Original Article

An Integrated Clinical Score to Predict Remission in Cushing's Disease

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Abstract

Objective: To derive a clinical score from parameters that favor remission of Cushing's disease (CD) after pituitary surgery. **Methods:** This is an analysis of 11 clinical, hormonal, and post-operative parameters that each favored remission in a cohort of 145 patients with CD treated by trans-sphenoidal surgery (TSS). Each parameter was designated as a categorical variable (presence/absence), and several favorable parameters present for each patient were calculated. From this, a median parameter score (clinical score) of the entire cohort was derived, which was then compared to the event of remission/persistence of CD. **Results:** The median number of favorable parameters present in the entire cohort was 3 (0–7). The significant count of patients in remission increased with the increasing number of parameters. The receiver-operator characteristic curve showed that the presence of ≥3 parameters was associated with remission in CD with a sensitivity of 84.2% and a specificity of 80%. Patients with a clinical score ≥3 had significantly higher remission rates (88.9%) than those who had persistent disease (27.3%; $P = 0.001$). **Conclusion:** A clinical score of ≥3 predicts remission in CD treated by TSS; however, it requires validation in other large cohorts. Rather than assessing individual parameters to predict remission in CD, an integrated clinical score is a better tool for follow-up and patient counseling.

Keywords: Clinical score, Cushing's disease, remission

Background

Cushing's disease (CD) is an endocrine disorder of chronic cortisol excess driven by autonomous tumoral production of adrenocorticotrophin hormone (ACTH) at the level of the pituitary. CD presents with characteristic metabolic, musculoskeletal, neuropsychiatric, and dermatological manifestations.[1] Trans-sphenoidal surgery (TSS) for CD is the treatment of choice, which has a mean remission rate of 78% (25–100%) and a relapse rate of 13% (0–65.6%) during the follow-up period of 10 years after surgery.[2] Defining remission in CD is a herculean task because of the following reasons: First, during follow-up, patients with persistently high cortisol can enter remission (delayed remission).[3,4] Second, relapse of CD is known during 10 years after surgery.[5-9] Third, there are numerous parameters predicting remission including the surgeon's expertise,[10] the tumor which is localized (imaging or intra-operative),[11,12] evidence of tumor on histopathology,[9,12,13] low immediate post-operative (day 1-7) cortisol,[9,12,14,15] urinary free cortisol (UFC) that is low or normal,[6,7,16] low ACTH,[17] and prolonged requirement of glucocorticoid replacement.[9,15] Individually, these parameters lack the precision to predict long-term remission. We hypothesized that a clinical score derived from the parameters favoring remission in our previous study[18] could better predict and overcome the dilemma of remission in CD.

Methods

This is a study from a single center of 145 CD patients who were treated with TSS over the last 35 years (1984 to 2019) and a prospective follow-up of patients from 2004 onward with the retrieval of retrospective data from the medical records

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department from 1984 to 2003. This study had the approval of our hospital Institutional Ethics Committee. Voluntary informed prospective written consent was obtained only from the participants who were on follow-up.

We extracted baseline demographics and clinical characteristics including age at admission, sex, weight, body mass index (BMI), symptom duration before the presentation, and the clinical manifestations of the disease. Cortisol dynamics, including 8 am and 11 pm cortisol with ACTH, dexamethasone suppression test (DST) including 1 mg overnight (ONDST), and 2 days 2 mg test low dose dexamethasone suppression test (LDDST) and 2 days 8 mg high-dose dexamethasone suppression test (HDDST), were performed as per laid down standard procedure.[19] Until 2009, in-house radioimmunoassay (RIA) was used for measuring ACTH and cortisol, and electro-chemiluminescence immunoassay (Roche Diagnostic, Germany) was used after that. Acceptable inter- and intra-assay coefficients of variation for RIA and ECLIA and the technique of sample collection have already been described previously.[20,21] Neuroimaging of the pituitary gland was performed by dedicated sellar magnetic resonance imaging protocols (CEMRI, 1.5 and 3 Tesla; Siemens Magnetom). Post-operative 8 am cortisol (from day 1 to 7), histopathology of the tumor tissue, anterior pituitary hormones post-operatively, cortisol at 3 months (8 am and 11 pm cortisol, and overnight 1 mg dexamethasone suppression test if found hypercortisolemic), clinical resolution and resolution of metabolic derangements, pituitary neuroimaging, duration of corticosteroid replacement post surgery, and hypothalamic-pituitary-adrenal (HPA) axis recovery function were assessed. Remission in the early post-operative period was defined as an 8 am cortisol (day 1 to 7) of ≤138 nmol/L. Late remission after surgery was defined as 8 am cortisol of <350 nmol/L at 3 months with normal 11 pm cortisol (<207 nmol/L) or a suppressed cortisol (<50 nmol/L) after overnight 1 mg dexamethasone suppression test.[18] The requirement of hydrocortisone replacement for more than 3 months (>90 days) was taken as the cutoff for scoring.

The median follow-up duration was 6 years, ranging from 3 months to 15 years. At the end of the first year during follow-up, 95 (65.5%) patients had remission of CD, and 50 had persistent disease. From our cohort, we identified 11 clinical, laboratory, and imaging parameters [Tables 1 and 2] favoring remission in CD treated by TSS. Among these, we excluded the non-visualization of tumors on follow-up imaging and recovery of the HPA axis due to a shortage of data for these parameters. The remaining nine parameters were transformed into categorical variables (presence/absence) and then assigned to each patient of the cohort. Thereafter, the number of favorable (existent) parameters present per patient was estimated. From this, a median parameter score (clinical score) for the cohort was calculated. The cohort was divided into two groups (less than or greater than the clinical score) to compare the event of remission of CD.

Statistical analysis

An analysis of the data obtained was carried out using IBM SPSS version 22.0 (IBM Corp., Armonk, NY). Categorical variables are presented as numbers and percentages, and continuous variables as median and range. We used Spearman's Rho to analyze the relationship between two continuous variables and the Kruskal–Wallis H test to analyze the relationship between two categorical variables. An analysis of multivariate logistic regression was conducted to determine what factors were associated with remission and persistence. A receiver-operator characteristic (ROC) curve analysis was done to find the cut-off values for various parameters and to arrive at the (best) clinical score associated with remission, along with sensitivity/specificity analysis. A significance level of $P < 0.05$ was used for all statistical tests.

Table 1: Parameters found to favor remission in CD in our previous study

Short duration of symptoms before presentation (<2 years)
Proximal muscle weakness[18]
Post-operative (days 1–7) 8 am cortisol ≤138 nmol/L[12,16]
Three month 8am cortisol less than 350 nmol/L[18]
Non-visualization of tumor on follow-up imaging[22]
Histopathological confirmation of tumor[2,9,13]
New onset hypogonadism[18]
Duration of glucocorticoid replacement[9,15]
Resolution of diabetes[14]
Resolution of hypertension[23,24]
Recovery of HPA axis[16]

Ethical Clearance Statement

Ethical clearance was taken from Institutional Ethics Committee (Postgraduate Institute of Medical Education and Research, Chandigarh), approval number INT/IEC/2017/85, dated 07/08/2017.

Also written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The study was conducted following the principles of Declaration of Helsinki (1964).

Results

We previously reported that from the ROC curve analysis, the cutoff values for immediate post-operative cortisol at 8 am and 3-month cortisol to predict remission were 159.85 nmol/L and 384.9 nmol/L, with sensitivity/specificity of 77%/84.1% and 81.6%/61.4%, respectively. We also found that with immediate post-op 8 am cortisol cutoff of 49.7 nmol/L, the sensitivity and specificity were 33.3% and 93.2%, respectively, to predict remission ($P = 0.002$). In a logistic regression analysis of the effects of the aforementioned parameters on remission likelihood in CD, 70.1% (Nagelkerke R2) of the variance was explained and 91.5% of cases were correctly classified as remission. If the duration of steroid replacement was >90 days and if there was resolution of hypertension post-surgery, then those patients were 15.8 times ($P = 0.033$) and 12.2 times ($P = 0.003$) more likely to enter remission.[18]

The median number of parameters favoring remission in the cohort was 3 (0–7). The number of patients in remission increased with the rising number of parameters [Figure 1]. The trend for increased remission was evident at ≥3 parameters (19/24; 79.2%); however, all patients with ≥5 parameters (n = 45; 100%) were found to be in remission [Figure 1].

ROC curve analysis showed that the presence of ≥3 parameters (C: 0.821, 95% CI: 0.744–0.898) was associated with remission in CD with a sensitivity of 84.2% and a specificity of 80%. ROC curves were also derived for the presence of ≥4, ≥5, ≥6, and ≥7 parameters, but the area under the curve was highest for ≥3 parameters. The presence of ≥5 parameters had a specificity of 100% but a low sensitivity of 47.4%. Based on the (derived) clinical score of 3, we sub-divided our cohort into patients with ≥3 parameters (n = 90) and patients with <3 parameters (n = 55). Patients with ≥3 parameters had a significantly higher remission rate (80/90; 88.9%) than the latter group (15/55 = 27.3%; $P < 0.001$) [Figure 2].

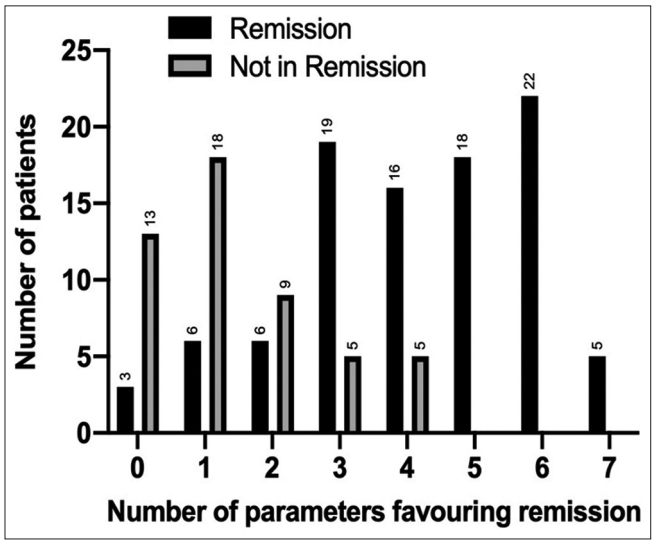

Figure 1: Stratification of patients of CD based on total number of favorable parameters present (range 0–7). A trend of increased remission was evident at ≥3 parameters

Among patients with ≥3 parameters who were in remission (n = 80), the frequency (in descending order) of various parameters favoring remission was as follows: histological confirmation of tumor (n = 73/80; 91.3%), 3-month 8 am cortisol <350 nmol/L (71/80; 88.8%), new-onset hypogonadism (n = 58/70; 82.9%), presence of proximal myopathy at presentation (n = 65/79; 82.3%), immediate post-operative 8 am cortisol ≤138 nmol/L (63/79; 79.7%), duration of glucocorticoid replacement >90 days (60/79; 75.9%), resolution of hypertension (57/76; 75%), short duration of symptoms until presentation <2 years (36/80; 45%), and resolution of diabetes (11/75; 14.7%).

Discussion

Remission in CD is a prospective realization and is rather elusive even 10 years after surgery.[5-9] Defining remission is important to dictate post-operative management (glucocorticoid replacement, redo surgery, medical therapy, radiotherapy, and/or adrenalectomy), monitor complications, and allay patients's anxiety. In our cohort of patients, we discovered that diverse pre- and post-operative clinical and biochemical parameters

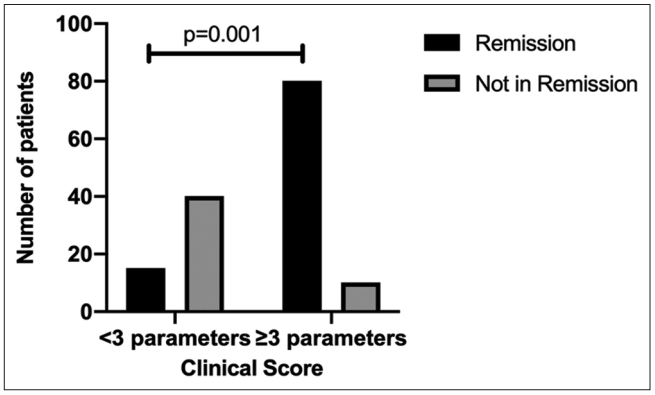

Figure 2: Patients with a clinical score ≥3 parameters had a significantly higher remission rate than those with <3 parameters ($P < 0.001$)

Table 2: Comparison of the baseline clinical, biochemical, and imaging characteristics between patients in remission and patients with persistent disease at 1 year

Parameter	Remission (*n*=95)	Persistence (*n*=50)	*P*
Short duration of symptoms before presentation (months) (*n*=49/144)	24 (12-48)*	36 (24-60)*	0.009
Proximal muscle weakness	70.9%	29.1%	0.038
Post-operative (day 1-7) 8 am cortisol (nmol/L)	76.7 (40-150.8)*	437 (207-628)*	<0.001
Three month 8 am cortisol less than 350 nmol/L	76.5%	23.5%	<0.001
Non-visualization of tumor on follow-up imaging	64.3%	35.7	0.003
Histopathological confirmation of tumor	70%	30%	0.045
New onset hypogonadism	75%	25%	<0.001
Duration of glucocorticoid replacement (>90 days)	96.8%	3.2%	<0.001
Resolution of diabetes	85.7%	14.3%	<0.001
Resolution of hypertension	85.7%	14.3%	<0.001
Recovery of HPA axis	87%	3%	0.018

*Denotes values in median and IQR

could favor remission in a large cohort of CD treated by TSS.[18] We studied nine parameters, such as short duration of symptoms before presentation, weakness of the proximal muscles, post-operative (days 1–7) 8 am cortisol, 3 month 8 am cortisol less than 350 nmol/L, histopathological confirmation of tumor, new onset hypogonadism, duration of glucocorticoid replacement (>90 days), resolution of diabetes, and resolution of hypertension [Table 1], to see if they had a relationship with remission or relapse. A low post-operative 8 am cortisol is a well-known indicator of remission. Two cut-offs, <50 nmol/L and <138 nmol/L, have been used to predict remission in the literature. Based on the ROC analysis, we obtained values of 49.7 nmol/L and 159.85 nmol/L, respectively, with sensitivity/specificity of 33.3%/93.2% and 77%/84.1%, which indicates patients with borderline values might enter delayed remission or relapse and thus need monitoring. For 3 months cortisol, the value to favor remission was 384.9 nmol/L with sensitivity/specificity of 81.6%/61.4%. Regarding histological confirmation of the tumor, it has been reported to have a high remission rate of 82.1%.[2] The findings in our cohort were almost similar (88%); however, adenoma was identified in 72% of patients with persistent disease. This may happen due to partial resection of the tumor. Additionally, patients in remission without histological confirmation may have lost tissue due to tumor necrosis or tissue handling. The duration of steroid replacement is an important predictor of remission and successful surgery.[15] Results of our study also suggest that glucocorticoid replacement for >90 days predicts remission. Cushing remission reduces medication doses for diabetes and hypertension, the metabolic manifestations of CD due to hypercortisolemia.[14,23,24] We found that resolution of diabetes (77%) and hypertension (71%) at 3 months predicted remission at 1 year in our cohort.

Except for clinical parameters including the presence of proximal muscle weakness, a short duration of symptoms until presentation, and new-onset hypogonadism (novel findings of our study), the listed parameters have been well described previously.[2,6,7,9,12-15] Proximal muscle weakness and a short duration of symptoms may denote increased severity of disease, leading to early diagnosis and early treatment. A relationship between the duration of symptoms and remission of disease has been described previously and is considered one of the most important predictors of remission.[25] However, disease duration may not be correlated with the recurrence of CD.[26] New onset hypogonadism after surgery has also been found to favorable for remission in our study. The reason for this is not exactly known, but there are some risk factors affecting gonadal axis other than hypercortisolemia. It could be due to tiny pituitary tumors having increased surgical difficulty, leading to damage to normal pituitary tissues.[27]

Although each of the parameters listed in Table 1 was found to be significantly different between patients who were in remission and patients who had a relapse in our study when combined in a regression analysis, only prolonged need of glucocorticoid replacement (>90 days) post-TSS and control of hypertension post-surgery significantly predicted remission. The likelihood of these patients entering remission was 15.8 times ($P = 0.033$) and 12.2 times ($P = 0.003$) higher if the duration of steroid replacement was > 90 days and hypertension was resolved after TSS. In this study, we quantified our results in the form of a clinical score to better predict remission in CD, a strategy that has not been described previously.

This study effectively objectified the remission criteria in patients of CD treated by TSS. Among the previously identified 11 parameters favoring remission, a clinical score of ≥3 parameters in a patient of CD treated by TSS predicts remission. With the rising number of parameters (≥3), the chances of remission increase substantially. Our results showed that a higher score (≥3) or increasing number of parameters was associated with an increased chance of being in remission. The ROC curve analysis firmly established ≥3 parameters as a cut-off for remission based on which we could see a significantly higher remission rate (88.9%; $P < 0.001$).

The strength of this study lies in objectifying the criteria for remission of CD based on parameters derived from a single center with a large cohort of patients. The limitations of the study include data unavailability for some parameters (post-operative imaging, recovery of HPA axis) and the assumption that each parameter has equal weightage to suggest remission while calculating the clinical score.

Conclusion

Parameters favoring remission in patients of CD treated by TSS can be integrated to create a clinical score that predicts long-term remission better than any of the individual parameters. In this study, a clinical score of ≥3 parameters could predict remission in patients of CD. This clinical score can be further modified and/or validated in other published cohorts of CD to predict remission.

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Conflicts of interest

There are no conflicts of interest.

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