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Long-Term Outcome of Bilateral Laparoscopic Adrenalectomy Measured by Disease-Specific Questionnaire in a Unique Group of Patients with Cushing's Syndrome

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Abstract

Background.—Laparoscopic bilateral adrenalectomy (LBA) is recommended for patients with bilateral adrenal disease and occult or unresectable ectopic Cushing's syndrome (CS). There are limited data on long-term outcomes after LBA, partly due to the lack of disease-specific tools for the measurement of impact on patients' health and quality of life.

Methods.—We used a disease-specific questionnaire covering all major clinicopathologic characteristics of CS. We compared the outcome from LBA to a control group of 60 patients who had thyroidectomy (matched for age, gender, and time of surgery, 2:1 control-to-CS).

Results.—Twenty-eight patients (20 women and 8 men) underwent LBA for CS. Of them, 24 patients (86 %) provided responses to our questionnaire. Ninety-two percent of patients' responses indicated a significant improvement of general Cushing's physical features with complete resolution reported in 59 % of responses. Significant improvement of associated biochemical abnormalities and comorbidities was reported in 83 % of patients' responses including complete reversal in 58 %. Significant improvement in emotional-behavioral symptoms was reported in 84 % of patients' responses with complete recovery in 53 %. All patients expressed satisfaction with LBA and significant improvement in their general health and self-reported quality of life. All of the improvements after LBA were statistically significant compared with the control group.

CONFLICT OF INTEREST Authors have no conflict of interest to declare.

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Conclusions.—Our disease-specific questionnaire enables a clearer understanding of the association between the clinical, metabolic, and emotional-behavioral features of CS, its treatment with LBA, and long-term impact on patient-reported quality of life. This disease-specific questionnaire may be useful for future studies in patients with CS.

Endogenous Cushing's syndrome (CS) is a complex heterogeneous disorder resulting from chronic exposure to excess glucocorticoids produced by the adrenal cortex.¹ Approximately 80 % of CS cases are adrenocorticotrophic hormone (ACTH)-dependent with the vast majority caused by ACTH-producing pituitary tumors, known as Cushing's disease (CD).^{2–4} Less commonly, ACTH-dependent CS can be caused by ACTH-secreting or very rarely corticotropin-releasing hormone (CRH)-producing nonpituitary neoplasms, known as ectopic CS. Approximately 15–20 % of Cushing's patients have ACTH-independent CS with unilateral functional adrenocortical adenoma or carcinoma accounting for the majority of cases.^{5,6} The familial and sporadic forms of bilateral macronodular and micronodular adrenal hyperplasia, including its variant—primary pigmented nodular adrenocortical disease (PPNAD)—are less common causes of ACTH-independent CS.^{7,8} The awareness, understanding of the genetics, and clinical importance of these uncommon causes of hypercortisolism have increased significantly during the past several decades.^{9,10}

The ultimate goal of treatment of CS is to reverse the signs, symptoms, and comorbidities resulting from excessive cortisol production and to improve patient's quality of life and prognosis. While laparoscopic bilateral adrenalectomy (LBA) has been recommended for patients with primary bilateral adrenal disease and occult or unresectable ectopic ACTH- or CRH-producing tumors refractory to medical management, the optimal management strategy for these patients remains controversial, and many important issues remain to be addressed.^{1,2,11–15} First, while the long-term outcomes of LBA for refractory CD have been studied by a number of investigators, including a recent systematic review, the long-term outcomes of LBA for less common causes of CS remain poorly characterized.^{7,16–24} Second, until recently, the impact of LBA on patients' health-related quality of life has been assessed by using quality of life questionnaires, such as the short-forms 36 and 12 (SF-36 and SF-12), but there are limited or no long-term follow-up data using a disease-specific questionnaire.^{25,26} Third, even though reliable disease-specific instruments, such as Tuebingen CD-25 and Cushing quality of life questionnaires are now available, they primarily deal with measuring the psychopathological, cognitive, and daily physical activity domains, while specific categories concerning the Cushing's clinical phenotype, metabolic syndrome, and disease-specific comorbidities are lacking.^{27,28} Lastly, most studies evaluating the long-term outcomes of LBA in patients with CS are uncontrolled, and the few controlled studies use reference data from healthy controls making it impossible to exclude a placebo effect of having an operation.^{23–25,29}

The objectives of this study were: (1) to design a concise, yet comprehensive, patient-reported outcome instrument (PRO; questionnaire) that encompasses major clinical characteristics of CS, (2) to test the disease-specificity of this questionnaire and conduct a pilot study for measuring long-term outcome of LBA in a unique group of patients with less common forms of CS, and (3) to assess the perioperative and surgical outcomes.

METHODS

Study Cohort

We conducted a review of electronic database and records of patients admitted to the National Institutes of Health (NIH) from 2010 to 2013 under clinical protocols NCT00005927, NCT01005654, and NCT02001051. LBA performed for occult or unresectable ectopic ACTH- or CRH-secreting tumors and familial or sporadic ACTH-independent bilateral macronodular or micronodular hyperplasia of the adrenal cortex were studied.

Disease-Specific Questionnaire

The study design is summarized in Fig. 1. We designed a patient-reported outcome instrument with items and domains developed based on literature review, and expert opinion. The framework of the instrument was constructed to enable measurement of the general concept: the long-term effect of LBA in improving signs, symptoms, comorbidities, and patient's quality of life measured by patients' overall satisfaction with the surgical results (Supplemental Fig. 1, CS-specific Questionnaire).

Cushing's symptoms were stratified into three main domains (categories): General Cushing's Physical features (GCP) (4 items, "a" through "d"); Biochemical Abnormalities and Comorbidities (BAC) (4 items, "a" through "d"); and Emotional-Behavioral features (EB) (4 items, "a" through "d"). Data were collected by an independent interviewer who asked the patients to describe their symptoms both preoperatively and at the time of the interview (postoperatively) on an ordinal scale of 1 point (no symptom), 2 points (mild symptom), 3 points (moderate symptom), and 4 points (severe symptom). At the end of the interview, patients were asked to describe their health-related satisfaction with surgery on an ordinal scale from 1 point (not satisfied at all), 2 points (somewhat satisfied), 3 points (satisfied), and 4 points (very satisfied).

To test the disease and procedure specificity of the patient-reported outcome instrument, the questionnaire scores of the study cohort were compared to the scores of a control group of 60 patients (matched 2:1 for age, gender, and time of surgery) who underwent thyroidectomy for benign or malignant thyroid disease. Using thyroidectomy patients enabled us to compare and closely match CS patients to a control group of patients who had surgery for a disease in the same disease category (endocrine disorders). In addition, these patients had total thyroidectomy (matching bilateral/total adrenalectomy in CS patients) and were started on life-long hormonal replacement therapy (matching hormonal replacement therapy of CS patients after LBA).

Statistical Methods

Statistical analyses were performed to determine the significance of the preoperative versus postoperative survey in patients with CS to assess the same outcome measures in the control group and to compare the difference between the two groups. Because the data were coded as 1 through 4 representing increasing level of symptoms, they were analyzed as ordinal values. Specifically, to assess the significance of the change pre-operative-to-postoperative,

the data were constructed into a 4×4 matrix and a Marginal Homogeneity test was used to determine if there is a significant difference in the responses postoperative versus preoperative.³⁰ To compare the difference between patients with CS and controls, the pretreatment survey values were subtracted from the posttreatment survey values, and then the distributions of these differences were compared using a Cochran–Armitage test for trend.³⁰ Thus, negative values in these latter comparisons indicate improvement. Kruskal–Wallis test was used for subgroup analysis of patients’ characteristics, and early postoperative outcomes with Dunn’s test applied for subsequent evaluations. Results are presented as median (value range) and mean $\pm$ standard deviation throughout the text with the level of significance set at $p < 0.05$.

RESULTS

Demographic and Clinical Characteristics

Patients’ clinical and demographic characteristics are provided in detail in Table 1. In brief, a total of 28 patients with a male-to-female ratio of 1:3, mean age of 39 ± 18 years, were included in the analysis. Twenty-two patients (79 %) were adults and six (21 %) were children. On initial evaluation, all patients reported having one or more physical features of CS, including weight gain, wasting and/or weakness of the proximal muscles, thinning of the skin (with easy bruising and pink or purple striae), increased acne, facial hair growth, and/or skin pigmentation (acanthosis). In regards to the disease-specific biochemical abnormalities and comorbidities: 22 patients (77 %) had hypertension, 9 (32 %) patients had diabetes mellitus or glucose intolerance, and 9 of 11 female patients (82 %) reported irregular menstrual cycle. Fifteen patients (54 %) reported one or more neuropsychiatric and emotional-behavioral symptoms, including depression, anxiety, mood swings, easy fatigability, and forgetfulness.

Short-Term Adrenalectomy Outcomes

The short-term surgical outcomes (30-days postoperatively) are summarized in Table 2. In brief, the time from the onset of signs and symptoms of CS to LBA was variable with a median of 24 (range 3–132) months. There was no conversion to an open adrenalectomy procedure. Postoperative complication rate was 7 % (1 patient with pneumonia and 1 with deep vein thrombosis). There was no 30-day postoperative mortality. Biochemical resolution of hypercortisolemia according to a recent consensus statement was tested and achieved postoperatively in all 28 patients.¹³ Before discharge patients were switched to 0.5 mg of dexamethasone daily for testing purposes, and 24-h urinary-free cortisol and diurnal serum cortisol were measured 24 and 48 h after dexamethasone initiation, respectively. Undetectable serum cortisol ($<1 \mu\text{g/dL}$) and 24-h urinary free cortisol ($<1.3 \mu\text{g/24 h}$) was consistent with cure.

Patient education regarding management of adrenal insufficiency including instructions for stress dose of glucocorticoid and intramuscular injection of hydrocortisone was developed by the patient care staff of the Clinical Center at the NIH and provided to all patients during the post-operative stay. All patients were provided with medical alert bracelets and

hydrocortisone sodium succinate vials for emergency use as described in detail in (http://www.cc.nih.gov/ccc/patient_education/pepubs/mngadrins.pdf).

Long-Term Adrenalectomy Outcomes Based on Disease-Specific Questionnaire

Twenty-four of the 28 patients (86 %) provided responses to our questionnaire and were included in the long-term outcome analyses. One female patient with ectopic CS died from widely metastatic and progressive, ACTH-producing tumor, and three other patients (two females; one male) were lost to follow-up. The median follow up was 24 (range 8–50) months. There were no cases of life-threatening Addisonian crises; however, three patients (12.5 %) reported doubling their steroid doses for upper respiratory tract infections with fever (two of them also required a stress-dose injection). One patient reported two emergency room visits, one for emotional distress, and one for diarrhea not requiring steroid dose adjustment or stress-dose injection. There was one case of myocardial infarction 2 years after LBA. Interestingly, a clinically silent recurrence of endogenous cortisol production was observed 3 years after LBA in one patient (4 %) with ectopic CS in the setting of MEN1. Before bilateral adrenalectomy, this patient had distal pancreatectomy for an ACTH and CRH-secreting pancreatic neuroendocrine tumor (PNET) metastatic to loco-regional lymph nodes. On routine annual follow-up imaging she was found to have a new enlarging, retroperitoneal left renal hilum mass. Adrenal rest or remnant and PNET metastasis were considered in the differential diagnoses, and she underwent exploratory laparotomy with retroperitoneal dissection. The final pathology showed that the mass was a hyperplastic, ectopic, completely encapsulated, retroperitoneal adrenal rest.

The long-term outcomes are shown in Fig. 2 and summarized in detail in Supplemental Table 1. There was a significant improvement of symptoms and signs of all major CS categories. Ninety-two percent of patients' responses indicated a significant improvement of General Cushing's physical features with complete resolution reported in 59 % of responses. Significant improvement of associated biochemical abnormalities and comorbidities was reported in 83 % of patients' responses including complete reversal in 58 %. Significant improvement in emotional-behavioral symptoms was reported in 84 % of patients' responses with complete recovery in 53 %. All 24 patients (100 %) were on steroid replacement therapy [hydrocortisone (mean 15 ± 3 mg in the morning and 5 ± 2 mg in the evening) and fludrocortisone (100 µg/day)]. There were no patients dissatisfied with the results of LBA.

Comparative Analysis

A group of 60 patients who underwent thyroidectomy for benign or malignant thyroid disease and remained on thyroid hormone replacement therapy postoperatively were used to control for disease- and procedure specificity of the questionnaire (Fig. 1). All 60 patients had the same questionnaire by an independent interviewer who was blinded to the answers of patients from the study cohort. Analysis of the data showed no statistically significant difference between preoperative and postoperative symptom levels in any of the general Cushing's syndrome categories reported by the patients from the control group.

To compare the difference between CS patients and patients from the control group, the pretreatment (before surgery) survey scores were subtracted from the post-treatment (long-

term postsurgery) survey scores. Negative values indicated improvement. The analysis of the distributions of differences between the LBA group and control group showed that there was a significantly greater declining level of symptoms (more changes were negative) among CS patients with LBA than among patients from control group. This was observed in all items of all three major CS categories (Fig. 3; Supplementary Table 2).

DISCUSSION

Our understanding of CS has improved dramatically since 1932 when Harvey Cushing described the symptoms and signs of hypercortisolism.³¹ There have been several consensus statements on screening, diagnosis and treatment of CS; however, the complexity and heterogeneity of this condition continue to present a considerable management challenge, and establishing the best treatment modality for patients with CS is a work in progress.^{1,4,5,13,15} The short-term outcomes of various management approaches have been investigated and compared in multiple studies, and, as a result, LBA has been recognized and accepted as the treatment of choice for patients with primary bilateral adrenal disease and occult or unresectable ectopic ACTH-or CRH-producing tumors.^{7,11,17,22,29,32–49} However, there are limited data regarding the long-term clinical outcome, prognosis and quality of life after LBA in patients with CS.^{8,10,20,45,50,51} This is, in part, because of the rarity of these conditions and the lack, until recently, of disease-specific tools for the measurement of the impact of CS and its management on patients' health and quality of life.

We designed a patient-reported outcome instrument to enable the measurement of the long-term effect of LBA on clinical, metabolic, and emotional-behavioral aspects of CS and patient-perceived quality of life. Analysis of patients' responses showed that 92 % of patients' responses showed a significant improvement of general Cushing's physical features with a complete cure of symptoms and signs reported in 59 % of responses. Significant improvement of associated biochemical abnormalities and comorbidities was reported in 83 % of patients' responses including complete reversal in 58 %. Significant improvement in emotional-behavioral symptoms was reported in 84 % of patients' responses with complete recovery in 53 %. All interviewed study patients with CS reported that the instructions were adequate and questions were clear, easy-to-understand, not redundant, and relevant to their condition and management. All patients expressed satisfaction with LBA reflecting significant improvement in their general health and self-perceived quality of life after surgery. As expected, the analysis of responses from the control group showed that the majority of patients did not have symptoms in either one of the three general Cushing's categories. The majority of these patients were very satisfied with the results of thyroidectomy. While they also found that the items of the questionnaire were clear and easy-to-understand, many felt that the questions were less relevant to their disease and management. These findings supported the CS specific nature of the questionnaire.

We believe the questionnaire developed and applied in the current study offers several important advantages over previously used questionnaires:^{23,27,28} (1) it consists of subdomains designed to cover major Cushing's features, (2) enables a clearer understanding of the association between the clinical, metabolic, and emotional-behavioral features of CS, its treatment, and patient-perceived quality of life; (3) in contrast to previous studies which

provide reference data from healthy controls only, we tested the disease- and procedure-specificity of our questionnaire by comparing the study cohort to a control group of patients who did not have CS but had operation for a different disease. This approach also allowed us to control for a placebo effect of having an operation. Additional strength of this study is using a cohort of young and adult patients who clearly had hypercortisolism prior to LBA, which enabled us to encompass the entire age spectrum of CS and exclude the confounding aspect of postoperative steroid replacement therapy.

Among the limitations inherent in a cross-sectional observational study is that the current study lacks comprehensive objective measures of CS and does not provide data on the prevalence and reversal of metabolic complications of CS at different time points after LBA. Also, the patient's responses were collected at a single postoperative time point, so that it is possible that their memory of events while hypercortisolemic was not correct. The duration of follow-up is short, however, despite this, improvement was significant. In addition, due to the lack of an established "gold standard" measure of long-term clinical course after LBA for CS, we were not able to test the content, construct, and criterion validity of our new questionnaire. However, the control group comparison shows that the differences we observed are attributable to LBA in patients with CS.

Analysis of surgical outcomes in our study cohort is consistent with many studies that LBA is a safe and effective treatment for patients with bilateral adrenal disease or occult or unresectable ectopic CS in whom rapid and definitive cure of hypercortisolism is necessary or when other therapies have failed.^{19,32,52,53} Consistent with previously published data, we also found a low (7 %) risk of perioperative complications that resolved.^{17,22,25,26} Education of patients and patients' family members on adrenal insufficiency signs and symptoms including instructions on "sick day" dose adjustment and when and how to use emergency hydrocortisone injection are among the possible explanations for improved outcomes of management of post-operative adrenal insufficiency and no life-threatening events encountered in this study.

One of the interesting findings of this study is the excellent long-term outcome of LBA in patients with ectopic CS, because many have suggested that these high-risk patients have a poor prognosis. It is possible that patients with overt tumors were referred less often to the NIH than those with occult or unresectable disease, which could lead to an accrual bias; nevertheless, 88 % of patients with occult or unresectable ectopic CS were alive and well at the time of follow-up (30 months on average) and were very satisfied with the results of LBA. These findings support previous evidence that regardless of the prognosis, no patient with ectopic CS should suffer from the effects of persistent hypercortisolism, because it can readily and safely be controlled with LBA, especially when refractory to medical therapy.^{11,54,55}

CONCLUSIONS

Our disease-specific questionnaire enables a clearer understanding of the association between the clinical, metabolic, and emotional-behavioral features of CS, its treatment with

LBA, and long-term impact on patient-reported quality of life. We believe our disease-specific questionnaire may be a useful tool for future studies in patients with CS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIG. 1.

Schematic of study design. ¹ CS—Cushing's syndrome, ² LBA—Laparoscopic bilateral adrenalectomy, ³ Control group patients matched for age, gender, time of surgery (thyroidectomy), and needed postoperative hormone replacement therapy

FIG. 2.

Long-term effect of LBA on symptoms and signs of CS. Percentage of responses calculated based on responses of patients who had symptoms preoperatively, *CS* Cushing's syndrome, *LBA* laparoscopic bilateral adrenalectomy, *GCP* General Cushing's physical features, *BAC* biochemical abnormalities/comorbidities, *EB* Emotional-Behavioral Features

FIG. 3.

Comparison of scores of patients with CS versus control group. *Blue bars*—Cushing's syndrome cohort; *Yellow bars*—control group, *GCP* General Cushing's physical features; *a* tendency to gain weight unevenly ($p < 0.0001$); *b* weakness and wasting of proximal muscle groups ($p = 0.0008$); *c* had thinning and easy bruising of the skin with pink or purple striae ($p < 0.0001$); *d* worsening acne, facial hair growth/scalp hair loss (in women) and skin darkening ($p = 0.0002$); *BAC* Biochemical Abnormalities/Comorbidities; *a* hypertension (HTN) preoperatively ($p < 0.0001$); *b* menstrual cycle irregularity ($p < 0.0001$); *c* secondary hyperglycemia ($p < 0.0001$); *d* history of recurrent low-trauma fractures ($p < 0.0001$); *EB* Emotional-Behavioral Features; *a* generalized fatigue and malaise ($p < 0.0001$); *b* anxiety ($p = 0.0008$); *c* depression ($p = 0.007$); *d* mood swing; level of symptoms ($p < 0.0001$)

TABLE 1

Study cohort clinical characteristics

Demographic and clinical characteristics	Value
Total patients	28
Sex	
Male <i>n</i> (%)	8 (29)
Female <i>n</i> (%)	20 (71)
BMI (kg/m ²), mean (SD)	32 (7)
Age at surgery (years), mean (SD)	39 (18)
Cause of CS	
ACTH-independent bilateral micronodular adrenal hyperplasia	11 (39)
Familial (PPNAD/Carney complex) <i>n</i> (%)	8 (29)
Sporadic <i>n</i> (%)	3 (11)
ACTH-independent bilateral macronodular adrenal hyperplasia <i>n</i> (%)	8 (29)
Ectopic ACTH <i>n</i> (%)	8 (29)
Ectopic CRH <i>n</i> (%)	1 (4)
Time from diagnosis to LBA (mo), median (range)	24 (3–132)
Previous treatment with adrenolytics and/or enzyme inhibitors <i>n</i> (%)	7 (25)

BMI body mass index, *SD* standard deviation, *CS* Cushing's syndrome, *ACTH* adrenocorticotrophic hormone, *CRH* corticotropin-releasing hormone, *LBA* Bilateral laparoscopic adrenalectomy

TABLE 2

Short-term surgical outcomes

Characteristics	Value
LBA approach <i>n</i> (%)	28 (100)
Transperitoneal <i>n</i> (%)	23 (82)
Synchronous retroperitoneal <i>n</i> (%)	4 (14)
Conversion from retroperitoneal to transperitoneal <i>n</i> (%)	1 (4)
Operating time	
Transperitoneal BLA (min), median (range)	197 (115–452)
Retroperitoneal BLA (min), median (range)	129 (104–193)
Blood loss	
<50 ml <i>n</i> (%)	24 (86)
51–200 ml <i>n</i> (%)	3 (10)
>200 ml <i>n</i> (%)	1 (4)
Adrenal gland weight (entire group) (g) (SD)	
ACTH-independent bilateral micronodular adrenal hyperplasia (g) (SD)	16 (11.4)
ACTH-independent bilateral macronodular adrenal hyperplasia (g) (SD)	55 (29.3)
Ectopic CS (g) (SD)	24.1 (12.6)
Length of stay (days), mean (SD)	2 (1.2)
Mortality <i>n</i> (%)	0
Morbidity <i>n</i> (%)	2 (7) ^a

Short term outcomes—30 days post-surgery

LBA Bilateral laparoscopic adrenalectomy

SD standard deviation

^aMorbidity—pneumonia (*n* = 1), deep vein thrombosis (*n* = 1)