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ORIGINAL ARTICLE

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

Chun-Heng Kuo [a,b,f], Shyang-Rong Shih [a,c,d,f], Hung-Yuan Li [a,c], Szu-Chi Chen [a,b], Po-Ju Hung [a,e], Fen-Yu Tseng [a,c,*], Tien-Chun Chang [a,c,d,*]

[a] *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*
[b] *New Taipei City Hospital, New Taipei City, Taiwan*
[c] *National Taiwan University College of Medicine, Taipei, Taiwan*
[d] *Center of Anti-aging and Health Consultation, National Taiwan University Hospital, Taipei, Taiwan*
[e] *Department of Internal Medicine, Taipei Hospital, Ministry of Health and Welfare, New Taipei City, Taiwan*

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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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* Corresponding authors. Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan.
E-mail addresses: fytseng@ntu.edu.tw (F.-Y. Tseng), tienchunchang@ntu.edu.tw (T.-C. Chang).
[f] These authors are co-first authors.

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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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