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Recovery of Hypopituitarism after Neurosurgical Treatment of Pituitary Adenomas

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ABSTRACT

Surgery is the treatment of choice for many pituitary tumors; pituitary function may suffer after operation, but relief of pressure on the normal pituitary may also favor postoperative recovery of hypopituitarism. The aim of this study was to investigate the frequency of new appearance and recovery of hypopituitarism after neurosurgery and try to identify features associated with it. Pre- and postoperative anterior pituitary functions were investigated in 234 patients with pituitary adenomas (56 nonfunctioning, 71 PRL-secreting, 66 GH-secreting, 39 ACTH-secreting, 1 LH/FSH-secreting, and 1 TSH-secreting tumors). Eighty-eight new postoperative pituitary hypofunctions appeared in 52 patients (12 NF, 14 PRL-secreting, 15 GH-secreting, 10 ACTH-secreting, and 1 LH/FSH-secreting adenomas). They corresponded to 27% ACTH deficiencies (in 29 of the 107 patients with normal preoperative ACTH in whom postoperative evaluation was complete), 14.5% (15 of 103) new GH deficiencies, 10.5% (15 of 143; $P < 0.0005$, significantly less than ACTH deficiency) new TSH deficiencies, 16.5% (20 of 121) new gonadotropin deficiencies, and 13% (9 of 71) new PRL deficiencies. Preoperatively, 93 were deficient in at least 1 pituitary hormone; after surgery, 45 (48%) recovered between 1 and 3 hormones. The 2 patients with LH/FSH- and TSH-secreting macroadenomas did not recover pituitary function. Factors associated with a higher probability of postoperative pituitary function recovery were: no tumor rests on postoperative pituitary imaging ($P = 0.001$) and no neurosurgical ($P = 0.001$) or pathological evidence ($P = 0.049$) of an invasive nature. Tumor size did not differ significantly between those who did and those who did not recover pituitary function after surgery.

Even if clear hypofunction is observed at initial work-up, patients should be reassessed after surgery without substitution therapy, because practically half the preoperative pituitary hormone deficiencies recover postoperatively, eliminating the need for life-long substitution therapy. (*J Clin Endocrinol Metab* **84:** 3696–3700, 1999)

HYPOPITUITARISM may be found at initial work-up of patients harboring pituitary adenomas. Little is known about the pathophysiology of these pituitary hormone deficiencies. It is usually considered to be due to compression and destruction of the normal pituitary gland by the expanding mass; focal necrosis due to compression of the portal circulation is also possible (1). The outcome of initial hypopituitarism is unclear, because once a clear deficiency has been demonstrated, patients are often left on replacement therapy without assessing possible recovery from hypopituitarism.

It has also been speculated that concomitant pituitary hyperfunction may determine the degree of pituitary hypo- or normofunction; GH-secreting adenomas have been reported to induce less hypofunction than nonfunctioning (NF) adenomas (2). Hyperprolactinemia is known to produce hypogonadism, which is corrected by lowering serum PRL to normal levels either surgically (3) or medically (4, 5). Other factors such as pituitary size are believed to determine postoperative outcome, although this is not always the case (2). The degree of remaining viable normal pituitary, evaluated by basally normal or elevated PRL and a positive response of TSH to TRH, has also been considered to be predictive of postoperative pituitary function recovery (1).

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Transsphenoidal surgery is the treatment of choice in the majority of patients with functioning and NF pituitary adenomas. Apart from removing the adenoma, this technique makes it possible to preserve normal pituitary tissue in many cases. Even though it may induce new pituitary insufficiencies, it has also been shown in small series to improve initial pituitary hypofunction in NF (1, 2, 6, 7) and GH-secreting tumors (2, 8).

We decided to investigate pituitary function before and after neurosurgery in 234 patients with pituitary neoplasms to evaluate postoperatively both recovery and new induction of hypopituitarism and try to identify related features.

Subjects and Methods

Between 1982 and 1997, 234 patients underwent neurosurgery for pituitary adenoma; 23 were operated by the transcranial route, and the remaining patients were operated by the transsphenoidal route; 22 patients underwent more than 1 operation. There were 89 men and 145 women; the tumor size and secretory nature are shown in Fig. 1. Pituitary type was defined by the presence or absence of clinical and biochemical evidence of hormonal hyperproduction into NF and ACTH-, GH-, PRL-, TSH-, and gonadotropin (LH-FSH)-secreting adenomas. Postoperative immunohistochemistry confirmed the clinical/hormonal classification in cases of functioning tumors; NF adenomas classified on clinical grounds often presented some degree of positive immunohistochemistry, mainly gonadotropins, but were still classified as NF. Mean age was 41 ± 15.1 yr; however, patients with NF (47.8 ± 16.2 yr) and GH-secreting adenomas (44.6 ± 12.9 yr) were older than those with prolactinomas (34.6 ± 14.4 yr; $P < 0.0001$ and $P < 0.001$, respectively) and ACTH-secreting adenomas (35.6 ± 12.6 yr; $P < 0.0001$ and $P < 0.02$, respectively).

Assessment of anterior pituitary function was carried out preoper-

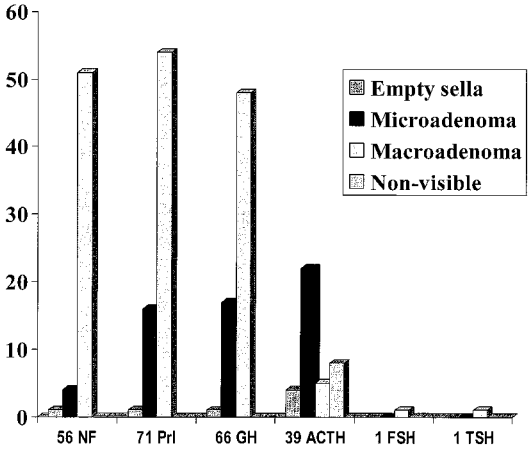

FIG. 1. Secretory type and tumor size in patients with operated pituitary adenomas. Published by permission of BioScientifica (Webb SM, Rigla M, Wägner A, Oliver B, Bartumeus F 1998 Impact of the expanding mass of a pituitary tumour on pituitary function. In: Webb SM, ed. Pituitary tumours: epidemiology, pathogenesis and management. Bristol: BioScientifica; 151–160).

atively as well as 1–6 months postoperatively. Basal hormonal measurements were obtained for all patients, and in 55% of the patients, complete dynamic testing of the pituitary-gonadal, pituitary-thyroidal, and pituitary-adrenal axes and GH reserve was performed. The following criteria were used to define pituitary hormone deficiency or excess.

PRL

PRL levels above 27 μg/L were considered elevated and below 4 μg/L were considered low.

ACTH

Pituitary ACTH deficiency was diagnosed when serum 0800 h cortisol levels were low (<3.6 μg/dL; 100 nmol/L) or cortisol peaked below 18 μg/L (500 nmol/L) in response to insulin-induced hypoglycemia (<40 mg/dL) or 1 mg glucagon, sc, or below 21 μg/dL (600 nmol/L) in response to synthetic ACTH stimulation (250 μg, iv) together with an increase from basal of less than 220 nmol/L (8 μg/dL).

Thyroid hormones

Hypothyroidism was diagnosed when a subnormal serum free T_4 (FT_4) level (<9 pmol/L) was associated with a low or normal TSH (0.3–5 mU/L) level.

Gonadotropins

In males hypogonadism was diagnosed when serum levels of testosterone were low (<10 nmol/L) in the presence of low or normal levels of gonadotropins (<10 IU/L). In postmenopausal women, hypogonadism was diagnosed when serum LH and/or FSH levels were inappropriately low for age (<20 IU/L). In premenopausal women, gonadotropin deficiency was diagnosed in the presence of amenorrhea or oligomenorrhea and infertility, when gonadotropins were basally low or low normal (normal: LH, 2–15 IU/L; FSH, 2–10) associated with persistently low estradiol levels (<30 pg/ml; <0.11 nmol/L). In case of doubt, a GnRH test was performed; a normal response to 100 μg GnRH, iv, was defined as a doubling of LH from baseline and a 50% increase in FSH.

GH

Severe GH deficiency was defined as a GH peak below 3 μg/L after insulin-induced hypoglycemia (<40 mg/dl) or 1 mg glucagon, sc.

All hormones were measured at least in duplicate with commercially available kits. The analytical methods used to measure the various hormones varied over the years (RIA until 1988, immunoradiometric assays until 1992, and nonisotopic methods, such as enzyme chemiluminescence, chemiluminescence, and enzyme-linked immunosorbent assay, since 1992); therefore, the parameters used to determine the normality or abnormality of a hormonal parameter were based on whether the results fell within or outside of the reference range for each method.

Neuroradiological studies included initially computed tomography with contrast enhancement and/or magnetic resonance imaging in the last decade. Studies were performed before and between 3–12 months after surgery and were evaluated as previously described (9). The presence of a microadenoma (maximum diameter, <10 mm), a macroadenoma (maximum diameter, >10 mm), an empty sella or normal pituitary was noted; the extension of the adenoma (intrasellar or with extrasellar extension, inferior, right or left lateral, or superior) as well as the presence of postoperative tumor rests were also analyzed.

The neurosurgical reports were reviewed for indications of an invasive appearance and the impression of having performed a complete neurosurgical excision. The pathology report disclosed the immunohistochemical characteristics of the adenoma; additionally, evidence of an invasive nature of the tumor to the surrounding structures (meninges, sella turcica, sphenoid, or cavernous sinuses) was noted.

Statistical analysis

Initially descriptive statistics were performed. In those relevant percentages, 95% confidence intervals were used to analyze data followed by a χ^2 test. Differences in age between the adenoma groups were analyzed by an ANOVA followed by *post-hoc* Scheffe's test. To analyze the relationship between two qualitative variables, a table of contingence was constructed. Statistical differences were analyzed using the χ^2 test or Fisher's exact test. In all cases a difference was considered significant when $P < 0.05$. The statistical package used was SPSS/win 8.0 (SPSS, Inc., Chicago, IL).

Results

Basal hormonal measurements were obtained for all patients. Complete pre- and postoperative pituitary reserve evaluations were available in 55% and 62% of the subjects, respectively (Table 1A). Pituitary function evaluation according to the secretory nature of the tumor is also shown in Table 1B.

New cases of postoperative hypofunction

Globally, 98 patients had normal preoperative pituitary function and complete postoperative evaluation; in 30 patients (corresponding to 3 NF and 9 PRL-, 9 GH-, and 9 ACTH-secreting tumors), 56 new postoperative hypofunctions appeared. Additionally, in 22 patients of the 79 who preoperatively had at least 1 pituitary hormone deficiency, a further 32 deficiencies appeared. Taking the pituitary hormones individually, new deficiencies were seen for ACTH in 27% of evaluable cases, for GH in 14.5%, for TSH in 10.5%, for LH/FSH in 16.5%, and for PRL in 13% (Fig. 2). New ACTH deficiencies were significantly more frequent than TSH deficiencies ($P < 0.0005$), but no further differences were observed. Macroadenomas (n = 39; 75% of the 52 patients who developed new pituitary deficiencies) caused new hypopituitarism more frequently than microadenomas (n = 13; 25%, of which in 2 pituitary imaging did not disclose the small adenoma identified at surgery; $P < 0.0005$).

Postoperative recovery of initial pituitary hypofunction

Ninety-three patients had preoperative hypofunction; NF adenomas tended to present a higher prevalence of hypopituitarism than the functioning tumors (52% *vs.* 44% in

TABLE 1. Patients (percentage of the total) with complete pre- and postoperative pituitary function evaluation expressed as hormonal axes (A) and secretory type (B)

	Preoperative	Postoperative
A		
Thyroid axis	85.5	82.5
PRL	83.3	79.9
Gonadal axis	79.9	82.5
Adrenal axis	77.4	80.8
GH	71.4	76.9
Complete	55.0	62.0

Type	NF (n = 56)	PRL (n = 71)	GH (n = 66)	ACTH (n = 39)	TSH (n = 1)	Gn (n = 1)
B						
Preoperative	24 (42.9)[a]	39 (54.9)	44 (66.7)	20 (51.3)	1	1
Postoperative	30 (53.6)	48 (67.6)	46 (69.7)	20 (51.3)	1	0

[a] Percentages are in *parentheses*.

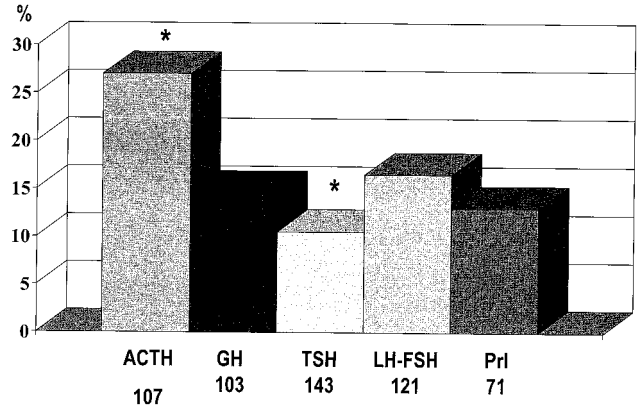

FIG. 2. New cases of postoperative hypofunction (percentage) in patients whose respective pituitary hormone was preoperatively considered to be normal and with complete postoperative evaluation. New cases of ACTH deficiency were significantly more frequent than new TSH deficiency ($P < 0.0005$).

PRL-secreting, 39% in GH-secreting, and 18% in ACTH-secreting adenomas); 45 (48.4%) of these 93 recovered 1–3 pituitary hormones postoperatively (Table 2). Recovery tended to be less common in NF adenomas than in prolactinomas, acromegalics, or ACTH-secreting adenomas, although differences did not attain statistical significance ($P = 0.079$).

In those patients in whom a preoperative deficiency was evidenced and postoperative evaluation was available, recovery of pituitary function was observed for all hormones, without significant differences between the different axes (Fig. 3).

Correlation between pituitary tumor size and postoperative recovery of hypopituitarism

In the 93 patients with preoperative pituitary deficiencies, pituitary tumor size (12 microadenomas and 81 macroadenomas; $P < 0.005$) was not correlated with postoperative recovery of hypopituitarism. Four microadenomas did not recover, whereas 8 (66%) recovered 1 (n = 7) or 2 (n = 1) pituitary hormones. Of the 81 macroadenomas, 44 (54.3%) did not recover pituitary function, whereas 30 (37%) recovered 1, 6 (7.4%) recovered 2, and 1 (1.2%) recovered 3 pituitary functions after surgery (P = NS).

TABLE 2. Relation between postoperative recovery of initial pituitary hypofunction and pituitary secretory type; 45 patients (48.4%) recovered pituitary function, whereas 48 (51.6%) did not

Secretory type	No. of postoperative axes recovered			
	0	1	2	3
NF (n = 29)[a]	19 (65)	10 (35)	None	None
PRL (n = 31)	16 (52)	11 (35)	3 (10)	1 (3)
GH (n = 26)	11 (42)	14 (54)	1 (4)	None
ACTH (n = 7)	2 (29)	2 (29)	3 (43)	None
Total (n = 93)	48	37	7	1

Percentages are given in *parentheses*.

[a] In the NF tumors, there was a significant difference ($P < 0.046$) in the recovery of pituitary function depending on whether the neurosurgeon considered the adenoma invasive (no patient recovered) or noninvasive (50% recovered pituitary function).

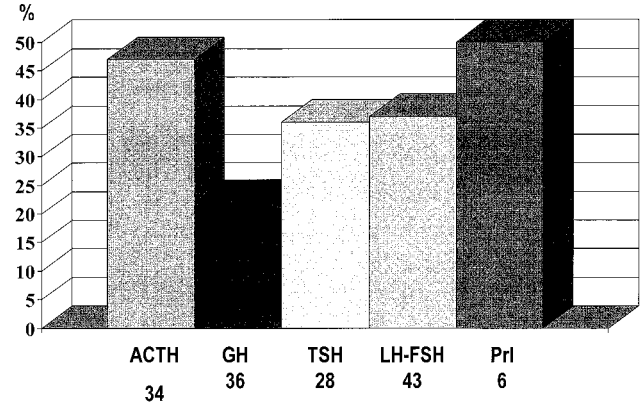

FIG. 3. Postoperative recovery (percentage) of initial hypofunction for the different pituitary hormones.

The two patients with large TSH- and LH/FSH-secreting neoplasms, with preoperative ACTH deficiency, associated in the second patient with TSH and GH deficiencies, did not recover pituitary function; postoperatively, the latter patient was also gonadotropin deficient.

Correlation between neurosurgical outcome and pituitary hypofunction recovery

When the neurosurgical report indicated that the tumor was invasive to the surrounding tissue, it was associated with a lower probability of pituitary function recovery after

TABLE 3. Features related to pituitary hypofunction recovery

Pituitary hormone	Neurosurgically invasive		Complete neurosurgical excision		Postop. X-r tumor rests		Histological invasion	
	Yes	No	No	Yes	Yes	No	Yes	No
ACTH	3/9	5/8	2/4	8/16	3/10	5/8	1/3	7/14
TSH	1/8	4/7	1/6	5/11	2/9	5/8	0/4	6/12
GH	1/8	3/8	0/4	5/16	1/8	3/7	0/3	4/13
LH-FSH	3/12	9/16	3/8	9/21	4/16	7/10	2/5	12/24
PRL	0/12	3/4	0/1	3/5	0/2	2/3	0/1	4/6
Total	8/39	24/43	6/23	30/68	10/45	22/36	3/16	33/69
Percentage	20	56	26	44	22	61	19	48
P value	0.001		NS		0.001		0.049	

The neurosurgical impression or histological evidence of no tumor invasion to surrounding structures or the absence of postoperative radiological (X-r) tumor rests were significantly related to postoperative pituitary hypofunction recovery.

surgery than if it was considered noninvasive ($P = 0.001$; Table 3). Similar results were found when the neurosurgeon reported having performed an incomplete excision (26% postoperative recovery) or a complete excision (44% recovery), although it did not reach statistical significance ($P = 0.146$). Even though it is well known that postoperative radiological findings often do not confirm the neurosurgeon's impression of having performed a complete excision, we did observe how those patients with evidence of residual tumor recovered pituitary hypofunction less (22%) than those without radiological evidence of tumor rests (61%; $P = 0.001$). Finally, when there was pathological evidence of surrounding tissue invasion by the tumor, this was also associated with a lower probability of pituitary hypofunction recovery after surgery (19%) than if the tumor was noninvasive (48%; $P = 0.049$).

Comparison of postoperative pituitary hypofunction recovery in NF and GH-secreting macroadenomas

As Greenman (2) reported that independently of pituitary tumor size, GH-secreting macroadenomas spared anterior pituitary function relatively more than NF macroadenomas, we investigated whether in the NF and GH-secreting macroadenomas with some degree of preoperative pituitary hypofunction there were any differences in the number of endocrine axes initially deficient that recovered after surgery. Hypopituitarism was present preoperatively in 50% of NF adenomas (28 of 56), but only in 30% of GH-secreting tumors (20 of 66; P = NS). Although 18 (64%) NF macroadenomas did not recover function postoperatively, 10 (36%) did, as well as 11 (55%) GH-secreting macroadenomas. ACTH was the pituitary hormone that most commonly recovered (6 of 28 patients, 21%, in NF and 5 of 20, 25%, in GH-secreting adenomas), but there were no significant differences between hormone recovery in either tumor type.

Discussion

Pituitary function may be affected in patients with large pituitary lesions by a primary mass effect of the adenoma on the portal system, inducing pituitary hypofunction and slight hyperprolactinemia; interruption of the portal circulation may also induce focal ischemic necrosis in normal pituitary cells. After surgical decompression normalization of hyperprolactinemia and recovery of hypopituitarism are possible if normal pituitary tissue is still present. Given the scarce regeneration potential of pituitary tissue, limited recovery after surgical decompression may be anticipated if the tumor is very large or long-standing. Nevertheless, in a small series, 40–65% of patients harboring large NF pituitary adenomas have been shown to recover pituitary function after surgical decompression (1, 6, 7). However, others have reported deterioration of gonadal, adrenal and thyroid function after surgery in 100 acromegalic patients, with no improvement (10).

These findings led us to analyze our surgical series of 234 pituitary adenomas to determine how many improved pituitary function after surgery and, additionally, how frequent postoperative deterioration was. In 30.6% of patients with complete normal preoperative hormonal evaluation and in an additional 27.8% of patients who preoperatively exhibited at least 1 pituitary hormone deficiency, new deficiencies appeared after surgery affecting all hormones (less frequently for TSH and most for ACTH); 75% of these patients had macroadenomas, but the remainder had small lesions. At the same time, however, we confirmed that nearly half of the 93 patients with 1–3 hormone deficiencies before surgery recovered endocrine function. NF adenomas tended to recover pituitary hormones less than secreting tumors. As also reported by others (1, 6, 7) ACTH was the hormone that most frequently recovered, although gonadotropins, TSH and GH, also improved, as did 3 of 6 PRL deficiencies. Preoperative hypopituitarism was more frequent in macroadenomas than microadenomas; however, postoperative recovery was not significantly related to tumor size.

The existence of preoperative TSH stimulation by TRH and normal to high basal PRL levels has been considered predictive of pituitary function recovery after surgery in NF adenomas, supporting the existence of both viable thyrotroph and lactotroph cells and compression of the portal circulation leading to hypopituitarism (1). We were unable to verify whether the TSH response to TRH was predictive, as we stopped performing this test routinely 10 yr ago, and our experience with basal PRL was not as clear. When initial PRL was low, the same number of patients did as did not recover hypopituitarism, and no clear differences were observed when comparing the low PRL group with the high or normal PRL groups (data not shown); furthermore, the number of pituitary hormones that recovered when PRL was normal or

high did not differ from that when PRL was low. These differences may be due to the fact that Arafah (1) only analyzed NF tumors, and we included both secreting and NF adenomas.

We tried to identify other features related to postoperative recovery of pituitary hypofunction. If the tumor was depicted as not invasive (by both the neurosurgeon and the pathologist), and postoperative radiology did not identify tumor rests, the probability of improving hypopituitarism was higher than when this was not the case. All of these features tend to correlate with the invasive nature of the lesion; however, tumor size alone (usually considered to reflect the degree of aggressivity) was not found to explain the higher prevalence of pituitary hypofunction in NF macroadenomas than in GH-secreting macroadenomas (2). After surgery, pituitary function recovery occurred in both Greenman's (2) and our patients, but hypopituitarism was still more prevalent in NF (68% in Greenman's series and 64% in ours) than in GH-secreting (17% and 45%, respectively) macroadenomas. There is no clear explanation for the lower rate of hypopituitarism in GH-secreting *vs.* NF macroadenomas. It may de due to the fact that the unique features of acromegaly lead to an earlier diagnosis than in NF tumors, which are clinically more quiescent; alternatively, differences in age (greater in NF adenomas) or prior medical treatment in acromegalics might have preserved pituitary function better. Finally, either GH or insulin-like growth factor I could exert a proliferative effect on pituitary cells (2), as described in thyroid cells (11, 12).

The main aim in treating a new patient with a pituitary tumor is to control the pituitary mass and hyperfunction, but as both surgical and medical decompression of a pituitary mass can facilitate pituitary hypofunction recovery, it is relevant to clinical practice to develop a treatment strategy aimed at preserving and recovering pituitary function and preventing irreversible hypofunction. In the case of medical treatment for prolactinomas, it would seem logical to retest pituitary function either after a substantial reduction in circulating PRL or after a marked reduction in pituitary mass. It would also be interesting to analyze whether tumors other than prolactinomas recover pituitary hypofunction after successful medical treatment. These are issues that deserve attention in the future prospective management of patients with pituitary masses.

This is clearly different from what was observed after radiotherapy, the third therapeutic option in pituitary tumors, which is associated with progressive hypopituitarism related to dose and time since irradiation. After 5 yr all patients were GH deficient, 90% were gonadotropin deficient, 77% were ACTH deficient, and 42% were TSH deficient (13).

As nearly half of the initial pituitary hypofunctions normalized after surgery for pituitary adenomas, we anticipate a greater number of recoveries to be identified if the clinician is aware of this possibility; this would eliminate unnecessary life-long substitution therapy in a number of patients, which in itself may be harmful.

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