Transsphenoidal surgery for Cushing's disease

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Based on Pharmacia Lecture to Section of Endocrinology, 16 May 1984

Summary

A series of 101 patients with Cushing's disease underwent transsphenoidal surgery. Diagnosis was fundamentally based on dynamic testing, mainly on the dosage-dependent suppression of cortisol after dexamethasone. The effect of surgery was monitored by intraoperative ACTH measurements. In 96 out of 101 patients a microadenoma of the pituitary was identified and removed selectively. In 74% of patients there was a clinical and endocrinological remission of Cushing's disease. Four 'operative failures' after selective adenomectomy underwent hypophysectomy in a second operation and each remitted. Thus the overall remission rate was 77%. In general, bilateral adrenalectomy was performed in patients who had failed to remit after selective adenomectomy.

Although there is a considerable mortality and morbidity in patients with Cushing's syndrome, complications attributed to surgery were low. Two patients died postoperatively. In general, an improvement of disturbed pituitary function was noted after selective adenomectomy.

Introduction

In his classic study of the basophilic adenomas of the pituitary body, Cushing[1] built upon his original report[2] to provide a precise clinical description of the new syndrome. He also drew attention to 'minute' pituitary adenomas in some of these cases as an autopsy finding[3]. Subsequent experience confirmed that in patients with pituitary-driven hyperadrenalism the pituitary adenomas usually were relatively small, but it emerged that basophilism of the adenoma was not a prerequisite of ACTH secretion[4]. Although Cushing initially championed the transsphenoidal approach, he himself never operated on a patient with the disease that now bears his name. Later, the establishment of the diagnosis of the cause of cortisol oversecretion was advanced by Liddle[5] and others[6,7]. These workers described a regimen of dynamic endocrine testing, based upon the suppressibility of serum cortisol by dexamethasone, which could be used to differentiate Cushing's disease from other causes of Cushing's syndrome, such as the ectopic ACTH syndrome or adrenal neoplasms.

Experience has shown that in most patients the cause of Cushing's syndrome lies in the hypothalamo–pituitary axis, and that in the majority of patients it is due to a pituitary adenoma. The introduction of optical magnification systems for microsurgery and the development of new devices and instruments for microsurgical techniques[8], led to the revival of the transsphenoidal surgical approach[8,9]. The discovery that microadenomas, defined as tumours less than 10 mm in diameter[8], could be visualized and removed with high selectivity and without generalized permanent impairment of pituitary function has stimulated interest and controversy about the results of operation in patients with Cushing's disease.

0141-0768/86/050262-08/$02.00/0

Methods

Patients

Between January 1971 and February 1984, 101 consecutive patients presumed to have Cushing's disease underwent a transsphenoidal exploration of the pituitary. From 1971 to November 1982, patients were treated in the Neurosurgical Clinic, University of Munich, and from December 1982 to February 1984 in the Neurosurgical Clinic, University of Erlangen-Nürnberg. Only 4 patients were operated on before 1976.

Seventy-three patients were female and 28 were male, their ages ranging between 13 and 64 years at the time of surgery (average 37.4 years). In 16 patients disease onset was during childhood or adolescence, and 14 of these underwent operation before the age of 20 years. Six patients had a unilateral adrenalectomy and 2 a subtotal bilateral adrenalectomy before transsphenoidal surgery. No patient received radiotherapy before operation.

The follow up period was 3.2 years in patients having a clinical remission after surgery and 1.6 years in patients regarded as operative failures. None of the patients was followed up for less than 8 months.

Neuroradiological assessment

In all patients preoperative studies included plain skull X-rays, sagittal and coronal 2 mm polytomograms and, from 1975, a CT scan. As conventional CT scanning proved to be generally uninformative, all patients treated after December 1982 ($n=26$) had thin collimation computerized tomography with sagittal and coronal reconstructions generated by a Siemens Somatom DR 3 scanner, with studies before and after injection of contrast medium.

The majority of patients (68/101=67%) had a sella turcica of normal size on plain skull X-rays. Conventional sella polytomography revealed abnormalities in 34 of 68 patients (50%) who did not have pathological changes on plain skull X-rays. The most common abnormalities were an elongation of the sagittal diameter of the sella turcica and a circumscribed bulging of the sella floor.

Thin collimation CT scanning provided the most reliable neuroradiological information, with 22 of the 26 patients assessed by this technique showing signs of a microadenoma. Indirect signs such as a deviation of the pituitary stalk were detected in 55% of patients. In 42% the microadenoma could be visualized as a relatively hypodense intrasellar lesion

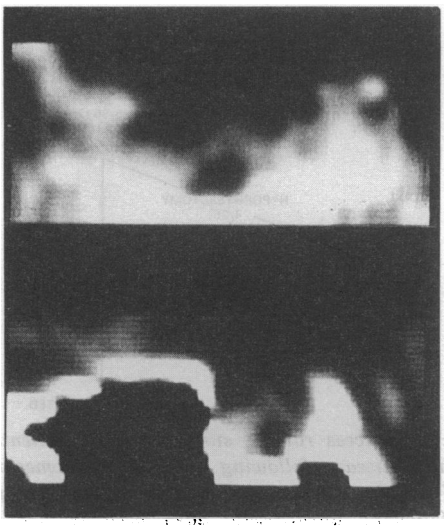


Figure 1. Typical appearance of a pituitary microadenoma in thin collimation CT scan reformations, documented by the findings in a 46-year-old female patient. The region of diminished alteration ('low density zone') is highly suspicious of a microadenoma, confirmed by surgery in this case. The normal pituitary appears to be hyperdense in relation to the adenoma (diameter at operation = 7 mm)

(Figure 1). A herniation of the optico-chiasmatic cistern into the intrasellar space ('partially empty sella') was observed in 50% of cases. Compared with the intraoperative findings, the predicted location of the microadenomas was good in 42% of cases.

Endocrinological assessment

Central ACTH-dependent Cushing's disease was diagnosed by endocrine function tests. The diagnosis was routinely based on: (1) elevated plasma cortisol levels without circadian rhythm; (2) the non-suppressibility of serum cortisol or urine steroids during administration of low-dose (2 mg) dexamethasone overnight; but (3) the suppressibility by at least 50% of serum cortisol levels or urine steroids with high-dose (8 mg or in some cases 16 mg) dexamethasone; (4) the presence of normal or slightly elevated ACTH-levels, despite hypercortisolism; (5) stimulation of cortisol and ACTH release by lysine-vasopressin (LVP) or by corticotropin-releasing factor (CRF).

Anterior pituitary reserve was tested by a stimulation test using 250 µg ACTH, 100 µg LRH and 200 µg TRH and determinations of levels of prolactin, growth hormone, TSH, LH and FSH before and 30 minutes after stimulation pre- and post-surgery.

The secretion dynamics of cortisol and growth hormone were tested by insulin-induced hypoglycaemia. A growth hormone increase of more than 7 ng/ml was regarded as normal[10,11]. In order to monitor the effectiveness of the surgical procedure, pre-, intra- and postoperative ACTH measurements were performed in 86 patients. ACTH was determined by radioimmunoassay using the extraction method of Müller[12]. The normal range was between 20 and 50 pg/ml. Endocrinological testing was repeated 5–6 days after surgery, at 2–3 months and again at 6 months. Endocrinological remission was claimed only when the clinical signs and symptoms of Cushing's syndrome had remitted and a normal suppressibility of serum cortisol after low-dose (2 mg or 3 mg) dexamethasone overnight was documented or a secondary adrenocortical-insufficiency was present.

Responses of ACTH and cortisol to a bolus injection of 0.1 mg ovine CRF (Bachem, Switzerland) were tested in 20 patients preoperatively, all of whom were assessed again after surgery.

Operative technique

The transsphenoidal operation was carried out via a sublabial unilateral paraseptal midline approach, thus sparing the nasal mucosa. The patient was positioned supine with the surgeon sitting at the patient's head; this technique is a modification of Cushing's original method, and is more convenient than operating with the patient in a sitting position[8]. Microsurgery was used as soon as the vomer was exposed. Radiofluoroscopic control was employed to establish the correct site for the opening of the sella floor. The intrasellar space and the walls of the cavernous sinus were carefully and systematically explored in order not to miss parts of an adenoma. Alcoholic solutions were not used to treat the tumour bed.

In no case was subtotal hypophysectomy or resection of periadenomatous tissue performed. In 96 patients an adenoma was removed selectively. In 5 patients an adenoma could not be found; one had a total hypophysectomy performed. As soon as an adenoma was found and removed, hydrocortisone was given intraoperatively in order to avoid relative acute adrenocortical failure. Usually the sella floor was closed by a fascia lata transplant. Nasal tamponade was inserted and removed about 24 hours later.

Results

Intraoperative findings and surgical pathology

In 96 patients an adenoma of the pituitary was found during operation and a selective adenomectomy attempted. In 5 patients an adenoma could not be detected. In one of these cases a hypophysectomy was performed at the first operation. Another patient, for whom information about ACTH levels was not available at the time of surgery, was later found to be suffering from Cushing's syndrome due to ectopic ACTH-secretion by a malignant tumour. Generally we recommended bilateral adrenalectomy either when an adenoma was not found or when the adenomectomy had failed to correct hypercortisolism.

In one patient not included in this series, abnormal dural venous sinus bleeding prevented exposure of the pituitary. This patient later had a bilateral adrenalectomy.

Eight patients underwent a second transsphenoidal operation. Four patients had a hypophysectomy after an unsuccessful initial selective adenomectomy. Four patients were operated upon again for recurrences of hypercortisolism, after an initially successful surgical procedure which had led to a normalization of cortisol secretion for a period.

Thus a total of 100 selective adenomectomies and 5 hypophysectomies were included in the retrospective analysis of these 101 patients (Figure 2). Three patients had a macroadenoma, and in 93 a microadenoma was found. The smallest tumour detected was 2 mm in diameter; 47 of 93 (50%) microadenomas were less than 5 mm in diameter, the remainder having a diameter ranging from 5 to 10 mm. Fifty-one tumours were located in the centre of the pituitary; 25 (26%) were lateralized and 33 had both central and lateral extensions. Six tumours were

found outside the sella. A high percentage of tumours (59/96 = 61%) were well circumscribed; the others were more or less dumb-bell shaped or without well defined borders. In almost all cases tumour tissue appeared to be white and soft. Histopathology with classical staining techniques demonstrated an adenoma of the pituitary in 75 of 96 (78.1%) cases. The majority of these adenomas were chromophobe (20/75 = 26.6%), basophilic (19/75 = 25.3%) or mixed type (12/75 = 16%). Diffuse hyperplasia was found in 6 cases, 5 of whom had a remission after the operation. In 8 cases neither an adenoma nor hyperplasia was found in the classical staining; 5 of these were assessed by immunohistochemistry or cell-culture studies and in each ACTH secretion was demonstrated. In 12 cases no tumour tissue was available for conventional histology.

An evaluation by dispersed cell culture studies[13,14] and immunohistology was performed in 62 cases. ACTH-secreting cells were found in 54 cases. Immunohistochemically the occurrence of ACTH precursors like the pro-opiocortins, β-endorphins, β-lipotrophins, MSH and 16-k fragments could be detected in microadenomas as well as in biopsies from periadenomatous tissue of patients included in this series, as has been reported elsewhere[15].

In 3 patients a haemorrhage into the adenoma was detected. In another 3 histology revealed an increased mitosis rate. All of them had a clinical and endocrinological remission following adenomectomy but were submitted to radiotherapy.

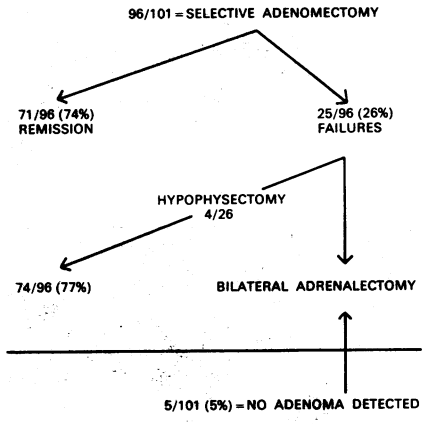


Figure 2. Success rate of surgery in 101 patients with Cushing's disease following selective adenomectomy of ACTH-secreting adenomas. Four patients had hypophysectomy following unsuccessful adenomectomy: one patient had a remission after primary hypophysectomy (not included in this figure) performed because no adenoma could be detected; the 4 other patients without adenomas had bilateral adrenalectomy after exploration of the pituitary.

Operative results

Figure 2 gives an overview of the outcome after operation. Of 96 patients who had a selective adenomectomy, 71 patients (74%) had a clinical and endocrinological remission documented either by secondary adrenocortical insufficiency, expressed by low basal cortisol and ACTH levels, or normal

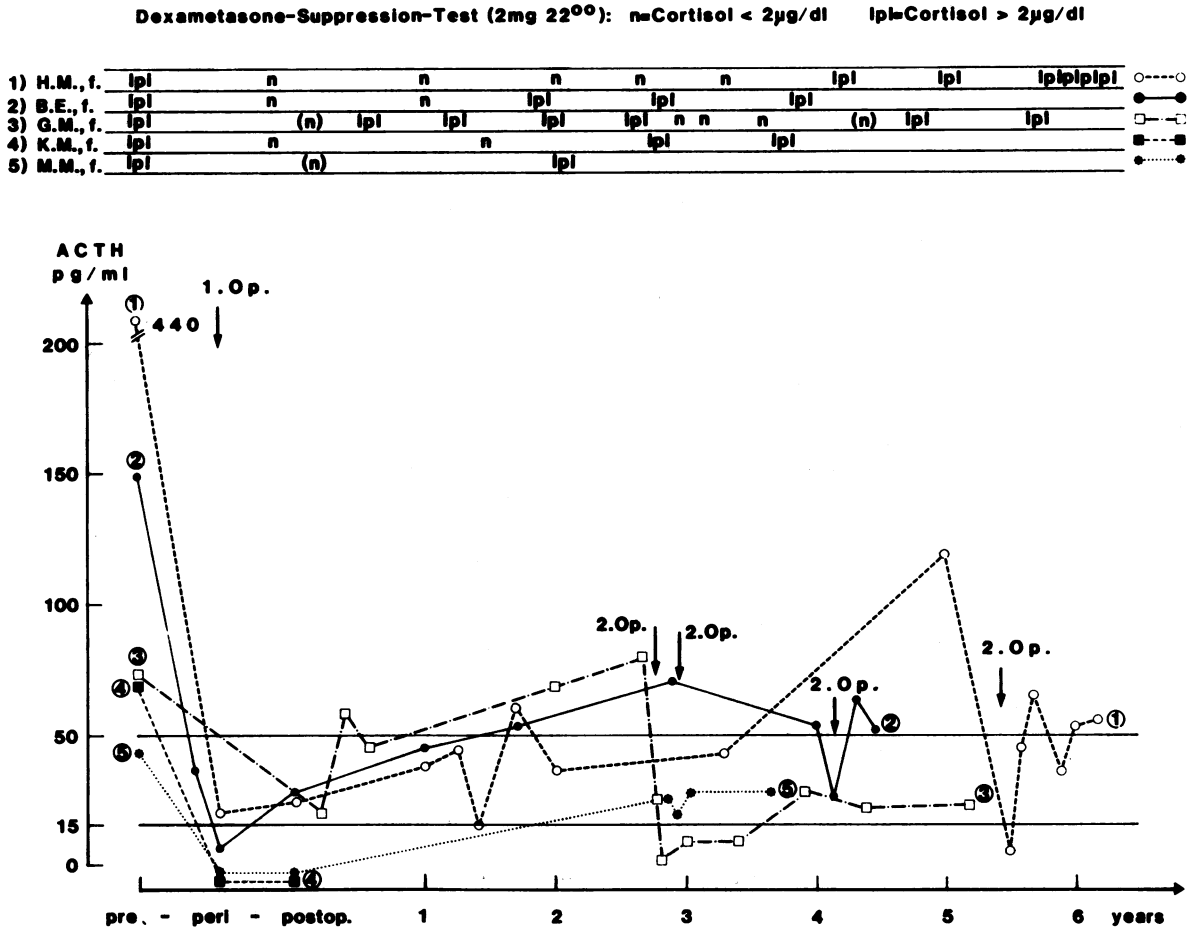


Figure 3. ACTH-levels and results of the low-dose dexamethasone suppression test in 5 patients with recurrent Cushing's disease following successful selective adenomectomy. After initial normalization of ACTH and suppressibility of cortisol after 2 mg dexamethasone (n), *recurrence of Cushing's disease and pathological suppressibility* (p) *were encountered. The pathological response of the 2 mg dexamethasone suppression test preceded clinical recurrence of Cushing's disease. After a second transsphenoidal operation a complete remission was only observed in patient No. 3, who then later had another recurrence.*

suppressibility of cortisol to below 2 μg/dl following 2 mg dexamethasone. A successful microadenomectomy customarily was followed by hypocortisolism, but this usually did not last longer than 6 months. Eight patients required cortisol substitution therapy for more than one year.

One patient in whom a microadenoma was not found at operation had a total hypophysectomy performed. Four others had total hypophysectomy after an unsuccessful attempted adenomectomy. Except for one patient, who died following the second surgical procedure, hypercortisolism remitted in all these patients.

Five patients had a recurrence of Cushing's disease after a first transsphenoidal operation had been documented to be successful either by transient secondary adrenocortical-insufficiency or by normal cortisol suppression after low-dose dexamethasone (Figure 3). Four of these patients had a second operation and in one another remission was achieved, but recently this patient has developed another recurrence.

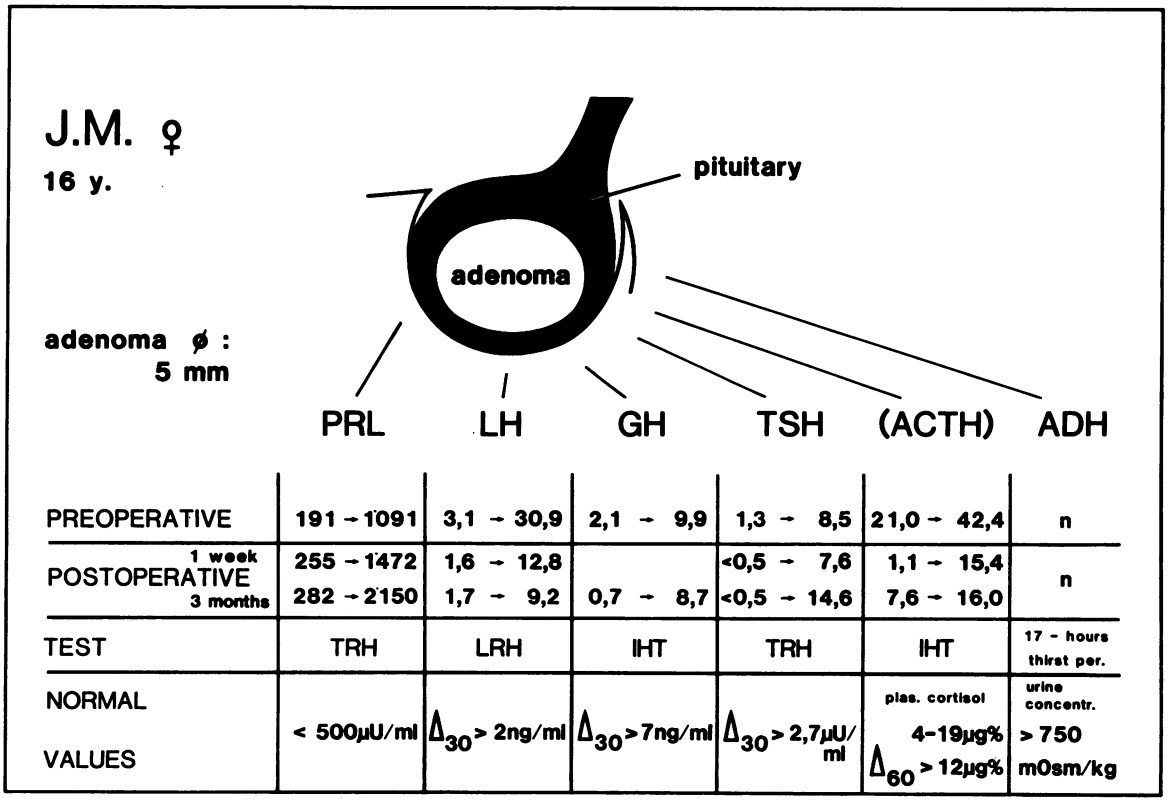
Two patients died from unrelated causes 1.5 and 2 years respectively after surgery. All the other patients have no clinical or endocrinological evidence of recurrent hypercortisolism.

Twenty-one patients have been followed up for more than five years. The longest follow-up period is 14 years in one patient who still has no evidence of recurrent Cushing's disease. Eight pregnancies in 5 women occurred during follow up.

'Catch-up' growth or resumption of a normal growth rate was seen in 8 out of 11 juvenile patients with deficient growth prior to surgery. These functional results are the clinical evidence of the selectivity of the surgical procedure. Clinical and endocrinological remission occurred in 13 out of 14 (93%) children and adolescents operated on before the age of 17 years. Thus the results in juvenile patients were more favourable than in adults.

Generalized anterior pituitary deficiency was not observed in any of the patients who had selective adenomectomy (Figure 4), but was seen in all patients having hypophysectomy. Apart from secondary adrenocortical insufficiency, which occurred in most patients, but which had usually resolved by 6 months after operation, no other permanent damage of anterior pituitary function could be observed in those treated by selective adenomectomy.

In an attempt to establish criteria for predicting the prognosis after operation, 86 patients had ACTH levels measured peri- and postoperatively. A decrease to subnormal levels (<10 pg/ml) was seen in 47 patients, all of whom had clinical remission initially. When there was only a moderate decrease of ACTH, so that it remained within the normal range postoperatively, only 13 out of 21 patients had normal regulation of cortisol following 2 mg dexamethasone. When ACTH levels did not fall much below the initial values or were still elevated (>50 pg/ml) after surgery, only one out of 15 patients had normal regulation of cortisol secretion following insulin-induced hypoglycaemia and dexamethasone. However, in one patient who had a later recurrence of hypercortisolism, ACTH levels were



PREOPERATIVE	191 - 1091	3,1 - 30,9	2,1 - 9,9	1,3 - 8,5	21,0 - 42,4	n
POSTOPERATIVE 1 week	255 - 1472	1,6 - 12,8		<0,5 - 7,6	1,1 - 15,4	n
POSTOPERATIVE 3 months	282 - 2150	1,7 - 9,2	0,7 - 8,7	<0,5 - 14,6	7,6 - 16,0	
TEST	TRH	LRH	IHT	TRH	IHT	17 - hours thirst per.
NORMAL VALUES	< 500μU/ml	Δ_{30} > 2ng/ml	Δ_{30} > 7ng/ml	Δ_{30} > 2,7μU/ml	plas. cortisol 4-19μg% Δ_{60} > 12μg%	urine concentr. > 750 mOsm/kg

*Figure 4. Selective adenomectomy of an ACTH-secreting microadenoma of the pituitary in a 16-year-old girl. As documented by dynamic endocrine testing (ACTH, LRH, TRH-stimulation test and insulin-induced hypoglycaemia) there is no impairment of either anterior or posterior pituitary functions. (*n = *normal*; PRL = *prolactin*; LH = *luteinizing hormone*; GH = *growth hormone*; TSH = *thyroid-stimulating hormone*; ACTH = *adrenocorticotrophic hormone (cortisol-levels indicate ACTH-influence)*; ADH = *antidiuretic hormone*; IHT = *insulin-induced hypoglycaemia testing*)*

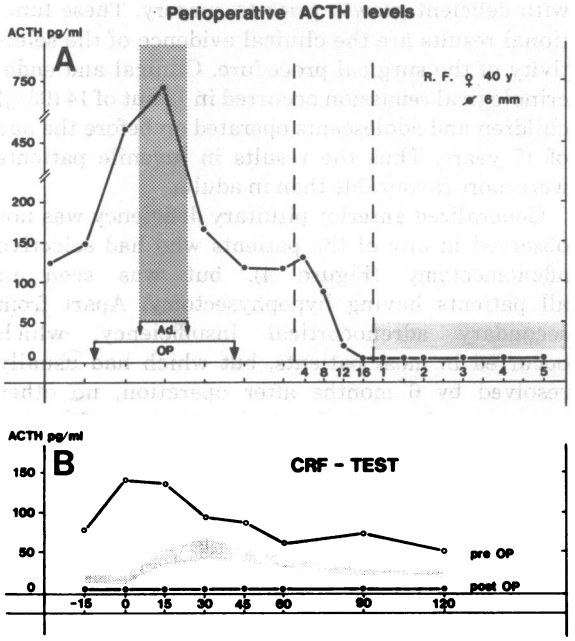


Figure 5. Perioperative ACTH levels (A) *and results of CRF testing* (B) *in a 40-year-old patient.* A: *There was a rapid decrease of preoperatively elevated ACTH-levels into the subnormal range (< 10 pg/ml) after the adenomectomy.* B: *While there was a normal response of ACTH to CRF injection before the operation* (pre OP) *there was no increase of the subnormal ACTH-levels after CRF postoperatively. But subnormal cortisol levels could be suppressed further by low-dose dexamethasone, thus demonstrating successful surgery*

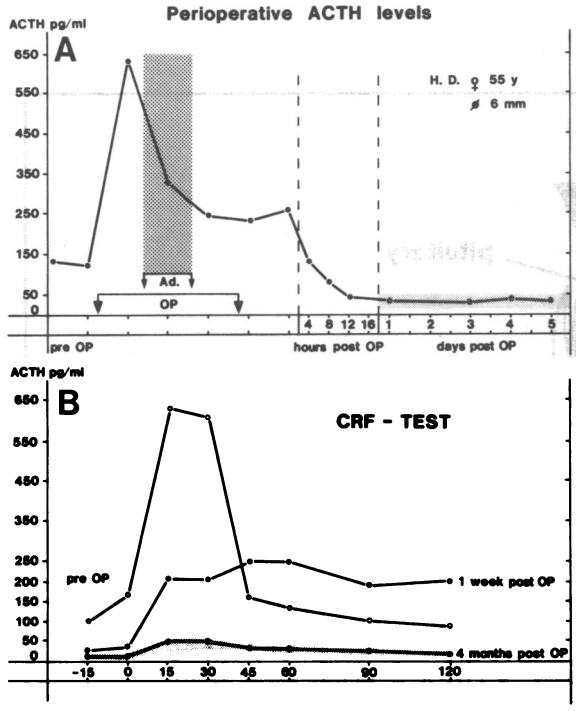


Figure 6. Perioperative ACTH levels (A) *and results of CRF testing* (B) *in a 55-year-old female patient.* A: *There is a rapid decrease of preoperatively elevated ACTH levels into the normal range 20 hours after the adenomectomy* (Ad. = *adenomectomy;* OP = *operation).* B: *Preoperatively* (pre OP) *the elevated ACTH levels responded strongly to CRF. Even one week after surgery there was still a strong response of ACTH, thus demonstrating that CRF regulation was still disturbed. Three months after adenomectomy the response was in the normal range and there was a normal suppression of serum cortisol after low-dose dexamethasone, there having been an abnormal test one week postoperatively*

subnormal for some days after operation but thereafter increased over a period of 6 months, indicating operative failure. Despite such exceptional cases, we feel that perioperative ACTH monitoring can be helpful in predicting the prognosis of operative therapy in ACTH-secreting microadenomas of the pituitary.

Lamberts *et al.*[16] suggested that patients with Cushing's disease whose cortisol was suppressed after acute administration of dopamine agonists had a poor response to transsphenoidal surgery. We tested the dopaminergic sensitivity of ACTH hypersecretion in 14 patients in this series, but found no correlation between the results of surgery and the response of ACTH to lisuride[17].

By contrast, the results of the CRF test seemed to correlate very well with perioperative ACTH levels. To date, 20 patients have been tested by evaluation of the ACTH and cortisol response to bolus injection of 0.1 mg ovine CRF (Figures 5 & 6). Nine patients had subnormal ACTH levels postoperatively and an absent ($n = 5$) or a blunted response to CRF. All had a remission of hypercortisolism, the results of CRF testing showing adrenocortical failure. The CRF test revealed normal basal and stimulated ACTH levels in 4 patients postoperatively, one of whom was an operative failure.

Complications

There was only one death amongst patients having selective adenomectomy or negative sella exploration as the initial surgical procedure. In a total of 106 sella explorations of 101 patients, 2 patients died as a direct consequence of surgery. Both had pneumonia. One young patient died after an apparently successful endocrinologically selective adenomectomy: preoperatively he had suffered from the respiratory distress syndrome and obesity (106 kg), and one week after operation he developed pneumonia which was resistant to antibiotic treatment. The other patient died from pneumonia and meningitis after hypophysectomy performed as a second surgical procedure following an unsuccessful attempted microadenomectomy. These postoperative deaths may be attributed to the fact that we never refused to operate upon a patient, regardless of the severity of disease.

Plebothrombosis and pulmonary embolism were seen in 4 patients following surgery; meningitis was observed in 3 others. There was no CSF fistula. Transient III or IV nerve palsies were seen in 2 cases with an extrasellar location of the adenoma. Transient diabetes insipidus was observed in about 30% of cases whose adenomas were in close proximity to the posterior lobe, but this was permanent in only 2 patients.

Discussion

Neurosurgical treatment has long been impeded by the small size of the pituitary adenomas associated with hypercortisolism, and the difficulties of detecting them. Furthermore, the pathogenesis of the disease still remains controversial. Treatment in the past was generally by either bilateral adrenalectomy or pituitary irradiation[18]. It is still not known if the pituitary microadenomas secreting ACTH and causing hypercortisolism arise as primary neoplasms in the pituitary[19] or secondary to a dysregulation of

hypothalamic CRF secretion[20,21]. Nevertheless, their selective removal via the transsphenoidal approach has proved to be associated with clinical and endocrinological remission.

To select patients suitable for surgery and to rule out other causes of Cushing's syndrome, the diagnosis of ACTH-dependent Cushing's disease must be made on the basis of endocrinological dynamic tests. The response of cortisol to low and high doses of dexamethasone[5] is still the most valuable test[7,22,23] and is only very occasionally misleading[24]. Although an assessment of the ACTH and cortisol response to CRF may be useful in differentiating Cushing's disease from ectopic causes of Cushing's syndrome[10,25], it is not a reliable way to distinguish between the hypothalamic and pituitary origins of Cushing's disease.

Some years ago we suggested[12,26] that perioperative ACTH monitoring might provide a tool to predict the endocrinological outcome shortly after surgery. In practice, almost all patients found to have a secondary adrenocortical insufficiency immediately postoperatively had a sustained remission. But even when subnormal ACTH levels were measured[23], failures and recurrences were seen in exceptional cases. Recurrence after an obviously successful operation, which was followed by normalization of clinical and endocrinological parameters, may favour the concept of a hypothalamic origin of Cushing's disease in some cases. This is particularly likely when multiple recurrences and remissions occur after transsphenoidal surgery[23].

When the findings of dynamic endocrinological tests are equivocal, selective venous sampling of plasma ACTH may solve the diagnostic dilemma[27]. Our current experience suggests that modern thin collimation computerized tomography may reveal intrasellar abnormalities, even in a sella turcica of normal size and without pathological changes in sellar polytomography[28]. Certainly, a normal sella turcica should not preclude patients with an endocrinological diagnosis of Cushing's disease being treated by operation. As reported previously, partially empty sellas occur in association with pituitary microadenomas[29,30], and an enlarged sella turcica in our series was usually due to an accompanying herniation of the basal cisterns into the intrasellar space. The minute size of the adenomas, and their variable location and structure, mean that a meticulous exploration of the intrasellar space is necessary during surgery. Only the transsphenoidal approach, using microinstruments, provides an opportunity of directly inspecting and dissecting the pituitary in order to resect all the tumour tissue selectively and to spare normal pituitary tissue.

In this series, and in the experience of Hardy[31], the majority of the adenomas arose in the central region of the pituitary. It is the opinion of Lamberts *et al.*[16] that central tumours found adjacent to the posterior lobe actually represent intermediate lobe tumours. In contrast to our findings, Boggan *et al.*[32] found the majority of tumours in the lateral wings of the pituitary. In practice, tumours of dumb-bell shape or with extension throughout the pituitary may be defined as central or lateral by different surgeons. The variability of pituitary microadenomas in respect of tumour consistency and outline, and also the frequent occurrence of poorly circumscribed tumours, mean that a selective adenomectomy of an ACTH-secreting microadenoma is the most sophisticated transsphenoidal operation, which challenges even the experienced neurosurgeon.

If an adenoma is not detected during surgery, some authors recommend that a partial or total hypophysectomy should be performed[8,31–33]. This

Table 1. Results of transsphenoidal operations for Cushing's disease

Author	*Centre*	*No. of cases*	*Adenomas found*	*Operative procedure*	*Success rate*	*Recurrences*	*Mean follow up (years)*
Salassa *et al.*[34]	Rochester	18	17 (94%)	Selective adenomectomy	16/18 (88%)	Not stated	1.5
Hardy[31]	Montreal	75	60 (80%)	Selective adenomectomy or subtotal hypophysectomy●	53/63 (84%)	Not stated	Not stated
				Partial or total hypophysectomy■	10/12 (83%)	2	1.75
Kageyama *et al.*[35]	Nagaya	90	85 (94%)	Selective adenomectomy	82/85 (96%)	5	Not stated
				Partial or subtotal hypophysectomy	1/5 (20%)	Not stated	Not stated
Lüdecke[37]	Hamburg	75	66 (88%)	Selective adenomectomy	59/66 (89%)	Not stated	Not stated
Boggan *et al.*	San Francisco	100	85 (85%)	Selective adenomectomy	74/85 (87%)	4	4.6
				Hypophysectomy	7/8 (87%)	Not stated	Not stated
Present series	Munich Erlangen	101	96 (96%)	Selective adenomectomy	71/96 (74%)	5 (0/28)	3.2 (>5)
				Hypophysectomy	4/5 (80%)	(0/4)	(>3)

● adenomas detected histologically
■ no adenoma found on histology

was only occasionally done in our series, for it usually leads to life-long dependency on replacement therapy. Instead we advocate total adrenalectomy if transsphenoidal surgery is not successful.

Experienced neurosurgeons (Table 1) report cure rates ranging from 74% to 93% after selective adenomectomy, but the rate of surgical success seems to depend not only on the experience of the centre where patients are treated[37] but also on the endocrinological criteria for remission and on the constitution of the patient population. In a recent survey[37], the rate of recurrences was found to range from 0% to 100%. Younger people seem to respond more favourably, whatever the treatment used: transsphenoidal microsurgery[38], conventional pituitary irradiation[39], or implantation of Y-90 or Au-198[40]. None of the drugs presently available is suitable as a permanent treatment of Cushing's disease[41]. The selectivity of microsurgical adenomectomy has been demonstrated by endocrinological functional testing[42,43]. Clinical findings, such as the pregnancies observed in our series after operation, attest to the presence of an undamaged anterior pituitary.

Patients with Cushing's disease have a higher mortality than those with other functioning microadenomas[44,45]. This is because of the lowered resistance and poor general condition in many cases. Nevertheless, the overall complication rate is low[31,32,34,46]. Therefore, a transsphenoidal operation, with the aim of a selective adenomectomy of a pituitary microadenoma, should be the first step in treatment as soon as the diagnosis of central, ACTH-dependent, hypothalamo-pituitary Cushing's disease has been established.

Acknowledgments: We thank Drs G K Stalla, Medizinische Klinik Innenstadt, University of Munich, and Dr U Schrell, Neurochirurgische Klinik, University of Erlangen, for their help with the serum ACTH determinations; Drs H L Fehm and K H Voigt, Medizinische Klinik and R Martin, Sektion für Elektronenmikroskopie, University of Ulm, as well as Drs E Adams and K Mashiter, Endocrine Unit, Hammersmith Hospital, London, for the immunohistology and cell culture studies; Dr G Joplin for his initiative of cooperation and advice; and Professor G Teasdale, Glasgow, for his help in preparing the manuscript.

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(Accepted 7 October 1985. This paper is dedicated to Prof Dr Frank Marguth, of Munich, on his 65th birthday)