Adrenocorticotropin levels do not change during early recovery of transsphenoidal surgery for ACTH-secreting pituitary tumors

F.R. Pimentel-Filho*,**,***, A. Cukiert*, F. Miyashita*, M.K.P. Huayllas*, M. Knoepfelmacher***, L.R. Salgado*,***, and B. Liberman*,***

*Division of Endocrinology and Neurosurgery, Hospital Brigadeiro; **Division of Endocrinology, UNOESTE, Presidente Prudente; ***Hypothalamus-Pituitary Unit, Endocrinology, University of São Paulo Medical School, São Paulo-SP, Brazil

ABSTRACT. In patients with ACTH-secreting pituitary tumor the peri-tumoral normal corticotrophs were supposed to be suppressed by cronic hypercortisolemia since frequently they develop transient secondary adrenal insufficiency after pituitary tumor resection and during early postoperative days. We evaluated the ACTH dynamics during transsphenoidal surgery in 16 patients with ACTH-secreting pituitary tumors (6 cured by surgery, 8 not cured Cushing's disease patients and 1 cured by surgery and 1 not cured Nelson's syndrome patients) and tested the hypothesis that in these patients, ACTH secretion from the peri-tumoral normal corticotrophs is inhibited and hence removal of the entire tumor should result in subtle postoperative reduction in plasma ACTH. Blood samples for ACTH determination were obtained from 14 Cushing's disease patients immediately before pituitary gland manipulation and 10, 30, 60, 90, 120, 150 and 300 min after pituitary tumor resection and on postoperative day one. In Nelson's syndrome patients the blood sample was obtained only after tumor removal. All patients received intravenous hydrocortisone during surgery and on the first postoperative day. Patients were considered cured by surgery if they presented adrenal insufficiency after hydrocortisone withdrawal. Mechanical pituitary manipulation induced increase in ACTH level. In all 14 Cushing's disease patients (cured and not cured), mean plasma ACTH levels were significantly greater 10 min after pituitary tumor resection (54.4±12.8 pmol/l) than in the pre-manipulation period (ACTH=26.3±5.3 pmol/l) (p=0.005). In Cushing's disease patients, the ACTH levels did not change significantly until 300 min after pituitary tumor resection either in those 6 patients cured by surgery (at 10 min after pituitary tumor resection ACTH was 54.4±12.8 pmol/l for all 14 Cushing's disease patients and at 300 min after tumor removal ACTH was 39.0±12.6 pmol/l for cured and 41.3±15.7 pmol/l for not cured Cushing's disease patients). The ACTH level also persisted high until 300 min after complete pituitary tumor resection in one cured patient with Nelson's syndrome. ACTH level does not change in the early recovery period after ACTH-secreting pituitary tumor, even in those cured patients, and probably peri-tumoral normal corticotrophs are not completely suppressed by cronic hypercortisolemia (and acute glucocorticoid administration) when these patients are under intense stress, like transsphenoidal surgery. Mechanical pituitary manipulation may induce ACTH release in patients with ACTH-secreting pituitary tumors but probably does not interfere in the maintenance of high ACTH-levels during the early postoperative period, since ACTH half-life is only 8-15 min. In patients with ACTH-secreting pituitary tumors, the behavior of the human hypothalamic-pituitary-adrenal system during transsphenoidal surgery does not conform to the specifications of a negative feedback mechanism.

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Correspondence: Dr. Bernardo Liberman, Division of Endocrinology, Hospital das Clínicas, Universidade de São Paulo, C. Postal: 3671, 01060-970 São Paulo, Brasil.

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INTRODUCTION

The most important endocrinological response to surgical stress includes activation of the hypothalamic-pituitary-adrenal and sympathetic systems. No major hormonal change occurs during anesthesia and surgical exploration. However, during anes-

thesia reversal, endotracheal extubation and in the immediate postoperative recovery period a strong activation of the hypothalamic-pituitary-adrenal axis and adrenomedullary sympathetic system can be observed with substantial increases in plasma ACTH, cortisol and epinephrine (1). A limited number of papers that studied the responses of these systems to surgical stress had included patients with pituitary tumors (2, 3), but no previous study had evaluated, in these patients, the influences on ACTH and cortisol secretion rates of the mechanical pituitary manipulation. Graham *et al.* (3) suggested previously that intraoperative ACTH levels during transsphenoidal surgery for Cushing's disease do not predict cure. In that study no glucocorticoid was administered before or after surgery. However, until recently several authors recommended that Cushing's disease patients should be given larger than normal doses of glucocorticoid replacement intraoperatively and postoperatively to avoid symptoms and signs of acute steroid withdrawal (4-6). In patients with ACTH-secreting pituitary tumor the peri-tumoral normal corticotrophs were supposed to be suppressed by cronic hypercortisolemia since frequently they develop adrenal insufficiency after pituitary tumor resection.

In this paper we evaluated the mechanical pituitary manipulation influences on ACTH release and also studied the pituitary-adrenal ACTH dynamics during and after pituitary tumor resection by transsphenoidal surgery in patients with ACTH-secreting pituitary tumor who received glucocorticoid through the procedure and during the immediate postoperative day.

SUBJECTS AND METHODS

Sixteen patients with pituitary tumors were evaluated before and after transsphenoidal surgery. Imaging of the pituitary tumors was obtained by magnetic resonance (MR; General Electric - Sigma; 1.5 Tesla) in all patients. All patients received identical sedative and anesthetic agents during the procedure. Suggestive tumor tissue was visualized and resected by the same neurosurgeon (AK) using the same surgical technique for all patients. Histological examination and immunohystochemistry confirmed the diagnosis in all patients. Informed consent was obtained from all patients and the research protocol was approved by the Institutional Review Board.

Fourteen patients had Cushing's disease (age= 36.4±3.2 years; 1 male and 13 females) and two had Nelson's syndrome (1 male and 1 female, with age of 16 and 42 years, respectively). They received intravenous hydrocortisone (HC) during surgery and on the first postoperative day: 200 mg during the day of surgery (PO-i)(50 mg immediately before pituitary manipulation, 50 mg 10 min after pituitary tumor resection and 50 mg b.i.d.) and 100 mg (50 mg b.i.d.) during the first postoperative day (PO-1). Nelson's syndrome patients received the same schedule of HC administration of Cushing's disease patients, but the first dose was administered before anesthesia and they were not included for statistical analysis. Six patients with Cushing's disease (group I) were considered cured by surgery. They presented adrenal insufficiency after HC withdrawal with serum cortisol less than 2 µg/dl (<55 nmol/l) (3, 5). In the other eight patients (group II) the hypercortisolism persisted after surgery and they were considered not cured. Only one Nelson's syndrome patient was considered cured in the postoperative period.

The ACTH dynamics were studied before and after pituitary tumor resection in all 16 patients. Blood samples for ACTH determination were obtained immediately before pituitary gland manipulation (and before HC administration for Cushing's disease patients) and 10, 30, 60, 90, 120, 150 and 300 min after pituitary tumor resection and on postoperative day one. Plasma ACTH levels were measured by an automated chemiluminescent enzyme immunoassay kit (IMMULITE, Diagnostic Products Corp., Los Angeles, CA) and the reference range was 2.2-10.2 pmol/l. The inter- and intra-assay coefficients of variance for ACTH were 7.2% and 2.9%, respectively.

Data were analyzed by the Mann-Whitney test (for comparisons between groups), Wilcoxon test (for comparing values before and after pituitary manipulation) and Friedman repeated measures analysis of variance on ranks and Kelss-Newman's multiple range test (for analysis after pituitary tumor resection). Results were reported as mean±SE. *P*-values below 0.05 were considered statistically significant.

RESULTS

In all 14 Cushing's disease patients (groups I and II), mean plasma ACTH levels were significantly greater 10 min after pituitary tumor resection (54.4±12.8 pmol/l) than in the pre-manipulation period (ACTH=26.3±5.3 pmol/l) (p=0.005). This occurred despite the iv administration of 50 mg of HC before pituitary manipulation.

In patients from groups I and II no differences in mean plasma ACTH concentration were found within the first 300 min after tumor resection either in the 6 patients (group I) with complete tumor resection (proved later by the remission of hypercor-

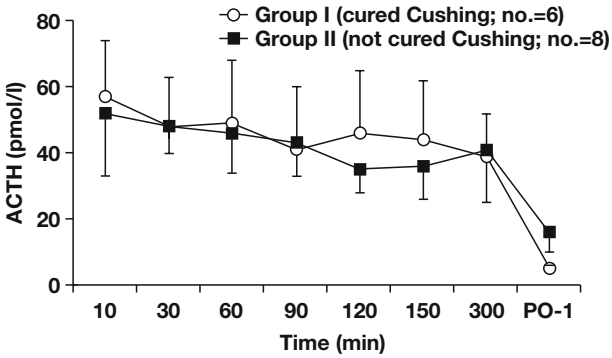

Fig. 1 - *Plasma ACTH (mean±SE) after pituitary tumor resection in patients with Cushing's disease. ○ represents cured patients (group I) and ■ represents not cured patients (group II).*

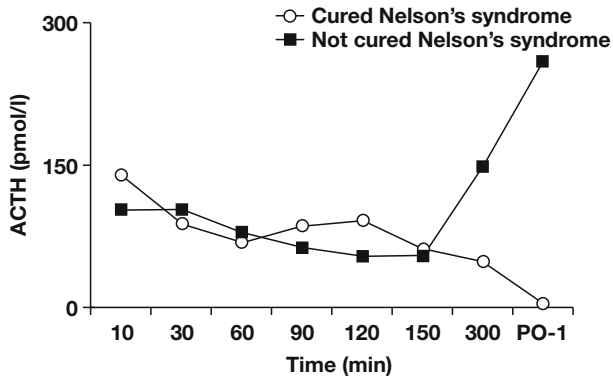

Fig. 2 - *Plasma ACTH level in cured (○) and not cured (■) Nelson's syndrome patients after pituitary tumor resection.*

tisolism) or in the other 8 patients not cured by surgery (group II) (Fig. 1). Only in PO-1 a significant decrease in ACTH level was observed in both groups. The mean plasma ACTH level at 300 min after tumor removal was 39.0±12.6 pmol/l for cured (group I) and 41.3±15.7 pmol/l for not cured (group II) Cushing's disease patients (p=0.95). In PO-1 the mean plasma ACTH was 5.1±0.9 pmol/l for cured and 16.2±5.7 pmol/l for not cured patients (p=0.029). The ACTH level also persisted high until 300 min after complete pituitary tumor resection in one cured patient with Nelson's syndrome (Fig. 2). The other Nelson's syndrome patient was not cured by surgery and the ACTH level at PO-1 evaluation was 259.9 pmol/l.

DISCUSSION

Increased ACTH and cortisol secretion during anesthesia reversal, endotracheal extubation and early recovery has been well documented in some reports dealing with major surgical procedures (1, 2, 7). They are considered the main periods of stress to the patient. It is well known that in normal subjects in a resting state steroid administration supresses ACTH. We also found previously in 8 patients with bilateral adrenalectomy and ACTH-secreting pituitary tumors (6 Cushing's disease and 2 Nelson's syndrome) under non-stressful circumstances that HC (50 mg iv) may partially suppress ACTH secretion which did not return to basal level until 8 hours after HC administration (data not showed). On the other hand, in normal subjects under conditions of surgical stress, corticotrophs may secrete high amounts of ACTH in spite of excess of glucocorticoid administration, suggesting that during stress the behavior of the human hypothalamic-pituitary-adrenal system may not conform to the specifications of a rigid negative feedback mechanism (7). In the present study, Cushing's disease (groups I and II) and Nelson's syndrome patients were submitted to intense surgical stress and showed no change in the ACTH release until 300 min after pituitary tumor resection. Similar results were obtained by Graham *et al.* (3). Recently, they have shown ACTH disappearance curves during the first 60 min after ACTH-secreting pituitary tumor removal and also did not observe significant change in ACTH level either in cured or in not cured patients. This behavior in Cushing's disease was different from those observed in a group of 9 patients (age: 39±5 years; 3 males and 6 females) with non-ACTH-secreting pituitary tumors and normal hipothalamic-pituitary-adrenal axis, in whom a similar ACTH dynamics was studied without glucocorticoid administration (data not showed). A robust ACTH release (approximately 3 folds greater than that of Cushing's disease patients) was observed during the first 300 min after pituitary tumor removal and anesthesia reversal. In these patients the ACTH peak (120 min after pituitary tumor resection) was 182±65 pmol/l while in cured and not cured Cushing's disease patients the ACTH level at the same time (120 min) was only 46±19 and 35±7 pmol/l, respectively. The smaller ACTH release observed in Cushing's disease patients during surgical stress, like in the present study, could not be attributed only to HC administered during the procedure, since in Graham's study (3) the Cushing's disease patients did not receive HC and presented the same pattern of ACTH release. Moreover, Arafah *et al.* (2) observed that ACTH levels, in patients who recovery the pituitary-adrenal function after pituitary macroadenoma resection, reached normal values in spite of glucocorticoid administration, suggesting that subtle use of HC does not interfere in

stressful ACTH secretion. Probably, the chronic (and not acute) hypercortisolemia in Cushing's disease may be responsible for the smaller ACTH release during postoperative stress. Actually, in patients with ACTH-secreting pituitary tumor (Cushing's disease and Nelson's syndrome) an abrupt decline in ACTH level should be expected within 15-30 min (at least one half-life) (8) if tumor resection was complete and peri-tumoral normal corticotrophs were totally suppressed by cronic hypercortisolemia. However, in the present study, we observed that even in those 7 patients cured by surgery (including 1 patient with Nelson's syndrome) the ACTH levels did not change for at least 300 min after tumor resection, suggesting that in these patients (under stress) the pituitary-adrenal system may not follow the feedback mechanism, like in normal subjects or in Arafah's study (2). In addition, this also could suggest that peri-tumoral normal corticotrophs may not be totally suppressed in patients with Nelson's syndrome or Cushing's disease under intense stressful circumstance, like surgery. This hypothesis was previously proposed by Graham *et al.* (3) since they also did not observe a rapid and uniform reduction in ACTH levels during the first 60 min after ACTH-secreting pituitary tumor resection in 11 cured Cushing's disease patients. However, we cannot exclude, only with these data, the possibility that the ACTH measured during this early recovery period reflects secretion by surviving cells or tumor tissue that could infarct with time, as previously suggested by Orth *et al*. (6) and Graham *et al*. (3). Mechanical pituitary manipulation may justify the early rise in ACTH levels, as shown in the present study, but it could not explain the maintenance of high ACTH levels for hours (ACTH half-life=8-15 min) (8). Simmons *et al*. (9) demonstrated that serum cortisol was still elevated 360 min after surgery in a great number of patients (12 of 17 patients) who had achieved remission after transsphenoidal surgery for Cushing's disease and did not receive glucocorticoid during the procedure. Obviously, this cortisol secretion was induced by ACTH secreted during this period, as suggested in this study and by Graham's data (3).

It is not clear which ACTH-releasing factor could be leading to this abnormally set feedback mechanism during surgical stress. Several substances secreted during surgical stress may induce ACTH release such as CRH, vasopressin, angiotensin-II, catecholamines and interleukin-1 and 6 (1, 10). Some of these substances could be acting as potent ACTH-releasing factors. Derijk *et al.* (11) showed that administration of a supra-physiological dose of HC (80 mg) suppressed the lipopolysaccharide-induced interleukin-1β, interleukin-6 and tumor necrosis factor (TNF) α production, whereas administration of a physiological dose (20 mg) of HC suppressed only TNF-α production. In the present study, a similar supra-physiological dose of HC was administered to patients and it is possible that all 3 citokines were suppressed during surgical stress. At least in these cases, the persistent ACTH release could not be exclusively due to these citokines. Udelsman *et al.* (1) demonstrated ACTH and cortisol hypersecretion in the postoperative period of neck exploration procedures despite the absence of increased circulating CRH. These authors (1) also showed significant increase in epinephrine and in plasma renin activity during this period and they should be considered potentially important ACTH-releasing factors. However, plasma elevations of catecholamines during acute glucocorticoid deficiency after surgical treatment for Cushing's disease are not enough to induce an adequate increase in ACTH and cortisol levels (12). Moreover, we observed (unpublished data) in 2 patients with cortisol-secreting adrenal adenoma that the ACTH level was undetectable during the first 300 min after surgery (documented at the same time of that in transsphenoidal surgery), suggesting that in this situation corticotrophs were completely suppressed or that some ACTH-releasing factors secreted during transsphenoidal surgery were not released during adrenalectomy. When neural connections from the operative site are interrupted, such as by sectioning of the spinal cord or epidural anesthesia, the ACTH and cortisol responses to surgery can be abolished, suggesting that afferent nerve impulse mediates the response (6). Persistent ACTH secretion during the immediate postoperative period in patients with ACTH-secreting pituitary tumors may be induced by so far unknown ACTH-releasing factors.

We conclude that ACTH level does not change in the early recovery period after ACTH-secreting pituitary tumor resection, even in those cured patients, and that probably peri-tumoral normal corticotrophs are not completely suppressed in patients with Cushing's disease during the immediate postoperative stress period despite the administration of high doses of glucocorticoids and cronic hypercortisolism. ACTH-releasing factors other than the traditional ones may be responsible in these patients for the persistent ACTH release during transsphenoidal surgery. In patients with ACTH-secreting pituitary tumors the behavior of the human HPA system during transsphenoidal surgery does not conform to the specifications of a negative feedback mechanism, as can be seen in patients

with non-ACTH-secreting tumors. Mechanical pituitary manipulation probably does not interfere in the maintenance of high ACTH-levels during the early postoperative period.

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