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Received, January 10, 2008.

Accepted, June 2, 2008.

PITUITARY HORMONAL LOSS AND RECOVERY AFTER TRANSSPHEOIDAL ADENOMA REMOVAL

OBJECTIVE: Transsphenoidal adenomectomy carries the possibility of new pituitary failure and recovery. Herein, we present rates and determinants of postoperative hormonal status.

METHODS: All consecutive patients who underwent endonasal transsphenoidal adenoma removal over an 8-year period were analyzed. Those with previous sellar radiotherapy were excluded. Pre- and postoperative hormonal status (at least 3 mo after surgery) were determined and correlated with clinical parameters using a multivariate statistical model.

RESULTS: Of 444 patients (median age 45 years, 75% macroadenoma, 19% with multiple operations), 9 had preoperative panhypopituitarism. Of the remaining 435 patients, new hypopituitarism occurred in 5.5% of patients (anterior loss in 5%; permanent diabetes insipidus in 2.1%; including 2 patients who had total hypophysectomy). Of 346 patients with preoperative hormonal dysfunction, 170 (49%) had improved function. "Stalk compression" hyperprolactinemia resolved in 73% of 133 patients; recovery of at least 1 other anterior axis (excluding isolated hypogonadism associated with "stalk compression" hyperprolactinemia) occurred in 24% of 209 patients. Multivariate analysis showed that new hypopituitarism was most strongly associated with larger tumor diameter ($P = 0.04$). Of 223 patients with an endocrine-inactive adenoma, new hypopituitarism was seen in 0, 7.2, and 13.6% of patients with tumor diameters of <20 , 20 to 29, and ≥ 30 mm, respectively ($P = 0.005$). Multivariate analysis revealed that resolution of hypopituitarism was related to younger age (39 versus 52 years, $P < 0.0001$), absence of an intraoperative cerebrospinal fluid leak and, in patients with an endocrine-inactive adenoma, absence of systemic hypertension (24% versus 6%, $P = 0.009$).

CONCLUSION: After transsphenoidal adenomectomy, new unplanned hypopituitarism occurs in approximately 5% of patients, whereas improved hormonal function occurs in 50% of patients. The likelihood of new hormonal loss or recovery appears to depend on several factors. New hypopituitarism occurs most commonly in patients with tumors larger than 20 mm in size, whereas hormonal recovery is most likely to occur in younger, nonhypertensive patients and those without an intraoperative cerebrospinal fluid leak.

KEY WORDS: Endonasal surgery, Hyperprolactinemia, Hypopituitarism, Pituitary adenoma, Pituitary hormonal function, Transsphenoidal surgery

Neurosurgery 63:709–719, 2008

DOI: 10.1227/01.NEU.0000325725.77132.90

www.neurosurgery-online.com

Postoperative hypopituitarism and hormonal recovery are well-known consequences of transsphenoidal pituitary adenoma removal. In most reports, the rate of new long-term pituitary failure is less than 10% (11, 24, 37, 38), with higher rates reported in cases

of pituitary apoplexy and reoperations for Cushing's disease (41, 43). Although most transsphenoidal surgical series cite rates of new hypopituitarism, there have been few systematic analyses looking at rates across different tumor types and potential predictors of

ABBREVIATIONS: CSF, cerebrospinal fluid; DI, diabetes insipidus; GH, growth hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; UCLA, University of California, Los Angeles

either new pituitary failure or recovery of hormonal function after adenoma removal.

In this report, we analyze 444 consecutive patients treated over an 8-year period with transsphenoidal adenoma removal. Patients who received previous radiation therapy to the sella or parasellar area were excluded, given the known long-term impact of radiotherapy on pituitary function (31, 40, 46). Using a multivariate model, potential predictors of change in hormonal status included tumor pathology and size, previous or multiple surgeries, preoperative hormonal status, intraoperative events, and surgical complications. Preoperative diabetes mellitus, hypertension, and smoking, all of which are risk factors for cerebrovascular disease and stroke, were also included in the risk factor analysis (21, 39). The impact of surgery on "stalk compression" hyperprolactinemia and related hypogonadism was also analyzed (28, 29).

PATIENTS AND METHODS

Patient Cohort

From July 1998 to June 2006, all patients in the University of California, Los Angeles (UCLA) Pituitary Tumor database who underwent endonasal transsphenoidal removal of a pituitary adenoma at UCLA or Harbor-UCLA Medical Centers were included in this retrospective analysis. All operations were performed by the same neurosurgeon (DFK). Patients' medical records were reviewed to document pre- and postoperative hormonal status, pathology reports, magnetic resonance imaging for tumor size and location, operative notes, postoperative events, and clinic follow-up notes. Patients were excluded if they received preoperative cranial or sellar radiotherapy, had less than a 3-month postoperative hormonal evaluation, or had missing pre- and postoperative hormonal data. However, a subset of patients with missing postoperative prolactin levels (in non-prolactin-secreting patients) or insulin-like growth factor 1 (IGF-1) levels (in nonacromegalic patients) were included in the overall analyses. In the subset of patients ($n = 40$) who received postoperative radiotherapy, postoperative hormonal status was determined before radiotherapy. This analysis was approved by the UCLA and the Harbor-UCLA Medical Centers Institutional Review Board.

Surgical Technique

As described previously, the endonasal transsphenoidal approach with the operating microscope was used in all cases; endoscopic assistance was used in selected cases (20, 33, 49). In all patients, a selective adenectomy was attempted with the additional goal of preserving the normal pituitary gland. In patients with Cushing's disease, when the preoperative magnetic resonance imaging scan and the inferior petrosal sinus sampling did not indicate the adenoma location, the gland was explored through several vertical incisions. If no tumor was found from gland exploration, then a partial hemihypophysectomy was performed on the most suspicious side; total hypophysectomy was performed in only 2 cases (20).

Over the past 6 years, full-strength (3%) hydrogen peroxide has been irrigated directly into the sellar tumor bed for up to 5 minutes to aid in hemostasis and for its tumoricidal effect. The effects of hydrogen peroxide are potentially important, given a recent study showing that it is tumoricidal to glioma and pituitary adenoma cell lines and has local deleterious effects on normal tissue (35). Peroxide was initially used

only for small functional adenomas, but in the last 3 years of the series, it was used for almost all adenomas unless there was a large surgical defect in the diaphragma sellae. In this analysis, we also sought to determine whether hydrogen peroxide irrigation was deleterious to pituitary gland function.

Pre- and Postoperative Hormonal Assessment

Because many patients who were referred for surgery came with complete hormonal testing from outside laboratories, a standard reference range was not used; instead the patients' results were interpreted as normal or abnormal based on the available normal reference range from the outside laboratory. Although not all patients had identical evaluations, the following pre- and postoperative tests (at least 3 mo after surgery) were used to assess the different hormonal axes.

The corticotroph axis evaluation included morning plasma adrenocorticotropic hormone (normal range, 9–52 pg/mL [2–11.4 pmol/L]) and serum cortisol (normal range, 8–25 μ g/dL [221–690 pmol/L]) levels; in patients with Cushing's disease, 24-hour urinary free cortisol levels were obtained. Dynamic testing of the hypothalamic-pituitary axis (via either cosyntropin or metyrapone) was done in a subset of patients who had subnormal serum cortisol levels, and/or those with clinical features suspicious for adrenal insufficiency.

The thyrotroph axis evaluation included serum levels of thyroid-stimulating hormone (normal range, 0.3–4.7 mIU/L), total T4 (normal range, 4.9–11.4 ng/dL [63–147 pmol/L]) and/or free T4 (normal range, 0.7–2.2 ng/dL [9–28.3 pmol/L]).

The gonadotroph axis evaluation in women included serum levels of luteinizing hormone (LH) (normal premenopausal range, 2–15 IU/L), follicle-stimulating hormone (FSH) (normal premenopausal range, 2–23 IU/L), and estradiol. In premenopausal women, hypogonadism was diagnosed if amenorrhea and/or infertility was present and if gonadotropins were low or below normal in the setting of low estradiol levels (<21 pg/mL [<77.1 pmol/L]). Hypogonadism was diagnosed in postmenopausal women when serum LH (normal postmenopausal range, 16–63 IU/L) and/or FSH (normal postmenopausal range, 21–106 IU/L) were low. In men, LH (normal range, 2–12 IU/L) and FSH (normal range, 1.6–9 IU/L) were assessed; total testosterone (normal range, 250–1100 ng/dL [8.7–38.2 nmol/L]) and/or free testosterone (normal range, 35–155 pg/mL [1213–5374 pmol/L]) were also assessed. Secondary hypogonadism was diagnosed in men if total or free testosterone was low in the setting of normal or low LH and FSH.

The lactotroph axis was assessed with serum prolactin levels (normal range, 5–20 ng/mL [5–20 μ g/L] for men and 5–25 ng/mL [5–25 μ g/L] for women).

The somatotroph axis evaluation included random serum growth hormone (GH) (normal range, 0–6 ng/mL [0–6 μ g/L]) and age- and sex-adjusted IGF-1 levels (normal ranges for age/sex not shown); stimulation tests with GH-releasing hormone-arginine or the insulin tolerance test was performed postoperatively on patients in whom the IGF-1 levels were near or below the lower limit of normal, or when other anterior pituitary axes were deficient. In the absence of stimulation testing for GH deficiency, any patient who had three other anterior hormonal axis deficiencies (corticotroph, thyrotroph, and gonadotroph) was categorized as being GH-deficient, whether in the pre- or postoperative state (2–4, 16).

Posterior pituitary function was assessed based on urine specific gravity, serum sodium, and urine output. Patients were diagnosed as having diabetes insipidus (DI) if urine specific gravity was 1.005 or less and urine volume was greater than 200 mL/h for at least 3 consecutive hours.

Characterization of Hormonal Dysfunction

Patients were categorized preoperatively according to which pituitary hormonal abnormalities were present, including hypoadrenalism, hypothyroidism, hypogonadism, “stalk compression” hyperprolactinemia (not from a prolactinoma), and DI (28, 29, 45). New pituitary dysfunction was defined as any abnormality occurring at least 3 months after surgery based on hormonal testing or new hormone replacement for a new deficiency. Recovery of dysfunction was categorized by hormonal axis. In patients with preoperative “stalk compression” hyperprolactinemia, the change in serum prolactin was assessed. Loss of the lactotroph axis (low prolactin levels) was not investigated in this analysis. Hypogonadism was categorized as occurring in association with other axis deficiencies (hypopituitarism) or without hyperprolactinemia, in isolation with “stalk compression” hyperprolactinemia (28, 29, 45), or in association with a prolactinoma.

Predictors of Postoperative Hypopituitarism or Gain of Hormonal Axis

Possible predictors of hormonal recovery or loss included patient age and sex, the comorbidities of treated hypertension, treated diabetes mellitus, and cigarette smoking (at least 5 cigarettes/d; 5 of 444 patients had no data on smoking history), and previous transsphenoidal or transcranial adenoma surgery. Preoperative hormonal status was documented by hormonal axis and number of axes affected (28, 29, 45).

Tumor-related data included tumor size (maximal tumor diameter, macroadenoma versus microadenoma, and size categories: <20 mm versus 20–29 mm versus \geq 30 mm), tumor type (acromegaly, Cushing’s disease, endocrine-inactive, prolactinoma, or thyroid-stimulating hormone-secreting), cavernous sinus invasion (seen on magnetic resonance imaging or intraoperatively), pituitary apoplexy, presence of an intraoperative cerebrospinal fluid (CSF) leak, and use of full-strength (3%) hydrogen peroxide irrigation.

Postoperative complications, including intrasellar hematoma requiring reoperation, CSF leak, and bacterial meningitis, were noted. The development of transient and permanent DI and delayed hyponatremia was noted (27, 50). Given our previous reports (20, 33, 49) on remission rates for patients with adenomas, and specifically for patients with endocrine-inactive adenomas and Cushing’s disease, these data are not presented in this report.

Statistical Analysis

Predictors of loss or recovery of pituitary axes after surgery were analyzed by univariate statistics, including a two-tailed Fisher’s exact test for dichotomous variables, Student’s *t* test for normally distributed continuous variables, and Mann-Whitney *U* test for variables that were not normally distributed. Average pre- and postoperative prolactin values were compared between groups using a Student’s *t* test for normally distributed values. The *P* value for significance was set at 0.05. A multivariate model was then used to further assess the variables in question. Because of the relatively small number of cases of hormonal loss (*n* = 22) and hormonal recovery (*n* = 51) and the large number of variables, a model including all variables could not be applied. Instead, each variable that was statistically significant on univariate analysis was explored for a best-fit model. For assessing hormonal loss, a 2-variable model was used, and for assessing hormonal gains, a 3-variable model was used. This process was repeated for each variable in question to produce the multivariate *P* values. Statistical analyses were performed using the R programming language, version 2.5.1 (R Development Core Team, Vienna, Austria) and SAS (SAS Institute, Inc., Cary, NC).

RESULTS

Study Cohort

Over an 8-year period, 444 patients (median age, 45 years; range, 9–84 years; 60% women) underwent 475 procedures for tumor removal and had sufficient data for study inclusion. Of these, 415 patients had 1 operation, 27 patients had 2 operations, and 2 patients had 3 operations performed by DFK; 61 patients (14%) had undergone previous transsphenoidal or transcranial tumor surgery at outside institutions. Overall, 86 patients (19%) underwent more than 1 operation. As shown in Table 1, of the 444 patients, 25% had a microadenoma and 75% had a macroadenoma. Postoperative radiotherapy or radiosurgery was given to 40 patients. Median follow-up was 16 ± 19 months (range, 3 months–8 years 10 months). Thirty-six additional patients were excluded: 18 with previous radiotherapy and 18 with insufficient hormonal data.

Preoperative Hormonal Status

Of 444 patients, 309 (70%) had hypopituitarism, 158 (36%) had “stalk compression” hyperprolactinemia, 121 (27%) had both hypopituitarism and “stalk compression” hyperprolactinemia, and 346 (78%) had hypopituitarism and/or “stalk compression” hyperprolactinemia. Preoperative hypopituitarism was observed in 66% of 61 patients with previous outside surgery and in 44% of 383 patients without previous surgery (*P* = 0.002). Nine patients (2%) had preoperative panhypopituitarism (including DI); of these, 5 (56%) had previous surgery and 1 had apoplexy. The rate of non-prolactin-related hormonal deficiencies (hypopituitarism) was highest in patients with endocrine-inactive adenomas (59 versus 34% for all other adenomas, *P* < 0.0001).

Preoperative Growth Hormone Deficiency

Of the 374 patients (84% of the cohort) with adequate data, 113 (30%) met the criteria for preoperative GH deficiency. This diagnosis was based on low IGF-1 for age in 91 patients (81%), preexisting loss of 3 other hormonal axes in 16 patients (14%), abnormal GH stimulation testing in 3 patients, and ongoing GH replacement therapy in 3 patients with previously diagnosed GH deficiency.

Postoperative Hormonal Loss: All Adenomas

As shown in Table 2, of all 435 patients who did not have preoperative panhypopituitarism, 24 (5.5%) had loss of 1 or more new pituitary axes postoperatively; if the 2 patients who underwent a planned total hypophysectomy for Cushing’s disease are excluded, the rate of new (unplanned) hypopituitarism is 5.1% (22 of 433 patients). Of these 24 patients, new anterior hypopituitarism occurred in 21 (5.2%) of 402 patients with at least 1 intact axis preoperatively (including new adrenal, thyroid, gonadal, and GH loss in 2, 1.5, 2, and 3%, respectively); new permanent DI occurred in 9 (2.1%) of 435 patients without preoperative DI. Excluding the 2 patients who had a planned hypophysectomy, new unplanned anterior hypopituitarism occurred in 19 (4.8%) of 400 patients, and new permanent DI

TABLE 1. Patient and tumor characteristics in 444 patients who had transphenoidal surgery^a

Characteristic	No. of patients (%)
Pituitary adenoma types (n = 444)	
Endocrine-inactive	231 (52%)
ACTH-secreting ^b	84 (19%)
Prolactinoma	73 (16%)
GH-secreting	53 (12%)
TSH-secreting	3 (1%)
Tumor size	
Microadenoma	113 (25%)
Macroadenoma	331 (75%)
Other tumor characteristics and clinical factors	
Cavernous sinus invasion	139 (31%)
Intraoperative CSF leak	247 (56%)
Intraoperative use of hydrogen peroxide	228 (51%)
Transient DI	107 (24%)
Delayed hyponatremia	32 (7%)
Prior surgery at outside hospital	62 (14%)
Radiotherapy after surgery	40 (9%)
Preoperative hormonal loss^c	
Adrenal (total n = 364; excludes Cushing's patients)	56 (15%)
Thyroid (total n = 441; excludes thyrotropinoma patients)	93 (21%)
Gonadal (total n = 444)	281 ^d (63%)
Growth hormone (n = 374; excludes acromegalic patients)	113 (30%)
"Stalk effect" hyperprolactinemia (n = 333)	158 (43%)
DI (n = 444)	9 (2%)
Any preoperative hormonal dysfunction (n = 444)	346 (78%)

^a ACTH, adrenocorticotropic hormone; GH, growth hormone; TSH, thyroid-stimulating hormone; CSF, cerebrospinal fluid; DI, diabetes insipidus.

^b Eighty patients with Cushing's disease and 4 with Nelson's syndrome.

^c Total number for each axis excludes functional tumors of that axis.

^d Including 64 prolactinomas.

occurred in 7 (1.6%) of 433 patients. Only 1 patient in the cohort (a 46-year-old man with a 40-mm adenoma) with normal preoperative pituitary function developed postoperative panhypopituitarism. He had borderline low free T4 (0.7 ng/dL) but otherwise normal baseline hormonal tests before surgery.

Postoperative Hormonal Recovery: All Adenomas

As shown in Table 2, of 346 patients (78% of the cohort) with preoperative hypopituitarism and/or "stalk effect"

hyperprolactinemia, 170 (49%) had improved postoperative function. No patients had recovery of DI. Recovery of hypopituitarism (excluding isolated hypogonadism associated with "stalk compression" hyperprolactinemia) occurred in 24% of 209 patients and involved 1, 2, 3, or 4 axes in 78, 14, 6, and 2%, respectively. By hormonal axis, recovery of adrenal, thyroid, gonadal, and somatotroph function occurred in 22, 14, 30, and 27%, respectively.

Of 217 patients with hypogonadism who did not have a prolactinoma, gonadal axis recovery occurred in 36 (22%) of 166 patients with other axis deficits or no hyperprolactinemia, and in 20 (39%) of 51 patients with isolated hypogonadism associated with "stalk compression" hyperprolactinemia (P = 0.017). Of 64 patients with a prolactinoma and hypogonadism, 27 (42%) had gonadal axis recovery.

Of 133 patients with "stalk compression" hyperprolactinemia and postoperative prolactin levels available, 97 (73%) had normalization, 23% had a decrease, 2% had further elevation, and 2% had no change in prolactin level (<5 ng/mL [5 µg/L] change). Of these 133 patients, mean prolactin decreased from 69 ± 57 ng/mL (69 ± 57 µg/L) to 20 ± 21 ng/mL (20 ± 21 µg/L; P < 0.0001) after surgery.

Endocrine-inactive Adenomas

Of 231 patients with endocrine-inactive adenomas, 194 (84%) had preoperative hormonal dysfunction, including 120 (54%) with "stalk compression" hyperprolactinemia. Postoperatively, 7% had new hypopituitarism and 48% had improved postoperative function (Table 3). Of patients with preoperative hypopituitarism (excluding those with isolated hypogonadism associated with "stalk compression" hyperprolactinemia), 18% regained at least 1 axis (ranging from 7% for thyroid to 21% for gonadal), and 73% had resolution of hyperprolactinemia. Gonadal recovery occurred in 16 (13%) of 120 patients with other axis deficiencies or no hyperprolactinemia, and in 16 (46%) of 35 patients with isolated hypogonadism associated with "stalk compression" hyperprolactinemia (P = 0.0001).

Predictors of New Hypopituitarism: Overall

After excluding the 2 patients with Cushing's disease who underwent a total hypophysectomy and 9 patients with preoperative panhypopituitarism, there were 433 patients for analysis of predictors of new hypopituitarism. On univariate analysis, older age, larger tumor size, endocrine-inactive tumors, and non-use of intraoperative hydrogen peroxide were all significant predictors of new pituitary failure (Tables 4 and 5). There was also a trend that cases earlier in the surgical series were more likely to result in new hypopituitarism, with a rate of new loss of 6.9% in the first half of patients and 3.2% in the second half of patients (P = 0.08). On multivariate analysis, only tumor size was independently predictive of new hypopituitarism. Average tumor size in patients who lost an axis was 28 mm, versus 20 mm in those who did not lose an axis (P = 0.002). Split into 3 size groups, 2.2, 5.2, and 11.7% of patients lost axes with maximal tumor diameter less than 20 mm, 20 to 29 mm, and 30 mm

TABLE 2. Change in pituitary function by tumor subtype^a

Tumor type	No change (%)	Any recovery of function ^b		Loss of function ^c (%)		
		No. of patients	%	Any	Anterior	Posterior
All adenomas (n = 444)	59%	346	49%	5.5%	5.2%	2.1%
Endocrine-inactive (n = 231)	53%	194	48%	7.4%	7.3%	3.1%
ACTH-secreting (n = 84) ^d	75%	51	32%	6%	6%	2.4%
Prolactinoma (n = 73)	60%	65	51%	0%	0%	0%
Acromegaly (n = 53)	55%	36	61%	3.8%	3.8%	0%

^a ACTH, adrenocorticotropic hormone.

^b Includes resolution of “stalk effect” hyperprolactinemia. The total number of patients reported for each axis includes only patients who had the potential for recovery of function in that axis.

^c The percentage of new hormonal loss is based on the total number of patients who had an intact axis preoperatively, and includes 2 patients who underwent a planned total hypophysectomy.

^d Includes 80 patients with Cushing’s disease and 4 with Nelson’s syndrome.

TABLE 3. Endocrine-inactive adenomas: change in pituitary function by axis

	No change (total n = 231) (%)	Recovery of function ^a		Loss of function ^a	
		No. of patients	%	No. of patients	%
Adrenal	93.5%	51	16%	180	4%
Thyroid	96%	72	7%	158	3%
Gonadal	46%	155	21%	76	5%
Growth hormone	92%	90	10%	141	6%
Posterior lobe	97%	8	0%	223	4%
Hyperprolactinemia ^b	2%		73%	Not assessed	

^a The number of patients reported (the denominator) for each hormonal axis only includes patients who had the potential for recovery or loss of function in that particular hormonal axis.

^b Of 106 patients with an elevated preoperative prolactin level (>20 ng/mL in men and >25 ng/mL in women), hyperprolactinemia resolved in 73%, improved in 23%, did not change in 2% (<5 ng/mL change), and worsened in 1%.

or larger, respectively ($P = 0.003$). Although the use of hydrogen peroxide irrigation after tumor resection was associated with a lower rate of new hypopituitarism (1.7 versus 8.7%; $P = 0.0015$), of patients in whom hydrogen peroxide irrigation was used, 67% had tumors smaller than 20 mm in size and 33% had tumors 20 mm or greater in size ($P < 0.00001$). Hydrogen peroxide was also used more frequently in the later half of the surgical series ($P < 0.001$).

Predictors of New Hypopituitarism: Endocrine-inactive Subgroup

In 223 patients, tumor size was the strongest predictor of new axis loss on both univariate and multivariate tests; the mean tumor diameter in patients who lost axes was 33 mm, versus 25 mm in those without axis loss ($P = 0.002$). Split into 3 groups, new hypopituitarism occurred in 0, 7.2, and 13.6% of patients with tumors less than 20 mm, 20 to 29 mm, and 30 mm or larger, respectively ($P = 0.005$). New hypopituitarism also occurred more often early in the surgical series (11% in the first half versus 4.3% in the second half; $P = 0.04$).

TABLE 4. Predictors of pituitary hormonal failure in 433 patients: continuous variables

Factor	No loss of axis	Loss of axis	Univariate P value
Premorbid factors			
Age (yr)	45	53	0.023 ^a
No. of axes lost preoperatively	1.18	0.96	0.28
Tumor characteristics			
Maximum tumor diameter (mm)	20	28	0.002 ^{b,c}

^a Age: $P = 0.18$, controlling for maximum tumor diameter.

^b Maximum tumor diameter: $P = 0.04$, controlling for age and endocrine-inactive tumor type.

^c Independently significant in a multivariate model.

TABLE 5. Predictors of pituitary hormonal failure in 433 patients: dichotomous variables^a

Factor	Loss of axis	Univariate P value
Premorbid factors and surgical history		
<i>Sex</i>		
Male	7.6%	0.07
Female	3.4%	
<i>Hypertension</i>		
HTN	5.9%	0.7
No HTN	4.6%	
<i>Diabetes mellitus</i>		
DM	5.2%	1.0
No DM	5.1%	
<i>Smoking</i>		
Smoker	4.8%	1.0
Nonsmoker	5.2%	
<i>Multiple operations</i>		
Yes	3.9%	0.8
No	5.3%	
<i>Surgical experience</i>		
1st half of series	6.9%	0.08
2nd half of series	3.2%	
Tumor characteristics		
<i>Tumor type</i>		
Endocrine-inactive	7.6%	0.015 ^b
All others	2.4%	
<i>Preoperative stalk compression hyperprolactinemia</i>		
Present	6.0%	0.6
Absent	8.1%	
<i>Cavernous sinus invasion</i>		
Present	5.3%	1.0
Absent	5.0%	
Operative and postoperative events		
<i>Intraoperative hydrogen peroxide</i>		
Used	1.7%	0.002 ^c
Not used	8.7%	
<i>Intraoperative CSF leak</i>		
Present	4.1%	0.4
Absent	6.3%	
<i>Transient DI</i>		
Present	2.8%	0.3
Absent	5.8%	
<i>Delayed hyponatremia</i>		
Present	0%	0.4
Absent	5.5%	

^a HTN, hypertension; DM, diabetes mellitus; CSF, cerebrospinal fluid; DI, diabetes insipidus.

^b Endocrine-inactive tumor type: in a multivariate model, $P = 0.18$, controlling for maximum tumor size.

^c Hydrogen peroxide: in a multivariate model, $P = 0.07$, controlling for age and surgical experience.

TABLE 6. Predictors of recovery of hypopituitarism in 209 patients: continuous variables^a

Factor	No gain of axis	Gain of axis	Univariate P value
Premorbid factors			
Age (yr)	52	39	<0.0001 ^{b,c}
No. of axes lost preoperatively	2.26	1.84	0.033 ^d
Tumor characteristics			
Maximum tumor diameter (mm)	25	22	0.15

^a Excludes patients with isolated hypogonadism associated with “stalk compression” hyperprolactinemia.

^b Age: $P < 0.0001$, controlling for growth hormone adenoma type and intraoperative cerebrospinal fluid leak

^c Independently significant in a multivariate model.

^d Number of axes lost preoperatively: $P = 0.4$, controlling for age and intraoperative cerebrospinal fluid leak.

Predictors of Hormonal Recovery: Overall

In total, 51 (24%) of 209 patients with preoperative hypopituitarism (excluding patients with isolated hypogonadism associated with “stalk compression” hyperprolactinemia) had partial or complete recovery (Tables 6 and 7). Factors associated with recovery included younger age, absence of hypertension, acromegaly, fewer hormonal deficits preoperatively, smaller tumor diameter, and absence of intraoperative CSF leak. On multivariate analysis, only younger age and absence of an intraoperative CSF leak were independently predictive of hormonal recovery.

Predictors of Hormonal Recovery: Endocrine-inactive Subgroup

In total, 24 (18%) of 137 patients with preoperative hypopituitarism (excluding patients with isolated hypogonadism associated with “stalk compression” hyperprolactinemia) had partial or complete hormonal recovery. On multivariate analysis, the factors of younger age (47 versus 56 years, $P = 0.006$), absence of a postoperative CSF leak ($P = 0.03$), and absence of hypertension ($P = 0.05$) were predictive of hormonal recovery. Only 6% of patients with hypertension recovered an axis, compared with 24% without hypertension (univariate analysis, $P = 0.009$).

DISCUSSION

Summary of Findings

In this study of 444 consecutive patients who had transphenoidal adenomectomy, new anterior pituitary failure occurred in 5% of patients and permanent DI occurred in 2% of patients. New loss of adrenal, thyroid, gonadal, and somatotroph function occurred in 2, 1.5, 2, and 3% of patients, respectively. The strongest predictor of new hypopituitarism was tumor size,

TABLE 7. Predictors of recovery of hypopituitarism in 209 patients: dichotomous variables^a

Factor	Gain of axis	Univariate P value
Premorbid factors		
Sex		
Male	22.2%	0.5
Female	26.7%	
Hypertension		
HTN	14.6%	0.0085 ^b
No HTN	30.7%	
Diabetes mellitus		
DM	16.1%	0.4
No DM	25.8%	
Smoking		
Smoker	33.3%	0.5
Nonsmoker	24.0%	
Multiple operations		
Yes	15.7%	0.13
No	27.2%	
Surgical experience		
1st half of series	20.0%	0.15
2nd half of series	29.3%	
Tumor characteristics		
Tumor type		
GH-secreting	57.9%	0.001 ^c
All others	21.1	
Endocrine-inactive	17.5%	0.002 ^d
All others	37.5%	

TABLE 7. continued

Factor	Gain of axis	Univariate P value
<i>Maximum tumor size</i>		
<20 mm	32.5%	0.046 ^e
≥20 mm	19.7%	
<i>Preoperative stalk compression hyperprolactinemia</i>		
Present	14.3%	0.27
Absent	22.4%	
<i>Cavernous sinus invasion</i>		
Present	20.8%	0.4
Absent	24.3%	
Operative and postoperative events		
<i>Intraoperative hydrogen peroxide</i>		
Used	29.6%	0.11
Not used	19.8%	
<i>Intraoperative CSF leak</i>		
Present	17.5%	0.009 ^{f,g}
Absent	33.7%	

^a HTN, hypertension; DM, diabetes mellitus; GH, growth hormone; CSF, cerebrospinal fluid. Excludes patients with isolated hypogonadism associated with “stalk compression” hyperprolactinemia.

^b Hypertension: in a multivariate model, $P = 0.17$, controlling for age and intraoperative CSF leak.

^c Growth hormone-secreting tumor: in a multivariate model, $P = 0.10$, controlling for age and intraoperative CSF leak.

^d Endocrine-inactive tumor type: in a multivariate model, $P = 0.9$, controlling for age and intraoperative CSF leak.

^e Tumor size of 20 mm or greater: in a multivariate model, $P = 0.7$, controlling for age and intraoperative CSF leak.

^f Intraoperative CSF leak: in a multivariate model, $P = 0.002$, controlling for age and maximum tumor size.

^g Independently significant in a multivariate model.

with a new axis loss occurring in 12% of all patients with adenomas of 30 mm or greater in diameter. Improved anterior pituitary function occurred in 49% of patients, including 24% with complete or partial resolution of hypopituitarism not attributable to hyperprolactinemia. The strongest predictors of resolution of hypopituitarism were younger age and no intraoperative CSF leak, as well as absence of hypertension in patients with endocrine-inactive adenomas. “Stalk compression” hyperprolactinemia resolved in 73% of patients. Hypogonadism, when occurring in isolation with “stalk compression” hyperprolactinemia, was significantly more likely to resolve than when occurring with other axis deficits or without hyperprolactinemia.

Previous Reports on New Hormonal Loss or Recovery after Transsphenoidal Adenomectomy

In case series from the past 2 decades, improved postoperative anterior pituitary function was seen in 35 to 50% of patients (32, 36, 38, 48), whereas resolution of DI has not been reported. New anterior pituitary failure has ranged from 2 to

22% (1, 5, 12, 18, 38, 48), and permanent DI has ranged from 0.4 to 15% but is typically 3% or less (1, 8, 10, 12, 18, 19, 24, 25, 37). Pituitary failure after endocrine-inactive adenoma removal has tended to be higher, as documented in the present series, but has ranged widely from 1.5 to 40% (17, 38, 48). In patients undergoing surgery for Cushing’s disease, the rate has generally ranged from 2 to 9% (14, 20, 24, 44) but has been as high as 53% in series in which total hypophysectomy was frequently used (13, 34, 42, 47). The variability in rates of new hypopituitarism likely reflects several factors, including different surgical strategies with respect to normal gland manipulation and preservation, transsphenoidal surgical experience, and hormonal testing protocols.

Clinical Predictors of Hormonal Loss

Using a multivariate model, the present study indicates that larger tumor size is the single strongest predictor of new pituitary failure and that the risk of new hypopituitarism increases significantly at a tumor diameter threshold of 20 mm. Notably, however, even with large adenomas of 30 mm in diameter or

greater that cause severe gland compression, hormonal function can be preserved in over 85% of such cases. Older age and the endocrine-inactive tumor subtype were also associated with a higher rate of pituitary failure in univariate analyses. However, older patients tended to have larger endocrine-inactive tumors, so these 3 factors of advanced patient age, larger tumor size, and an endocrine-inactive tumor are often linked in a given patient. The importance of tumor size as a risk factor for postoperative hypopituitarism in univariate analyses has been reported by others (36, 38). Interestingly, previous studies have found that high intrasellar pressures at the time of adenoma removal correlate with preoperative hypopituitarism and headaches, but not with tumor size (7, 30). Nonetheless, the relatively severe degree of gland compression and thinning typically caused by large macroadenomas suggests that intrasellar hypertension and compromised portal vasculature likely contribute to the vulnerability of the gland to postoperative dysfunction.

There was also a trend of less hormonal loss in the second half of the series overall and in the endocrine-inactive cohort. Other studies have shown that with increasing transsphenoidal experience, outcomes generally improve and complication rates are lower (9, 10, 15). Finally, irrigation with hydrogen peroxide in the tumor resection cavity was not associated with deleterious effects on gland function and, in fact, was associated with a lower rate of new hypopituitarism. This seemingly beneficial effect can likely be explained by the fact that hydrogen peroxide was used on average on smaller tumors and more often later in the series, both factors associated with lower rates of new hypopituitarism. Whether hydrogen peroxide actually reduces the risk of tumor recurrence is unclear, although its tumoricidal effect on adenoma cell lines has been well demonstrated (35).

Clinical Predictors of Hormonal Recovery

In the multivariate analysis, the strongest predictors of pituitary functional recovery were younger age, absence of hypertension (in the endocrine-inactive cohort), and absence of an intraoperative CSF leak. The deleterious effects of advancing age and hypertension on the potential for gland recovery likely relate to the known association of these 2 factors on cerebrovascular disease in general and their specific impact on the hypothalamic-pituitary vascular supply (21, 22, 39). A higher rate of hormonal recovery was also noted in acromegalic patients in the univariate analysis; this has been reported before and may be related to the fact that the GH-secreting tumors tended to be smaller and to occur in younger patients, both factors that are associated with a higher likelihood of hormonal recovery (23). Nomikos et al. (38) also found in univariate analysis that, in patients with endocrine-inactive tumors, smaller tumor size was associated with a greater likelihood of hormonal recovery, but this analysis did not take into account factors of age or systemic hypertension. The finding that an intraoperative CSF leak reduces the chance of hormonal recovery likely reflects a greater degree of surgical manipulation of the infundibulum and gland. In support of

this concept, Nemergut et al. (37) also showed that an intraoperative CSF leak was predictive of permanent DI in patients undergoing transsphenoidal surgery.

This study also shows that isolated hypogonadotropic hypogonadism occurring in association with "stalk compression" hyperprolactinemia (28, 29) is 2 to 3 times more likely to resolve than hypogonadism occurring in the absence of hyperprolactinemia or in association with other axis deficits. Previous series have not addressed this dichotomy in recovery of gonadal function (1, 5, 12, 18, 38, 48), although others have shown that "stalk compression" hyperprolactinemia is a relatively reliable indicator of reversible hypopituitarism (6, 7).

Study Limitations and Strengths

The major limitations of this study are its retrospective nature, lack of a uniform hormonal testing protocol, and missing hormonal data, particularly pre- and postoperative IGF-1 levels and postoperative prolactin levels. Given that many patients were referred from outside physicians with hormonal testing already performed and postoperative hormonal testing completed at outside facilities, missing data were unavoidable in some patients. The overall dataset, however, was complete. Data were available for all 444 patients for surgical events, hypertension, and diabetes mellitus, and only 5 patients (1%) had missing data regarding their smoking history. All 444 patients had complete pre- and postoperative data for adrenal, thyroid, gonadal, and posterior pituitary function status, and 84% of patients had sufficient data to assess for GH deficiency. The infrequent use of stimulation testing for diagnosing GH deficiency is admittedly problematic, because up to one-third of patients with a normal age-adjusted IGF-1 level will have GH deficiency when subjected to a GH-releasing hormone-arginine or insulin tolerance test (26). Thus, the rates of pre- and postoperative GH deficiency documented in this cohort, based predominantly on IGF-1 levels and on coexisting hormonal deficits, likely underestimate the true rate of GH deficiency.

The major strengths of the study are the relatively large patient cohort size and the multivariate assessment of multiple clinical factors associated with hormonal gains and losses. To our knowledge, no previous studies have assessed this spectrum of clinical factors associated with hormonal loss or recovery after adenoma removal in a multivariate fashion. For example, in so doing, these new data suggest that hypertension is a negative prognostic indicator for recovery of hormonal function. The large retrospective study of patients with an endocrine-inactive adenoma by Nomikos et al. (38) did assess tumor size and patient age as factors for hormonal recovery; however, no analysis for loss of hormonal axis was performed, and no data for somatotroph function were presented. In the study by Webb et al. (48) of 234 surgically treated patients, complete pre- and postoperative hormonal data were available for only 55 and 62% of the cohort, respectively. In the large study by Nemergut et al. (37) of 881 patients, the analysis focused on posterior lobe function only.

CONCLUSION

In this series of patients who underwent transsphenoidal adenomectomy, new unplanned hypopituitarism developed in 5% of patients, improvement in hypopituitarism occurred in 24% of patients, and "stalk compression" hyperprolactinemia resolved in over 70% of patients. These results indicate that several patient-specific and perioperative factors are predictive of postoperative pituitary function. The strongest predictor of new hypopituitarism appears to be tumor size, with rates of new hypopituitarism ranging from 0 to 2% for tumors smaller than 20 mm in maximal diameter, and increasing to 12 to 14% for tumors larger than 30 mm in diameter. In contrast, hormonal recovery is most likely to occur in younger patients without hypertension and in those who do not sustain an intraoperative CSF leak.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials or devices described in this article.

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Acknowledgments

We thank the nurses of the neurosurgical units at both medical centers and the General Clinical Research Center at Harbor-UCLA Medical Center (supported by National Institutes of Health Grant RR00425) for care of the patients. We also thank Charlene Chaloner, R.N., and Diana Evans, N.P., for their assistance with data collection.

COMMENTS

Fatemi et al. reviewed a fair-sized group of patients who underwent transsphenoidal surgery for pituitary adenomas. The article has limitations as one would expect from a retrospective study, but the data are interesting and worthwhile. Overall, the results are quite good with new hormone deficiencies seen in 5.5% and improvement in preoperative hormone dysfunction in 49%, a significant percentage of which was resolution of hyperprolactinemia from stalk compression.

The data here show the significant opportunity for improvement in pituitary deficiencies. In some patients presenting with only partial hypopituitarism but no neurologic deficit or hypersecretory syndrome, surgery should be discussed and considered for the opportunity to improve pituitary function and negate the need for replacement therapy. In this article, Fatemi et al. provided valuable data enabling some statistics on the likelihood of improvement. For the group with endocrine-inactive adenomas, 18% gained at least one hormonal axis improvement, whereas 73% had resolution of hyperprolactinemia. Only 7% of this group had new hormonal deficits. The information on which patients are more likely to develop new deficits is less helpful as it correlates with larger size, more traumatic surgery with cerebrospinal fluid (CSF) leak, and hypertension.

Kalmon D. Post
New York, New York

This is a very interesting retrospective study performed by a skillful neurosurgeon specially dedicated to pituitary surgery, together with his qualified group. In the article, Fatemi et al. give relevant statistical confirmation to some aspects we already knew, such as percentages of postoperative hormonal problems or recovery and the factors related to them. What gives particular value to the conclusions presented by Fatemi et al. is the homogeneous and contemporary series of patients who underwent surgery with up-to-date techniques and instrumentation with strict and, again, up-to-date criteria of cure. The correlation of hypertension and intraoperative CSF leak with the final outcome should be kept in mind by all of those involved in this type of surgery.

Paolo Cappabianca
Naples, Italy

Fatemi et al. performed a retrospective analysis of 444 patients who underwent transsphenoidal adenectomy at their institution over an 8-year period and had thorough pre- and postoperative endocrine analysis. They concluded that after pituitary surgery approximately 5.5% of patients have new-onset pituitary deficiencies and nearly 50% of patients have preoperative deficiencies (of all causes including those with hypogonadism owing to hyperprolactinemia of stalk compression) have some improved function. They also noted that preoperative tumor size is strongly associated with new-onset postoperative pituitary deficiencies and that recovery of pituitary function occurs most frequently in young nonhypertensive patients without a history of intraoperative CSF leaks.

Of particular note in this article is the observation that 18% of patients with nonfunctioning adenomas that have some preoperative pituitary dysfunction (excluding those with hypogonadism due to the hyperprolactinemia of stalk compression) recover at least one axis after pituitary tumor removal. This result is particularly useful because this analysis was performed in patients with true pituitary damage (i.e., excluding those who potentially had presurgical pituitary hormone suppression owing to the effects of hypersecretion of cortisol and/or

prolactin). This observation is noteworthy in that neurohypophysial tissue is generally thought to have a low degree of plasticity after damage. In contrast, as demonstrated in this article, the postoperative recovery rate of at least some pituitary function in nearly one-fifth of these patients speaks to the importance of long-term postoperative reevaluation of pituitary deficiencies. In other words, repeat pituitary hormone testing should be performed as late as 3 months after surgery (or longer) to avoid what might otherwise result in unnecessary life-long pituitary hormone replacement.

William H. Ludlam
Marc R. Mayberg
Seattle, Washington

This is a retrospective analysis of postoperative pituitary function after transsphenoidal surgery. There have been many studies of pituitary function after transsphenoidal surgery for pituitary adenomas, and these studies have reported nearly all of the findings of this study. Fatemi et al. points out that the major contribution of this article is an assessment of the multiple clinical factors associated with hormonal gains and losses and that this analysis yields new data suggesting that hypertension is a negative prognostic indicator for recovery of hormonal function. I agree and applaud this finding.

Accurate assessment and management of pituitary function are key factors in optimizing quality of life in patients after pituitary surgery.

Nelson M. Oyesiku
Atlanta, Georgia

In this descriptive study, Fatemi et al. summarized data gathered by a single surgeon over an 8-year period, which represents a commendable effort to better understand the effects of transsphenoidal surgery on postoperative pituitary function.

Demographic factors, select comorbidities, hormone levels, tumor size, and other variables were studied with a view toward defining risk factors for postoperative pituitary dysfunction and characteristics predictive of improved pituitary function after surgery.

Fatemi et al. found that 5% of patients have worsening pituitary function after surgery, with larger tumors being associated with an increased risk of postoperative dysfunction when controlling for other variables. Apparent increases in postoperative hypopituitarism in older patients and in patients with endocrine-inactive tumors were

confounded by tumor size. Of patients with preoperative pituitary dysfunction, 50% demonstrated a recovery of hormonal function in at least one axis. In this report, young patients without high blood pressure and intraoperative CSF leak were more likely to recover function, although the influence of blood pressure seems to be less significant compared with that of age and CSF leaks. That absence of intraoperative CSF leak should herald improved likelihood of functional anterior pituitary restoration resonates with prior reports describing the relevance of intraoperative CSF on outcome. CSF leak has been studied specifically regarding posterior pituitary function and was shown in a series of more than 800 patients to significantly predict permanent diabetes insipidus (1). Finally, the inclusion of the use of peroxide in the analysis will be of interest to those who routinely use this agent for hemostasis. In this report, its increasing use later in the series—as the senior surgeon gained experience—confounds its effect on pituitary function. The results of the article could have been enhanced by an elaboration of Table 2 and a more complete annotation of Table 7.

The article adds to the literature in the range of axes studied in this fashion and in the analytical approach taken, and the rates of postoperative pituitary function are largely consistent with those of prior reports. Among the strengths of this report are the large number of patients and the data set, although a more homogeneous hormone testing algorithm is preferred, as Fatemi et al. suggested. An additional strength is that all patients were operated on by a single surgeon. Although data gathered in a prospective controlled fashion are preferable, these data nevertheless offer surgeons additional information to aid in the management of patients undergoing transsphenoidal surgery. An additional provocative study—alluded to in this report by the inclusion of a handful of endoscopic cases—would involve the acquisition of similar data on microscopic and endoscopic transsphenoidal approaches in a prospective randomized fashion to compare the effects of these surgical approaches on pituitary function.

Ian F. Dunn
Edward R. Laws, Jr.
Boston, Massachusetts

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SUBMISSIONS, PEER-REVIEW, AND DISCLOSURE

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