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Biochemical Predictors of Outcome of Pituitary Surgery for Cushing's Disease

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Key Words
Cushing's disease · Pituitary adenoma · Pituitary surgery · Cortisol · Metyrapone · Corticotropin-releasing hormone

Abstract
Objective: Transsphenoidal surgery (TS) is the primary therapy for Cushing's disease (CD). The aims of this retrospective study were twofold: (i) investigate early and late results of TS for CD, and (ii) evaluate various postoperative tests in order to predict the outcome of TS. ***Methods:*** We reviewed the long-term outcome in 79 patients with CD who underwent TS (median follow-up 84 months, range 6–197). Within 2 weeks after surgery, morning serum cortisol concentrations were obtained (n = 78) and corticotropin-releasing hormone (CRH) (n = 53) and metyrapone tests (n = 72) were performed. Three groups of outcome were identified: sustained remission, early failure (persistent CD), and late relapse. ***Results:*** Immediate postoperative remission was achieved in 51 patients (65%), whereas 28 patients (35%) had persistent CD after TS. Ten patients developed recurrent CD after initial remission (20%). *Morning cortisol:* all relapses but one recorded serum cortisol >50 nmol/l. A cortisol threshold value of 200 nmol/l has a positive predictive value of 79% for immediate surgical failure (negative predictive failure [NPV] 97%). *CRH test:* CRH-stimulated peak cortisol ≥600 nmol/l predicted early failure in 78% (NPV 100%). All relapses recorded CRH-stimulated peak cortisol ≥485 nmol/l. *Metyrapone test:* 11-deoxycortisol ≥345 nmol/l predicted an early failure in 86% of cases (NPV 94%). ***Conclusion:*** Predictive factors of surgical failure are morning cortisol ≥200 nmol/l, 11-deoxycortisol ≥345 nmol/l after metyrapone and CRH-stimulated cortisol ≥600 nmol/l. CRH and/or metyrapone testing are not superior to morning cortisol concentration in the prediction of outcome of TS. Careful long-term follow-up remains necessary independent of the outcome of biochemical testing.

Introduction

Cushing's disease (CD) is caused by adrenocorticotropin (ACTH)-secreting pituitary tumors. Transsphenoidal surgery (TS) is the first choice of treatment for CD. Although being a safe treatment, with a reported 30-day mortality in experienced hands of less than 1%, surgical cure is not achieved in all patients [1–3]. The reported initial success rate for pituitary surgery for CD varies between 60 and 86%, however the true rate tends to be low-

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Table 1. Patient characteristics of 79 patients with Cushing's disease

	Sustained remission (n = 41)	Early failure (n = 28)	Late relapse (n = 10)
Mean age in years (SE)	42.3 ± 2.0	39.9 ± 2.5	38.3 ± 4.0
Sex			
Male	11	4	1
Female	30	24	9
Mean follow-up months (SE)	75.9 ± 7.2	91.9 ± 10.2	120.9 ± 19.8
Deaths	4	3	1
Lost to follow-up	4	1	1
Adenoma on MRI			
Macroadenoma	7	12	2
Microadenoma	34	16	8
Visible	27	10	7
Non-visible	7	6	1
BIPSS	17	12	3
Pretreatment			
Ketoconazole	31	23	5
Metyrapone	0	1	0
Postoperative pituitary insufficiency			
No hormonal deficiency	31	19	7
1 axis	4	4	2
2 axes	3	4	1
3 or more axes	3	1	0
Morning cortisol (n = 78)	40	28	10
≤50 nmol/l	18	0	1
50–200 nmol/l	15	1	5
>200 nmol/l	7	27	4
Metyrapone test (n = 72)	37	27	8
11-deox <50 nmol/l	18	0	2
11-deox 50–150 nmol/l	8	0	1
11-deox 150–350 nmol/l	7	3	3
11-deox >350 nmol/l	4	24	2
CRH test (n = 53)	32	18	3
Max. cortisol ≤600 nmol/l	27	0	2
Max. cortisol >600 nmol/l	5	18	1
Max. ACTH ≤10 pmol/l	22	3	0
Max. ACTH >10 pmol/l	2	9	2

er since up to 25% of patients suffer from recurrence after apparent remission [4–12]. Moreover, success and recurrence rates per center largely depend on biochemical criteria which can differ per center. Immediately after successful resection of the autonomous corticotropic adenoma, the remaining corticotropic cells are still suppressed in the majority of patients. Therefore, low or undetectable postoperative serum cortisol levels are associated with long-term remission [1, 6, 12–16]. Inability to increase the secretion of ACTH (and subsequently 11-deoxycortisol secretion) after administration of metyrapone, an 11β-hydroxylase (CYP11B1) blocker, may also indicate complete surgical excision of the pituitary adenoma [17]. Since corticotropic pituitary adenomas are generally susceptible to stimulation by corticotropin-releasing hormone (CRH), responsiveness to CRH in the early postoperative phase may reflect incomplete resection of adenoma and an increased risk of recurrence [6, 7, 18–21].

The objective of this survey was twofold: (i) to investigate the early and late results of pituitary surgery for CD, and (ii) to compare the predictive values of three early postoperative tests (morning serum cortisol concentration, CRH test, and metyrapone test) in the individual assessment of outcome defined by 24-hour urinary free cortisol (UFC) excretion and 1 mg overnight dexamethasone testing at 12 weeks after pituitary surgery.

Patients and Methods

Patients

Seventy-nine consecutive patients underwent primary pituitary surgery for CD at the Erasmus Medical Centre Rotterdam between 1991 and 2006. We reviewed our data retrospectively. The study was approved as an institutional case-note review. The mean age of patients at the time of surgery was 40.8 years (SE 1.46). The median follow-up period was 84 months (range 7–121). Sixty-three patients were female (80%). Clinical characteristics of patients are detailed in table 1.

All patients were diagnosed preoperatively with CD according to the following criteria: clinical features, elevated excretion of free cortisol in 24-hour urine samples on at least two occasions, insufficient suppression of serum cortisol after 1 mg overnight dexamethasone (cutoff 50 nmol/l), loss of normal circadian rhythm of cortisol secretion and non-suppressed plasma ACTH levels in the presence of normal or elevated serum cortisol levels. Radiological imaging of the pituitary was performed by magnetic resonance imaging (MRI). Macroadenoma was defined as a pituitary tumor with a diameter of >1 cm in any dimension on radiological imaging [22]. Pituitary adenomas not visible on preoperative MRI or adenomas <1 cm in diameter were classified as microadenomas. The study population consisted of 21 patients with macroadenomas and 58 patients with microadenomas. Fourteen microadenomas could not be visualized preoperatively by MRI. Bilateral inferior petrosal sinus sampling (BIPSS) was performed if the size of the adenoma was <6 mm, or if no adenoma was present on radiological imaging. Basal bilateral petrosal sinus-to-peripheral plasma ACTH ratio of >2.0 or post-CRH stimulation ratio ≥3.0 were used to demonstrate pituitary ACTH hypersecretion [23].

Presurgical treatment with adrenal enzyme inhibitors, such as ketoconazole (n = 59) and metyrapone (n = 1), was given during 3 months until 1 day before pituitary surgery. Four different neurosurgeons operated on the patients in our series. A transsphenoidal selective adenomectomy was performed when the tumor was radiologically identified or, in cases of negative sellar imaging, hemihypophysectomy was performed on the side with ACTH lat-

Table 2. Clinical characteristics of patients who died (n = 8) and who were lost to follow-up (n = 6)

Pat. No.	Follow-up status	Cause of death/ reason lost to FU	Age when lost to FU/at time of death, years	Duration of follow-up months	Outcome of initial surgery	Second-line therapy	Active CD when lost to FU/death
1	died	colorectal cancer	74	70	sustained remission	no	no
2	died	stroke	71	114	sustained remission	no	no
3	died	myocardial infarction	54	37	sustained remission	no	no
4	died	cervical cancer	39	131	sustained remission	no	no
5	died	myocardial infarction	83	103	early failure	RT	no
6	died	unknown	62	48	early failure	RT, Bi-ad	no
7	died	myocardial infarction	40	6	early failure	repeat TS, RT, Bi-ad	no
8	died	cervical cancer	62	50	late relapse	repeat TS, RT, Bi-ad	no
9	lost	myocardial infarction	32	19	sustained remission	no	no
10	lost	unknown	39	72	sustained remission	no	no
11	lost	myocardial infarction	57	86	sustained remission	no	no
12	lost	unknown	35	94	early failure	RT, Bi-ad	no
13	lost	unknown	50	138	early failure	RT	no
14	lost	moved elsewhere	35	92	late relapse	RT	no

FU = Follow-up; CD = Cushing's disease; TS = transsphenoidal surgery; RT = radiotherapy; Bi-ad = bilateral adrenalectomy.

eralization during BIPSS. On the day of surgery the patients received 200 mg of hydrocortisone, which was tapered off to no dose within 4 days. In 1 patient, hydrocortisone could not be tapered postoperatively due to severe glucocorticoid withdrawal symptoms, such as fatigue, nausea and hypotension. All patients received antibiotic prophylaxis (amoxicillin) in the perioperative period [24, 25].

Postoperative Assessment

Between days 7 and 10 postoperatively, morning serum cortisol (n = 78) was measured at 08:00 h, 72 h after the last dose of hydrocortisone. Subsequently, a metyrapone test (n = 72) and, from 1998 onwards, a CRH test (n = 53) were performed in the following days. Human CRH (Ferring BV, Hoofddorp, The Netherlands) was used during the CRH test. At 07:00 h, an indwelling forearm cannula was inserted and 30 min later 1 μg/kg CRH was administered intravenously. Serum cortisol was measured at 15-min intervals for 2 h. Plasma ACTH was also measured in 38 patients at 15-min intervals for 2 h. During the CRH test, patients were restricted to bed rest. The metyrapone stimulation test was performed after an overnight fast. The metyrapone stimulation test is routinely performed in our hospital after pituitary surgery in order to test the ACTH reserve. Following the measurement of morning serum cortisol, patients received 6 oral doses of 750 mg metyrapone (Alliance Pharmaceuticals Ltd, Chippenham, Wilts., UK) at 4-hour intervals. On the second day of the test, a fasting blood sample was taken for determination of 11-deoxycortisol, 4 h after the last metyrapone dose [17]. Pending the results of the postoperative tests, patients were discharged on hydrocortisone replacement therapy (40 mg/day). Patients who recorded 11-deoxycortisol levels <350 nmol/l in the metyrapone test were considered to have secondary adrenal insufficiency and continued hydrocortisone replacement therapy until further notice [26]. Clinical remission was defined as a continued need for corticosteroid replacement for >6 months after TS. Biochemical remission was defined as suppression of serum cortisol <50 nmol/l after 1 mg overnight dexamethasone and a normal UFC excretion (reference <850 nmol/24 h). All patients in remission after surgery (both clinical and biochemical remission) had resolution of symptoms of CD (weight loss, improvement of glucose tolerance, hypertension and emotional lability). Three groups of outcome were identified: sustained remission, early failure (persistent CD), and late relapse (recurrence of disease after initial remission). During follow-up all patients were re-evaluated initially at 12 weeks after surgery, followed by 6-monthly intervals in the first 2 years after surgery and at least annually thereafter. Endocrine evaluation consisted of measurement of serum cortisol after 1 mg overnight dexamethasone and 24 h UFC excretion along with assessment of anterior pituitary hormone function. Hypopituitarism was defined as the presence of hypothyroidism, hypogonadism, growth hormone deficiency or permanent diabetes insipidus. Patients were considered to be growth hormone-deficient if serum insulin-like growth factor-1 levels were below the normal range at two different intervals or when an impaired response was seen during growth hormone stimulation tests. Eight patients died during follow-up. Causes of death were cardiovascular events and stroke (4 patients), colorectal cancer (1 patient), cervical cancer (1 patient) and unknown (2 patients). Six patients were lost to follow-up in the study period. None of the patients who died or who were lost to follow-up during the study period suffered from active CD (table 2).

Laboratory Assays

Serum cortisol and 24-hour UFC excretion were measured using a chemiluminescence-based immunoassay (Immulite 2000, Siemens, Los Angeles Calif., USA; inter- and intra-assay coefficients of variation, respectively below 15 and 7%). Urines were analyzed without prior solvent extraction.

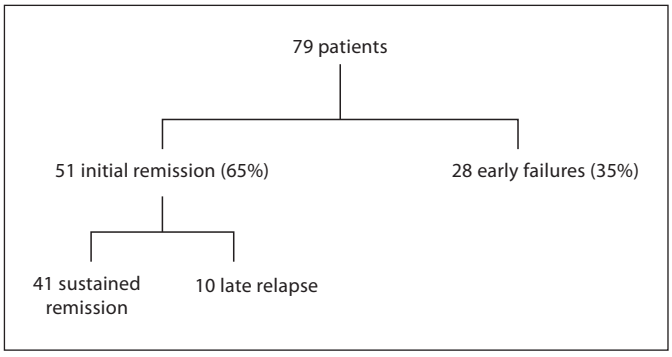

Fig. 1. Clinical outcome of TS for CD in the Erasmus Medical Centre Rotterdam, The Netherlands (1991–2006).

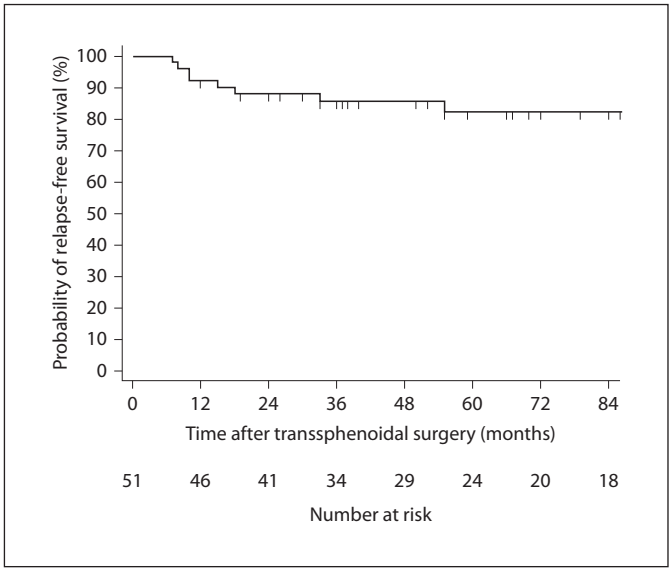

Fig. 2. Kaplan-Meier curve showing relapse-free survival of patients in initial remission after pituitary surgery for CD in the Erasmus Medical Centre Rotterdam, The Netherlands (1991–2006).

Plasma ACTH (reference 0–11 pmol/l) was measured using a chemiluminescent enzyme immunometric assay (Immulite 2000, Siemens, inter- and intra-assay coefficients of variation, respectively below 6.5 and 5.5%). Serum 11-deoxycortisol was measured by RIA after extraction (antiserum from Radioassay Systems Labs, Carson, USA; inter- and intra-assay coefficients of variation, respectively below 13 and 12%).

Statistical Analysis

Descriptive statistics were calculated for continuous variables. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each test using 2×2 tables (patients in sustained remission were compared with patients with early failure of surgery). Relapsing patients were not considered. PPV was defined as the likelihood that a subject with a positive test had persistent CD after pituitary surgery (treatment failure). NPV was defined as the likelihood that a subject with a negative test would remain in remission after surgery. Cutoff levels were increased stepwise to determine the optimal combination of PPV and NPV. Statistical analysis and graphing were performed using GraphPad Prism version 3.0 (GraphPad Software, San Diego, Calif., USA) and MedCalc version 9.6.3 (MedCalc Software, Mariakerke, Belgium).

Results

Patient characteristics and test results are shown in table 1. During the study period, 51 patients (65%) achieved immediate postoperative remission. CD recurred in 20% of patients after initial successful pituitary surgery (fig. 1). The probability of relapse-free survival of patients in immediate remission after pituitary surgery was 92% at 12 months, 88% at 24 months, 86% at 36 months and 83% at 84 months (fig. 2). Median time to relapse was 16.5 months (range 7–121). Failure to remove the adenoma completely, resulting in persistent CD, occurred in 28 patients (35%). These patients received second-line therapy, including repeat pituitary surgery, fractionated stereotactic radiotherapy and/or bilateral adrenalectomy.

Macroadenomas accounted for 43% in the early failure group. Moreover, in 21% of early failures no adenoma could be identified on preoperative MRI. In patients successfully operated, the percentage of macroadenomas was only 17%.

Overall, 22 patients (28%) were left with partial or complete hypopituitarism. Ten patients in sustained remission (24%) developed partial or complete hypopituitarism after TS compared with 9 of those with surgical failure (32%). Deficiency of one or more pituitary hormones was found in 30% of late relapses (3 patients). The thyrotropic axis was most frequently affected (17 patients), followed by gonadotropic (13 patients) and somatotropic (7 patients) axes. Permanent diabetes insipidus occurred in 2 patients.

Morning Serum Cortisol

Early postoperative morning serum cortisol levels were obtained in 78 patients (fig. 3). Morning serum cortisol levels <200 nmol/l were seen in 33 of 40 patients in sustained remission (83%). Seven patients in sustained remission recorded postoperative morning serum cortisol

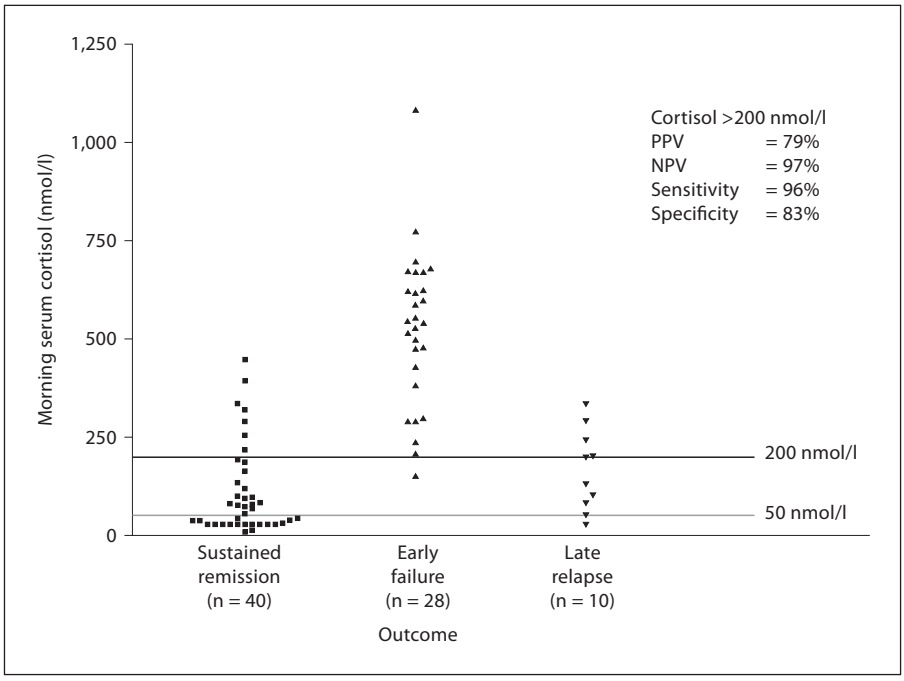

Fig. 3. Morning serum cortisol levels of 78 patients after pituitary surgery for CD. A cutoff level of 200 nmol/l predicts early failure of surgery in 79% of patients. All relapses, except one, recorded early postoperative morning serum cortisol levels >50 nmol/l.

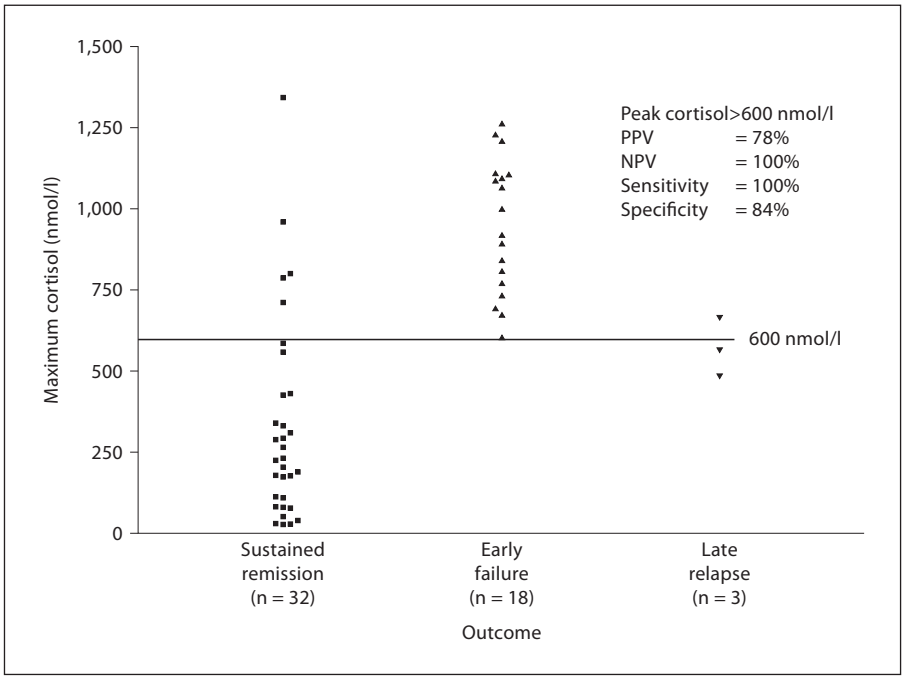

Fig. 4. Peak serum cortisol concentrations of 53 patients in response to human CRH administration after TS for CD. A threshold value of 600 nmol/l results in a PPV of 78% for immediate surgical failure (NPV 100%).

levels in excess of 200 nmol/l (median follow-up 66 months, range 40–154). Six of these 7 patients had received pretreatment with ketoconazole. Cortisol levels >200 nmol/l were seen in 96% of patients with persistent CD (early failures). All patients with recurrent CD, except one, had morning serum cortisol concentrations of at least 50 nmol/l. In our series, a threshold value of 200 nmol/l for morning serum cortisol obtained within 2 weeks after pituitary surgery resulted in a PPV of 79% for immediate postoperative failure (NPV 97%).

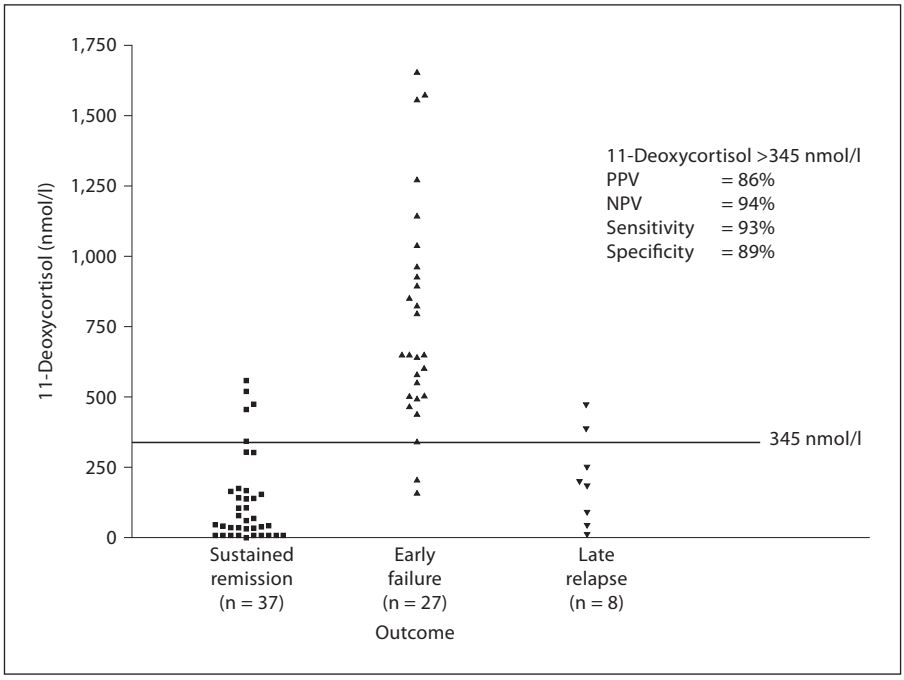

Fig. 5. Early postoperative 11-deoxycortisol levels after metyrapone (6 × 750 mg) in 72 patients with CD. The metyrapone test has a PPV of 86% to detect immediate failure of pituitary surgery when a cutoff value of 345 nmol/l is used (NPV 94%).

CRH Stimulation Test

The responsiveness to CRH (human CRH 100 μg i.v.) was studied in 53 patients postoperatively. Results of the CRH stimulation test are shown in figure 4. All patients with persistent hypercortisolism (18 early failures) showed absolute peak cortisol levels >600 nmol/l after CRH administration. Only 5 of 32 patients in sustained remission also had cortisol values in excess of 600 nmol/l (median follow-up 55 months, range 40–70). All 5 had received ketoconazole treatment prior to pituitary surgery and also recorded morning serum cortisol concentrations >200 nmol/l in the early postoperative phase. All patients with recurrent CD (n = 3) recorded peak serum cortisol levels >485 nmol/l after CRH administration. In the present study, absolute peak serum cortisol levels >600 nmol/l after CRH predicted immediate surgical failure in 78% of cases (NPV 100%). Measurement of plasma ACTH and calculation of the incremental changes in cortisol and ACTH did not improve discrimination between groups (data not shown).

Metyrapone Stimulation Test

Metyrapone test was performed in 72 subjects. The results of the postoperative metyrapone test are shown in figure 5. 89% of patients in sustained remission (33 out of 37) recorded 11-deoxycortisol levels <345 nmol/l after 6 × 750 mg metyrapone. However, metyrapone-stimulated 11-deoxycortisol concentrations of >345 nmol/l were seen in 4 patients in sustained remission (median follow-up 77 months, range 55–114); 3 of these 4 patients had been treated with ketoconazole before TS. 93% of patients with persistent CD after surgery (n = 25) noted 11-deoxycortisol levels >345 nmol/l. Although 11-deoxycortisol levels ranged from 12 to 470 nmol/l in patients with recurrent disease after apparent remission, the majority of patients (75%) had 11-deoxycortisol concentrations of <345 nmol/l. In the present study, serum 11-deoxycortisol levels of >345 nmol/l in response to metyrapone predicted early failure of TS in 86% of cases (NPV 94%).

Combined Assessment

In 49 patients (29 patients in sustained remission, 18 early failures, and 2 relapses) all three postoperative tests were performed (morning serum cortisol, CRH test, and metyrapone test). Of the 29 patients in sustained remission who underwent all three tests, 12 recorded postoperative morning serum cortisol levels <50 nmol/l. All of these 12 patients with 'undetectable' postoperative cortisol concentrations showed relative unresponsiveness to CRH stimulation, with peak cortisol concentrations ranging from 28 to 80 nmol/l. Furthermore, all 12 also showed an impaired response to metyrapone administration with serum 11-deoxycortisol levels varying from 10 to 78 nmol/l.

Only 1 patient in the early failure group measured a postoperative morning serum cortisol level (152 nmol/l) below the cutoff value of 200 nmol/l. She also recorded an insufficient response to metyrapone administration (11-deoxycortisol 208 nmol/l). In the CRH test however, she showed a significant cortisol response (677 nmol/l) exceeding the cutoff point of 600 nmol/l.

Two patients with recurrent CD underwent all three postoperative tests. One patient had a suppressed morning serum cortisol value of 51 nmol/l and reached an absolute serum cortisol peak concentration of 485 nmol/l in the CRH test. Response in the postoperative metyrapone test was also subnormal (11-deoxycortisol 200 nmol/l). The second patient with recurrent disease had a postoperative morning cortisol value of 386 nmol/l and also showed a substantial response in both CRH test (peak cortisol 568 nmol/l) and metyrapone test (11-deoxycortisol 470 nmol/l).

Discussion

The ultimate goal of a selective transsphenoidal adenomectomy in CD is a complete removal of the corticotropic adenoma without causing loss of normal pituitary functions. After TS, however, a substantial number of patients have persistent CD or develop recurrent tumors during follow-up. We examined early and late outcome of pituitary surgery as well as predictive values of early postoperative tests in a large cohort of patients with CD during a median follow-up period of 84 months.

Early and Late Outcome of Pituitary Surgery

The immediate postoperative and overall remission rates in the current paper fall at the lower end of the reported outcome data from other centers [4–12, 27]. This may be explained by a number of reasons. Firstly, variability in remission rates can be attributed to the different criteria used to define postoperative remission. We used adequate suppression of serum cortisol after 1 mg overnight dexamethasone in combination with a normal UFC excretion as definition of biochemical remission. Thus, remission or failure were defined independently of the tests that were examined. Secondly, there is considerable difference in duration of follow-up between published studies. Prolonged follow-up leads to lower cure rates, as the incidence of relapse increases with time. In our study, recurrent CD occurred >10 years after initially successful pituitary surgery in 1 patient, indicating that lifelong follow-up of patients with CD is mandatory. Thirdly, we report the surgical outcome of a heterogeneous group of adenomas, i.e. both micro- and macroadenomas, whereas some clinical series only report results of TS in microadenomas [4, 27]. Remission rates are lower in patients with macroadenomas [1, 28, 29]. This finding is confirmed in the present survey in which 43% of patients with surgical failure had a corticotropic macroadenoma. Finally, extensive surgical exploration, as performed in some centers, may result in higher cure rates. However, this is at the expense of postoperative pituitary function loss. Hypopituitarism after pituitary surgery is associated with an impaired health-related quality of life [30, 31]. The trend towards more conservative surgery in our center, aimed at preserving pituitary functions, has resulted in a relatively favorable hypopituitarism rate. Overall, we found 28% of patients to have postoperative hormonal disturbances compared to 26–52% reported elsewhere [11, 15, 16, 32].

Prediction of Surgical Outcome

Which biochemical parameters most reliably predict the long-term outcome after TS is still a matter of debate. Immediate postoperative recognition of patients with persistent CD or at risk for relapse would allow additional therapeutic measures to be undertaken at an early stage. When judged by long-term outcome, a postoperative serum cortisol level <50 nmol/l has been regarded as the best predictor for long-term remission and is associated with a 10-year recurrence rate of approximately 10% [1, 6, 12–16, 33]. This finding was confirmed in the present study in which remissions were associated with suppressed morning serum cortisol levels. 89% of relapses recorded postoperative morning cortisol levels >50 nmol/l. Thus, persistently detectable serum cortisol concentrations in the early postoperative phase can be indicative of incomplete resection of the corticotropic adenoma and an increased risk of recurrence. It must be emphasized, however, that detectable morning cortisol levels (>50 nmol/l) are not necessarily followed by recurrence of CD, which might in part be explained by preoperative treatment with ketoconazole (see below). Moreover, our study confirms that relapse can occur even in the presence of postoperative hypocortisolism.

The CRH test is a widely used non-invasive test to discriminate CD from Cushing's syndrome due to ectopic ACTH secretion [34–36]. Both ovine and human CRH have been used in clinical studies, although there is no consensus on the response criteria. In the current survey, we studied the results of the early postoperative human CRH test. Compared to peak ACTH level and incremen-

tal changes in cortisol and ACTH concentration, the absolute peak cortisol concentration after CRH stimulation gave the best diagnostic accuracy in predicting outcome of pituitary surgery. All failures and recurrences showed a significant rise in serum cortisol during the time course of the test using a cutoff value of 600 nmol/l. In accordance with previously reported literature, we found that suppressed responses to CRH during the early postoperative period are indicative of long-term remission of CD [6, 7, 18–21]. However, similar to morning cortisol levels, a subset of patients who were in sustained remission exhibited post-CRH cortisol levels >600 nmol/l which may in part be related to ketoconazole treatment before TS (see below).

Metyrapone blocks cortisol synthesis by competitively inhibiting 11β-hydroxylation in the adrenal cortex. This stimulates ACTH secretion, leading to increased production of cortisol precursors such as 11-deoxycortisol. Therefore, the metyrapone test can be used in establishing the diagnosis of secondary adrenal insufficiency [37–39]. We studied the results of the metyrapone test carried out in patients after pituitary surgery for CD in order to establish its usefulness in the assessment of surgical outcome. Postoperatively, the majority of patients with persisting CD had markedly increased levels of metyrapone-stimulated 11-deoxycortisol compared to patients in sustained remission. Previously, van Aken et al. [17] reported in a small number of patients 100% sensitivity for the early postoperative metyrapone test in detecting patients at risk for recurrent CD when an 11-deoxycortisol cutoff value of 150 nmol/l was used. However, in the present study, we found great variability of 11-deoxycortisol levels in patients with recurrent CD, ranging from 12 to 470 nmol/l. Therefore, according to the current data, the usefulness of the metyrapone test in the early prediction of relapse is limited.

Combining the results of all three postoperative tests (serum cortisol, CRH test, and metyrapone test) we found that patients in sustained remission with suppressed postoperative morning serum cortisol concentrations also showed a relative concordant unresponsiveness to CRH stimulation and metyrapone administration. Comparison of PPVs and NPVs of the investigated tests shows that the additional value of CRH and metyrapone testing to measurement of morning serum cortisol levels is limited.

Pretreatment with Cortisol-Lowering Drugs

CD is associated with diabetes, hypertension, poor wound healing, hemorrhagic diathesis and increased tissue fragility. In order to control hypercortisolemia and minimize perioperative risks, medical therapy with ketoconazole prior to surgery is used in several centers. In previous studies on postoperative biochemical testing in CD, results have not been interpreted in relation to eventual preoperative treatment with cortisol-lowering drugs [7, 12, 32]. In the present study, 75% of patients were pretreated with ketoconazole. Interestingly, 6 of the 7 patients in sustained remission with postoperative serum cortisol levels >200 nmol/l received presurgical treatment with ketoconazole. It is possible that these patients, after an apparent remission, will ultimately develop recurrence of CD. However, the median follow-up of these patients was 5.5 years, making recurrent CD in future still possible but less likely. However, an alternative explanation is that the treatment with ketoconazole prior to surgery could have resulted in higher postoperative basal and CRH-stimulated cortisol levels in these patients due to early recovery of suppressed non-tumor corticotropic cells and subsequent restoration of pituitary-adrenal function. Future studies should investigate the possible relationship between preoperative achievement and duration of normocortisolism after ketoconazole pretreatment and the postoperative recovery of the pituitary-adrenal axis.

Conclusions

In our study we identified undetectable morning serum cortisol concentrations and an impaired responsiveness to CRH and metyrapone stimulation in the early postoperative period as biochemical predictors of long-term remission. Recurrent CD seems to be associated with higher morning serum cortisol levels and an unsuppressed CRH-stimulated cortisol response. However, there is considerable overlap between patients who do and those who do not relapse. In our series we could not clearly identify the benefits of performing additional CRH and/or metyrapone tests in the postoperative assessment of patients with CD. In addition, pretreatment with cortisol-lowering drugs may influence the results of different postoperative biochemical tests. Future studies are necessary to determine the effects of preoperative ketoconazole treatment on the recovery of the hypothalamic-pituitary-adrenal axis in patients who are in remission after pituitary surgery.

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