The hypothalamic-pituitary-gonad axis in male Cushing’s disease before and after curative surgery

Hangping Zheng1 · Qi Wang1 · Qiaoli Cui1 · Quanya Sun1 · Wei Wu1 · Lijin Ji1 · Min He1 · Bin Lu1 · Zhaoyun Zhang1 · Zengyi Ma2 · Ming Shen2 · Xuefei Shou2 · Yongfei Wang2 · Yao Zhao2 · Yiming Li1 · Hongying Ye1 · Shuo Zhang1

Received: 1 April 2022 / Accepted: 16 May 2022 / Published online: 31 May 2022
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract
Objective Gonadal and sexual disturbances are commonly encountered in patients with Cushing’s disease. Nevertheless, the prevalence of hypogonadism in male Cushing’s disease, the risk factors as well as the recovery time have been scarcely reported. Therefore, we aimed to explore the prevalence of hypogonadism at baseline and its determinants. In addition, the recovery time of hypogonadism and risk factors for unrecovered gonadal axis in male Cushing’s disease with biochemical remission were investigated.

Methods We reviewed medical records of males with Cushing’s disease managed between 2010 and 2020. Fifty-two male patients were enrolled according to the criteria. Each case attained biochemical remission after transsphenoidal surgery. Demographic details, clinical features, 24-hour UFC, hormonal profile [serum PRL, FSH, LH, TT, ACTH, cortisol, TT4/FT4, TT3/FT3, TSH and IGF-1] were measured at baseline and during follow-up. The maximal tumor diameter on MRI was recorded at diagnosis.

Results Hypogonadotropic hypogonadism was observed in thirty-nine patients (75%) at diagnosis. Total testosterone was negatively correlated with ACTH and 24-hour UFC. Midnight serum ACTH level at diagnosis was significantly associated with hypogonadism after adjusting for confounding factors. Thirty-two (80%) patients achieved eugonadism within 12 months after the surgery, of which twenty-eight (87.5%) achieved eugonadism within 3 months. Seven patients were persistently hypogonadal during the follow-up (≥1 year), mainly due to the hypopituitarism as a complication of the therapies such as surgery.

Conclusion Hypogonadotropic hypogonadism is frequent in male Cushing’s disease, but it is reversible in most cases within one-year follow-up after remission.

Keywords Hypogonadism · Cushing’s disease · Testosterone · Recovery

Abbreviations
UFC urinary free cortisol; PRL prolactin; FSH follicle-stimulating hormone; LH luteinizing hormone; TT total testosterone; ACTH adrenocorticotropic hormone; TT4 total thyroxine; FT4 free thyroxine; TT3 total triiodothyronine; FT3 free triiodothyronine; TSH thyroid-stimulating hormone; IGF-1 insulin-like growth factor 1; HH hypogonadotropic hypogonadism; BMI body mass index.

These authors contributed equally: Hangping Zheng, Qi Wang

Hongying Ye
yehongying@huashan.org.cn

Shuo Zhang
zhangshuo@huashan.org.cn

1 Department of Endocrinology and Metabolism, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai 200040, China

2 Department of Neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai 200040, China
Introduction

Gonadal and sexual disturbances are commonly encountered in patients with Cushing’s disease. Decreased libido and potency are generally recorded in male Cushing’s disease [1, 2]. Nevertheless, the prevalence of hypogonadism in male Cushing’s disease as well as the risk factors have been scarcely reported. In this study, we assessed the plasma levels of testosterone and gonadotropins prior to and after therapy of the Cushing’s disease in males. We explored the prevalence of hypogonadism at diagnosis and its determinants. In addition, the recovery time of hypogonadism and risk factors for unrecovered gonadal axis in male Cushing’s disease with biochemical remission were investigated.

Subjects and methods

This combined cross-sectional and longitudinal cohort study was conducted at Huashan Hospital, Shanghai, China. The study was approved by the Human Investigation Ethics Committee at Huashan Hospital (No.2017M011). Medical records of males with Cushing’s disease managed between 2010 and 2020 were reviewed. Inclusion criteria included (1) willingness to participate in the study, (2) age ≥18 years, (3) receiving regular follow-up, (4) diagnosis of Cushing’s disease according to the updated diagnostic criteria [3] and (5) attaining biochemical remission after transsphenoidal surgery. Exclusion criteria included (1) Cushing’s syndrome other than pituitary origin, (2) loss of follow up, (3) uncured or relapse during the follow up, (4) with primary gonadal disease, (5) after radiation therapy and (6) with medication affecting androgens. Fifty-two patients were enrolled after their informed consent. Patients were followed for more than 1 year after transsphenoidal surgery.

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)] were recorded at diagnosis (pre-surgery) as well as during the follow-up (1, 3, 6, 12, 15, 18, 24 months after surgery). Maximal tumor diameter on MRI of each patient at diagnosis was noted.

Central hypothyroidism was defined as low FT4 (<12 pmol/L) with a low, normal, or mildly elevated TSH [4]. IGF-1 index was defined as the ratio of measured value to the respective upper limit of the reference range for age and sex. Hypogonadotropic hypogonadism (HH) was defined as low (<6.68 nmol/L) morning serum TT with low/normal serum FSH and LH levels. Biochemical remission of Cushing’s disease was defined as morning serum cortisol <2 μg/dL (<55 nmol/L) within the week after surgery and disappearance of clinical signs and symptoms of hypercortisolism [3, 5, 6]. All patients were administered with 20 mg of hydrocortisone 3 times daily after surgery to avoid steroid withdrawal syndrome, with a 10-day taper afterward [7]. When hydrocortisone was reduced to 10 mg once a day for 10 days, the patient was followed up for the first time after surgery. The adrenal axis was evaluated with a morning cortisol level obtained before that day’s glucocorticoid dose at each visit, followed by an ACTH stimulation test starting when the level is 2–10 μg/dL (55–276 nmol/L). The adrenal axis has recovered if the baseline more than 10 μg/dL (276 nmol/L) or stimulated level is approximately 18 μg/dL (500 nmol/L) or greater [6, 8, 9]. Hormonal measurements were carried out by chemiluminescence assay (Advia Centaur CP). Intra-assay and inter-assay coefficients of variation were less than 8% and 10%, respectively, for the estimation of all hormones.

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp. Categorical variables are expressed in actual numbers and percentages. Continuous variables were checked for normality prior to analysis, presented as means ± SD for normally distributed variables and median, 25th percentile, and 75th percentile (Median [P25, P75]) for variables without a normal distribution, respectively. Both anthropometry and biochemical measurements were compared between groups using independent t-tests for normally distributed continuous data and non-parametric tests for variables without a normal distribution. Multivariate logistic regression analysis was performed to evaluate the association between HH and specific variables after adjusting for confounding factors. The correlation between serum ACTH concentration, 24-hour UFC and TT was examined by Pearson’s correlation analyses. P < 0.05 was considered as statistically significant.

Results

Overall cohort

Fifty-two males with Cushing’s disease were included. The mean age at diagnosis was 36.5 ± 13.7 years. HH was observed in thirty-nine patients (75%) at diagnosis. Thirty-two (80%) patients achieved eugonadism within 12 months after the surgery, of which twenty-eight (87.5%) achieved eugonadism within 3 months, while seven were persistently
hypogonadal during the follow-up (≥1 year). 14, 14, 3 and 1 patient(s) achieved eugonadism in 1, 3, 6, 12 month(s) after the surgery, respectively.

Comparison of patients with eugonadism vs. hypogonadism at diagnosis

As shown in Table 1, age and maximal tumor diameter at diagnosis were not significantly different between patients of the two groups. Patients with eugonadism had lower midnight serum cortisol [17.4 (13.6, 30.4) μg/dL, p = 0.036] as well as lower ACTH levels at baseline than those who were diagnosed with hypogonadism. No significant differences were found between the two groups in PRL, FSH, LH, TSH, FT4, TT3 and IGF-1 index (Table 1).

Total testosterone was negatively correlated with ACTH and 24-hour UFC

To further explore the correlation between TT and the cortisol level, Pearson’s correlation analyses was performed. As shown in Fig. 1, Total testosterone was negatively correlated with midnight serum ACTH level (r = −0.427, p = 0.0025) and 24-hour UFC (r = −0.334, p = 0.022).

ACTH was independently associated with hypogonadism at diagnosis

To go deep into the association between the prevalence of hypogonadism and serum ACTH levels, we divided the 52 patients into three groups according to tertiles of ACTH levels. Compared to individuals with low levels of 8 a.m. ACTH (Fig. 2), 16 p.m. ACTH (Fig. 3), and 24 p.m. ACTH (Fig. 4), the prevalence of hypogonadism in those with high levels of ACTH was significantly higher. The multiple logistic regression model shown in Table 2 demonstrated that plasma levels of midnight ACTH at diagnosis was significantly associated with hypogonadism, even after adjusting for age, body mass index (BMI), maximal tumor diameter, LH, FSH, TT4, PRL and midnight serum cortisol at diagnosis (Table 2).

Comparison of patients achieving eugonadism vs. persistent hypogonadism

It turned out that patients with persistent hypogonadism had a higher percentage of hypothyroidism (71.4% vs 3%, p < 0.001) as well as a higher prevalence of permanent central diabetes insipidus (42.9% vs 0%, p < 0.001) than those who attained eugonadism after remission of Cushing’s disease, while none was diagnosed with hypothyroidism and central diabetes insipidus.

Table 1 Comparison of characteristics between patients with eugonadism vs. hypogonadism at diagnosis

| Variable                  | Patients with eugonadism | Patients with hypogonadism | P value |
|---------------------------|--------------------------|----------------------------|---------|
| Number                    | 13                       | 39                         | /       |
| BMI (kg/m^2)              | 24.8 ± 2.8               | 27.0 ± 3.5                 | 0.032   |
| HbA1c (%)                 | 5.9 ± 0.6                | 6.5 ± 1.3                  | 0.067   |
| Age (years)               | 30 (19.5, 39.0)          | 32 (28, 47.5)              | 0.164   |
| Maximum tumor diameter (mm)| 4 (2.5, 6.0)            | 5 (3, 6.75)                | 0.147   |
| 8 a.m. serum cortisol (μg/dL)| 28.1 ± 9.0             | 30.7 ± 13.8                | 0.409   |
| 16 p.m. serum cortisol (μg/dL)| 26.5 ± 11.3            | 28.3 ± 13.2                | 0.637   |
| 24 p.m. serum cortisol (μg/dL)| 17.4 (13.6, 30.4)       | 23.8 (15.2, 34.9)          | 0.036   |
| 24-hour UFC (μg/24-hour) | 537.9 (360.0, 760.0)     | 789.4 (432.5, 1726.4)      | 0.095   |
| 8 a.m. ACTH (pg/mL)      | 65.6 (26.0, 110.2)       | 114.0 (67.7, 159.0)        | 0.014   |
| 16 p.m. ACTH (pg/mL)     | 70.5 (52.4, 100.9)       | 92.3 (79.3, 150.3)         | 0.024   |
| 24 p.m. ACTH (pg/mL)     | 53.2 (27.4, 78.4)        | 99.4 (64.5, 145.1)         | 0.001   |
| TSH (mIU/L)               | 0.91 (0.57, 1.74)        | 0.76 (0.33, 1.42)          | 0.328   |
| FT3 (pmol/L)              | 4.77 ± 1.31              | 3.66 ± 0.80                | 0.010   |
| FT4 (pmol/L)              | 15.05 ± 3.18             | 14.53 ± 2.51               | 0.631   |
| TT3 (nmol/L)              | 1.59 ± 0.72              | 1.20 ± 0.34                | 0.071   |
| TT4 (nmol/L)              | 87.77 ± 18.21            | 74.85 ± 19.38              | 0.041   |
| IGF-1 index               | 0.69 ± 0.35              | 0.64 ± 0.23                | 0.687   |
| FSH (IU/L)                | 5.81 (4.67, 6.86)        | 5.47 (2.88, 7.91)          | 0.643   |
| LH (IU/L)                 | 4.53 (3.24, 5.58)        | 4.44 (2.09, 5.48)          | 0.317   |
| TT (nmol/L)               | 10.7 (7.7, 14.8)         | 5.06 (3.89, 5.60)          | <0.001  |
| PRL (ng/mL)               | 15.5 ± 4.1               | 18.5 ± 11.8                | 0.352   |
diabetes insipidus at baseline before the surgery. The change in LH from last visit to baseline was significantly lower among patients with persistent hypogonadism compared to the other [−2.2 (−6.1, 0.3) vs 1.3 (−0.3, 2.8), p = 0.002]. No significant differences were found between the two groups in age, follow-up time, maximum tumor diameter, change in FSH, change in weight and combined drug use (Table 3). Characteristics of seven males with persistent hypogonadism after follow-up (≥1 year) were shown in Table 4. No obvious lesion was detected by MRI in Case1#. And the lesion of Case 4# was flat and thin. Case 2#, 5# and 6# suffered from pituitary macroadenomas. Case 7# had experienced two times of surgery. Case 1#, 3# and 5# attained adrenal axis recovery during the follow-up.

Discussion

In the present study, we reported that hypogonadotropic hypogonadism occurred in 75% male Cushing’s disease at diagnosis. The negative correlation found between plasma testosterone and ACTH, 24-hour UFC (Fig. 1) in our study reinforced the role of hypercortisolism playing on the suppression of gonadal axis. Midnight serum ACTH level at

Table 2 24 p.m. ACTH was independently associated with hypogonadism at diagnosis

|                 | B (SE)   | P value | Exp (B) (95% IC) |
|----------------|---------|---------|------------------|
| Model 1        | 1.778 (0.671) | 0.008   | 5.92 (1.59, 22.04) |
| Model 2        | 1.653 (0.688) | 0.016   | 5.22 (1.36, 20.10) |
| Model 3        | 1.801 (0.846) | 0.033   | 6.06 (1.15, 31.82) |
| Model 4        | 1.968 (0.996) | 0.048   | 7.15 (1.02, 50.35) |

Data are odds ratios (95% confidence interval)
Model 1: unadjusted
Model 2: adjusted for age, midnight serum cortisol and BMI at diagnosis
Model 3: model 2 further adjusted for LH, PRL and maximum tumor diameter at diagnosis
Model 4: model 3 further adjusted for FSH and TT4 at diagnosis
diagnosis was significantly associated with hypogonadism after adjusting for age, maximum tumor diameter and other confounding factors.

Eugonadism occurred spontaneously in 80% male Cushing’s disease who achieved biochemical remission after the surgery over a median follow up of twelve months, and most of which (87.5%) achieved eugonadism within 3 months. Seven were persistently hypogonadal during the follow-up (≥1 year) after remission. As listed in Table 4, there were some risk factors affecting gonadal axis recovery other than hypercortisolemia. Firstly, it would be more likely to damage normal pituitary tissue since recurrent pituitary surgery and too tiny/unclear/flat pituitary tumors also increased surgical difficulty and risk of impaired pituitary function. It should be noticed that most patients with persistent hypogonadism developed hypopituitarism including central hypothyroidism and central diabetes insipidus after curative surgery, suggesting hypogonadism mainly due to the hypopituitarism as a result of surgical complications. Secondly, pituitary macroadenoma compressing normal tissue resulted in hypopituitarism.

Shekhar S’s team studied the pre- and post-surgical characteristics of the gonadal and thyroid axis hormones in 23 adult Cushing syndrome patients who received curative surgery with follow-up for 6–12 months. But only two men were enrolled in their study. It turned out that one was already taking testosterone at baseline and the other one received gonadal axis recovery at 6-month follow up [10]. The recovery time reported by Shekhar S’s team was consistent with our study.

The spontaneous recovery of hypogonadism after resolution of hypercortisolism suggested that a wait-and-watch approach may be reasonable during the follow up less than one year when surgical remission is anticipated. In addition, our study may also help clinicians for timely initiation of testosterone/gonadotropin treatment if male patients were

### Table 3
Comparison of characteristics between patients achieving eugonadism vs. with persistent hypogonadism

|                  | Patients achieving eugonadism | Patients with persistent hypogonadism | P value |
|------------------|-------------------------------|--------------------------------------|---------|
| Number           | 32                            | 7                                    | /       |
| Age (years)      | 37.5 ± 13.7                   | 41.4 ± 9.9                           | 0.397   |
| Follow-up time (month) | 12.0 (3.0, 24.0)         | 12.0 (12.0, 18.0)                     | 0.375   |
| Maximum tumor diameter (mm) | 5.0 (3.0, 6.0)            | 5.0 (3.0, 35.0)                      | 0.419   |
| Involvement of thyroid axis, n (%) | 1 (3%)                     | 5 (71.4%)                            | <0.001  |
| Prevalence of permanent central diabetes insipidus, n (%) | 0 (0%)                     | 3 (42.9%)                            | <0.001  |
| Change in testosterone (nmol/L) | 8.29 (5.75, 14.08)       | -4.13 (-4.76, 1.50)                  | <0.001  |
| Change in LH (from last visit to baseline, IU/L) | 1.3 (-0.3, 2.8)          | -2.2 (-6.1, 0.3)                     | 0.002   |
| Change in FSH (from last visit to baseline, IU/L) | -2.1 (-3.6, -0.2)        | -2.4 (-6.0, -0.5)                    | 0.382   |
| Change in weight (from last visit to baseline, kg) | -2.0 (-6.5, 0.0)         | -4.5 (-9.0, -0.25)                   | 0.280   |
| Aspirin (%)      | 1 (3.1%)                      | 0 (0%)                               | 0.636   |
| ACEI/ARB (%)     | 4 (12.5%)                     | 3 (42.9%)                            | 0.058   |
| Calcium-channel antagonist (%) | 6 (18.8%)                | 2 (28.6%)                            | 0.560   |
| Metformin (%)    | 1 (3%)                        | 1 (14.3%)                            | 0.225   |

### Table 4
Characteristics of 7 males with persistent hypogonadism after follow-up (≥1 year)

| Patient | Age (years) | Maximum tumor diameter (mm) | Times of surgery | Involvement of thyroid axis | Present with central diabetes insipidus | Recovery of adrenal axis | Follow-up (months after surgery) |
|---------|-------------|-----------------------------|------------------|----------------------------|-----------------------------------------|--------------------------|----------------------------------|
| 1       | 51          | Unclear                     | 1                | /                          | /                                       | Yes                      | 24                               |
| 2       | 48          | 36                          | 1                | Yes                       | Yes                                     | /                        | 18                               |
| 3       | 36          | 4                           | 1                | Yes                       | /                                       | Yes                      | 15                               |
| 4       | 53          | 5                           | 1                | /                          | /                                       | /                        | 12                               |
| 5       | 43          | 15                          | 1                | Yes                       | /                                       | Yes                      | 12                               |
| 6       | 31          | 35                          | 1                | Yes                       | Yes                                     | /                        | 12                               |
| 7       | 28          | 3                           | 2                | Yes                       | Yes                                     | /                        | 12                               |
persistent hypogonadism during the follow up more than one year, especially patients with macroadenoma, too tiny pituitary tumors and recurrent pituitary surgeries.

Our study has several strengths. It is the most comprehensive and largest longitudinal study to date describing the gonadal function status of male Cushing’s disease before and after curative surgery. Secondly, we analyzed multiple markers of hypercortisolism, including maximum tumor diameter, 24-hour UFC and the circadian rhythm of cortisol and ACTH. Thirdly, we were able to demonstrate the dose-response relationship between baseline hypercortisolism and gonadal hormone abnormalities.

The main limitation of the present study is the lack of analysis data on semen and free testosterone. In addition, the extrapolation of the conclusions of our study is limited because ethnic differences might play a role in gonadal axis suppression. Since a further follow-up is crucial to prove whether gonadal axis recovery would occur over time in those with persistent hypogonadism, the follow-up duration in our study was comparatively shorter. Thus, larger scale clinical trials with longer follow-up duration, including various ethnic groups, are required to further validate the conclusions.

In conclusion, the retrospective study demonstrated that hypogonadotropic hypogonadism was common among male Cushing’s disease at diagnosis. Midnight serum ACTH level at diagnosis was significantly associated with hypogonadism after adjusting for confounding factors. Hopefully, hypogonadotropic hypogonadism is reversible in male Cushing’s disease in most cases within one year follow-up after remission.

Data availability

The data analyzed during the study are not publicly available due to relevant regulations, but are available from corresponding authors on reasonable request.

 Acknowledgements The authors are indebted to the patients who participated in this study and all the doctors contributing to the diagnosis and treatment of these patients.

Author contributions H.P.Z and Q.W. analyzed the data and wrote the manuscript. Q.Y.S., Q.L.C., W.W. and L.J.J. collected the data. Z.Y.M., M.S., X.F.S., Y.F.W. and Y.Z. performed transsphenoidal surgeries. Y.M.L. and Z.Y.Z. revised the study and manuscript. B.L. and M.H. recruited patients. H.Y.Y. and S.Z. conducted the study design and quality control. All authors read and approved the final manuscript.  

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. A.G. Smals, P.W. Kloppenborg, T.J. Benraad, Plasma testosterone profiles in Cushing’s syndrome. J. Clin. Endocrinol. Metab. 45(2), 240–245 (1977)
2. J.P. Luton, P. Thiebaut, J.C. Valcke, J.A. Mahoudeau, H. Bricaire, Reversible gonadotropin deficiency in male Cushing’s disease. J. Clin. Endocrinol. Metab. 45(3), 488–495 (1977)
3. M. Fleseriu, R.J. Auchus, I. Bancos, A. Ben-Shlomo, J. Bertherat, N.R. Biemmasz, C.L. Boguszewski, M.D. Bronstein, M. Buchfelder, J.D. Carmichael et al. Consensus on diagnosis and management of Cushing’s disease: a guideline update. Lancet Diabetes Endocrinol. 9(12), 847–875 (2021)
4. M. Fleseriu, I.A. Hashim, N. Karavitsak, S. Melmed, M.H. Murad, R. Salvatori, M.H. Samuels, Hormonal replacement in hypopituitarism in adults: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 101(11), 3888–3921 (2016)
5. A. Dutta, N. Gupta, R. Walia, A. Bhanasali, P. Dutta, S.K. Bhadada, R. Pivonello, C.K. Ahuja, S. Dhandapani, A. Hajela et al. Remission in Cushing’s disease is predicted by cortisol burden and its withdrawal following pituitary surgery. J. Endocrinol. Invest. 44(9), 1869–1878 (2021)
6. Chinese Pituitary Adenoma Cooperative Group, Consensus of Chinese experts on diagnosis and treatment of Cushing’s disease. Natl. Med. J. China 96(11), 835–840 (2016)
7. E.V. Varlamov, G. Vila, M. Fleseriu, Perioperative management of a patient with cushing disease. J. Endocrinol. Soc. 6(3), bvac010 (2022)
8. L.K. Nieman, B.M. Biller, J.W. Findling, M.H. Murad, J. Newell-Price, M.O. Savage, A. Tabarin; Endocrine Society, Treatment of cushing’s syndrome: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 100(8), 2807–2831 (2015)
9. M.D. Hurtado, T. Cortes, N. Natt, W.F. Young Jr, I. Bancos, Extensive clinical experience: Hypothalamic-pituitary-adrenal axis recovery after adrenalectomy for corticotropin-independent cortisol excess. Clin. Endocrinol. (Oxf) 89(6), 721–733 (2018)
10. S. Shekhar, S. Gubbi, R. McGlotten, L. Nieman, SAT-459 Hypothalamic-Pituitary-Gonadal (HPG) and Hypothalamic-Pituitary-Thyroid (HPT) axes in Cushing Syndrome (CS): a retrospective cohort study. J. Endocrine Soc 3(Suppl 1), SAT-459 (2019).