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Transsphenoidal microsurgical treatment of Cushing disease: postoperative assessment of surgical efficacy by application of an overnight low-dose dexamethasone suppression test

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Object. Transsphenoidal adenomectomy with resection of a defined pituitary adenoma has been the treatment of choice for CD for the last 30 years. Surgical resection, however, may not always result in long-term remission of CD. This is particularly important in light of the high risk of morbidity and mortality in patients in the unsuccessfully treated cushingoid state. As such, it is interesting to identify prognostic factors that may predict the likelihood of long-term remission.

Methods. The authors review their series of 174 patients who have undergone transsphenoidal procedures for CD over a period of 20 years with minimum follow-up periods of 5 years. Selection of these patients was based on clinical, imaging, and laboratory criteria that included serum cortisol levels, loss of diurnal variation in serum cortisol levels, urinary free cortisol concentration, and results of a dexamethasone suppression test, petrosal sinus sampling, and corticotroph-releasing hormone stimulation tests as indicated. All patients who met the biochemical criteria underwent transsphenoidal microsurgery.

The authors found an overall rate of remission of 74% at 5 years postoperatively. Patients in whom morning serum cortisol concentrations were lower than 3 μg/dl (83 nmol/L) on postoperative Day 3, following an overnight dexamethasone suppression test, had a 93% chance of remission at the 5-year follow-up examination. Patients with cortisol concentrations higher than this level uniformly failed to achieve long-term remission.

Conclusions. Transsphenoidal microsurgery is an effective means of control for patients with adrenocorticotrophic hormone–producing microadenomas. Clinical outcome correlated well with the size of the tumor, as measured on preoperative imaging studies, and with postoperative morning cortisol levels following an overnight dexamethasone suppression test. Postoperative cortisol levels can be used as a useful prognostic indicator of the likelihood of future recurrence following transsphenoidal adenomectomy in CD.

Key Words • Cushing disease • pituitary tumor • transsphenoidal approach • cortisol • outcome • survival

Cushing disease is caused by the excessive secretion of ACTH from a pituitary adenoma. Lack of treatment in cases of CD leads to complications from the resulting hypercortisolism including habitus changes, immunosuppression, impaired wound healing, diabetes, hypertension, left ventricular hypertrophy, and psychiatric effects. Patients with untreated CD survive a median of 5 years according to data in the literature.

Treatment options for CD include neurosurgical intervention, adrenalectomy, drug therapy, and radiosurgery. Since the early 1970s, TSA has been the preferred mode of treatment for CD.

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; CD = Cushing disease; CI = confidence interval; CRH = corticotropin-releasing hormone; CSF = cerebrospinal fluid; CT = computerized tomography; IPS = inferior petrosal sinus; MR = magnetic resonance; TSA = transsphenoidal adenomectomy; UFC = urinary free cortisol.

Despite advances in neurosurgical treatment of CD, successful therapy remains a significant challenge. The overall published rate of remission following transsphenoidal microsurgery has been reported to be in the range of 70 to 90%.[4,6,7,12,16,19,23,34] Significant prognostic factors associated with the success of surgery have included the size and invasiveness of the tumor.

Because of the significant rate of recurrence or persistence of the disease and the attendant morbidity, it is of interest to determine factors that may correlate with long-term outcomes following surgical intervention. Patients in whom failure of TSA is likely may, therefore, be considered candidates for repeated pituitary surgery, adrenalectomy, drug therapy, radiotherapy, or radiosurgical treatment. Parameters including postoperative cortisol level,[3,5] 24-hour urine cortisol concentration,[1] absence of a cortisol response to CRH,[3,37] and the need for long-term glucocorticoid substitution[3] have been described as useful prognostic indicators.

TABLE 1

Demographics of patients who underwent transsphenoidal craniotomy for CD

Factor	No. of Patients
patients enrolled from 1973 to 1993	174
patients w/ 5-year follow up	152
lost to follow up	10
no. of deaths*	4
nondiagnostic surgical explorations	12
patient age range (yrs)	8–57
sex (152 patients)	
male	48
female	104
ethnicity (152 patients)	
caucasian	131
Latin-American	18
Asian	2
African-American	1

* Four patients died: three of coronary disease and one of stroke.

The purpose of the present study is to review our series of patients harboring ACTH-secreting pituitary adenomas, who were treated with transsphenoidal surgery in view of 5-year remission rates and complications. In particular, we have investigated postoperative morning cortisol levels measured after an overnight low-dose dexamethasone suppression test to predict outcome following TSA.

Clinical Material and Methods

Patient Population

Data from the clinical records of all patients with ACTH-secreting adenomas who presented to the senior author (M.H.W.) from 1973 to 1993 were analyzed. The total series consisted of 174 patients. This cohort was chosen to allow a minimum long-term follow-up period of 5 years. Ten patients were lost to follow up and four patients died within the follow-up period. In 12 patients the surgical explorations were nondiagnostic. A subset of 152 patients with CD confirmed by surgical exploration completed the 5-year follow up or died within the follow-up period. These patients form the study population. The demographics of these patients are summarized in Table 1.

A diagnosis of CD was based on the following criteria: loss of diurnal variation in serum cortisol levels; elevated concentration of 24-hour UFC; serum level of ACTH at the upper limit of normal or slightly elevated; and failure to suppress the serum cortisol level after a low-level (2-mg) dexamethasone test. High-level dexamethasone suppression was seen in most cases, although in several 16 mg of dexamethasone was required. Abnormal findings of CT, MR imaging, and/or IPS and cavernous sampling studies were also used as criteria for exploration. In 22 cases, MR imaging, CT scanning, and IPS sampling yielded nondiagnostic findings and the patients underwent surgical exploration on the basis of abnormal biochemical findings alone. Imaging studies were performed in all patients in this series. No tumor could be identified on imaging studies in 42 patients. During surgical exploration of 162 patients we found microadenomas in 133 patients (82%) and macroadenomas in 29 patients (18%).

Surgical Technique

Microsurgical TSAs were performed via the sublabial approach in all patients, as previously described.[10] In 12 patients no tumor was found during exploration and hemihypophysectomy was then performed. Exploration consisted of three vertical incisions in the gland and a midlevel horizontal incision; this dissected the gland into eight segments for exploration. In the event that no tumor was found, we performed hemihypophysectomy, which consisted of resection of the lateral lobe on one side and the inferior segment of the midline mucoid wedge. In all patients in whom the arachnoid membrane was preserved, dehydrated ethanol was instilled in the tumor bed to treat potential microscopic rests of tumor cells. In patients in whom perforation of the arachnoid and egress of CSF was encountered, no alcohol was used. In these patients, we performed grafting by using autologous adipose tissue and/or fascia lata followed by lumbar puncture with dural fenestration.

Postoperative Management and Follow-Up Protocol

In the perioperative period, patients were treated according to our standard protocol. On the 1st postoperative day, they were intravenously given 50 mg of hydrocortisone in the morning and 25 mg in the evening. On the 2nd day, they were given 50 mg of hydrocortisone in the morning and 1 mg of dexamethasone in the evening at 10 p.m. Blood was withdrawn from the patient at 8 a.m. on the 3rd postoperative morning and a fasting serum cortisol level was measured and recorded. Following this procedure, hydrocortisone replacement was resumed. Corticoid medications were then tapered as tolerated by the patient. This generally took 2 weeks to 1 year.

During the immediate postoperative period, the patients were carefully observed for diabetes insipidus or syndrome of inappropriate secretion of antidiuretic hormone. Nasal packings were removed on the 2nd postoperative day and patients were discharged on the 3rd or 4th postoperative day.

An initial routine follow-up clinical evaluation was obtained 6 weeks postoperatively and thereafter at 6-month intervals. At these visits, fasting cortisol levels were obtained at 8 a.m. and 4 p.m. If patients demonstrated normal 8 a.m. and 4 p.m. serum cortisol levels with normal diurnal variation, they were not required to undergo a repeated 24-hour test of UFC. If the morning and late afternoon cortisol levels did not demonstrate a normal diurnal variation, however, a 24-hour UFC test was performed to confirm normal cortisol secretion. In the later years of the study, all patients underwent 24-hour UFC tests at least once postoperatively, even if normal diurnal variation was present. Patients suspected of disease recurrence (loss of normal diurnal variation, elevated serum cortisol level, or elevated 24-hour UFC concentration) underwent a full endocrinological workup.

Statistical Analysis

Life tables were assembled to calculate 5-year disease-free survivals. Confidence intervals were calculated using the Greenwood method. Contingency tables were analyzed using the Fisher exact test as implemented in the algorithm of Mehta and Patel.[21] Other statistical analyses were conducted with the aid of a commercially available software package (Statistica '98; StatSoft, Inc., Tulsa, OK).

TABLE 2

*Overall short-term outcomes for patients who underwent transsphenoidal craniotomy for ACTH-secreting tumors segregated by initial postoperative cortisol levels and surgical findings**

Patient Group	All Patients	Patients W/ Microadenomas	Patients W/ Macroadenomas
Group I	128	123	5
Group II	14	9	5
Group III	20	1	19
negative exploration	12	NA	NA
total	174	133	29

* NA = not applicable.

TABLE 3

Complications following transsphenoidal microsurgery

Complication	No. W/ ACTH-Secreting Tumor (215 patients)	No. W/ Other Disease (2142 patients)	p Value*
CSF leak	0	24	0.16
grafts	72	733	0.88
meningitis	0	9	1.00
donor-site infection	3	14	0.19

* Probability values were calculated using the Fisher exact test.

Results

Role of IPS Sampling

Inferior petrosal sinus sampling was used in 20 patients, in whom no evidence of tumor had been identified on imaging studies.

In the 18 patients in whom the results of the IPS sampling were positive, all were found to have an adenoma on exploration. In five of these patients, however, a higher ACTH level was found contralateral to the side where the adenoma was found. These results are consistent with and confirm the results of previous investigators.[18,25,39]

Initial Response to Surgery

As shown in Table 2, patients' initial outcomes were categorized into three groups based on serum cortisol levels obtained on postoperative Day 3 following a low-dose overnight dexamethasone suppression test. Group I contained patients with cortisol levels lower than 3 μg/dl (< 83 nmol/L), Group II contained patients with low-to-normal postoperative ranges of cortisol (3–8 μg/dl), and Group III contained patients in whom the cortisol level (> 8 μg/dl) clearly indicated that surgery had failed.

Of the 162 patients in whom surgery revealed tumors, 128 (79%) had morning cortisol levels lower than 3 μg/dl on postoperative Day 3 following the low-dose dexamethasone suppression test. The size of the tumor was a highly significant factor in the likelihood of biochemical success. Although 123 (92%) of 133 patients with microadenomas had immediate postoperative morning cortisol levels below 3 μg/dl, only five (17%) of 29 patients with macroadenomas had immediate postoperative cortisol levels lower than 3 μg/dl ($p < 0.0001$). Fourteen patients had postoperative cortisol levels between 3 and 8 μg/dl following the low-dose dexamethasone suppression test. Overall short-term outcomes are summarized in Table 2.

Complications From Surgery

Complications were rare in this series. In 72 patients, fat and/or fascia lata grafting was required. In no patient did a CSF leak requiring reoperation occur or meningitis develop. Three patients did, however, sustain infections at graft donor sites. In all such instances, the isolated organism was *Staphylococcus aureus*. These results were largely judged not to be statistically significant when compared with the overall series of patients undergoing transsphenoidal microsurgery (Table 3). Similarly, no statistical significance was seen for the incidence of fat graft requirements. There were no perioperative deaths or complications leading to new neurological deficits in this series. Although an intensive postoperative assessment of the endocrinological axis was not performed on a routine basis following surgery, no patient to our knowledge has required treatment for a new endocrinological deficit following selective TSA. Interestingly, no patient who underwent the hemihypophysectomy described earlier experienced pituitary insufficiency as a consequence of this procedure.

Long-Term Results

Overall Survival. A 5-year follow-up period was obtained in 152 patients (87%). Ten patients were lost to follow up before the 5-year period, but these patients were included in the actuarial analysis to comprise a total series of 162 patients. Four patients died during the accrual period, three of coronary artery disease and one of stroke (Table 4). Twelve additional patients, in whom surgical explorations were not diagnostic, were not included in the analysis. These data allow a calculation of an actuarial 5-year life survival rate of 97.3% (95% CI 94.8–99.9%).

Disease Remission. For all 162 patients in whom surgery uncovered a tumor, 118 (72.8%) experienced remission from hypercortisolism (normal morning and late afternoon cortisol levels with diurnal variation or normal 24-hour levels of UFC) at 5 years (95% CI 87.9–57.7%). A Kaplan–Meier curve demonstrating disease-free remission in all patients in whom surgery revealed a tumor is presented in Fig. 1.

Initial postoperative cortisol levels correlated well with the likelihood of long-term remission. For the 121 patients in Group I who had completed a 5-year follow-up period, 113 had normal fasting 8 a.m. and 4 p.m. serum cortisol lev-

TABLE 4

Causes of death for four patients in this series

Case No.	Cause of Death	Initial Cortisol Level (μg/dl)	Mos to Death	Disease in Remission at Death
1	heart disease	5.4	49	no
2	heart disease	8.2	40	no
3	heart disease	2.3	58	yes
4	stroke	2.8	50	yes

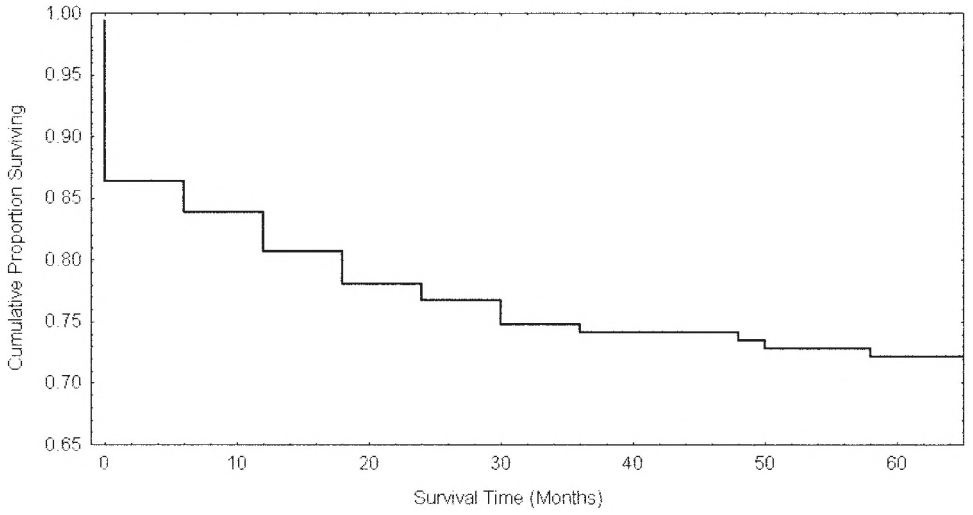

FIG. 1. Kaplan–Meier curve demonstrating actuarial recurrence-free survival for all patients in this series in whom surgical explorations revealed a tumor.

els with diurnal variation or normal 24-hour UFC levels at the end of the 5-year follow up, yielding a long-term actuarial remission rate of 93% (95% CI 88.7–97.3%).

Of the 14 patients in the initial cohort of Group II, 11 completed the 5-year follow up. None of these patients continued to experience remission at the end of 5 years. For these patients, the median time to treatment failure was 18 months. A Kaplan–Meier graph of recurrence-free survival is presented in Fig. 2.

After we separated out the patients with microadenomas from Group I, 112 of 116 patients continued to have disease remission at 5 years postoperatively, yielding a long-term actuarial remission rate of 96.5% (95% CI 93.2–99.8%). In the patients with macroadenomas, continued disease remission was found in only one of five at 5 years. For patients in Group I in whom disease recurred, the median time to recurrence was 27 months with a range of 6 to 48 months.

No patient who ceased taking corticoid medications less than 6 weeks postoperatively achieved disease remission. All these patients had postoperative Day 3 morning cortisol levels greater than 5 μg/dl (138 nmol/L).

Characteristics and Management of Disease Recurrence

In patients with initially low cortisol levels, recurrences of disease were observed 6 months to 4 years postoperatively. Of the four original macroadenomas that recurred, recurrent or residual tumor was found on MR imaging studies in all cases. These tumors were reexplored; however, remission was not reestablished in any of these patients by the second surgery. Of the four original microadenomas that recurred, one was identified as recurrent tumor on imaging. This tumor was reexplored and remission was again established by the second surgery. Failed treatments included three adrenalectomies accompanied by application of radiation to the sella turcica, one application of radiation to the sella plus a regimen of ketoconazole, and one regimen of ketoconazole alone.

Treatment of Patients With Failed Explorations

For the 12 patients in whom surgical exploration was nondiagnostic, none achieved disease remission postoperatively from performance of a hemihypophysectomy alone. Eight of the 12 patients subsequently underwent adrenalectomy with fractionated external beam radiotherapy directed to the sella turcica. There were no deaths in this subgroup and all patients achieved remission of their CDs. Seven of eight patients did have panhypopituitarism, however. The remaining four patients underwent total hypophysectomies, which were performed early in this series. Three of these patients experienced total hypopituitarism as a result of the second procedure, and one patient experienced persistent hypercortisolemia and was treated with radiation directed to the pituitary, subsequent to an attempted total hypophysectomy. There were no patients in whom Nelson syndrome developed in this series.

Discussion

Surgical Management of CD

Extensive experience over the last quarter of a century has demonstrated the high safety and efficacy of transsphenoidal surgery in the treatment of CD.[5,28,34,36] Improvements in surgical technique since the advent of the operating microscope have improved, to a significant extent, outcomes following pituitary surgery.

The present study confirms the efficacy of transsphenoidal microsurgical resection for CD and identifies factors that correlate with outcome at a standardized end point of 5 years.

Despite excellent results in the majority of patients, surgical therapy will fail in a significant minority. In many of these patients, treatment failures clearly manifest themselves only months or years following the initial surgical intervention. The complications of a continued cushingoid state are well known, and include diabetes, changes in habitus, and depression. It is useful, therefore, to have the means to identify patients who are at higher risk of disease recurrence following transsphenoidal surgery. Patients who are at clear risk for disease recurrence may potentially benefit from a closer follow up and early adjuvant therapy.

In accordance with previously published data, factors associated with poorer outcomes have been identified to include tumor size larger than 1 cm in diameter and tumor invasiveness.[2,4,15]

In the present series, the initial remission rate, as operationally defined by dexamethasone-suppressed serum cortisol levels of 3 μg/dl on postoperative Day 3, was 80%, which is comparable to the initial response rates published by other groups.[5,19,28,34,35] The overall 5-year survival rate of greater than 97% is substantially better in comparison with a historical control series in which the 5-year mortality rate was calculated to be as high as 50%, and is similar to the recent results of Swearingen, et al.[33]

Prognostic Factors for Recurrence and the Role of Serum Cortisol

Previous investigators have used a variety of indices to determine the likelihood of disease recurrence. Each of these indices has certain advantages and disadvantages in the clinical setting. Arnott and coworkers[1] examined the predictive value of the 24-hour urine cortisol level in 26 patients 1 to 4 weeks following pituitary surgery. They found that, in all patients with suppressed 24-hour urine cortisol levels, long-term remissions could be expected. Unfortunately, the mean follow-up period in that study was less than 2 years.

Several investigators have analyzed the role of postoperative cortisol levels as an early prognostic indicator of surgical success. Trainer and coworkers[35] examined the nonsuppressed postoperative morning cortisol level in 48 patients who had undergone TSA and were followed for a mean of 40 months. They found that no patient with a postoperative serum cortisol level of 50 nmol/L (1.8 μg/dl) or less had recurrence of CD. Recent data, however, have contradicted the main conclusion of this publication.[38] Fahlbusch and coworkers[12] have recommended that postoperative ACTH levels be considered in the evaluation of postoperative patients. A parameter that is related to postoperative cortisol suppression is the need for replacement with exogenous corticoid medications. In a multicenter retrospective study, Bochicchio, et al.,[3] found the need for postoperative cortisol replacement to be a factor predictive of long-term disease remission. Vignati and associates[37] examined the role of the postoperative CRH stimulation test in 30 patients who were followed between 9 months and 10 years after surgery. Continued suppression of a normal response was considered predictive of remission.

Our protocol for postoperative evaluation has concentrated on the use of early postoperative dexamethasone-suppressed morning serum cortisol levels. We have found this test to be easily obtainable and a useful predictor of long-term disease-free survival. In this group, 93% of patients with a postoperative cortisol level lower than 3 μg/dl experienced remission at the 5-year follow up. Postoperative morning cortisol levels have the advantage of being widely available and simple to obtain in comparison with other predictive indices.

Nugent and coworkers[24] and Pavlatos, et al.,[26] initially described the low-dose overnight dexamethasone suppression test for the rapid diagnosis of Cushing syndrome. When used in the diagnostic setting, there are relatively high false-positive and false-negative rates,[9,13,32] especially when used in patients in whom concurrent illness may lead to a reduction in the suppressibility of the adrenal axis. The results of the present study suggest, by contrast, that in the postoperative setting the findings of low morning cortisol levels after an overnight low-dose dexamethasone suppression test has a high sensitivity for patients who will experience a long remission following transsphenoidal surgery, and a high specificity for those in whom the intervention will fail within a 5-year follow-up period. In contrast to the diagnostic setting, all the patients included in this series had proven hypercortisolism due to pituitary disease rather than to other disease states such as depression or chronic illness. Patients with ACTH-secreting pituitary adenomas have chronically suppressed pituitary axes and, in the setting of a successful removal of tumor, would be expected to have below normal levels of cortisol after a low-dose dexamethasone challenge. The remaining nonsuppressed cortisol function would be due to residual ACTH-secreting tissue in this highly selected population. This hypothesis was largely borne out by the observations of the present study. Low plasma cortisol levels were a good, but not a completely reliable indicator of long-term remission, with 5% of patients experiencing recurrence of their disease within a 5-year period. Dexamethasone-suppressed postoperative cortisol levels higher than 3 μg/dl, however, were a reliable indicator of long-term surgical failure.

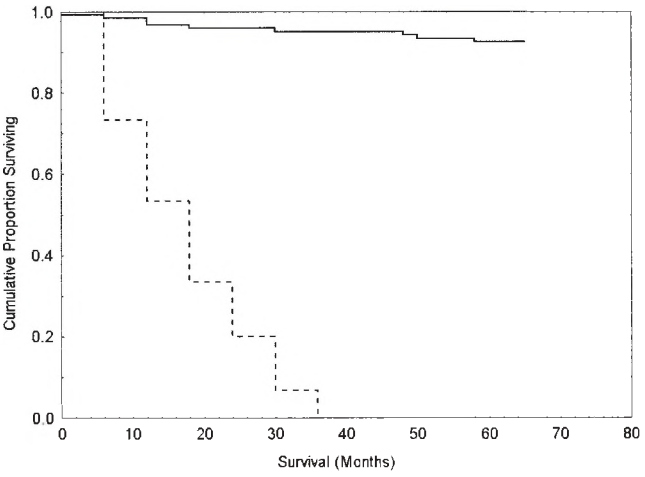

FIG. 2. Kaplan–Meier graph comparing recurrence-free survival for patients in Group I *(solid line)* and Group II *(broken line)*.

Similar results were obtained by Imaki, et al.,[17] in their series of 30 patients who had undergone successful initial procedures. One of 25 patients in whom the dexamethasone-suppressed plasma cortisol level was lower than 2 μg/dl experienced recurrence of disease, whereas three of five patients with cortisol levels higher than 2 μg/dl experienced recurrence during a median follow-up period of 87.6 months. Recently, Yap and colleagues[38] reported their experience in 66 patients who initially had undetectable nonsuppressed serum cortisol levels. In their study the authors noted an 11.5% incidence of disease recurrence was noted over a median 36-month follow-up period.

We have routinely used perioperative cortisol replacement to avoid an acute symptomatic addisonian state in the postoperative period. The morning cortisol concentration obtained in the early postoperative course following an

overnight low-dose dexamethasone suppression test can be used to determine the residual production while reducing the severity of postoperative symptoms. We do recognize, however, that there are groups that do not routinely give patients immediate postoperative cortisol replacement, which may affect the ability to compare our results directly with those of others. In a recent report[30] the authors suggested that postoperative cortisol replacement is not routinely indicated following transsphenoidal surgery on the 1st postoperative day. It is unclear, however, whether this recommendation can be continued to the 3rd postoperative day, the time at which the cortisol sampling took place in our protocol. Certainly, even with postoperative cortisol replacement, many of our patients did have symptoms of cortisol withdrawal including nausea and headaches. On the basis of the present results, it does not appear that our use of dexamethasone-suppressed values of cortisol adversely affect the sensitivity and specificity of postoperative cortisol testing in comparison with the nonsuppressed values obtained by other groups.[8,35,38] Whether routine postoperative cortisol replacement should be used, however, continues to be unclear, and further research is warranted in this area.

Treatment of Patients in Whom the Initial Surgical Exploration has Failed

Our results show that no patient with a postoperative cortisol level greater than 3 μg/dl achieved long-term remission of their disease. We believe that these patients should be considered as likely treatment failures and should be monitored vigilantly. Surgical reexploration should be considered,[14,27,35] as should adjuvant therapy. Adjuvant therapy may include drug therapy,[31] adrenalectomy,[20] fractionated external beam radiation,[11] or stereotactic radiosurgery.[22,29] Such measures are reasonable in the management of uncontrolled CD with its high incidence of morbidity and demonstrated 5-year mortality rate.

Conclusions

We found the early postoperative morning cortisol level to be a very good, but not absolute prognostic indicator for patients treated by transsphenoidal craniotomy for CD. Patients with postoperative serum cortisol levels below normal (< 3 μg/dl) had a 93% chance of disease remission at the 5-year follow up. No patient with a normal postoperative cortisol level (3–8 μg/dl), however, experienced disease remission. These patients should be informed of their poor prognosis for remission and an appropriate intervention should be taken.

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