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ORIGINAL ARTICLE

Adrenocorticotropic hormone levels before treatment predict recurrence of Cushing's disease

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Background/Purpose: Cushing's disease (CD) is the most common cause of endogenous Cushing's syndrome. Transsphenoidal surgery (TSS) is the first choice of treatment. Predicting prognosis after treatment can benefit further strategies of management, but currently there is no convenient predictor. This study aims to investigate characteristic changes after treatment and to identify potential prognostic predictors.

Methods: We retrospectively studied the records of CD patients presenting to the National Taiwan University Hospital, Taipei, Taiwan between 1992 and 2011. They were categorized according to treatment response. Clinical features and examination findings were compared between groups.

Results: Forty-one patients with CD were included. The follow-up time was 0.26–19.3 years. The time interval between the onset of symptoms and diagnosis was 2.1–120.0 months. The initial remission rate of CD after the first treatment was 82.9%. Mean body mass index (BMI) was 27.4 kg/m^2 before treatment and 26.0 kg/m^2 3 months after treatment. The patients in remission had a greater decrease in BMI after treatment and lower dehydroepiandrosterone

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sulfate (DHEAS) levels before treatment, compared with the recurrent group (both $p < 0.05$). Adrenocorticotropic hormone (ACTH) levels before treatment showed a significant positive correlation with recurrent diseases ($p < 0.05$).
Conclusion: A larger decrease in BMI after treatment and lower DHEAS levels before treatment were noted for the patients who stayed in CD remission. Higher ACTH levels before treatment predicted a recurrence of CD. These are potentially simple and practical predictors of prognosis.

Introduction

Cushing's disease (CD) is the most common cause of endogenous Cushing's syndrome (CS).[1] Transsphenoidal surgery (TSS) is the first choice of treatment.[1] Untreated CD has been significantly associated with increased mortality;[2,3] the 5-year survival rate is around 50% during the natural course of the disease.[2] Moreover, male sex, older age at diagnosis, type 2 diabetes mellitus, depression, hypertension, dyslipidemia, and obesity are all associated with cardiovascular disease in CD.[4,5] According to the literature, the presence of cardiovascular disease, longer duration of glucocorticoid (GC) exposure, older age at diagnosis, and higher preoperative adrenocorticotropic hormone (ACTH) levels are all associated with mortality in CD.[4,5] Patients who achieve remission after treatment have a much better survival rate than those with persistent or recurrent disease, and they do not have increased mortality rates compared with the general population.[6,7] Whether CD is persistent, recurrent, or in remission affects prognosis; therefore predicting the prognosis after treatment is important, and will affect further strategies of management.

In a recent large-scale study of 346 patients, none of the variables studied [including age, sex, comorbidities at diagnosis, immediate postoperative serum cortisol levels, pituitary magnetic resonance imaging (MRI) findings, and pathology] were predictors of CD recurrence.[4] Another study suggested that if tumors could be identified in both preoperative images and pathologic specimens, remission of CD was more likely to be achieved.[8] In other words, if a tumor cannot be identified and resected, it is more difficult to achieve remission. Other studies have shown that very low/undetectable postoperative serum cortisol levels are a good predictor of long-term remission;[8–10] only 7% of patients with very low postoperative serum cortisol levels had recurrent CD.[8–10] Low urinary free cortisol levels 6 weeks after TSS treatment have also been associated with remission.[8] In the above studies, serum and urine cortisol levels should be obtained under conditions where there is no GC supplementation. However, it is sometimes not feasible in clinical practice because patients receive a GC supplement when symptoms/signs of adrenal insufficiency develop after surgery. That surgeons think the tumor has been totally removed or the pituitary gland has been damaged so much that adrenal insufficiency would develop also warrants GC supplementation. Other strategies that have been proposed to predict long-term remission include measuring cortisol levels after suppression with loperamide or dexamethasone, or after stimulation with corticotropin-releasing hormone, desmopressin, or metyrapone.[3,11–15] However, it is difficult to interpret the results of these studies because of differences in the testing protocol, time at which the tests were performed, and the dose of the GC supplement before and during the tests.[9] To our knowledge, current predictors for CD recurrence after treatment are not good enough. This study aims to investigate the characteristic changes after CD treatment and to identify other potential prognostic predictors, which should be simple and practical for clinical usage.

Methods

This study was approved by the Institutional Review Board of the National Taiwan University Hospital (NTUH; Taipei, Taiwan; protocol number 201305026RINC).

We retrospectively searched for all CD patients who presented to NTUH between January 1992 and December 2011. Fifty-two patients were identified. In order to comprehensively review all the details of medical records, we selected the patients who received treatment for CD at NTUH for further study ($N = 42$). The patients who received any treatment in other hospitals were excluded ($N = 10$). We also excluded the patient who received radiotherapy in NTUH ($N = 1$). The 41 patients who were enrolled for analysis all received TSS as their first treatment for CD.

Diagnosis

CS was suspected at first presentation among all the patients included in the study because of the presence of associated symptoms and signs. Diagnostic tests for CS included the baseline serum ACTH and cortisol levels, serum cortisol levels after 1 mg dexamethasone suppression test (DST), and low-dose DST (0.5 mg dexamethasone every 6 hours for 48 hours, with post dexamethasone morning serum cortisol levels > 2 μg/dL as the diagnostic criteria for CS). Clinicians diagnosed CD based on the results of the following tests: high baseline serum ACTH levels in patients with CS, pituitary MRI, high dose DST (2 mg dexamethasone every 6 hours for 48 hours, with post dexamethasone morning serum cortisol levels $< 50\%$ of the baseline cortisol level preferring the diagnosis of CD), and inferior petrosal

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sinus sampling of ACTH after intravenous injection of desmopressin. DST and inferior petrosal sinus sampling were not performed in all patients. Patients with ACTH-independent CS or ectopic CS were excluded from the study.

Measuring outcomes

Initial remission after first treatment was defined according to the following criteria: (1) improved symptoms and signs of CS; (2) normal or lower than normal ACTH and cortisol levels within 3 months after treatment (or need for continued GC supplementation for general well-being within 3 months after treatment); and (3) no visible pituitary tumor on the follow-up MRI (if data were available). Patients who failed to meet any of the above criteria were classified as having persistent CD and were assigned to the persistent group. Patients were classified as having recurrent CD and were assigned to the recurrent group if they achieved initial remission but subsequently developed CD recurrence during follow-up. The patients who achieved initial remission and had no recurrence during follow-up were assigned to the remission group.

Long-term remission was defined by the following criteria: (1) normal or lower than normal ACTH and cortisol levels without GC supplementation at the latest follow-up (or need for continued GC supplementation for general well-being); (2) no evidence of pituitary tumors on most recent MRI; and (3) follow-up for more than 3 years after initial treatment.

Statistical analysis

Results are expressed as mean $\pm$ standard deviation or median (range). To analyze changes in characteristics before and after treatment, a paired samples t test was used for parametric data, while the Wilcoxon signed-rank test was employed for nonparametric data.

Data on patients with persistent CD were compared with the remission group. One-way analysis of variance was used for univariate analysis, and a logistic regression model was used for the multivariate analysis. The Pearson Chi-square test and Fisher's exact test were used to analyze categorical variables for parametric and nonparametric data, respectively. The Cox proportional hazards model was used for time-to-event analyses and to determine harzard ratios of variables under study to predict recurrent CD. Stata/SE 11 for Windows (StataCorp LP, College Station, TX, USA) was used for statistical analysis. A p value ≤ 0.05 was considered statistically significant.

Results

Clinical features and signs

Patients' characteristics are listed in Table 1. The median age at diagnosis was 36 years (range, 5—66 years). There were 36 (87.8%) female patients. Time between the onset of symptoms and diagnosis was 2.1—120.0 months (median, 18.4 months). The most common presentations were as follows: moon face (80.5%), weight gain (65.9%), obesity (63.4%), menstrual disturbance (47.2% of women), acne (46.3%), buffalo hump (41.5%), thin skin or easy bruising (34.2%), purple striae over the abdomen or thighs (29.3%), increased hair on the face, torso, or extremities (29.3%), plethora (24.4%), edema (22.0%), mood disorder or insomnia (22.0%), proximal muscle weakness (17.1%), lumbago (14.6%), hyperpigmentation (14.6%), headache (9.8%), blurred vision or visual field defects (9.8%), and hair loss (7.3%). Common comorbidities included dyslipidemia (58.5%), hypertension (56.1%), hyperglycemia (39.0%), osteopenia or osteoporosis (22.0%), fracture (14.6%), and urolithiasis (12.2%).

According to the definition of the Health Promotion Administration in Taiwan, patients were categorized as underweight [body mass index (BMI) < 18.5 kg/m^2], normal weight (BMI 18.5—23.9 kg/m^2), overweight (BMI 24.0—26.9 kg/m^2), or obese (BMI $\geq$ 27 kg/m^2).[16] Before treatment, more than half of the patients were overweight (14.6%) or obese (48.8%). Thirty-two percent of patients had higher ACTH levels than normal (normal, 10—65 pg/mL). All patients had baseline ACTH levels higher than 10 pg/mL. Ninety-three percent of patients had lost their diurnal rhythm of serum cortisol.

Tumor diameter was 2—17 mm with a median diameter of 5 mm. More than 90% of tumors showed lateralization on MRI (right side, 46.3%; left side, 46.3%).

Complications

Complications are shown in Table 1. Patients with symptoms, signs, and laboratory results indicating hypothyroidism or adrenal insufficiency, as well as those who needed to continue thyroxin or GC supplementation due to pituitary-directed therapy were categorized as having hypopituitarism. Patients with symptoms, signs, laboratory results, or imaging results that indicated diabetes insipidus (DI) and those who needed to continue desmopressin supplementation were classified as having DI. The most common complications after TSS were hypopituitarism, DI, and cerebral spinal fluid leakage. Less common complications included infection of the central nervous system or the surgical wound, hemorrhage of the residual tumor or the wound, and seizure.

Outcome

The follow-up periods for patients were 0.26—19.3 years (median, 5.1 years). The initial remission rate after the first treatment was 82.9% (Table 1). Sixty-nine percent of patients went into long-term remission after all the treatments they received.

Changes of characteristics after initial treatment

Characteristics analyzed included clinical features, body weight, blood pressure, and biochemical data, both before treatment and within 3 months after initial treatment (Table 2). Significant changes were observed in body weight, BMI, serum cortisol and ACTH levels, white blood cell count, and glucose levels. Blood pressure tended to

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Table 1 Clinical characteristics of patients in remission, patients with persistent CD, and patients with recurrent CD.

	Remission	Persistent	Recurrent	*p*
N	27	7	7	
Follow-up time or time to persistence or recurrence (mo)	42.3 (3.2–203.1)	2.6 (0.4–7.0)	39.9 (12.7–131.9)	—
Age (y)	34.1 ± 15.0	37.7 ± 13.8	29.9 ± 11.4	0.6
Sex (M/F)	4/23	0/7	1/6	0.8
Diameter of pituitary tumor (mm)	6.6 ± 3.8	6.8 ± 3.0	6.4 ± 2.4	>0.99
Body weight (kg)				
Before treatment	66.9 ± 19.5	70.0 ± 19.5	61.4 ± 19.0	0.7
At 3 mo after treatment	59.6 ± 18.7	68.8 ± 22.3	62.4 ± 17.7	0.6
Weight loss 3 mo after treatment	4.4 ± 3.4	1.6 ± 5.6	0.2 ± 4.3	0.1
BMI (kg/m^2)				
Before treatment	27.9 ± 5.9	26.5 ± 7.2	25.9 ± 6.7	0.7
At 3 mo after treatment	26.2 ± 4.9	25.6 ± 7.9	26.0 ± 6.5	>0.99
Decrease in BMI 3 mo after treatment	2.2 ± 1.4	0.6 ± 1.9	0.2 ± 1.8*	0.03
Cortisol at 8 am (μg/dL)				
Before treatment	26.6 ± 11.6	23.5 ± 9.4	30.3 ± 10.7	0.5
After treatment[a]	13.6 ± 14.7	24.1 ± 8.5	10.1 ± 4.3	0.1
ACTH at 8 am (pg/mL)				
Before treatment	47.5 ± 29.1	50.1 ± 23.4	65.8 ± 22.9	0.3
After treatment[a]	12.9 ± 11.8	43.0 ± 26.6*	17.8 ± 10.4**	<0.001
DHEAS before treatment (μmol/L)	6.1 ± 4.3	10.2	13.3 ± 2.0*	0.1
White blood cell count (K/μL)				
Before treatment	10.00 ± 3.30	9.74 ± 2.45	9.12 ± 2.04	0.8
After treatment	7.58 ± 1.56	8.49 ± 2.10	7.17 ± 2.11	0.4
Plasma glucose (mg/dL)				
Before treatment	112.5 ± 55.9	102 ± 27.1	97.6 ± 23.5	0.8
After treatment	93.0 ± 35.8	85.2 ± 13.2	97.7 ± 21.0	0.7
Initial treatment				
TSS	27	7	7	—
Short-term complications[a]				
DI	3 (11.1)	0 (0)	0 (0)	>0.99
Hypopituitarism	21 (77.8)	5 (71.4)	4 (57.1)	0.6
Long-term complications[b]				
DI	0	0	0	—
Hypopituitarism	5 (33.3)	2 (40)	2 (33.3)	>0.99

Data are presented as *n* (%), mean ± standard deviation, or median.
* $p < 0.05$ versus remission.
** $p < 0.05$ versus persistent.
ACTH = adrenocorticotropic hormone; BMI = body mass index; CD = Cushing's disease; DHEAS, dehydroepiandrosterone sulfate; DI, diabetes insipidus, TSS = transsphenoidal surgery.
[a] Within 3 months.
[b] Lasting > 3 months.

decrease after treatment, although this change was not statistically significant.

Predictors of recurrent or persistent disease

We analyzed the relationship between clinical characteristics and outcomes (Tables 1,3 and 4). Twenty-seven patients stayed in remission during follow-up. These patients had a significantly greater decrease in BMI and lower dehydroepiandrosterone sulfate (DHEAS) levels before treatment, compared with patients who had recurrent CD (both $p < 0.05$). They also had significantly lower ACTH levels within 3 months after initial treatment compared with patients who had persistent CD ($p < 0.05$; Table 1). However, DHEAS levels were only measured in 37.0% of patients in the remission group and in 21.4% of patients in the other groups. Higher ACTH levels within 3 months after initial treatment were related to a persistent disease [odds ratio adjusted for age, 1.09; 95% confidence interval (CI): 1.02–1.16; $p < 0.01$; Table 3]. Higher ACTH levels before treatment predicted disease recurrence during follow-up (hazard ratio adjusted for age, 1.04; 95% CI: 1.00–1.07; $p < 0.05$; Table 4). Mean diameters of the pituitary tumors in three groups had no difference, and thus they were not potential predictors for prognosis (Table 1).

Discussion

This study highlighted the changes of clinical characteristics and outcomes of CD after treatment. It demonstrated

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Table 2 Changes of characteristics within 3 months after initial treatment.

	Before treatment $N = 41$	After treatment $N = 41$	p
Body weight (kg)	65.1 ± 20.1	62.4 ± 18.9	0.0036
BMI (kg/m^2)	27.3 ± 6.2	26.0 ± 5.8	0.0009
Systolic blood pressure (mmHg)	137 ± 24	135 ± 20	0.7
Diastolic blood pressure (mmHg)	91 ± 17	87 ± 13	0.5
Serum cortisol at 8 am (μg/dL)	26.2 ± 11.0	14.7 ± 13.2	0.0001
Serum ACTH at 8 am (pg/mL)	49.7 ± 28.6	19.1 ± 18.7	<0.0001
White blood cell count (K/μL)	9.86 ± 3.27	7.66 ± 1.81	0.0002
Plasma glucose (mg/dL)	115.3 ± 56.9	90.3 ± 27.5	0.0042

Data are presented as mean ± standard deviation.
ACTH = adrenocorticotropic hormone; BMI = body mass index.

Table 3 Odds ratio (95% confidence interval) for predictors of persistent CD.

	Crude	Adjusted model
Age (y)	1.02 (0.96–1.09)	0.98 (0.89–1.08)
Weight loss 3 mo after treatment (kg)	0.92 (0.73–1.15)	—
Decrease in BMI 3 mo after treatment (kg/m^2)	0.71 (0.41–1.25)	—
Cortisol at 8 am before treatment (μg/dL)	0.97 (0.89–1.05)	—
Cortisol at 8 am after treatment (μg/dL)	1.06 (0.99–1.13)	—
ACTH at 8 am before treatment (pg/mL)	1.00 (0.97–1.03)	—
ACTH at 8 am after treatment (pg/mL)	1.09 (1.02–1.16)*	1.09 (1.02–1.16)*
DHEAS before treatment (μmol/L)	1.15 (0.71–1.87)	—

Patients with initial remission were used as the reference group (odds ratio = 1); * $p < 0.01$.
ACTH = adrenocorticotropic hormone; BMI = body mass index; CD = Cushing's disease; DHEAS, dehydroepiandrosterone sulfate.

Table 4 Hazard ratios (95% confidence interval) for predictors of recurrent CD.

	Crude	Adjusted model
Age (y)	0.97 (0.91–1.03)	0.96 (0.90–1.03)
Weight loss 3 mo after treatment	0.88 (0.72–1.08)	—
Decrease in BMI 3 mo after treatment	0.77 (0.49–1.20)	—
Cortisol at 8 am before treatment (μg/dL)	1.03 (0.96–1.11)	—
Cortisol at 8 am after treatment (μg/dL)	0.99 (0.93–1.06)	—
ACTH at 8 am before treatment (pg/mL)	1.03 (1.00–1.06)*	1.04 (1.00–1.07)*
ACTH at 8 am after treatment (pg/mL)	1.07 (0.98–1.16)	—
DHEAS before treatment (μmol/L)	1.29 (0.80–2.09)	—

Patients with remission were used as the reference group (hazard ratio = 1); * $p < 0.05$.
ACTH = adrenocorticotropic hormone; BMI = body mass index; CD = Cushing's disease; DHEAS = dehydroepiandrosterone sulfate.

that patients in remission had a larger decrease in BMI after treatment and lower DHEAS levels before treatment, compared with the recurrent group. Higher ACTH levels before treatment could predict CD recurrence during follow-up.

In our study, 69.2% of the patients achieved long-term remission. This result was higher than the 67.2% reported in a study of 61 patients in England in 2001,[8] but lower than the 72% reported in a study of 80 patients in the United Kingdom in 2012,[7] and the 71.1% reported in a study of 346 patients in the United States in 2013.[4] Clinical features and comorbidities in our study were similar to those reported in the aforementioned studies.[4,7]

In terms of diagnostic tests for CD, ACTH levels, cortisol levels, or diurnal changes do not have 100% screening sensitivity. Observation of all three of these factors is crucial for accurate diagnosis. We suggest using 2 μg/dL of cortisol as the cut-off point when an overnight dose of 1 mg of dexamethasone is used for screening CS, because two patients in our study had false negative results when we used 5 μg/dL of cortisol as the cut-off point. In terms of other dynamic studies, we suggest that suppressible cortisol levels after 48 hours of low-dose DST or non-suppressible cortisol levels after 48 hours of high-dose DST cannot be used to rule out a CD diagnosis. A diagnosis of CD requires the clinician's careful observation and full alertness, as well as the assistance of laboratory tests.

In our study, the initial remission rate after TSS alone was 82.9%, which was similar to previous studies[17–19]; however, the recurrence rate was much higher (20.6%) than other studies. This may be due to the reduced

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aggressiveness of TSS, given that rates of transient DI (7.3%) and permanent DI (0%) were also lower in our study. The remission rate among patients who encountered recurrent or persistent disease after the second round of TSS was approximately 80%, a rate that compares favorably with other management. In our experience, TSS (if feasible) stands out as the first choice of treatment in the management of recurrent or persistent CD.

Higher ACTH levels before treatment were found to be related to recurrence of CD in this study. There were higher mean ACTH levels before treatment in the recurrent group, compared with the remission group. Higher ACTH levels before treatment may indicate much larger tumor burden and local aggressiveness, which increases the difficulty of complete tumor resection. Thus, the recurrence rate increases when there are potential residual tumors. Another potential predictor for prognosis is ACTH levels after treatment; though we did not find statistical significance in Cox regression analyses. Lower ACTH levels after treatment would indicate a more complete treatment of the ACTH-secreting tumor or more destruction of the pituitary gland. However, in our study, patients received a supplemental dose of GC postoperatively when surgeons believed that tumors were completely resected and adrenal insufficiency would occur without GC supplementation. In our clinical practice, the dosage and regimen of GC prescription varied between different surgeons. GC supplementation affects ACTH and cortisol levels and thus is a potential confounder and may interfere with the analyses. It is important for patients with potential adrenal insufficiency to receive this treatment, and it should not be abandoned simply to attempt to predict outcome. Further study design with a fixed dosage of GC supplement or certified protocols of GC withdrawal before blood sampling may help to clarify this potential disease predictor.

Lower DHEAS levels before treatment were also shown in the remission group, compared to the recurrent group in this study. DHEAS is an adrenal androgen.[1] Although an additional cortical androgen-stimulating hormone other than ACTH may exist, ACTH plays a role in stimulating the adrenal cortex to secrete DHEAS.[20,21] Therefore, higher serum DHEAS levels may indicate higher levels of ACTH secretion from pituitary tumors. This may be the reason why DHEAS levels were higher in patients with persistent or recurrent CD. Unlike ACTH, DHEAS levels remain the same throughout the day.[20] This means that DHEAS may be a better marker than ACTH for prediction of CD recurrence. A recent study showed that DHEAS levels, along with ACTH and cortisol levels, decreased after TSS in all patients with CD except in those with persistent disease.[22] Burkhardt et al[22] have also suggested DHEAS levels as a novel biomarker for CD. Although DHEAS levels before treatment were found to be significantly higher in patients with CD recurrence in our study, the number of patients for whom DHEAS data was available was too small to come to a definite conclusion. This is worthy of further study.

In terms of body weight, patients with CS are known to have increased central adiposity owing to the fact that GC plays an essential role in regulating metabolism and body composition.[23,24] A study of 14 patients showed that nearly all fat deposits, including visceral fat, fat in pelvic bone marrow, subcutaneous fat of the trunk and limbs, and total fat, reduced after CD remission.[25] After treatment, body fat redistribution was associated with favorable cardiovascular risk. However, most patients remained overweight or obese even after remission.[25] In our study, average BMI decreased from 27.4 kg/m^2 to 26.0 kg/m^2 after treatment of CD. Further, BMI significantly decreased in the remission group, compared to the recurrent group ($p = 0.03$). Although the number of patients was not high enough to reach a definite conclusion, the results indicated that BMI could easily be applied in clinical practice and may be a predictor of CD recurrence.

Many studies pointed out that serum cortisol levels after surgery correlated well with long term remission; however, we found that they were not good predictors for persistent or recurrent disease in our study. Some investigators suggested that delayed resolution of adrenal autonomy resulted in persistent postoperation hypercortisolism, even after successful pituitary adenoma resection.[26–28] During further follow-up, there was a gradual decrease in serum cortisol levels in these disease-free patients. However, serum ACTH has a shorter half-life than serum cortisol and would be decreased soon after successful pituitary adenoma resection. If the serum ACTH level after surgery remained high, we found that it was a better predictor for persistent CD.

Limitations of this study include the small sample size, retrospective study design, the different postoperative GC supplementation regimens and dosage, and the small percentage of patients for whom DHEAS levels were available. Prospective and well-designed studies should be conducted to verify our observations.

In conclusion, the accurate and timely diagnosis of CD requires careful observation and high levels of alertness, accompanied by laboratory and imaging studies. Patients in CD remission had a larger decrease in BMI after treatment and lower DHEAS levels before treatment. Higher ACTH levels before treatment predicted recurrence of CD. These are potential predictors of prognosis, and are simple and practical for clinical usage.

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