Clinical Endocrinology (2001) **54**, 617–626

Transsphenoidal pituitary surgery in Cushing's disease: can we predict outcome?

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(Received 14 July 2000; returned for revision 5 September 2000; finally revised 11 October 2000; accepted 9 January 2001)

Summary

OBJECTIVE To assess the results of transsphenoidal pituitary surgery in patients with Cushing's disease over a period of 18 years, and to determine if there are factors which will predict the outcome.

PATIENTS Sixty-nine sequential patients treated surgically by a single surgeon in Newcastle upon Tyne between 1980 and 1997 were identified and data from 61 of these have been analysed.

DESIGN Retrospective analysis of outcome measures.

MAIN OUTCOME MEASURES Patients were divided into three groups (remission, failure and relapse) depending on the late outcome of their treatment as determined at the time of analysis, i.e. 88 months (median) years after surgery. Remission is defined as biochemical reversal of hypercortisolism with re-emergence of diurnal circadian rhythm, resolution of clinical features and adequate suppression on low-dose dexamethasone testing. Failure is defined as the absence of any of these features. Relapse is defined as the re-emergence of Cushing's disease more than one year after operation. Clinical features such as weight, sex, hypertension, associated endocrine disorders and smoking, biochemical studies including preoperative and postoperative serum cortisol, urine free cortisol, serum ACTH, radiological, histological and surgical findings were assessed in relation to these three groups to determine whether any factors could reliably predict failure or relapse after treatment.

RESULTS Of the 61 patients included in this study, 48 (78·7%) achieved initial remission and 13 (21·3%) failed treatment. Seven patients suffered subsequent relapse (range 22–158 months) in their condition after apparent remission, leaving a final group of 41 patients (67·2%) in the remission group. Tumour was identified at surgery in 52 patients, of whom 38 achieved remission. In comparison, only 3 of 9 patients in whom no tumour was identified achieved remission. This difference was significant ($P = 0{\cdot}048$). When both radiological and histological findings were positive, the likelihood of achieving remission was significantly higher than if both modalities were negative ($P = 0{\cdot}038$). There were significant differences between remission and failure groups when 2- and 6-week postoperative serum cortisol levels ($P = 0{\cdot}002$ and 0·001, respectively) and 6-week postoperative urine free cortisol levels ($P = 0{\cdot}026$) were compared. This allowed identification of patients who failed surgical treatment in the early postoperative period. Complications of surgery included transitory DI in 13, transitory CSF leak in 8 and transitory nasal discharge and cacosmia in 3. Twelve of 41 patients required some form of hormonal replacement therapy despite achieving long-term remission. Thirteen patients underwent a second operation, of whom 5 achieved remission.

CONCLUSIONS Transsphenoidal pituitary surgery is a safe method of treatment in patients with Cushing's disease. Operative findings, radiological and histological findings, together with early postoperative serum cortisol and urine free cortisol estimates may identify failures in treatment. Alternative treatment might then be required for these patients. Because of the risk of late relapse, patients require life-long follow-up.

Introduction

Transsphenoidal pituitary surgery (TSPS) has become the accepted form of treatment for patients suffering from pituitary-dependent Cushing's syndrome (Fahlbusch & Buchfelder, 1986; Nakane *et al*., 1987; Melby, 1988; Orth, 1995). It is the only form of treatment that allows removal of an ACTH-producing adenoma without the need for long-term replacement therapy. In the hands of skilled surgeons, success

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rates have varied from 70 to 90%, although this figure drops to less than 70% in series with longer follow-up periods due to late relapses.

We report a series of 69 patients with clinical Cushing's disease who underwent transsphenoidal pituitary surgery. The aim was to report the surgical results, to determine if there are any predictive factors as to outcome and to describe preoperative, peri-operative and postoperative findings.

Patients

Data were collected from patient medical records and updates by letter from referring primary physicians. Sixty-nine consecutive patients presented with presumed pituitary-dependent Cushing's syndrome from 1980 to 1997. Of these, 7 patients were excluded from the analysis due to insufficient or missing medical records. In one further patient exploratory surgery was negative and subsequent investigations suggested ectopic ACTH-dependent Cushing's syndrome. This left 61 patients who underwent a total of 78 operations. The analysis is based mainly on the first operation unless stated. The female to male ratio of 45 : 16 was comparable to other series. The average age at presentation was 37·3 years (range 12–69) of whom 6 patients were below the age of 18. Follow-up periods ranged from 7 to 211 months (median 88).

Five patients had had previous treatment for Cushing's syndrome, one for adrenal adenoma (see under Associated endocrine disorders); two had had pituitary surgery 6 and 9 years previously elsewhere and both had had histological confirmation of an ACTH adenoma. One had been treated with radiotherapy and relapsed the following year. One patient had refused any surgical intervention previously and was medically blocked.

Methods

Diagnosis of Cushing's syndrome

The diagnosis of Cushing's syndrome was made on clinical grounds together with confirmation of:

(a) raised urinary free cortisol (UFC) (normal range < 355 nmol/24 h);

(b) loss of diurnal circadian rhythm (midnight cortisol > 200 nmol/l); and

(c) loss of suppression of UFC and serum cortisol on oral low-dose dexamethasone suppression test (serum cortisol remaining above 100 nmol/l, serum ACTH remaining above 15 ng/l after administration of 0·5 mg dexamethasone every 6 h for 48 h).

The diagnosis of pituitary-driven Cushing's syndrome was made on the following criteria, although not all tests were carried out on every patient:

(a) suppression of UFC and serum cortisol on oral high-dose dexamethasone suppression test (UFC and serum cortisol suppressed by more than 50% of baseline after administration of 2 mg dexamethasone every 6 h for 48 h);

(b) intravenous dexamethasone suppression test (fall of serum cortisol level by more than 190 nmol/l from baseline after administration of 1 mg intravenous dexamethasone per hour for 7 h) (Biemond *et al.,* 1990);

(c) high or normal serum ACTH;

(d) exaggerated or normal response of serum cortisol and ACTH on intravenous h-CRH stimulation (serum cortisol increased by more than 20% of baseline, serum ACTH increased by more than 50% after administration of 100 μg h-CRH at 0930 h, values derived from personal data);

(e) positive demonstration of an adenoma on pituitary imaging (CT with intravenous contrast and/or MRI scans); or

(f) inferior petrosal sinus sampling (IPSS) after administration of CRH (basal ACTH IPS : plasma ratio greater than or equal to 2·0 or peak ACTH IPS : plasma ratio greater than or equal to 3·0).

Assay measurements and statistics

The measurements of urine free cortisol and plasma cortisol depended on the use of biochemical assays. Unfortunately, three different assays were used for each estimate (i.e. UFC and plasma cortisol) over the past 18 years. With different ranges for normal values, it was difficult to compare estimates between various assays. To overcome this problem, a few assumptions were made for each assay used.

1. The assay estimations have a normal distribution.
2. The lower and upper limits of the normal range would encompass 97% of all normal estimates.
3. The lower and upper limits would be two standard deviations from the mean.
4. From this, each value could be expressed in terms of standard deviations and compared. For univariate analysis, the Fisher's exact test was used. To achieve a 2×2 table, the patients in the failure and relapse groups were combined as one and compared with patients in the remission group (see under Definitions). For multivariate analysis, logistics regression was employed. The Mann–Whitney test was used for non-parametric data analysis. A *P*-value of 0·05 or less was considered statistically significant.

Data with normal distribution were expressed as mean ± standard error of the mean (SEM) while data not following a normal distribution were expressed as median and range. To compare means between different groups of patients, the

Table 1 Protocol for postoperative assessment of Cushing's disease

Days 1 and 2	Plasma cortisol 09·00 h and 0000 h Plasma ACTH 09·00 h and 0000 h 24 h UFC × 2 Basal bloods—T4, E2, progesterone or testosterone, FBC, U and E
Day 3	TRH and GnRH tests—TSH, PRL, LH/FSH at 0′, 20′, 60′ Short Synacthen test (SST)—cortisol at 0′, 30′, 60′
Day 4	IST (0·1 U/kg)—glucose, cortisol, GH at 0′, 30′, 60′, 90′, 120′ 2 mg dexamethasone at 2200 h
Day 5	Plasma cortisol and ACTH at 0900 h

Hydrocortisone was discontinued 48 h prior to testing.

Kruskal–Wallis test was used for non-parametric data and one-way ANOVA for parametric data.

Surgical technique

All patients underwent transsphenoidal pituitary surgery by the same surgeon (D.B.M). The aim of surgery was to remove all disease tissue and to leave normal pituitary gland behind if possible. All patients received antibiotics for 1 week starting peroperatively. The sublabial route was used in 56 patients while the pernasal route was used in the remaining five. Image intensification was used to confirm surgical landmarks before entering the pituitary fossa. The majority of patients had spongestan packing of the pituitary fossa after exploration, unless bleeding or a CSF leak warranted muscle packing. All patients received steroid replacement and antibiotics post-operatively (see below).

Postoperative assessment

The postoperative endocrine assessment concentrated on the evaluation of cortisol secretion in the early postoperative period. Data of cortisol estimations and UFC levels at 2 weeks, 6 weeks and 1 year were collected. The values were expressed in SDs and compared using Mann–Whitney test. As in all retrospective studies, the difficulty was that of missing data.

On discharge, the patients were given replacement hydrocortisone in reducing dosage and instructed to return 6–8 weeks later for a more thorough endocrine assessment after discontinuation of hydrocortisone. This protocol is shown in Table 1. Subsequent to the initial tests, UFC and 0900 h cortisol levels were performed at regular intervals, to monitor for recurrence. The overnight dexamethasone suppression test was used in some patients. When adequate suppression was not obtained (usually 1·5 mg dexamethasone given at 2200 h the previous night and 0900 h cortisol levels failed to suppress to below 100 nmol/l), patients were then subjected to a formal low-dose dexamethasone suppression test.

The hypothalamic–pituitary–adrenal (HPA) axis was assessed by short Synacthen test (SST) (250 μg Synacthen, serum cortisol estimations taken at 0, 30 and 60 min) and insulin stress test (IST) (Actrapid insulin 0·1 U/kg administered i.v. at 0900 h and serum cortisol estimations taken at 0,

Table 2 Summary of clinical, radiological, histopathological and operative results

	Remission	Failure and relapse	
Smoking and hypertension			$P = 0{\cdot}085$
Positive history (17)	11	6	
Negative history (16)	15	1	
Radiology			$P = 0{\cdot}153$
Positive finding (37)	27	10	
Negative finding (17)	11	10	
Histology			$P = 0{\cdot}134$
Positive finding (41)	31	10	
Negative finding (19)	10	9	
Operative findings			$P = 0{\cdot}048$
Positive findings (52)	38	14	
Negative findings (9)	3	6	
Tumour size			$P = 1{\cdot}00$
Microadenoma (20)	13	7	
Macroadenoma (10)	7	3	
Histology and radiology			$P = 0{\cdot}038$
Both positive (26)	20	6	
Both negative (9)	3	6	
Histology, radiology and operative findings			$P = 0{\cdot}074$
All positive (26)	20	6	
All negative (2)	0	2	

All *P*-values derived from Fisher's exact test. Values from failure and relapse groups were combined to create a 2 × 2 table.

30, 60, 90 and 120 min) according to Hurel *et al*. (1996). A satisfactory response in the SST for this purpose was considered to be a peak cortisol of more than 550 nmol/l. In the IST, adequate hypoglycaemia was a blood glucose level of less than 2 mmol/l and a satisfactory response was defined as a cortisol level above 550 nmol/l (Plumpton & Besser, 1969).

Non-corticotroph anterior pituitary function was assessed postoperatively with basal serum prolactin (PRL), TSH, LH and FSH levels about 6–8 weeks postoperatively (see Table 1). Releasing hormone tests were also performed postoperatively where indicated.

Definitions

Outcome. The patients were divided into three groups depending on the outcome of their operation. If a patient had more than one operation, the outcome of their first operation would determine the placement. Patients were placed in the remission groups when there was a biochemical reversal of hypercortisolism with re-emergence of diurnal circadian rhythm, resolution of clinical features and adequate suppression on low-dose dexamethasone testing (see under Methods). Reversal of hypercortisolism is defined as the reduction of serum cortisol levels to within normal range for both morning and midnight values. Patients in whom there was absence of any of these parameters formed the failure group. Patients who were placed in the 'relapse group' achieved apparent remission for at least 12 months only to develop evidence of clinical and biochemical Cushing's disease subsequently.

Radiology. Any tumour smaller than 10 mm was considered a microadenoma. Any tumour 10 mm or larger or extending superior to the diaphragm sellae regardless of size was considered a macroadenoma.

Results

Clinical features

Sixteen features in the clinical history were recorded at the time of presentation. These included weight change, striae, acne, hirsutism, pigmentation, bruising, menstrual disturbances, hypertension, diabetes mellitus, muscle weakness, visual disturbances, depression, headache, associated endocrine problems, family history of endocrine disorders and smoking.

Weight change

The average weight at presentation among the 61 patients was 80 kg. Of these, only 54 stated that they had noticed a significant gain in weight in the preceding months. In the remission group, the average weight at presentation was 80·6 kg compared to the failure and relapse groups which was 82·6 and 70·6 kg, respectively. More significantly, the weight loss at about 1 year postoperatively was noted. In the remission and relapse groups, patients lost 9·8 and 8·6 kg on average at 1 year postoperatively compared to the failure group, where the average weight loss was only 3·4 kg. When this was converted to percentage loss of weight, the remission and relapse groups lost 11·7% and 14·1% of their preoperative weight, respectively, at 1 year as compared to 3·4% in the failure group. The differences were not significant.

Hypertension

Hypertension was defined as diastolic pressure greater than 90 mmHg, requiring antihypertensive medication for control. Of the 41 patients in the remission group, 22 had hypertension preoperatively, which resolved spontaneously in 11 patients (50%). In comparison, 11 of 13 patients and 4 of 7 patients in the failure and relapse groups had hypertension preoperatively (not significant). Of these, hypertension resolved spontaneously in only 4 of the 11 (36·4%) and 1 of the 4 patients (25%), respectively.

Associated endocrine disorders

Of the 61 patients, 5 (all in the remission group) had associated endocrine disorders, although these did not coincide in time with the Cushing's disease. They comprised parathyroid adenoma, Hurthle cell tumour, papillary carcinoma of the thyroid, congenital hypothyroidism and adrenal adenoma.

Smoking

A brief history of smoking was taken routinely from every patient. The exact amount was not recorded in the database, but simply whether or not the patient was a smoker. Fifteen of the 41 patients (36·6%) in the remission group were smokers compared with 7 of 13 (53·8%) and 3 of 7 (42·9%) in the failure and relapse groups. The difference was not significant.

Investigations

Preoperative low-dose dexamethasone suppression test. Forty-two patients had low-dose dexamethasone suppression tests performed, 7 of which showed suppression of 0900 h cortisol levels to less than 100 nmol/l and 35 did not (only one suppressed to less than 50 nmol/l). The median value was 322·5 nmol/l, with a range of 23–1094 nmol/l. The diagnosis of Cushing's disease in the 7 patients who showed suppression

was made on other parameters such as UFC, loss of diurnal rhythm and not on clinical features alone.

Preoperative high-dose dexamethasone suppression test. Once the diagnosis of Cushing's syndrome had been made, the high-dose dexamethasone suppression test was employed to differentiate the causes of Cushing's syndrome. Urine free cortisols (UFC) and 0900 h serum cortisols were considered to be suppressed adequately if the values decreased by more than 50% of the baseline value. Of the 32 patients who had UFCs measured, 31 showed adequate suppression. Of the 33 patients who had 0900 h serum cortisols measured, 30 had adequate suppression. The diagnosis of pituitary-dependent Cushing's disease in patients who did not show adequate suppression was made on other parameters such as suppression of UFC on high dose dexamethasone test, intravenous dexamethasone suppression test and positive findings on radiological imaging.

Intravenous dexamethasone suppression test. Seven patients underwent intravenous dexamethasone suppression test. All seven showed suppression of serum cortisol by more than 190 nmol/l of the baseline after administration of 1 mg dexamethasone per hour intravenously for 7 h (Biemond *et al.,* 1990).

Inferior petrosal sinus sampling (IPSS). IPSS with CRH was performed on 4 patients, of whom 3 had negative findings on radiology and 1 had no radiological study. In these 4 patients, IPSS was positive in three patients and indicated a pituitary cause of the Cushing's syndrome while the last one was inconclusive. In the 3 patients who tested positive, tumour was found in only 1 patient at the time of surgery.

Outcome

Of the 61 patients, 48 (78·7%) achieved and remained in remission at least 1 year after surgery and 13 were considered immediate failures. A summary is seen in Fig. 1. Of the 13 failures, 9 underwent repeat pituitary surgery, 2 had adrenalectomy and radiotherapy and 2 had radiotherapy alone. Seven patients suffered re-emergence of Cushing's disease more than 1 year after operation and were thus placed in the relapse group. This leaves a final remission group of 41 (67·2%). The average time for relapse in the 7 patients was 76·1 months (range 22–158). Of these, 4 underwent repeat pituitary surgery, 1 received medical blocking agents, 1 had an adrenalectomy and 1 had adrenalectomy and pituitary irradiation.

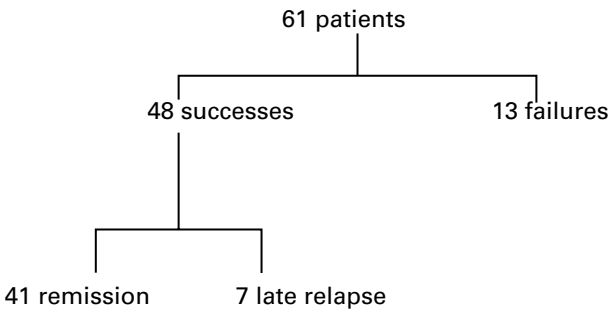

Fig. 1 Summary of outcome.

There were 45 females and 16 males in this series. Thirty-two females (71·1%) and 9 males (56·3%) achieved long-term remission. This difference was not significant (Fisher's exact test $P > 0{\cdot}05$).

Fifty-six patients are currently under follow-up, 2 have been lost to follow-up and 3 have died (1 from pituitary tumour extension, 1 from pulmonary embolus 1 month after hip replacement 10 months after pituitary surgery and 1 of cerebrovascular accident). Of the 41 patients in long-term remission, follow-up periods range from 14 to 211 months (median 83 months).

Radiological imaging

CT scans of the pituitary gland were the mainstay of imaging the pituitary fossa before 1989, after which MRI scanning predominated. All but 3 patients had some form of imaging performed. Thirty-eight patients had CT scans only, of whom 25 (65·8%) revealed a suspicious lesion. Of the 10 patients who had MRI scans only, 8 (80%) were reported as positive. Another 10 had both CT and MRI scans performed. Only 4 of these were positive, 1 on CT and 3 on MRI scanning. When both modalities were combined, 37 lesions were demonstrated while 21 patients had negative findings (Table 2).

Interestingly, no correlation was found between radiological and operative findings. Of the 37 patients who had positive imaging findings, 34 tumours were identified. Of the 21 patients who had negative imaging findings, 16 had tumour seen at operation. In the 16 patients in whom tumour was found despite negative imaging findings, 1 had MRI only, 9 had CT only and 6 patients had both CT and MRI.

When the size of tumour found on radiology was compared with outcome, no statistical difference was noted (Fisher's exact test $P > 0{\cdot}05$).

Operative findings

In 52 patients, an adenoma was thought to be identified of which 38 achieved remission. However, of the 9 patients in whom no tumour was identified, only 3 were in the remission group (Table 2). This difference was statistically significant ($P = 0{\cdot}048$, Fisher's exact test).

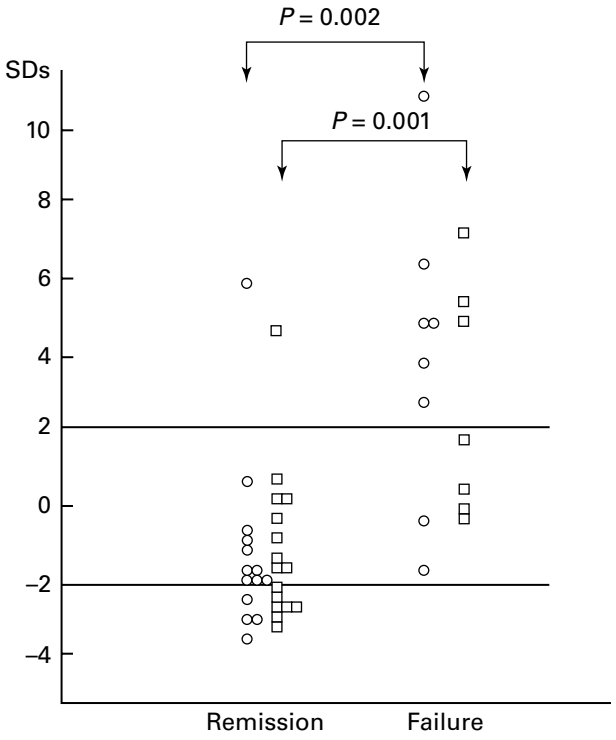

Fig. 2 2-week (circles) and 6-week (squares) postoperative plasma cortisol estimations expressed in standard deviations (SDs).

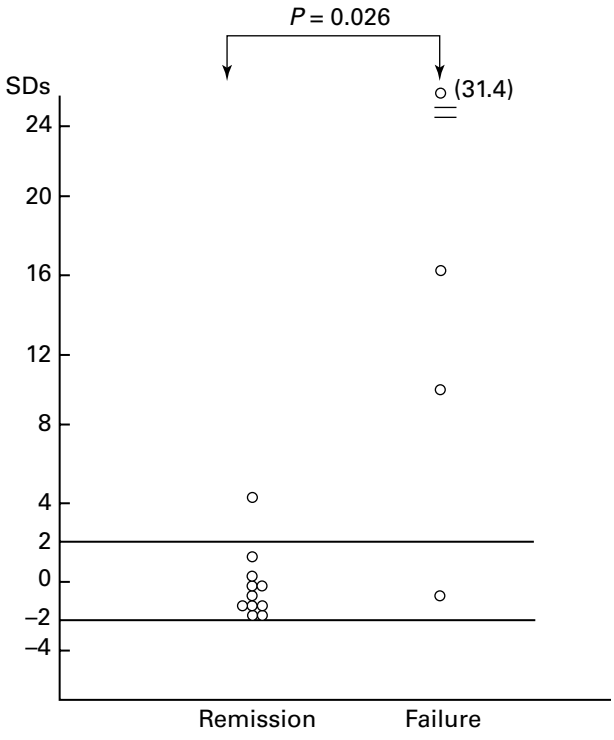

Fig. 3 6-week postoperative urine free cortisol levels expressed in standard deviations (SDs).

Histological findings

Specimens from 60 patients were removed during transsphenoidal surgery and subjected to histology and immunohistochemical staining for anterior pituitary hormones. Tissue was not obtained from 1 patient because of profuse bleeding at the time of operation. Forty-one demonstrated a positive adenoma (including 2 with hyperplasia) while 19 were negative. Of the 41 adenomas demonstrated, 4 did not show immunohistochemical staining for ACTH. In the group with histological evidence of an adenoma, the remission rate was 75·6% compared to the histology negative group, where the remission rate was only 52·4%. (Table 2)

Interesting observations were made when histology and radiology were compared with outcome. Of all the patients who had positive histology and radiology findings, 76·9% belonged to the remission group as compared to the group of patients with negative findings on both histology and radiology where only 33·3% belonged to the remission group. This was statistically significant ($P = 0{\cdot}038$). In simple terms, if a patient had a lesion identified on CT or MRI scan and histopathology confirmed the presence of a tumour, the patient had a significantly higher chance of remission when compared with a patient in whom both these investigations were negative.

However, when histology, radiology and operative findings were compared with outcome, no significant relationship was found. This could be accounted for by the very small number of patients ($n = 2$) in whom all three parameters were negative (Table 2).

Multivariate analysis of variables included smoking, hypertension, operative findings, histology, radiology and outcome was performed using logistic regression. Only operative findings showed a borderline significance ($P = 0{\cdot}052$). The outcome groups were divided into patients in remission and patients who had failed or relapsed in their condition.

Complications

Diabetes insipidus (DI) was the most common complication associated with pituitary surgery. Thirteen of 61 patients (21·3%) developed immediate postoperative DI. Five required desmopression (DDAVP) transiently and 8 resolved without DDAVP. Eight patients suffered CSF leaks (13·1%) during the first operation, all of which were noted at that time and dealt with intraoperatively with muscle packing in the pituitary

fossa. All resolved without further treatment. There were no reports of meningitis or death associated with the operation. Single cases of septal perforation, postoperative epistaxis, hypotension and ischaemic colitis and collapse were noted, the last two being thought to be secondary to Addisonian crisis due to omission of steroid replacement. Three patients complained of postoperative nasal discharge and cacosmia which subsequently resolved.

Postoperative endocrine function

A comparison of the 2- and 6-week postoperative plasma cortisol levels and the 6-week UFC estimations between patients in remission and failure are seen in Figs 2 and 3. The median values for 2- and 6-week postoperative plasma cortisol levels in the remission group were 162·5 nmol/l (range 31–1072) and 221 nmol/l (range 46–880), respectively. In comparison, the same values in the failure groups were 896·3 nmol/l (range 223·5–1622) and 577 nmol/l (range 332–1200), respectively. When the 6-week UFC values were analysed, the median value in the remission group was 134·5 mmol/24 h (range 44–946) compared to 1343·5 mmol/24 h (range 116–2965) in the failure group. These figures should be interpreted with caution since different assays were used throughout the study period. When expressed in SDs, they all show statistical significance. The single patient who showed elevated plasma cortisol level at 2 weeks subsequently tested normal and was placed in the remission group. Similarly, the patient who tested normal initially but subsequently showed elevated values was placed in the failure group.

ISTs were performed to assess the recovery of the HPA axis in 29 patients in remission. Sixteen patients showed suboptimal responses although only 4 subsequently required long-term steroid replacement. In comparison, SSTs were performed in 39 patients of whom 10 showed flat responses. Of these, 5 patients required steroid cover.

In the patients in whom remission was achieved, the recovery of other pituitary axes was assessed. Twelve patients required thyroxine replacement permanently. Four patients in our series have conceived and delivered healthy babies. Interestingly, of these 4 patients, only 1 had a formal GnRH test done and the response was flat. Even though 41 patients were in remission, only 29 patients of these are free from any hormonal replacement therapy, which means that 12 patients required some form of hormonal replacement therapy despite achieving remission.

Second (repeat) operations

Of the 61 patients who had TSPS, 20 patients suffered failure or subsequent relapse. Of these 20 patients, 13 (9 failures, 4 relapses) had a second (repeat) operation in an attempt to remove residual disease. Five of these 13 patients (38·5%) achieved subsequent remission. One was currently being investigated to assess success of the second operation. Three patients were subjected to a third exploration. None achieved remission.

The complication rate was higher in patients who had a repeat(s) operation. Six of 13 patients had CSF leaks (compared to 8 of 61 for first operations).

Is there is a learning curve?

The series of patients were divided into three groups according to the time each patient had their first operation performed. From 1980 to 1986 21 patients had TSPS, of whom 15 were in remission; from 1987 to 1991, remission rate was 12 of 19 and from 1992 to 1997, it was 14 of 21. It seemed that a learning curve was not present in this series of patients.

Discussion

Since Cushing described the finding of basophilic adenomas in the pituitary gland in cases of hypercortisolism in 1932, the search for the most suitable treatment has seen many changes. Pituitary irradiation, bilateral adrenalectomy and drug therapy have all been described (Atkinson, 1991). However, Hardy described the use of transsphenoidal pituitary surgery in 1969 and since then it has become the accepted form of treatment for pituitary-driven Cushing's syndrome. Unfortunately, the results are far from ideal, with failure rates ranging from 10 to 40% (Post *et al*., 1995; Giovanelli *et al*., 1996) and recurrence occurring in up to 25% of patients thought to have achieved permanent remission (Mampalam *et al*., 1988; McCance *et al*., 1993; Sonino *et al*., 1996). Furthermore, most of these series boast follow-up periods ranging from 21 to 80 months. As Tahir & Sheeler (1992) correctly stated, this recurrence rate will increase with longer follow-up periods. Our series boasts long follow-up periods of up to 211 months. This gives greater credence when analysis of the natural history of treated Cushing's disease is made. In addition, all patients were operated on by a single surgeon over the 18-year study period. Few series can make a similar claim. This feature removes the variability in surgical capability inherent in other series and injects a certain amount of consistency when analysing surgical results. To further emphasize consistency, no learning curve could be demonstrated over the 18-year study period. Also, our series attempts to predict outcome of surgery which is important as it could improve treatment. Of greater concern is the considerable percentage of patients left with pituitary endocrine deficiencies. This has led some

surgeons to suggest that adrenalectomy might be the best option in some patients with Cushing's disease (Burke *et al*., 1990; Lindholm, 1992). Bilateral adrenalectomy is associated with an almost 100% cure rate but leaves the patient with a life-long requirement for glucocorticoid replacement. Also, Nelson's syndrome, which is reported to occur in 8–45% of adrenalectomized patients (Burke *et al*., 1990; Etxabe & Vazquez, 1994), poses a therapeutic dilemma. It is for these reasons that proponents of TSPS persevere with attempts to improve on technique and identify factors that may predict potential failure or recurrence.

Before we can even consider how to improve cure rates and decrease the number of relapses, much has to be said about the non-uniformity, and indeed confusion at times, of the definition of cure. Most researchers use a combination of clinical and biochemical parameters (Hardy, 1982; Mampalam *et al*., 1988; McCance *et al*., 1993; Post *et al*., 1995; Bakiri *et al*., 1996; Sonino *et al*., 1996) while others depend solely on biochemical factors (Guilhaume *et al*., 1988; Burke *et al*., 1990; Robert & Hardy, 1991; Flack *et al*., 1992; Lindholm, 1992; Etxabe & Vazquez, 1994; Orth, 1995). Yet others depend solely on resolution of clinical features (Bigos *et al*., 1980). Clearly, any fervent attempt to compare cure rates between different series will be clouded by this lack of consensus.

Hence, much of the research performed on patients with pituitary-driven Cushing's disease have centred around the question on whether there are any factors that might identify patients in whom failure may be more likely after TSPS. The other question revolves round the identification of factors that might predict relapse in patients with Cushing's disease after apparently successful pituitary surgery.

Little attention has been paid to factors that identify patients who do poorly after TSPS. Most studies report their results and leave the reader to make inferences. Few are supported with statistical application. While most studies agree that preoperative variables such as sex, age, clinical symptoms, preoperative biochemical investigations such as serum cortisol, UFC and suppressibility of cortisol by dexamethasone have no bearing on the eventual outcome of surgery, there are others who suggest otherwise. Bochicchio *et al*. (1995) showed that patients with normal or exaggerated ACTH or cortisol response to CRH preoperatively had a significantly lower failure rate postoperatively when compared with patients who had no response. They also found that visualization of an adenoma on CT or MRI scan was a significantly good prognostic factor.

Histopathological confirmation of an adenoma has been claimed to be a good prognostic factor compared to the absence of confirmation. This has been shown by Arnott *et al*. (1990), Bakiri *et al*. (1996), Bochicchio *et al*. (1995); Guilhaume *et al*. (1988) and Sonino *et al*. (1996), all of whom showed statistical significance and supported by Post *et al*. (1995). In our series, when histological confirmation of tumour and radiological identification of tumour was assessed separately, they proved non-significant predictors of outcome. However, when assessed in combination, positive findings on histology and radiology predicted good outcome ($P = 0{\cdot}038$) compared to negative findings for these two investigations.

The size of adenoma noted at time of operation or on pathological analysis has a bearing on the outcome of surgery, larger ones being associated with poorer outcome. Indeed, Mampalam *et al*. (1988) not only agreed with this but also claimed that the presence of extrasellar extension is the main determinant of prognosis. We could not demonstrate this in our series.

In our present series, only the identification of tumour at operation proved a significant predictor of outcome ($P = 0{\cdot}048$). It seemed logical that if tumour could be seen at operation, then it could be removed with confidence. In contrast, when tumour is not seen at operation, blind surgical resection of the presumed tumour or partial hypophysectomy would result in poor curative rates. Our finding is contrary to that of Bakiri *et al*. (1996) and McCance *et al*. (1993), who found the presence of tumour at operation to be of no statistical significance with respect to eventual outcome.

When we looked at biochemical data, we found significant differences in the serum cortisol estimations at 2 and 6 weeks and the UFC estimation at 6 weeks postoperatively in the patients who sustained remission and those who subsequently failed treatment. This data is useful when considering early surgical re-exploration in patients who have failed treatment.

Another pertinent question to address is whether we can identify consistently patients at risk of recurrence after an apparent successful operation or in other words, identify those patients who are less likely to sustain a remission in the long term. The most often-reported parameter is the immediate postoperative endocrinological picture. Theoretically, when an offending adenoma is removed surgically, plasma cortisol and ACTH should fall to very low levels in the immediate postoperative period because normal pituitary tissue remains suppressed as a result of prior hypercortisolism. Similarly, if all adenomatous tissue has been removed, pituitary responsiveness to CRH should be blunted as compared when adenomatous tissue is left *in situ*. Avgerinos *et al*. (1987) and Schrell *et al*. (1987) tested this hypothesis and found that the recurrence rate was significantly higher in patients who showed normal response. Similarly, undetectable serum cortisol levels suggest all tumour tissue has been removed and that sustained remission should be achieved. However, Post *et al*. (1995) and Burke *et al*. (1990) reported 2 patients

each with initial undetectable serum cortisol levels who subsequently relapsed.

This evidence was considered so compelling that Trainer *et al*. (1993) reported the use of pituitary irradiation on 16 of 23 patients with detectable serum cortisols postoperatively and Ludecke & Niedworok (1985) suggested that the early postoperative serum cortisol levels can be used to decide on early re-operation. However, Bochicchio *et al*. (1995) reported only 33 of 135 patients with normal, hence detectable, serum cortisol levels had a relapse and concluded that normal cortisol levels after surgery were not necessarily followed by recurrence of disease. This made any aggressive policy of early re-operation and radiotherapy highly questionable.

More importantly, our series, with its long follow-up period, showed that patients can relapse as long as 158 months after initial treatment. This only serves to reinforce the notion that patients with Cushing's syndrome should have life-long follow-up after TSPS.

Conclusion

In the past, adrenalectomy was the main mode of treatment in patients with Cushing's syndrome. Although this achieved an almost 100% cure rate, it left the patient permanently dependent on hormonal replacement therapy and was associated with a significant risk of Nelson's syndrome or Addisonian crisis. TSPS is the only form of treatment that allows the successful treatment of Cushing's disease without the need for hormonal replacement therapy; it allows selective removal of tumour tissue leaving behind normal pituitary gland. Unfortunately, the success rate varies widely. In our series, although 48 patients (78·7%) achieved initial remission 7 patients relapsed, leaving only 41 of 61 patients (67·2%) in long-term remission. Positive identification both histologically and radiologically predicted a successful outcome, whereas the absence of surgical identification of tumour together with negative findings for both histological and radiological assessment predicted a significantly increased risk of failure of treatment. Those patients who were not adequately treated by TSPS were subjected to other forms of treatment and the Cushing's syndrome eventually eradicated. Our series also demonstrated that serum cortisol and urine free cortisol estimates performed 6 weeks postoperatively were reliable in identifying failures in treatment. This information is useful if these patients are considered for early surgical re-exploration.

Twenty-one patients (34·4%) suffered some form of complication, mostly transitory, or required replacement therapy after the first TSPS operation. There were no deaths, meningitis, significant haemorrhage or persistent CSF leaks.

Although the outcome of transsphenoidal pituitary surgery for pituitary Cushing's is not as good as we would hope, even in skilled hands, it is still to be recommended as the first-line treatment for most cases, provided tumour can be identified radiologically prior to surgery.

Acknowledgements

We would like to acknowledge the contributions made by Dr Keith Hall, Consultant Neuroradiologist, Ms Therese Collins for her efficient and expeditious secretarial work, the staff of PIU, Royal Victoria Infirmary and the Supra-regional Assay Service. Our gratitude also goes out to Ms Janine Gray, Medical Statistician, University of Teeside, Middlesbrough and Dr Dong Fang, Biostatistician, National University of Singapore for their work on the medical statistics.

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