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

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Summary

Background. The treatment of choice in Cushing's disease is transsphenoidal adenomectomy 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 adenomectomy, 17 enlarged adenomectomy 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 adenomectomy; 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 adenomectomy 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 adenomectomy [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 micro-adenoma and 5 with macro-adenoma) were operated on by pituitary adenomectomy 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 micro-adenoma 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 existence 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, 18, 24 months and then every year).

Plasma ACTH and serum cortisol/UFC 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 (n 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 transsphenoidal operation, while other 6 patients were treated by medical or irradiantion 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

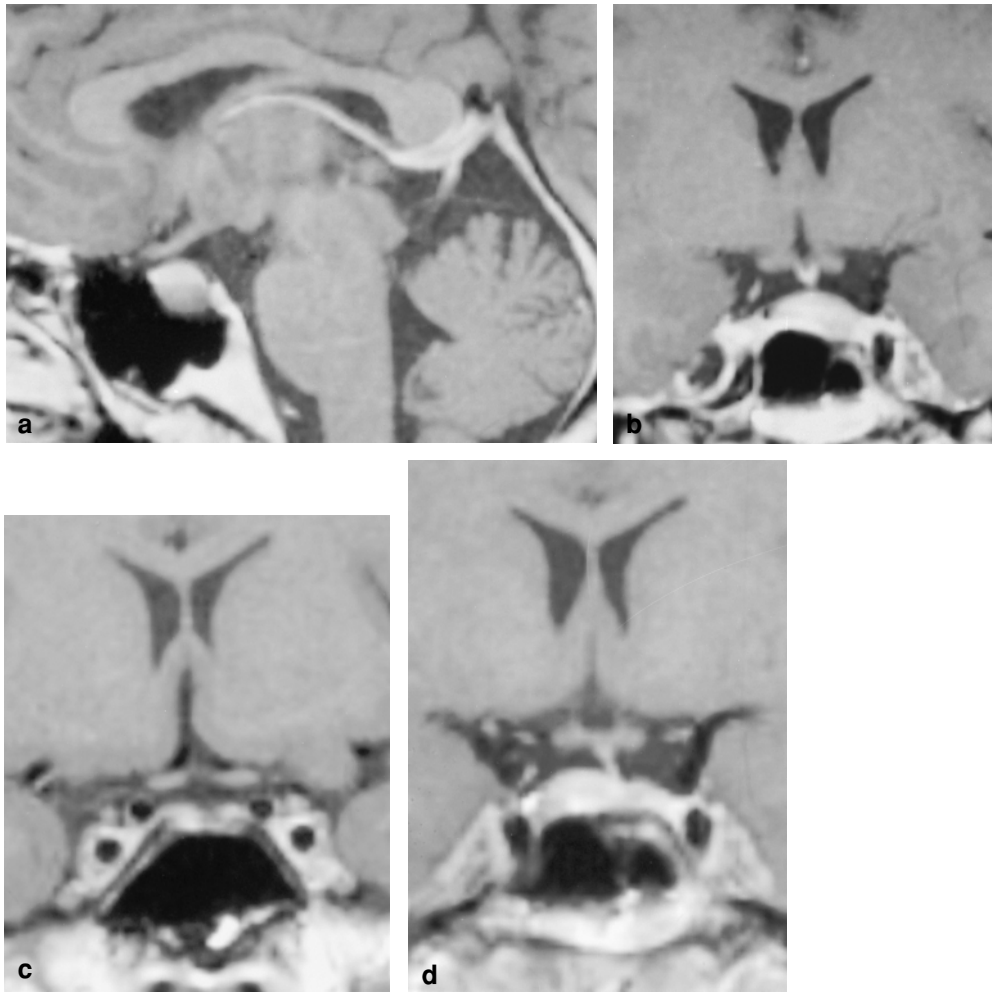

Fig. 1. The T1-weighted MR images in patient no. 13 are shown: pre-operatively a pituitary adenoma is present in the left lobe as shown in the sagittal scan (a) and in the coronal one (b); 12 months after transsphenoidal surgery the pituitary lesion has disappeared (c); 26 months after pituitary surgery a positive image of pituitary adenoma is present in the right lobe (d)

Table 1. *Outcome of Transsphenoidal Surgery and Pattern of Appearance of Relapse in 13 Patients who Recurred During the Follow-up*

Case	Outcome of TSS	Appearance of abnormal endocrine test (*months*)	Appearance of relapse (*months*)	MR/TC imaging at relapse	Treatment of relapse	Subsequent outcome
1	cured	CRH/dexa (*12–84*)	*84*	neg	TSS	cured
2	cured	CRH/dexa (*2–24*)	*60*	pos	TSS/RT/ADRX	hypo-adrenal
3	cured	CRH/dexa (*84*)	*84*	pos	TSS/medical	unchanged
4	cured	Lop/dexa (*40*)	*84*	neg	γ-knife	cured
5	cured	Lop/dexa (*23*)	*23*	pos	γ-knife/γ-knife	normalized
6	normalized	CRH/dexa (*10*)	*13*	neg	*	*
7	normalized	CRH/dexa (*26*)	*26*	neg	TSS/ADRX	hypo-adrenal
8	normalized	Lop/dexa (*7*)	*8*	neg	TSS	*
9	normalized	Lop/dexa (*1*)	*15*	pos	γ-knife/medical	unchanged
10	normalized	Lop/dexa (*1*)	*24*	pos	TSS/RT	cured
11	normalized	desmopressin (*1*)	*12*	neg	medical	unchanged
12	normalized	desmopressin (*1*)	*12*	pos	medical	unchanged
13	normalized	desmopressin (*1*)	*24*	pos	γ-knife/medical	unchanged

dexa Dexamethasone, *Lop* loperamide, *TSS* transsphenoidal surgery, *ADRX* bilateral adrenalectomy, *RT* radiotherapy, * lost at follow-up, *pos* positive, *neg* negative.

patients at risk for a relapse of Cushing's disease after transsphenoidal surgery is of great relevance.

In our experience 68% of patients had low ACTH/cortisol levels after operation and were considered as cured. These results are in agreement with many observations, showing that the early remission rate ranges between 70% and 90% [5, 8, 9, 11, 15]. A percentage of success of 69 and 76%, with a large variability of remission rates (from 52% to 100%), was found in two recent surveys concerning a large series of patients operated on in the last decades [2, 7]. It is well recognized that higher remission rates are increasingly obtained, thanks to the improved experience in the endocrine diagnosis and surgical approach to ACTH-secreting pituitary adenomas.

However, the most important and intriguing problem consequent upon transsphenoidal microsurgery for Cushing's disease is the appearance of recurrences during a long-term follow-up. The evidence of a true relapse, as defined by the reappearance of hypercortisolism in previously cured patients, is a more and more frequent phenomenon, which indicates the need of a cautious interpretation of surgical results.

The early postoperative assessment of cortisol secretion is highly predictive of long-term outcome. Indeed, it is known that not all surgically "successfully" treated patients present low cortisol levels soon after surgery and hypocortisolism is the most important factor predicting a persistent success. In some instances, indeed, plasma ACTH and cortisol levels are only normalized following operation without falling into the hypo-adrenal range, which should be the aim of treatment. The importance of hypocortisolism in the early postoperative period, as a marker of remission and late success, has been emphasized by many authors [2, 6, 7, 12, 16]; in fact, the recurrence rate increases from 4.3%, in patients with undetectable postoperative serum and urinary cortisol values, up to 26.3% in patients with high or normal levels [2, 14]. In our series hypercortisolism reappeared in 21% of operated patients. It is worth noting that 8 cases came out of the group of 15 patients who showed only a normalization of their ACTH and cortisol levels, while only 5 of 46 cured patients, who became hypo-adrenal soon after surgery and required substitution therapy, relapsed, as previously reported [2, 18]. No recurrences were seen in other series of patients with undetectable postoperative cortisol levels [10, 16]. On the whole, these observations do not indicate that patients with "normal" post-surgical levels are at risk of late recurrences, although the incidence of relapse in the latter patients is definitely higher than in cured ones (53% vs 11%).

The most relevant findings in this study are concerned with the hormonal modifications observed during the follow-up. The possibility of relapse has been suspected mainly on the basis of dynamic endocrine testing after surgery. The appearance of ACTH and/or cortisol hyperresponsiveness to CRH test is considered a valuable criterion for identifying patients at risk, as observed in 5 of the 13 patients who relapsed. This altered hormonal pattern has been previously reported also by other authors [13, 18]. The usefulness of desmopressin stimulation in the prediction of relapse has been recently demonstrated by us [3] and confirmed in the 3 patients of the present study who showed ACTH/cortisol responses in the early postoperative period. The ACTH releasing activity of this vasopressin analogue is probably mediated by the V3 receptors, recently cloned in the pituitary and over-expressed in corticotropinomas [4], and may be related to the persistence of adenomatous corticotrophs.

Furthermore, the lack of cortisol suppression after the opiate agonist loperamide observed in 5 patients with normal post operative cortisol levels, suggests that the alteration of the opioidergic control of ACTH secretion is also related to the presence of adenomatous corticotroph cells. In fact in active Cushing's disease there is a defect in the opioidergic control of ACTH secretion, which is reversible, since after successful surgery there is a recovery of a normal opioid inhibition of ACTH secretion [1]. It is of interest that this pattern of hormonal alterations preceded the appearance of the inadequate cortisol suppression after dexamethasone in these cases.

A positive imaging for pituitary adenoma by MRI/CT scan was documented only subsequently during the follow-up in 7 of the 13 patients who relapsed, without any difference between the two groups of patients with low or normal postoperative cortisol levels. Notwithstanding the aforementioned remarks concerning the "doubtful" usefulness of endocrine testing, our data do confirm that the alteration of hormonal responses to stimulatory and/or inhibitory challenges frequently occurs before the reactivation of the disease (in terms of clinical features and positive pituitary imaging). Accordingly, abnormal responses to other stimulatory tests, such as TRH, GnRH and metyrapone [2, 12, 17] have been also described.

In line with the progressive increase in the recur-

rence rate, documented in large series of cases [2, 7, 14], in the present study the appearance of relapse was also long-lasting, from 8 up to 84 months following adenomectomy.

In conclusion, in patients with Cushing's disease a long-term follow-up after pituitary surgery is mandatory: in fact, in surgically treated patients, either cured or with only normalized cortisol levels, a careful assessment of ACTH dynamics is needed. Although no single test can reliably predict the late outcome, individual patients at risk for relapse might be identified by abnormal responses to desmopressin, CRH and loperamide tests; particularly, the persistence of an ACTH/cortisol response to desmopressin stimulation may be considered as a criterion of risk for recurrence in patients who only normalized cortisol levels after pituitary surgery.

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Comments

The recurrence rates of ACTH-secreting pituitary adenomas is higher than those of other adenoma groups. Since Cushing's disease is a severe illness with a 5 year mortality of 50% in untreated cases, strict criteria for endocrinological remission have to be used in order to evaluate patients following surgery. Early diagnosis of recurrence of the disease is paramount. Parameters able to predict the late outcome and/or to identify patients at risk following surgery for Cushing's disease are very useful and are matter of a still ongoing discussion. In this manuscript, Barbetta *et al.* nicely present the close endocrinological follow-up examination in different groups of patients and were able to confirm parameters predicting the long-term outcome. Postoperative hypocortisolism has already been a well accepted and reliable predictor of outcome. The most relevant findings in this study rely on dynamic endocrine testing. Even if no single test can reliably predict the late outcome, the risk of recurrence of the disease correlates with the response to desmopressin, CRH and loperamide tests. The only matter of criticism is that the patients of group B with normalized serum and urinary free cortisol but without suppression during low-dose dexamethasone should not be reckoned as disease free but as surgical failures (persistent disease). For these patients, we suggest further treatment (e.g. re-operation in selected

cases, external radiation and/or adrenalectomy) due to the significantly higher rate of reappearance of clinical symptoms.

R. Fahlbusch and P. Nomikos

This is a very nicely crafted and carefully followed small series of 68 patients that the authors studied in a rigorous fashion with regard to preoperative endocrine testing and have some indication that they can predict relapse based on their endocrine tests. I do believe this information is a bit preliminary, and the testing scheme will probably not be adopted by the majority of surgeons treating Cushing's disease until more convincing endocrine data are available. Regardless of this, I think the information presented is provocative enough and useful enough.

E. R. Laws

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