acromegaly is rare, whereas a consistent subset of patients with PRL- or ACTH-secreting adenomas may recur, indicating that a careful endocrinological follow-up is mandatory, even many years after successful surgery.

Sommario *La chirurgia transfenoidale rappresenta un trattamento sicuro ed efficace nella cura degli adenomi ipofisari secernenti, tuttavia le percentuali del successo chirurgico ed il tasso di recidiva riportati sono altamente variabili in relazione ai criteri usati per definire la remissione biochimica dell'ipersecrezione ormonale. In questo studio riportiamo i risultati chirurgici a breve e lungo termine di una ampia casistica di pazienti operati per adenoma ipofisario secernente in accordo ai più recenti criteri utilizzati per definire il successo chirurgico degli stessi. Centoventicinque pazienti con adenoma secernente prolattina (42), GH (67) ed ACTH (16) sono stati considerati per questo studio. Il successo chirurgico è stato ottenuto nel 56% dell'intera serie, riguardando il 78% dei pazienti con microadenoma ed il 47% dei pazienti con macroadenoma. Le dimensioni dell'adenoma, i livelli ormonali e l'invasione della dura madre si sono dimostrati correlare negativamente con il successo chirurgico. Non si sono avuti casi di mortalità o complicazioni chirurgiche gravi. Il tasso di ricorrenza durante il follow-up postoperatorio è stato dello 0%, 9% e 24% per gli adenomi secernenti GH, ACTH e prolattina, rispettivamente. In conclusione, la chirurgia transfenoidale è sicura ed efficace nei tumori ipofisari secernenti e rappresenta il trattamento di scelta nei tumori secernenti GH ed ACTH, laddove nei pazienti con prolattinima viene riservata nei casi resistenti o intolleranti ai dopamino-agonisti.*

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