The recovery time of hypothalamic-pituitary-adrenal axis after curative surgery in Cushing’s disease and its predictor

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Abstract

Objective

Patients with Cushing’s disease (CD) experienced transient central adrenal insufficiency (CAI) after successful surgery. However, the reported recovery time of hypothalamic-pituitary-adrenal (HPA) axis varied and the risk factors which could affect recovery time of HPA axis had not been extensively studied. This study aimed to analyze the duration of CAI and explore the risk factors affecting HPA axis recovery in post-operative CD patients with biochemical remission.

Design and methods

Medical records of diagnosis with CD in Huashan Hospital were reviewed between 2014 and 2020. 140 patients with biochemical remission and regular follow-up after surgery were enrolled in this retrospective cohort study according to the criteria. Demographic details, clinical and biochemical information at baseline and each follow-up (within 2 years) were collected and analyzed.

Results

Overall, 103 patients (73.6%) recovered from transient CAI within 2 years follow-up and the median recovery time was 12 months [95% confidence intervals (CI): 10–14]. The age and midnight ACTH at baseline were significantly lower, while the TT3 and FT3 levels were significantly higher in patients with recovered HPA compared to patients with CAI at 2-year follow-up (p < 0.05). In persistent CAI group, more patients underwent partial hypophysectomy. TT3 at diagnosis was an independent predictor of the recovery of HPA axis, even after adjusting for gender, age, duration, surgical history, maximum tumor diameter, surgical strategy, and postoperative nadir serum cortisol level (p = 0.04, OR: 6.03, 95% CI: 1.085, 22.508). Among patients with unrecovered HPA axis at 2-year follow-up, 23 CAI patients (62%) were accompanied by multiple pituitary axis dysfunction besides HPA axis, including hypothyroidism, hypogonadism, or central diabetes insipidus.

Conclusion

HPA axis recovered in 73.6% of CD patients within 2 years after successful surgery, and the median recovery time was 12 months. TT3 level at diagnosis was an independent predictor of postoperative recovery of HPA axis in CD patients. Moreover, patients coexisted with other hypopituitarism at 2-year follow-up had a high probability of unrecovered HPA axis.

Introduction
Cushing disease (CD) is caused by adrenocorticotropic hormone (ACTH)-producing pituitary adenoma leading to cortisol overproduction, and the optimal treatment is trans-sphenoidal surgery (TSS) by an experienced pituitary surgeon\(^1\)–\(^3\). Generally, transient central adrenal insufficiency (CAI) occurs after successful TSS, therefore physiological hydrocortisone replacement is required until the recovery of hypothalamic-pituitary-adrenal (HPA) axis. Inadequate replacement may cause patients suffering from severe glucocorticoids withdrawal symptoms including adrenal crisis\(^3\). On the contrary, overdose replacement could result in side effects by excessive glucocorticoids. Therefore, it is necessary to explore the recovery time of HPA axis and relative predictors of HPA axis recovery in biochemical remission CD patients after TSS\(^4\). However, to date, there are no consistent conclusions in the literature on the recovery time in CD patients, varying from a couple of months to a few years, even lifelong replacement in some CD patients\(^3,5\)–\(^7\). Furthermore, the factors for predicting HPA axis recovery are scarcely reported.

Therefore, the aim of this study was to analyze the duration of HPA axis recovery form transient CAI and explore the factors for predicting HPA axis recovery in post-operative CD patients with biochemical remission.

**Subjects And Methods**

This study was a retrospective cohort study and was approved by the Human Investigation Ethics Committee at Huashan Hospital (No.2017M011). Medical records of patients with Cushing's disease managed between 2014 and 2020 were reviewed at diagnosis (pre-surgery) as well as during the follow-up (1, 3, 6, 12, 18 and 24 months after surgery).

**Inclusion And Exclusion Criteria**

Inclusion criteria included (1) willingness to participate in the study, (2) age \(\geq\) 18 years, (3) diagnosis of Cushing's disease according to the updated diagnostic criteria\(^8\), (4) biochemical remission after TSS, and (5) receiving regular follow-up visits (regular follow-up visits included 1, 3, 6, 12, 18 and 24 months after surgery and the enrolled patients should receive at least 4 follow-up visits within 2 years after surgery). Exclusion criteria included (1) uncured or relapse during the follow-up; (2) experiencing radiation therapy before the surgery and (3) with primary gonadal or thyroid disease.

**Clinical And Biochemical Methods**

Demographic details, clinical features, 24-hour urinary free cortisol (UFC), hormonal profile [serum prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (TT), adrenocorticotropic hormone (ACTH), cortisol, total thyroxine (TT4)/ free thyroxine (FT4), total triiodothyronine (TT3)/ free triiodothyronine (FT3), thyroid-stimulating hormone (TSH), insulin-like growth factor 1 (IGF-1)], body mass index(BMI), hemoglobin A1c (HbA1c), total cholesterol (TC), triglyceride (TG),
systolic blood pressure (SBP), and diastolic blood pressure (DBP) were recorded at diagnosis (pre-surgery) as well as during the follow-up.

Biochemical remission of CD included immediately postoperative remission [serum cortisol level < 2 µg/dL (138 nmol/L) within the first seven postoperative days] and although serum cortisol at 8:00 a.m. was ≥ 2 µg/dl or back to normal range immediate after surgery, it became hypocortisolemic at subsequent evaluation(s) and without relapse during the follow-up\(^8\)\(^–\)\(^10\). All patients with serum cortisol level < 2 µg/dL were administered with 20 mg of hydrocortisone 3 times a day after surgery to avoid steroid withdrawal syndrome, with a 10-day taper afterward. When hydrocortisone was reduced to 20 mg once a day for 10 days, the patient was followed up for the first time after surgery.

HPA axis was evaluated with 8:00 a.m. cortisol level obtained before that day's glucocorticoid intake, followed by an ACTH stimulation test starting when the level was 2 ~ 10µg/dL (55 ~ 276 nmol/L). The recovery of HPA axis was defined as 8:00 a.m. serum cortisol was more than 10µg/dL (276nmol/L) or stimulated level was approximately 18µg/dL (500 nmol/L) or greater\(^3\)\(^,\)\(^11\).

Central hypothyroidism was defined as low FT4 (< 12pmol/L) with a low, normal, or mildly elevated TSH\(^12\). IGF-1 index was defined as the ratio of measured value to the respective upper limit of the reference range for age and sex. Hypogonadotrophic hypogonadism was defined as low (< 6.68nmol/L) morning serum TT in males or irregular menstruation in females with low/normal serum FSH and LH levels.

**Statistical analysis**

Statistical analysis was done using IBM SPSS Statistics for Windows, Version 26.0. Continuous normal data were summarized as means and standard deviations; non-normal data as medians and interquartile ranges; categorical variables were expressed as frequency percentage. For independent bivariate comparisons, Student's \( t \) and the U-Mann Whitney test were used according to normality. Multivariate logistic regression analysis was performed to evaluate the association between TT3 and the recovery of HPA axis after adjusting for confounding factors. Kaplan-Meier curve was drawn by GraphPad Prism (version 8.0), and analysis by Log-Rank test. A two-tailed \( P \) value < 0.05 was considered statistically significant.

**Results**

**Overall cohort**

A total of 166 patients pathologically diagnosed with CD with regular follow-up after surgery were hospitalized in the Department of Endocrinology, Huashan Hospital from 2014 to 2020. Of these, 22 patients were excluded due to no biochemical remission after surgery or relapse during follow-up. Moreover, 4 patients who experienced radiation therapy before the surgery were excluded as well (Fig. 1). A total of 140 patients were included in our study, with a median age of 37 years (IQR, 29–47 y), 111
females (79%), and 29 males (21%). The median duration of CD symptoms was 2 years (IQR, 1–5 y), and 24 patients (17.1%) had received surgical therapy before the visit to our center. Baseline characteristics of the included patients were presented in Table 1.

Table 1
Clinical and biochemical characteristics of patients at diagnosis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>29(21%)/111(79%)</td>
<td>8a.m. serum cortisol(µg/dL)</td>
<td>25.4(18.1,31.8)</td>
</tr>
<tr>
<td>Age(years)</td>
<td>37(29,47)</td>
<td>16p.m. serum cortisol(µg/dL)</td>
<td>21.8(15.3,28.1)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>2(1,5)</td>
<td>24p.m. serum cortisol(µg/dL)</td>
<td>19.1(15.1,24.5)</td>
</tr>
<tr>
<td>Surgery history</td>
<td>24(17.1%)</td>
<td>24-hour UFC(µg/24-hour)</td>
<td>356(211,757)</td>
</tr>
<tr>
<td>body mass index (kg/m^2)</td>
<td>25.4(23.0,28.2)</td>
<td>8a.m. ACTH(pg/mL)</td>
<td>70.1(44.2,109.9)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>84(60%)</td>
<td>16p.m. ACTH(pg/mL)</td>
<td>66.6(46.4,93.3)</td>
</tr>
<tr>
<td>IGR &amp; DM (%)</td>
<td>63(45%)</td>
<td>24p.m. ACTH(pg/mL)</td>
<td>61.7(42.7,96.4)</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>31(22.1%)</td>
<td>serum cortisol after 1mg DXM(µg/dL)</td>
<td>18.4(11.6,24.2)</td>
</tr>
<tr>
<td>Osteopenia &amp; Osteoporosis (%)</td>
<td>36(25.7%)</td>
<td>Maximum tumor diameter(mm)</td>
<td>7(5,10)</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile ranges) or n (%). IGR= impaired glucose regulation; DM = diabetes mellitus, UFC = urinary free cortisol; ACTH = adrenocorticotropic hormone; DXM = dexamethasone.

Median HPA recovery time was 12 months

Overall, 103 patients’ (73.6%) HPA axis recovered during the 2 years follow-up. For those patients whose HPA axis recovered, 2, 1, 14, 57, 13, 16 patients recovered at 1, 3, 6, 12, 18, and 24 months postoperative follow-up, respectively (Fig. 2). We found that the duration of postoperative CAI was mostly ranged from 6 to 24 months, with only 3 patients recovered within 3 months after surgery. Importantly, about half of the patients (n = 57) recovered at 12 months postoperatively (95% CI: 10–14), which suggested that 12 months was a key time point for postoperative CD patients.

Among 103 patients, 9 patients were accompanied by central diabetes insipidus, 3 of whom with hypothyroidism, 5 with hypogonadism. In addition, among these 9 patients, 2 patients experienced 2 pituitary surgeries and 3 patients underwent extended pituitary tumor resection or partial hypophysectomy. Extended resection usually involved the removal of 1mm of tissue around the tumor. All the patients undergoing partial hypophysectomy were with suspicious tumor in MRI, which was also not
obvious during the operation, therefore, according to bilateral inferior petrosal sinus sampling results, partial hypophysectomy was performed.

**The differences between patients with HPA axis recovered and with persistent CAI at 2-year follow-up after surgery**

As shown in Table 2, the patients, who achieving biochemical remission after transsphenoidal surgery were divided into two groups according to whether HPA axis recovered at 2-year follow-up after surgery [central adrenal sufficiency (CAS) group and persistent CAI group]. Patients in CAS group were younger [34 (28, 46) vs 40 (34, 54), p = 0.026) and had lower midnight ACTH [57.3 (41.3, 84.2) vs 81.2 (54.3, 122.0) pg/mL, p = 0.021] level at baseline than those in persistent CAI group. While, there were not significantly differences in gender, disease duration, maximal tumor diameter seen in MRI, and history of surgery between the two groups at diagnosis.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CAS at 2 years</th>
<th>CAI at 2 years</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N(%)</strong></td>
<td>103(73.6%)</td>
<td>37(26.4%)</td>
<td>/</td>
</tr>
<tr>
<td><strong>male (%)</strong></td>
<td>25 24%</td>
<td>5(14%)</td>
<td>0.171</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>34 28,46</td>
<td>40 34,54</td>
<td>0.026*</td>
</tr>
<tr>
<td><strong>Disease duration (years)</strong></td>
<td>2.0 0.7,4.0</td>
<td>3.0 1.0,6.0</td>
<td>0.162</td>
</tr>
<tr>
<td><strong>History of surgery therapy</strong></td>
<td>15(15%)</td>
<td>9(24%)</td>
<td>0.177</td>
</tr>
<tr>
<td><strong>8a.m. serum cortisol[μg/dL]</strong></td>
<td>25.4 18.3,32.3</td>
<td>25.3 16.9,29.6</td>
<td>0.611</td>
</tr>
<tr>
<td><strong>16p.m. serum cortisol[μg/dL]</strong></td>
<td>22.1 15.4,28.1</td>
<td>21.5 14.3,29.4</td>
<td>0.795</td>
</tr>
<tr>
<td><strong>24p.m. serum cortisol[μg/dL]</strong></td>
<td>19.4 15.4,24.5</td>
<td>18.1 14.7,24.3</td>
<td>0.665</td>
</tr>
<tr>
<td><strong>24-hour UFC[μg/24-hour]</strong></td>
<td>361 226,749</td>
<td>300 182,821</td>
<td>0.839</td>
</tr>
<tr>
<td><strong>8a.m. ACTH[pg/mL]</strong></td>
<td>65.8 43.8,100.7</td>
<td>93.7 64.1,136.8</td>
<td>0.071</td>
</tr>
<tr>
<td><strong>16p.m. ACTH[pg/mL]</strong></td>
<td>63.4(46.2,86.9)</td>
<td>81.9(64.4,119.5)</td>
<td>0.074</td>
</tr>
<tr>
<td><strong>24p.m. ACTH[pg/mL]</strong></td>
<td>57.3(41.3,84.2)</td>
<td>81.2(54.3,122.0)</td>
<td>0.021*</td>
</tr>
<tr>
<td><strong>Maximum tumor diameter[mm]</strong></td>
<td>7 5,10</td>
<td>6 5,9</td>
<td>0.537</td>
</tr>
<tr>
<td><strong>Microadenoma%%</strong></td>
<td>84 81%</td>
<td>29 78%</td>
<td>0.675</td>
</tr>
<tr>
<td><strong>TSH[mIU/L]</strong></td>
<td>1.01 0.59,1.56</td>
<td>0.84 0.54,1.41</td>
<td>0.644</td>
</tr>
<tr>
<td><strong>TT3[fmol/L]</strong></td>
<td>1.21 1.02,1.46</td>
<td>1.07(0.9,1.24)</td>
<td>0.012*</td>
</tr>
<tr>
<td><strong>TT4[fmol/L]</strong></td>
<td>78.4 62.6,91.30</td>
<td>78.2(68.0,89.9)</td>
<td>0.976</td>
</tr>
<tr>
<td><strong>FT3[pmol/L]</strong></td>
<td>3.72(3.24,4.25)</td>
<td>3.49(3.11,3.95)</td>
<td>0.018*</td>
</tr>
<tr>
<td><strong>FT4[pmol/L]</strong></td>
<td>13.9(12.5,15.7)</td>
<td>15.0(13.1,16.5)</td>
<td>0.256</td>
</tr>
<tr>
<td><strong>Hypogonadism%%</strong></td>
<td>60(58%)</td>
<td>21(57%)</td>
<td>0.874</td>
</tr>
<tr>
<td><strong>PRL[ng/mL]</strong></td>
<td>18.6(14.3,29.4)</td>
<td>18.2(12.4,26.9)</td>
<td>0.597</td>
</tr>
<tr>
<td><strong>IGF-1 index</strong></td>
<td>0.78(0.58,0.91)</td>
<td>0.68(0.51,0.95)</td>
<td>0.824</td>
</tr>
<tr>
<td><strong>BMI [kg/m²]</strong></td>
<td>25.3 23.0,28.1</td>
<td>25.9 23.6,28.3</td>
<td>0.598</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>5.8 5.5,6.3</td>
<td>6.2 5.5,6.9</td>
<td>0.267</td>
</tr>
<tr>
<td><strong>TC[μmol/L]</strong></td>
<td>5.0 3.9,5.9</td>
<td>4.7 2.7,5.8</td>
<td>0.347</td>
</tr>
<tr>
<td><strong>TG[μmol/L]</strong></td>
<td>1.4 1.0,2.2</td>
<td>1.4 1.1,2.1</td>
<td>0.621</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>138±15.5</td>
<td>138±17.9</td>
<td>0.889</td>
</tr>
<tr>
<td>-------------</td>
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</tr>
<tr>
<td>DBP (mmHg)</td>
<td>91±13.6</td>
<td>91±16.0</td>
<td>0.985</td>
</tr>
<tr>
<td>Surgical approach (TES, %)</td>
<td>89 (88%)</td>
<td>34 (92%)</td>
<td>0.336</td>
</tr>
<tr>
<td>Tumor extended resection (%)</td>
<td>41(39%)</td>
<td>11(30%)</td>
<td>0.528</td>
</tr>
<tr>
<td>partial hypophysectomy (%)</td>
<td>4 3.9%</td>
<td>5 (13.5%)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile ranges) or n (%). CAI = Central adrenal insuciency; CAS = Central adrenal sufficiency; UFC = urinary free cortisol; ACTH = adrenocorticotropic hormone; TSH = thyroid-stimulating hormone; TT3 = total triiodothyronine; TT4 = total thyroxine; FT3 = free triiodothyronine; FT4 = free thyroxine; IGF-1 = insulin-like growth factor 1; PRL = prolactin; HbA1c = hemoglobin A1c; TC = total cholesterol; TG = triglyceride; SBP = systolic blood pressure, DBP = diastolic blood pressure. TES = transsphenoidal endoscopic surgery *p<0.05.

Notably, both TT3 [1.21(1.02,1.46) vs 1.07(0.9, 1.24) nmol/L, p = 0.012] and FT3 [3.72 (3.24, 4.25) vs 3.49 (3.11,3.95) pmol/L, p = 0.018] levels were significantly lower in patients of persistent CAI group compared with those of CAS group. No significant differences were found between the two groups in serum cortisol, TSH, PRL, IGF-1 index, the percentage of hypogonadism, and metabolic variables such as BMI, HbA1c, TC, TG, and BP.

What’s more, there were no significant differences between the two groups in surgical approach (endoscopic or microscopic transsphenoidal surgery) and undergoing extended resection of tumor or not. However, in persistent CAI group, more patients underwent partial hypophysectomy.

**TT3 level at diagnosis was an independent predictor of recovery of HPA axis**

Multiple logistic regression model was conducted to further explore the correlation between baseline TT3 level and the recovery of HPA axis. We found that TT3 level at diagnosis was an independent predictor of recovery of HPA axis at 2-year follow-up after surgery (p = 0.02, OR: 6.947, 95% CI:1.594,30.273), even adjusting for gender, age, duration at diagnosis, maximum tumor diameter, history of surgery, surgical approach (endoscopic or microscopic transsphenoidal surgery), adenomectomy range, and the minimal serum cortisol level within the first seven postoperative days (p = 0.04, OR: 6.03, 95% CI: 1.085, 22.508) (Table 3).
Table 3

TT3 level at diagnosis was independently associated with the recovery of HPA axis at 2 years post-operation.

<table>
<thead>
<tr>
<th></th>
<th>B (SE)</th>
<th>P value</th>
<th>Exp(B) (95% IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1.938(0.751)</td>
<td>0.01</td>
<td>6.947(1.594,30.273)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.882 (0.631)</td>
<td>0.02</td>
<td>6.564 (1.338,21.1941)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.797 (0.875)</td>
<td>0.04</td>
<td>6.03(1.085,22.508)</td>
</tr>
</tbody>
</table>

Data are odds ratios (95% confidence interval).

- Model 1: unadjusted
- Model 2: adjusted for gender, age, duration at diagnosis, maximum tumor diameter, and surgery history prior to the visit to our center
- Model 3: model 2 further adjusted for transsphenoidal endoscopic surgery, adenomectomy range (selective adenomectomy, enlarged adenomectomy, and partial hypophysectomy), and the minimal serum cortisol level within the first seven postoperative days

To go deep into the association between the baseline TT3 and the recovery of HPA axis, we divided the patients into two groups according to the median TT3 levels at diagnosis, with the cut-off value of 1.15 nmol/L. The corresponding Kaplan-Meyer analysis was shown in Fig. 3. The probability of HPA axis recovery within 2 years was 62% in the lower 50% quantile and 83% in the upper 50% quantile, and the median time to recovery was 18 months (IQR, 9-27m) and 12 months (IQR, 10-14m), respectively. In addition, we found that the risk of persistent CAI in the patients with lower TT3 level at diagnosis (less than 1.15 nmol/L) was significantly higher than the patients with higher TT3 (p = 0.011) (Fig. 3).

**Hypopituitarism at 2-year follow-up after surgery in patients with persistent CAI**

At 2-year follow-up after surgery, there were still 37 patients (26.4%) with unrecovered HPA axis. Among these patients, 23 CAI patients (62%) were diagnosed with multiple pituitary axis dysfunctions. There were 19 patients with hypothyroidism, 19 patients with hypogonadism, as well as 5 patients with central diabetes insipidus. The detailed distribution of hypopituitarism was shown in Fig. 4. There were 6 cases of macroadenomas and 13 cases with tumor size smaller than 6mm. In addition, 5 patients experienced 2 or more pituitary surgeries and 5 patients underwent extended pituitary tumor resection or partial hypophysectomy.

**Discussion**

In the current study, we reported that 73.6% (103/140) of patients with post-operative biochemical remission achieved recovery of HPA axis within two years follow-up after surgery. The median time of recovery was 12 months. Patients with CAI over 2 years have a high risk of postoperative persistent
hypopituitarism such as central hypothyroidism, hypogonadism, or diabetes insipidus. What's more, we found that the level of TT3 at diagnosis could be an independent predictor of the recovery of HPA axis after adjusting for confounding factors in CD patients with biochemical remission after surgery. This implied that 12 months was a key time point for postoperative evaluation of CD patients.

Previous study showed that the median duration of tertiary adrenal insufficiency was dependent on the etiology of Cushing Syndrome (CS). It was shortest in the ectopic CS, intermediate in CD, and longest in adrenal CS caused by unilateral cortisol producing adenoma. In CD, recovery times varied in different studies. In the guidelines, the time of glucocorticoid replacement was seldom mentioned. Our results suggested that the median time of recovery was 12 months. This was consistent with the previous study in children with CD, in which the full recovery rate was about 75% and the overall mean time of recovery was 12 months. In adults, Berr et al and Klose et al study groups showed the mean time of recovery was 17 and 24 months respectively, which were longer compared to ours. Besides, according to the conclusion in the guideline of CS, that most adults with transient CAI after surgery could return to normal and rarely failed to recover eventually. However, our results showed that the recovery rate was 73.6%, even with experienced neurosurgeons in our center, which was higher than that of previous studies (58% and 67% respectively). Notably, the patients enrolled in our study were from 2014–2020, later than previous studies, and the remission rate was increased, while HPA axis recovery time was shorter compared to previous study. These results might due the progress of surgery technology and the accumulation of experiences these years. In addition, the patients in this study received regular follow-up within 2 years after curative surgery, and detailed data were collected. At the same time, for CD, a rare disease, our patients’ number was relatively larger, thus the results were more representative and credible.

Besides, we found that age was also independently associated with the recovery of HPA axis (data not shown) and it was consistent with the conclusion of previous study. However, the correlation between serum thyroid hormone level and recovery of HPA axis hadn’t been investigated before. In this study we found that the risk that HPA axis unrecovered within 2 years after surgery was significantly higher in the group with lower TT3 level at diagnosis than patients in the group with higher TT3, and the cutoff value of TT3 was 1.15 nmol/L. To our knowledge, this was the first report about predictive value of TT3 for HPA axis recovery in Cushing’s disease with biochemical remission. It was well known that glucocorticoids inhibited function of hypothalamic–pituitary–thyroid (HPT) axis by decreasing the secretion of TRH and TSH. Furthermore, glucocorticoids also decreased the ratio of T3/T4 resulting from glucocorticoid-mediated inhibition of peripheral deiodination. Our previous study and the research of other group reported significant negative correlations between thyroid hormones and cortisol levels both before and after surgery. Thus, we proposed that the suppressed thyroid hormones, especially TT3 level not only revealed the inhibitory action of endogenous hypercortisolemia on HPT axis but also implied the severity of the prolonged negative feedback inhibition of the HPA axis. This might explain why pre-surgical TT3 level might predict HPA axis recovery in CD patients with biochemical remission after surgery.
The results of our study also showed that there were still thirty-seven patients did not recover from CAI at 2-year follow-up and there were no significant differences between the two groups (recovery or not) in the maximum tumor diameters seen in MRI, history of surgery, surgical approach (endoscopic or microscopic transsphenoidal surgery), and undergoing extended resection of tumor or not, except for undergoing partial hypophysectomy or not. Among them, twenty-three patients (62%) were diagnosed as hypopituitarism with multiple pituitary axis dysfunctions, most of whom with macroadenoma or tumor size smaller than 6mm. Previous reports documented that hypercortisolism could result in preoperative central functional central hypothyroidism and central hypogonadism, which could return to normal after 6 to 12 months after curative surgery. Other studies suggested that if more than one pituitary axis were injured, the recovery rate of HPA axis was very low, which were in line with our findings. Based on our findings, we thought that when the pituitary tumor was too large or too small (suspicious tumor in MRI), it increased the difficulty of surgery and more likely caused persistent CAI. Therefore, when pituitary surgery was more radical causing hypopituitarism, recovery of HPA axis function was rarely observed, most likely because of irreversible impairment of normal corticotroph cells. In other words, when the tumor was not obvious, it greatly affected the recovery of HPA axis, and preoperative accurate tumor localization by MRI images or other more advanced methods might help neurosurgeons preserve more pituitary residual tissue. Postoperative persistent hypothyroidism and/or hypogonadism suggested surgical-related hypopituitarism and unrecovered HPA axis, which could help clinicians with replacement strategies in postoperative CD patients.

The main limitation of this study was its retrospective nature. This could not prove the causality of TT3 level and HPA axis recovery, therefore prospective study should be conducted to explore it. However, in our study, the number of enrolled patients were relatively large, and the follow-up was regular, therefore the conclusion was credible and representative.

In summary, we reported that HPA axis recovered in 73.6% of CD patients within 2 years after successful surgery, and the median time of recovery was 12 months. Preoperative TT3 level might be an independent predictor of the postoperative duration of CAI in CD patients with biochemical remission after surgery. Moreover, patients coexisted with other hypopituitarism at 2-year follow-up had a high probability of unrecovered HPA axis. This could help doctors predict HPA axis function recovery time and adjust cortisone replacement treatment in postoperative CD patients.

**Abbreviations**

ACTH adrenocorticotrophic hormone; TT3 total triiodothyronine; FT3 free triiodothyronine; UFC urinary free cortisol; PRL prolactin; FSH follicle-stimulating hormone; LH luteinizing hormone; TT4 total thyroxine; FT4 free thyroxine; TSH thyroid-stimulating hormone; IGF-1 insulin-like growth factor 1; HbA1c hemoglobin A1c; TC total cholesterol; TG triglyceride; SBP systolic blood pressure; DBP diastolic blood pressure

**Declarations**
Data Availability

The data are available on request from the authors.

Funding

No.

Contributions

Qiaoli Cui analyzed the data and wrote the manuscript. Qiaoli Cui, Xiaoyu Liu, Quanya Sun, Wanwan Sun and Hangping Zheng collected the data. Zengyi Ma, Ming Shen, Yongfei Wang and Yao Zhao performed transsphenoidal surgeries. Yiming Li and Zhaoyun Zhang revised the study and manuscript. Shuo Zhang and Min He recruited patients. Hongying Ye and Shuo Zhang conducted the study design and quality control. All authors read and approved the final manuscript.

Declaration of interest

The authors declare that there is no conflict of interest.

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References


**Figures**

![Flowchart of included and excluded patients of the study.](image)

**Figure 1**

Flowchart of included and excluded patients of the study.
Figure 2

Cumulative percentage of patients with recovered HPA axis. The different grayscale bars from shallow to deep represented the percentage of patients recovered at 1, 3, 6, 12, 18, and 24 months postoperatively, respectively.
Figure 3

Cumulative probability of recovery of HPA axis in patients with basal TT3 level in the upper and lower 50% quantile.
Figure 4

Hypopituitarism at 2-year follow-up after surgery in patients with CAI. Among 37 patients with CAI, the percentages of hypothyroidism, hypogonadism, and central diabetes insipidus were 51% (n = 19), 51% (n = 19), and 14% (n = 5), respectively. CAI = Central adrenal insufficiency; HPA = hypothalamus pituitary adrenal axis; HPT = Hypothalamic-pituitary-thyroid axis; HPG = Hypothalamic-pituitary-gonad axis; DI = diabetes insipidus.