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The Complete Normalization of the Adrenocortical Function as the Criterion of Cure after Transsphenoidal Surgery for Cushing's Disease

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Transsphenoidal microsurgery is the standard treatment for patients with Cushing's disease. However, there is general lack of agreement regarding the definition of cure.

We studied 58 patients with corrected hypercortisolism after transsphenoidal surgery for Cushing's disease. Plasma and urinary cortisol levels were measured after surgery. After the postsurgical hypocortisolism stage (or periodically in patients without hypocortisolism), urinary free cortisol, plasma cortisol at 0800 h and 2300 h, morning cortisol after 1 mg dexamethasone, and cortisol response to insulin-induced hypoglycemia were performed. Patients were classified in 3 groups: group I, patients with transient hypocortisolism and normal hypothalamus-pituitary-adrenal axis afterwards; group II, patients with transient hypocortisolism and abnormalities in the circadian rhythm or the stress response afterwards; and group III, patients without postoperative hypocortisolism.

Thirty-three patients were included in group I, 8 in group II, and 17 in group III. Groups I and II were similar in postsurgical plasma cortisol (46.9 ± 30.3 *vs.* 60.7 ± 38.6 nM) and mean follow-up (69.8 *vs.* 68.8 months) but were significantly different in their recurrence rate (3.4% *vs.* 50%, $P < 0.001$). Patients in group III had normal postsurgical plasma and urinary cortisol but persistent abnormalities in circadian rhythm and stress response. After a mean follow-up of 39.1 months, their recurrence rate was similar to that of group II (64.7% *vs.* 50%).

The complete normalization of the adrenocortical function, which is always preceded by postsurgical hypocortisolism, is associated with a very low recurrence risk and should be considered, in our opinion, the main criterion of surgical cure in Cushing's disease. (*J Clin Endocrinol Metab* 86: 5695–5699, 2001)

TRANSSPHENOIDAL MICROSURGERY REMAINS the standard treatment for Cushing's disease, and hypercortisolism disappears immediately after surgery in at least 70% of patients (1–5). Despite the widespread acceptance of the procedure, there is general lack of agreement regarding a definition of cure.

In patients with Cushing's disease, high circulating levels of cortisol suppress both CRH secretion in the hypothalamus (6) and ACTH secretion by normal corticotroph pituitary cells. Thus, corticotroph adenoma function is independent from the hypothalamic regulation, so that patients have the characteristic absence of cortisol circadian rhythm and cortisol response to stress. Furthermore, if the excision of the adenoma is complete, ACTH secretion will decline to very low levels. The result is immediate adrenocortical insufficiency, which may persist for many months after surgery (7).

Different groups have tried to establish the degree of postoperative adrenocortical insufficiency that predicts an absence of relapses. We know that patients with higher postsurgical plasma cortisol levels, higher ACTH response to CRH, or shorter time of adrenal insufficiency, have a significantly higher risk of relapse, but there is a considerable overlap between values recorded in patients who do and those who do not relapse (8, 9). Cushing's disease may even recur during follow-up in patients with undetectable postoperative plasma cortisol (5). Some recent studies suggested that the desmopressin test could be useful for the early detection of patients at risk for relapse, but these preliminary results need to be confirmed (10). Given this difficulty in the definition of cure in the immediate postoperative period, some authors prefer the terms: remission, early cure, or apparent cure (2, 5, 8, 11–13).

After a phase of postoperative hypocortisolism, ACTH secretion is expected to be under hypothalamic control if only normal corticotroph cells are present. Thus, the activity of the adrenal axis should be completely normalized, including not only a quantitative restoration of the adrenal function (normal plasma and urinary cortisol values that are normally suppressible with dexamethasone) but also a qualitative normalization of the physiologic characteristics (circadian rhythm and response to stress). The achievement of quantitative and qualitative normalization of the adrenal function has been proposed as a reliable criterion of cure (14, 15); but, to our knowledge, no series of patients have been quantified according to these criteria. In this prospective study, we assess the long-term prognostic value of the complete normalization of the adrenocortical function in a series of patients with Cushing's disease treated with transsphenoidal surgery.

Subjects and Methods

Patients

Between January 1980 and April 2000, 198 patients with Cushing's disease underwent transsphenoidal surgery by the same neurosurgeon

(J. García-Uría). Eighty-nine of these patients have been followed elsewhere. Among the other 109 patients, 34 had persistent hypercortisolism after surgery and underwent pituitary irradiation (16), 9 patients are still in postsurgical secondary adrenal insufficiency, and 8 more patients are now considered as definitely having ACTH deficiency after more than 3 yr of adrenal insufficiency. Fifty-eight patients had surgically corrected hypercortisolism, with or without adrenal insufficiency, and are the subjects of this study.

The diagnosis of Cushing's syndrome was made on the basis of clinical features, the absence of a circadian rhythm in plasma cortisol concentrations, increased urinary cortisol excretion, and characteristic plasma cortisol responses to the administration of dexamethasone (17). The diagnosis of pituitary-dependent disease was usually established by findings of inappropriately high plasma ACTH concentrations, reduction of plasma cortisol concentrations in an overnight high-dose (8 mg) dexamethasone suppression test (18) or a traditional 2-d high-dose dexamethasone test (19), and imaging of the sella turcica with computed tomography or magnetic resonance. In 14 patients in whom the laboratory and radiologic findings were inconclusive, the diagnosis was based on the results of bilateral, simultaneous inferior-petrosal-sinus sampling (20).

Postoperative evaluation

On the day of operation, a steroid cover of 300 mg hydrocortisone was given, and this dose was gradually reduced and interrupted 24 h before any hormonal determination. Endocrinological evaluation was undertaken, 8–12 d after surgery, including plasma cortisol concentrations (4 samples through 24 h) and urinary free cortisol measurement. Patients with postoperative adrenal insufficiency were discharged on hydrocortisone treatment (30 mg/d) and were evaluated every 3 months, with determination of plasma cortisol between 0800 h and 0900 h, 24 h after the last hydrocortisone dose. Hydrocortisone dose was gradually reduced and stopped when plasma cortisol level was higher than 276 nM. Then, an assessment of the adrenal axis was done: urinary free cortisol, plasma cortisol at 0800 h and 2300 h, morning cortisol concentration after 1 mg dexamethasone at midnight and cortisol response to insulin-induced hypoglycemia were performed. Patients with normal plasma and urinary cortisol levels after surgery were discharged without corticosteroid-replacement therapy. They were evaluated 3 months after discharge and then every 6 months, with determination of urinary free cortisol, plasma cortisol at 0800 h and 2300 h, morning cortisol concentration after 1 mg dexamethasone at midnight, and cortisol response to hypoglycemia.

Other pituitary hormones were also studied in all the patients. Serum tiroxine, TSH, gonadotropins, and T or E2 levels were measured 3 months after surgery. GH response to hypoglycemia was studied, 3 months after surgery, in patients with postoperative normocortisolism and once the adrenal insufficiency was over in the patients with postoperative hypocortisolism.

A normal overnight suppression, after 1 mg dexamethasone, was considered when plasma cortisol concentration, at 0800 h, was below 138 nM. Plasma cortisol values at 2300 h that were less than 40% of the values at 0800 h were considered indicative of a normal circadian rhythm of cortisol secretion. The response to insulin-induced hypoglycemia was considered to be normal if the plasma cortisol concentration was above 497 nM at any time during the test (21).

Classification

Patients were then classified in three groups: group I, patients with transient adrenal insufficiency and with normal hypothalamus-pituitary-adrenal axis after the adrenal insufficiency stage [normal urinary free cortisol and recovery of cortisol suppressibility (after 1 mg dexamethasone), cortisol circadian rhythm, and response to hypoglycemia]; group II, patients with transient adrenal insufficiency but with abnormalities in the circadian rhythm or in the stress response afterwards; and group III, patients without adrenal insufficiency after surgery (normal plasma and urinary cortisol).

Long-term follow-up

Patients in groups I and II were followed on the basis of an annual visit in which clinical evaluation and an overnight 1 mg dexamethasone test were performed. Patients in group III were followed, every 6 months, with determination of urinary cortisol excretion, circadian rhythm of plasma cortisol, overnight 1 mg dexamethasone test, and cortisol response to insulin-induced hypoglycemia. A recurrence was considered when signs and symptoms of hypercortisolism reappeared, plasma cortisol after 1-mg dexamethasone test was not suppressed, and urinary cortisol excretion was persistently high.

Hormone assay

Plasma ACTH was measured by RIA before 1989 (Immuno Nuclear Corporation, Stillwear, MN) and thereafter by immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA). Plasma cortisol was measured by RIA until 1992 (ICN Biomedicals, Inc., Costa Mesa, CA; and Immunotech International, Marseille, France) and thereafter by time-resolved fluorescence immunoassay (Delfa System, Wallac, Inc. Oy, Turku, Finland). Cortisol was measured in unextracted urine at low pH by RIA (Diagnostic Systems Laboratories, Inc., Los Angeles, CA; and ICN Biomedicals, Inc.). Serum TSH was measured by immunoradiometric assay (Kodak Amerlite TSH-30 Ultrasensitive assay; Amersham International, Buckinghamshire, United Kingdom). Plasma E2 and T, serum LH, FSH, and PRL were measured with fluoroimmunoassays (Delfia System, Pharmacia). Serum GH was measured by RIA (Nichols Institute Diagnostics) until 1988 and by immunoradiometric assay (Immunotech International) thereafter.

Statistical analysis

Presurgical parameters (age, sex, urinary cortisol, ACTH, surgical findings) and postsurgical parameters (postsurgical plasma cortisol, time of adrenocortical insufficiency, urinary cortisol, plasma cortisol at 0800 and 2300 h, cortisol after 1 mg dexamethasone, response to hypoglycemia, follow-up) were compared between groups, using parametric ANOVA and nonparametric Kruskall-Wallis one-way ANOVA, as appropriate, both followed by the Tukey HSD multiple-comparisons test. The graphic presentation of cortisol circadian rhythm data was done using error-bar graphics, representing mean values and 95% confidence interval. The probability of hypercortisolism-free persistence was estimated by the product-limit method of Kaplan and Meier. Hypotheses for differences between groups were tested using the log-rank nonparametric test. Hypercortisolism-free follow-up was defined as the time elapsed between surgery and recurrence or until the last visit for patients that did not relapse. All tests were two-tailed. Values are given as means and SDs or percentage of patients, unless otherwise indicated. SPSS, Inc. (Chicago, IL) version 10.0 statistical software was used for data analysis.

Ethical approval was granted by the Hospital Ethics Committee. All patients gave informed consent for the realization of the insulin tolerance test.

Results

Following the classification criteria previously presented, 33 patients were included in group I, 8 patients in group II, and 17 patients in group III. Patients in different groups did not differ in any of the presurgical characteristics (Table 1). Interesting enough, no patients with a macroadenoma achieved the functional demands of group 1.

Surgical findings

A tissue thought to be a microadenoma was identified and resected in 40 patients; pathological studies confirmed the presence of an adenoma in 29 of these patients, because the excised pituitary tissue was apparently normal in 4 patients and was too small for adequate evaluation in the rest. A macroadenoma was removed and confirmed pathologically in 6 patients. Finally, in 12 patients, there was not clear evidence of tumor at surgery, and the surgeon carried on a systematical removal of two thirds of the pituitary gland. In 5 out of these 12, the pathological studies confirmed the

TABLE 1. Baseline characteristics of 58 patients undergoing transsphenoidal surgery for Cushing's disease

	All patients	Group I	Group II	Group III
Number of patients	58	33	8	17
Age	39.9 ± 12.6	38.7 ± 12.6	38 ± 9.5	43.1 ± 14
Female/male	48/10	27/6	8/0	13/4
UFC at diagnosis (nmol/d)[a]	1143.8 ± 828.5	1199.6 ± 812	1379.2 ± 1114.1	942.8 ± 737.2
Surgical findings (normal/micro/macro)	12/40/6	6/27/0	2/4/2	4/9/4
Histological findings (adenoma confirmed/not confirmed)	40/18	21/12	6/2	13/4

Classification criteria for different groups are detailed elsewhere in the text. Normal value, 55–331 nmol/d.
[a] UFC, Urinary free cortisol.

existence of an adenoma. Immunohistochemistry staining was done in 16 patients, and it was positive for ACTH in all of them.

The 18 patients without a histologically identifiable adenoma did not tend to fit the criteria for one group more often than another (Table 1).

Endocrinological evaluation

Postsurgical plasma cortisol was 46.9 ± 30.3 nM in group I and 60.7 ± 38.6 nM in group II; this difference was not statistically significant. Patients in group III had an average postsurgical plasma cortisol of 306.2 ± 91 nM ($P < 0.001$, compared with groups I and II) and urinary free cortisol of 149.5 ± 70.6 nmol/d. Patients in group I had a longer period of postsurgical adrenal insufficiency than patients in group II [18.2 (range, 6–34) *vs.* 10.4 (range, 2–15) months, $P < 0.01$].

When adrenal insufficiency resolved and patients were reevaluated, the following results were obtained. Urinary free cortisol was similar in the three groups (109 ± 49.7, 150 ± 85.8, and 149.5 ± 70.6 nmol/d in group I, II, and III, respectively). Plasma cortisol after 1 mg dexamethasone was 35.9 ± 27.6 nM in group I, 66.2 ± 41.4 nM in group II, and 91 ± 55.2 nM in group III ($P < 0.001$ for group I *vs.* group III, NS for other comparisons). Plasma cortisol was similar in all the patients at 0800 h (378 ± 143.5, 339.4 ± 104.8, and 342.1 ± 71.7 nM in groups I, II, and III, respectively, $P = 0.53$, NS), but significant differences were found between groups at 2300 h (63.5 ± 35.9, 215.2 ± 38.6, and 289.7 ± 80 nM in groups I, II, and III, respectively, $P < 0.01$ for all comparisons), indicating an absence of normal circadian rhythm of cortisol secretion in patients in groups II and III (Fig. 1). Cortisol response to hypoglycemia was normal in all the patients in group I, in 5 patients (71.4%) in group II, and in 1 patient (8.3%) in group III. The average increment in plasma cortisol after hypoglycemia was significantly lower in patients in group III (347.6 ± 154.5, 333.8 ± 303.5, and 41.4 ± 85.5 nM in groups I, II, and III, respectively, $P < 0.01$ for group III, compared with groups I and II).

This endocrinological evaluation was periodically performed for patients in group III: normal urinary cortisol excretion and dexamethasone suppressibility, but absence of a normal circadian rhythm, and a normal response to hypoglycemia did not change through follow-up.

Follow-up

Mean follow-up was 69.8 months (range, 18–175) in group I, 68.8 months (range, 15–198) in group II, and 39.1 months

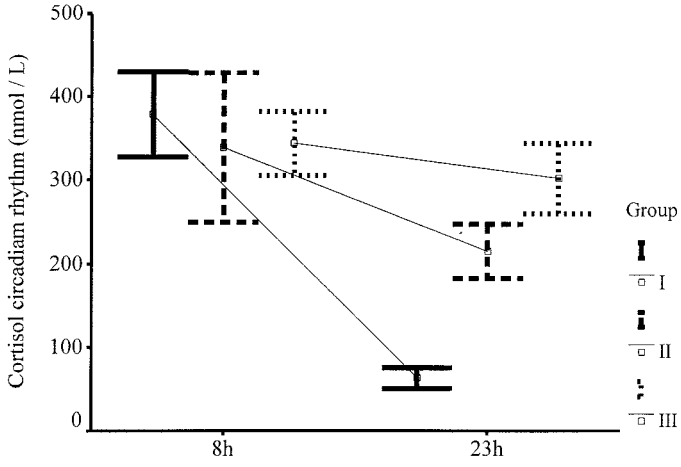

FIG. 1. Plasma cortisol values at 0800 h and 2300 h (mean and 95% confidence interval) in patients in groups I, II, and III. Plasma cortisol was similar in all the patients at 0800 h, but significant differences were found among groups at 2300 h ($P < 0.01$), indicating an absence of normal circadian rhythm of cortisol secretion in patients in groups II and III. Classification criteria for different groups are detailed elsewhere in the text.

(range, 6–103) in group III ($P < 0.05$ for group I *vs.* group III, NS for other comparisons). During this follow-up, 16 recurrences were registered: 1 patient (3.4%) in group I, 4 patients (50%) in group II, and 11 patients (64.7%) in group III ($P < 0.001$ for comparison between group I with groups II and III, NS difference between groups II and III, Table 2). According to the product-limit method, the actuarial probability of hypercortisolism-free survival, 5 yr after surgery, was 100% in group I, 73% in group II, and 23% in group III. Ten years after surgery, these probabilities were 83% for group I, 24% for group II, and 12% for group III (Fig. 2). Significant difference was found in the probability of hypercortisolism-free survival between group I and groups II and III ($P < 0.001$). No significant difference was found between groups II and III.

No significant differences were found between patients in group II who did and those who did not relapse in postsurgical plasma cortisol (46.9 ± 11 *vs.* 71.7 ± 85.5 nM), duration of postoperative adrenal insufficiency [8 (range, 2–12) *vs.* 12.7 (range, 8–15) months], or follow-up [52 (range, 15–84) *vs.* 86 (range, 43–198) months]. Similarly, no difference was found between patients in group III that relapsed and those who did not, in urinary cortisol excretion (143.5 ± 29.2 *vs.* 160 ± 65.1 nmol/d) or follow-up [37 (range, 12–71) *vs.* 43 (range, 12–103) months].

TABLE 2. Postsurgical plasma cortisol, time of adrenal insufficiency and percentage of recurrences during follow-up in 58 patients with corrected hypercortisolism after transsphenoidal surgery for Cushing's disease

	Group I	Group II	Group III
Number of patients	33	8	17
Post-surgical plasma cortisol (nM)	46.9 ± 30.3	60.7 ± 38.6	306.2 ± 91
Months of adrenal insufficiency	18.2 (6–34)	10.4 (2–15)	0
Recurrences, n (%)	1 (3.4)	4 (50)	11 (64.7)
Follow-up (months)	69.8 (18–175)	68.8 (15–198)	39.1 (6–103)

Classification criteria for different groups are detailed elsewhere in the text. Postsurgical plasma cortisol is presented as mean ± SD, duration of adrenal insufficiency and follow-up are presented as mean and range.

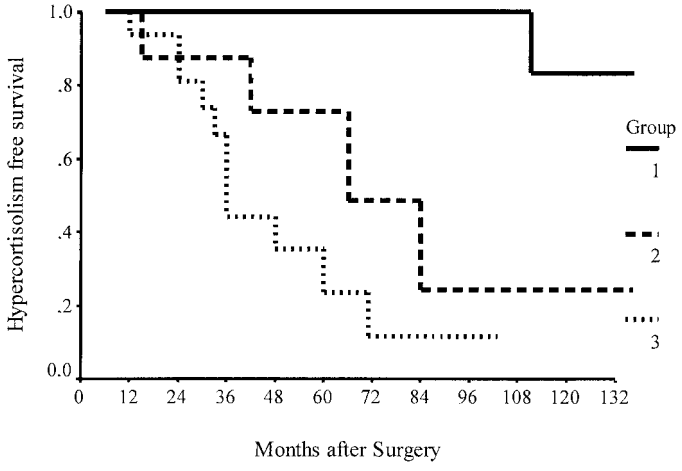

FIG. 2. Kaplan-Meier estimates of hypercortisolism-free survival after transsphenoidal surgery in 58 patients with Cushing's disease. Significant difference was found in the probability of hypercortisolism-free survival between group I and groups II and III ($P < 0.001$). No significant difference was found between groups II and III. Classification criteria for different groups are detailed elsewhere in the text.

Discussion

Postsurgical normalization of plasma and urinary cortisol and recovery of normal dexamethasone suppressibility have been considered as criteria for successful surgery in some series (2, 11, 12, 22, 23), but our results demonstrate that more strict criteria are needed. Patients in group III had quantitative normalization of adrenocortical function after surgery, but functional abnormalities characteristic of Cushing's disease (absence of circadian rhythm and stress response) persisted; and, in most cases (64%), hypercortisolism reappeared during follow-up. Adrenocortical function is dependent, in these patients, on corticotroph cells not inhibited in the immediate postsurgical period and with autonomous behavior, without hypothalamus-dependent characteristics. These findings must be related to persistence of tumoral cells after an incomplete tumor resection, whose subsequent growth is responsible for the relapse of the hypercortisolism. We could not find any parameter able to predict the long-term evolution of these patients. Postsurgical urinary cortisol and time of follow-up were similar in patients who recurred and those who did not. Moreover, the clinical symptoms improved in all cases; and, in our experience, pituitary irradiation effectiveness is not dependent on the time from surgery (16). Therefore, in our opinion, these patients should not receive any additional treatment until hypercortisolism recurs.

Postsurgical hypocortisolism does not always imply a good long-term prognosis in our series. Patients in group II achieved postsurgical adrenal insufficiency, some of them normalized the cortisol response to stress, but none normalized the cortisol circadian rhythm. In this group, hypercortisolism recurred in 50% of patients; actually, once the adrenal insufficiency is over, they are very similar to patients in group III, regarding abnormalities in cortisol circadian rhythm and in percentage of recurrences (50% *vs.* 64%). Differences between these groups (postoperative adrenal insufficiency and, in most cases, recovery of stress response in group II) are likely to depend on the quantity of residual tumor cells. In the patients in group II, these cells seem to be insufficient to prevent postsurgical hypocortisolism and to contribute, to a lesser extent, to the adrenal function at the moment the patients were evaluated, so that hypothalamic CRH is less inhibited and can respond, in most cases, to a potent pharmacological stimulus as hypoglycemia.

Our results confirm the impossibility of establishing which patients are really cured in the immediate postoperative period. No significant differences were found in postsurgical plasma cortisol between patients in groups I and II; and, even if adrenal insufficiency was significantly longer in patients in group I, there was a considerable overlap between both groups (Table 2). Differences between groups I and II became obvious after the adrenal insufficiency stage. Patients in group I had a complete normalization of the adrenocortical function, and their long-term prognosis was excellent, with only one case (3%) of recurrent disease 9 yr after surgery. The main difference between this group and the rest is the cortisol circadian rhythm recuperation. Our results suggest that this is the most sensitive test to detect persistent tumoral corticotrophs. Nocturnal ACTH secretion, responsible for the absence of cortisol circadian rhythm, is autonomous, independent from the hypothalamic regulation, and probably dependent on tumoral cells.

An undetectable postoperative plasma cortisol has been considered necessary for a favorable long-term prognosis in some series (24). Our results do not confirm this concept, because postoperative plasma cortisol in patients in group I is not necessarily undetectable.

No presurgical characteristics predict postoperative evolution; but in our series, none of the patients with a macroadenoma achieved the functional demands of group I. This confirms a greater difficulty in obtaining a complete surgical resection of macroadenomas (25).

Our study outlines the importance of long-term follow-up in patients with Cushing's disease. An immediate postsurgical evaluation can easily identify surgical failures (patients with persistent hypercortisolism or with normal plasma and

urinary cortisol). However, longer follow-up and a more complete evaluation of the functional recovery of the hypothalamus-pituitary-adrenal axis are needed, because parameters studied after the hypocortisolism stage have a higher prognostic value, compared with those obtained in the immediate postoperative period.

We conclude that the complete normalization of the adrenal function (including the normalization of urinary free cortisol, suppressibility after 1 mg dexamethasone, cortisol circadian rhythm, and response to hypoglycemia) is always preceded by postsurgical hypocortisolism, is associated with a very low recurrence risk, and should be considered, in our opinion, the main criterion of surgical cure in Cushing's disease.

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