Assessment of Cure and Recurrence After Pituitary Surgery for Cushing’s Disease

L. Barbetta¹, C. Dall’Asta¹, G. Tomei², M. Locatelli², M. Giovanelli³, and B. Ambrosi¹

¹Institute of Endocrine Sciences, Ospedale Maggiore IRCCS, University of Milano, Italy
²Institute of Neurosurgery, Ospedale Maggiore IRCCS, University of Milano, Italy
³Neurosurgical Clinic, Ospedale S. Raffaele IRCCS, Italy

Summary

Background. The treatment of choice in Cushing’s disease is transsphenoidal adenectomy with a recurrence rate ranging 9–23%. We investigated whether abnormal hormonal responses may predict the relapse in “operated” patients followed-up for a long period.

Method. Sixty-eight surgically treated patients with Cushing’s disease were followed-up for 12–252 months. Forty-eight patients underwent selective adenectomy, 17 enlarged adenectomy and 3 underwent total hypophysectomy. After surgery ACTH and cortisol levels were measured after stimulatory (desmopressin and CRH) and inhibitory tests (dexamethasone and loperamide).

Findings. After operation 46 patients were cured (group A), 15 patients only normalized cortisol levels (group B), 7 patients were surgical failures. During the follow-up, a disease-free condition was maintained in 48 of 61 cases (79%), while a recurrence occurred in 13 patients (21%, 5 of group A and 8 of group B).

In 5/13 patients who relapsed an absent inhibition after dexamethasone and an exaggerated response to CRH test preceded the recurrence. In 5 other patients the relapse was suspected by loperamide test. In the 3 remaining cases, positive responses to desmopressin preceded the recurrence. In 7/13 patients who relapsed the pituitary tumour was visualized by MRI/CT imaging.

Interpretation. During the follow-up a careful assessment of ACTH dynamics is needed. Although no single test can reliably predict the late outcome, individual patients at risk for relapse may be identified by abnormal responses to desmopressin, CRH and loperamide tests; particularly, the persistent responsiveness to desmopressin may be a criterion of risk for recurrence in patients who only normalized cortisol levels after surgery.

Keywords: Cushing’s disease; corticotropinomas; transsphenoidal surgery; ACTH; cortisol; pituitary adenectomy; recurrence.

Introduction

The hypersecretion of ACTH by a pituitary adenoma (Cushing’s disease) is the most common cause of endogenous hypercortisolism with an incidence in general population between 0.7 and 2.4 cases/million inhabitants per year.

Selective pituitary adenectomy by transsphenoidal microsurgery is widely considered the first choice approach for the treatment of Cushing’s disease. While the cure rate is of the order of 75–80%, a recurrence, defined as the reappearance of tumour and/or hormonal hypersecretion in previously cured patients, occurs in nearly 13% of the cases and progressively increases over the years [2]. Which parameters may herald a recurrence after successful surgery are still a matter of debate. Some epidemiological and hormonal criteria have been suggested as predictive factors of risk for relapse, as younger age, abnormal ACTH and cortisol elevations after TRH or GnRH tests [2], exaggerated responses to metyrapone after adenectomy [17], normal post-operative cortisol levels [6, 10, 16, 18]. After surgery, the persistence of normal basal and CRH-stimulated ACTH/cortisol levels seems to be correlated, although not necessarily, with a higher risk of recurrence; on the other hand, the longer the need for glucocorticoid replacement, the lower the probability of relapse. Whether the persistence of a positive ACTH/cortisol response to desmopressin may be considered as a further criterion of risk is currently under investigation: in fact, the ability of the peptide to raise ACTH/cortisol levels in Cushing’s disease has been reported as helpful for assessing the surgical outcome [3].

Some peri-operative variables, as type of surgery, tumour size and location, do not influence the outcome; on the contrary, patients with pre-operative visualization of the adenoma by MRI or CT scan show earlier recurrence after surgery, suggesting that the larger the adenoma, the higher is the probability that some adenomatous cells may remain and eventually cause a regrowth of the tumour [2].
In this study we report our experience with a large group of patients with Cushing’s disease treated by pituitary surgery who were followed-up for a long period of time after operation; it is shown that the post-surgical reappearance of abnormal hormone responses after endocrine testing are frequently predictive of the clinical recurrence.

**Methods and Patients**

In our Hospital 68 patients with Cushing’s disease (56 women, 12 men, aged 13–70 years, 63 with microadenoma and 5 with macroadenoma) were operated on by pituitary adenectomy and were followed-up for a period longer than 12 months (median 57.5, range 12–252 months). The diagnosis of Cushing’s disease was made on the basis of clinical features and standard hormonal criteria: high urinary free cortisol (UFC) excretion, normal or high plasma ACTH and serum cortisol levels, absent suppression after low-dose dexamethasone tests (1 mg orally overnight and/or 2 mg/day orally for 48 hours) but adequate suppression after high-dose dexamethasone tests (8 mg orally overnight and/or 8 mg/day orally for 48 hours), positive ACTH/cortisol responses after CRH (1 μg/kg iv) and desmopressin (10 μg iv) stimulation. Nuclear magnetic resonance imaging (MRI) and/or high resolution computed tomography (CT) of the sellar region showed a pituitary microadenoma in 40 cases (59%), while 5 patients (7%) had a macro-adenoma. Notably, CT imaging was positive in 63% (24/38) of the investigated cases, while MRI was more effective in detecting pituitary lesions, which were found in 72% (28/39) of the patients studied. Forty-eight patients (70%) underwent selective adenomectomy, 17 (25%) underwent enlarged adenomectomy (i.e. selective adenomectomy with thin layer resection of pituitary surrounding tissue and hemihypophysectomy) and the remaining 3 patients (5%) underwent total hypophysectomy. The diagnosis of Cushing’s disease was confirmed in all patients by the histological examination which showed the presence of adenomatous tissue, with positive staining for ACTH on immunohistochemical analysis.

Plasma ACTH and serum cortisol were measured in all patients after stimulatory (desmopressin and CRH tests) and inhibitory (dexamethasone and loperamide tests) challenges, either before or after pituitary surgery, as elsewhere reported [3].

Patients were repeatedly evaluated during the post-surgical follow-up (at 1, 6, 12, 24 months and then every year).

Plasma ACTH and serum cortisol/UCF levels were measured by IRMA (Nichols Institute, San Juan Capistrano, CA, USA) and RIA (Diagnostic Products, Los Angeles, CA, USA) methods, respectively.

**Results**

After operation 46 patients (68%) were considered as cured (group A), on the basis of clinical and hormonal criteria (serum cortisol and UFC below the normal limits soon after surgery, normal dexamethasone suppression and need for corticosteroid replacement therapy). Fifteen patients (22%) only normalized their cortisol and UFC levels (group B), while 7 patients (10%) were surgical failures.

During the follow-up of the 61 patients of groups A and B, a persistent disease-free condition was maintained in 48 cases (79%, 41 patients of group A and 7 of group B), while a recurrence occurred in 13 patients (21%): 5 of 46 (11%) from group A and 8 of 15 (53%) from group B. As far as the 13 patients who relapsed are concerned (Table 1), in 5 of them (1–3 of group A and 6, 7 of group B) a lack of cortisol inhibition after 1 mg dexamethasone and an exaggerated response to the CRH test preceded the elevation of urinary steroids and the clinical recurrence which appeared 13–84 months after operation.

In 5 other patients (n 4, 5 of group A and 8–10 of group B) the possibility of a relapse was firstly suspected on the basis of an inadequate ACTH/cortisol suppression after the administration of the opioid agonist loperamide and in 2 of them a concomitant exaggerated response to CRH was also present; thereafter, in all 5 cases an absent cortisol inhibition after dexamethasone and high UFC excretion were found. The clinical recurrence appeared 8–84 months following adenomectomy.

In the 3 remaining cases (n 11–13), who only normalized their cortisol levels soon after surgery (group B), persistent positive ACTH/cortisol responses after desmopressin were observed. Subsequently, high UFC excretion appeared and the clinical recurrence occurred 12–24 months after operation.

Only in 7 of the 13 patients who relapsed (n 2, 3, 5 of group A and n 9, 10, 12, 13 of group B), a visualization of the pituitary tumour by MRI or CT scan was found: the Fig. 1 shows the one and only female patient in whom the reappearance of the adenoma was on the contralateral side with respect to the first operation. Six patients underwent a second transphenoidal operation, while other 6 patients were treated by medical or irradiation therapy (Table 1): 3 cases were definitely cured, 1 case normalized cortisol secretion after γ-knife treatment, 5 were unchanged and were administered ketoconazole and 2 patients became hypo-adrenal after bilateral adrenalectomy.

**Discussion**

As the clinical features of hypercortisolism are serious and potentially lethal, the early identification of