

Gender differences in presentation and outcome of patients with Cushing's disease in Han Chinese

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Abstract. The purpose of this study was to assess gender-related distinction in the performance of Cushing's disease (CD) regarding clinical features, radiological findings, neurological and endocrine status, surgical outcome, and quality of life in Han Chinese. A retrospective study was conducted on 87 patients treated by trans-sphenoidal surgery, between 2006 and 2011, at a single treatment center in Shandong Provincial Hospital, China. Features of CD were compared and quality of life was analyzed between genders. The female-to-male ratio was 2.78: 1. Results showed that men have a younger age of diagnosis ($P < 0.001$), a larger adenoma diameter ($P < 0.001$), and a higher invasion rate ($P = 0.032$) and apoplexy rate ($P = 0.04$) than women. To be specific, compared with women, men are more prone to suffering from osteoporosis, hypokalemia, sexual dysfunction, and hypertension ($P < 0.05$), have significantly higher preoperative and postoperative (six months after surgery) cortisol levels ($P < 0.001$, $P = 0.003$) and a higher recurrence rate (30.43% vs. 7.81%; $P = 0.028$). No significant differences were seen in the CushingQoL scores between genders. Therefore, male patients with CD need more careful and long-term follow-up than female patients.

Keywords: Cushing's disease, gender differences, transsphenoidal surgery, CushingQoL scores

1. Introduction

One of the most common causes of endogenous hypercortisolism is Cushing's disease (CD). CD can result in both physical and psychological symptoms. Mass effect, hormone secretion dysfunction, and postoperative complications can severely impact a patient's life [1]. Treatment objectives are to eliminate possible mass effects of tumour, normalize possible hormonal and metabolic disturbances of patients, and to recover normal health-related quality of life (HRQoL) [2]. The CushingQoL questionnaire used was reliable and practicable, specifically designed for Cushing Syndrome (CS) [3].

CD is different from other types of pituitary adenomas because it is diagnosed more commonly in women than men [4], showing a pronounced female prevalence. However, whether this gender difference in Han Chinese has any relations with the performance and outcome is unknown. The purposes of this study were 1) to evaluate gender-related differences before and after surgery and 2) to

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use a CushingQoL assessment in a 5-year cohort of surgically treated patients. Therefore, our study focused on the differences between genders pertaining to the clinical symptoms and features, neurological and endocrine status, imaging performance, surgical outcome, and HRQoL in CD patients via a retrospective chart review. We believe that this study will provide innovative insights for this area of research as well as help to ameliorate gender-related diagnosis and treatment of CD.

2. Materials and methods

2.1. Patients

From 2006 to 2011, 87 patients suffering from an adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma had been managed at the *Department of Neurosurgery, Shandong Provincial Hospital* in Eastern China, with the male-to-female ratio being 1:2.78 (23 men and 64 women). All patients completed questionnaires during the follow-up. The inclusion criteria for patients are shown in Table 1. Data were collected including age, gender, clinical presentation, past medical history, imaging, neurological and endocrine status, intra-operative findings, and postoperative outcomes and questionnaires. Patients were divided into two groups based on gender. The definition interval was from onset of symptoms to diagnosis. Ethical approval was obtained through the *Ethics Committee of Shandong Provincial Hospital*. Informed consent was obtained from each individual.

2.2. Imaging and intra-operative characteristics

According to Lania et al. [5], the adenomas were subdivided into microadenomas (<10 mm) and macroadenomas (>10 mm). The invasiveness of adenomas was assessed according to the preoperative Magnetic Resonance Imaging (MRI) and operative findings. Cavernous sinus invasion (CSI) was diagnosed when the adenoma was seated to the internal carotid artery on MRI or when the cavernous sinus was found by operation [6]. The apoplexy was due to the expansion of a pituitary tumour by infarction, haemorrhage, or hemorrhagic infarction.

Table 1
Inclusion criteria for patients

Inclusion criteria	
1 Classical symptoms	6 Urinary free and/or serum cortisol suppressed by >50% of the baseline value after oral loading with 16 mg dexamethasones
2 Increased serum cortisol levels	7 Concordant ACTH increase by 50% of baseline in response to CRH
3 Loss of diurnal cortisol secretion	8 Adenoma with positive ACTH immunochemistry
4 Increased 24-hour urine-free cortisol	9 Presence of a pituitary mass on MRI
5 Normal/slightly elevated plasma ACTH and/or lack of suppression of urine-free and serum cortisol following oral Loading with 2 mg dexamethasones	

2.3. Endocrine assessment

Morning fasting basal hormone were assessed. Cortisol was measured using an electrochemiluminescent immunoassay kit (Roche Diagnostics GmbH, Mannheim, Germany) with a functional sensitivity of ≤ 8.5 nmol/L. Reference values of the laboratory were 171-536 nmol/L. The intra-assay and inter-assay variation coefficients were $\leq 10\%$ and $\leq 15\%$, respectively. Glucocorticoid replacement therapy was stopped three days before every evaluation.

2.4. Immunohistochemistry

Pathological evaluation was performed. Tissues were fixed in 10% formalin, stained using the hematoxylin-eosin method, embedded in paraffin, and examined after immunohistochemical staining with the antibodies against adrenocorticotrophic hormone (ACTH), prolactin, growth hormone, follicle-stimulating hormone, luteinising hormone, and thyroid-stimulating hormone.

2.5. CushingQoL questionnaire

Patients were requested to complete the questionnaire two years after surgery. The questionnaire followed a standard methodology with a time frame pertaining to the preceding four weeks. It included 12 relevant issues and answers based on five categories: 'Always' 'Often' 'Sometimes' 'Rarely' 'Never', or 'Very much' 'Quite a bit' 'Somewhat' 'Very little' 'Not at all' (scored from 1 to 5) [3]. According to Webb [3], the total score was calculated by adding each issue score (range: 12-60) and transformed from 0 to 100. Better Quality of Life was also represented by higher scores.

2.6. Statistical analysis

Analysis was performed by the SPSS 16.0 (Chicago, IL, USA), while a statistical level of significance of 0.05 was used. The measured quantitative data were presented as mean \pm standard deviation and compared by Mann-Whitney U test. Qualitative data were presented as percentages and compared using a Chi-square test.

3. Results

3.1. Demographic and tumour features

The clinical features of the patients and adenomas are shown in Table 2 and Table 3. In total, 87 patients (43.33 ± 10.63 years old ranging from 23 to 65 years) were studied. For men, the mean age and mean time interval were 30.33 ± 10.71 years (range: 23-65) and 55.92 ± 49.32 months (range: 0.5-84), respectively; the mean diameter of the adenomas was 1.56 ± 1.02 cm (range: 0.6-4.0); invasiveness was recognized to be 56.52% and the apoplexy rate be 17.39%. On the other hand, there were 64 women with a mean age of 48.00 ± 14.6 years (range: 23-55) and a mean time interval of 33.09 ± 34.25 months (range: 0.1-18). The tumour size was 0.97 ± 0.55 cm (range: 0.5-3.2) with an invasion rate and apoplexy rate of 31.25% and 3.12%, respectively, in female patients.

Table 2

Demographic and tumour characteristics of patients in the two groups

Variables	Men (n = 23)	Women (n = 64)	P
Mean age (years)	30.33 ± 10.71	48.00 ± 14.60	< 0.001
Time interval (months)	55.92 ± 49.32	33.09 ± 34.25	0.017
Tumour size (cm)	1.56 ± 1.02	0.97 ± 0.55	< 0.001

Table 3

Dexamethasone suppression test, invasiveness, and apoplexy in the two groups

Variables		Men (n = 23)	Women (n = 64)	P
Low-dose of dexamethasone	Suppression	2 (8.70%)	4 (6.25%)	0.653
	Non- suppression	21 (91.30%)	60 (93.75%)	
High-dose of dexamethasone	Suppression	14 (60.87%)	60 (93.75%)	0.001
	Non- suppression	9 (39.13%)	4 (6.25%)	
Invasiveness	+	13 (56.52%)	20 (31.25%)	0.032
	-	10 (43.48%)	44 (68.75%)	
Apoplexy	+	4 (17.39%)	2 (3.12%)	0.040
	-	19 (82.61%)	62 (96.88%)	

Overall, cases in men were younger than those presenting in women ($P < 0.001$). Tumour size appeared to be greater in men ($P < 0.001$). In addition, there were statistically significant differences in mean time interval ($P = 0.017$), high-dose dexamethasone suppression test ($P = 0.001$), invasiveness ($P = 0.032$) and apoplexy ($P = 0.04$) between the two groups. However, a study of low-dose dexamethasone suppression test did not demonstrate meaningful differences between the two groups.

3.2. Preoperative symptoms

Tumour-specific clinical features are presented in Table 4. The most frequent clinical signs encountered in the two groups were central obesity, moon faces, plethora and acne. Additionally, osteoporosis (65.22% vs 35.94%), hypokalemia (69.57% vs 43.75%), sexual dysfunction (78.26% vs 37.50%) and hypertension (91.3% vs 65.63%) occurred more frequently in men compared with women ($P < 0.05$).

Table 4

Clinical manifestations and symptoms in the two groups

Variables	Men (n = 23)	Women (n = 64)
Central obesity	18 (78.26%)	54 (84.38%)
Moon face	18 (78.26%)	53 (82.81%)
Plethora	17 (73.91%)	47 (73.44%)
Osteoporosis	15 (65.22%) ^a	23 (35.94%) ^a
Hypokalemia	16 (69.57%) ^a	28 (43.75%) ^a
Acne	16 (69.57%)	47 (73.44%)
Sexual dysfunction	18 (78.26%) ^a	24 (37.50%) ^a
Glucose metabolism dysfunction	2 (8.70%)	5 (7.81%)
Hypertension	21 (91.30%) ^a	42 (65.63%) ^a

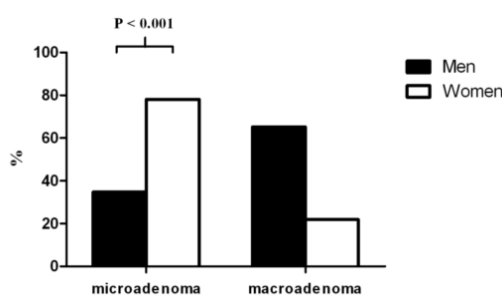


Fig. 1. Classification of tumours in the two groups.

Table 5

Pre- and postoperative cortisol levels in the two groups (unit: nmol/L)

Pre- and postoperative cortisol levels	Men (n = 23)	Women (n = 64)	P
Before surgery	839.88±308.47	544.77±200.63	<0.001
3 days after surgery	97.15±72.08	89.54±89.30	0.714
6 months after surgery	313.75±314.49	167.10±128.48	0.003

3.3. MRI

Approximately 78.12% women had microadenomas while 21.88% had macroadenomas (Figure 1). Approximately 34.78% men had microadenomas while 65.22% had macroadenomas. Therefore, macroadenomas were mostly associated with men rather than with women ($P < 0.001$).

3.4. Hormonal results before and after surgery

Cortisol levels in men decreased from 839.88±308.47 nmol/L before surgery to 97.15±72.08 nmol/L in 3 days, and then increased to 313.75±314.49 nmol/L in 6 months after surgery (Table 5). For women, cortisol levels decreased from 544.77±200.63 nmol/L before surgery to 89.54±89.30 nmol/L in 3 days, and then increased to 167.10±128.48 nmol/L in 6 months after surgery. One can see that the preoperative cortisol level in men was significantly higher than that in women ($P < 0.001$), and remains higher in 6 months after surgery ($P = 0.003$), however, there was no significant difference in cortisol levels in 3 days after surgery between the two groups ($P = 0.714$).

3.5. Follow up

The median duration of follow-up was 45 months (range: 13-121). The recurrence rates for men and women were 30.43% and 7.81% ($P = 0.013$), respectively. Based on postoperative hormone levels at 6 months, cortisol was controlled in 78.26% of men and 95.31% of women. The cortisol normalization rate in men was also significantly lower compared with women ($P = 0.028$).

Table 6
CushingQoL scores in the two groups

CushingQoL scores	Men(n = 23)	Women(n = 64)	P
Somnopathy	3.43±0.84	2.94±1.08	0.049
Have pain from leading a normal life	3.39±1.03	3.78±1.09	0.140
Take a long time to heal wounds	2.91±1.00	3.47±1.04	0.029
Bruise easily	3.00±0.90	3.89±0.91	<0.001
More irritable	3.70±1.15	3.09±0.94	0.015
Less self-confidence and more insecure	2.83± 1.07	2.98±1.06	0.542
Worried about physical changes due to illness	2.96±0.88	2.61±0.77	0.077
Less like going out	3.26±0.92	2.64±0.74	0.002
Had to give up social activities	3.17±1.03	3.20±0.84	0.893
Illness affects everyday activities	3.43±1.08	3.56±0.92	0.588
Difficult to remember things	3.91±1.00	4.05±0.84	0.536
Worried about health in the future	2.87±1.10	3.14±0.83	0.224

3.6. CushingQoL scores

CushingQoL scores in men and women were 55.98±17.88 and 57.00±15.32, respectively. No statistically significant difference was observed in the CushingQoL scores (Table 6).

4. Discussion

The research in this study depicted a pattern for Chinese Han patients with CD with men generally being diagnosed with greater tumours than women although the majority of patients were diagnosed in their thirties and forties, men appeared to be younger than women. These findings were consistent with those reported in the literature [7]. Furthermore, macroadenomas were mostly associated with men rather than with women, which might be due to the facts that a delayed diagnosis may allow tumours to grow larger [8], which men tend to feel uncomfortable complaining about their sexual problems, or that women usually present evident symptoms such as menstrual disorders. Caputo [9] and Nabarro [10] reported that premenopausal women may have smaller adenomas caused by menstrual abnormalities, while others showed that the rate of invasiveness and apoplexy were higher in men than in women. Further, in accordance with Cukiert [11], macroadenomas may be also related to cavernous sinus invasion. In the pituitary fossa, the absence of a bony interface could explain the invasion.

Our study showed that male patients tend to have a more severe clinical presentation than women. Chronic exposure to glucocorticoid may result in moon face, central obesity, hypertension, osteoporosis, fatigue, insomnia, depression, anxiety, cognitive problems [12]. Such manifestations (osteoporosis and psychosis of excessive cortisol production) were also more frequent in men than in women [13]. Some authors reported parallel data concerning the prevalence of osteoporosis in men, whereas others disagreed [14,15]. Feelders [1] identified hypertension and osteoporosis as significant risk factors in CD patients and revealed that a decrease in osteoblastic activity and an increase in osteoclastic bone resorption may result in osteoporosis. Additionally, our study suggested that males were found to be an independent risk factor for osteoporosis. We agree that hypertension also contributes to the markedly increased mortality of increased cardiovascular risk and that women are more likely to seek early medical advice because of the presentation of severe symptoms, such as

menstrual irregularities or changed appearance. Our results were also in accordance with those described by Vierhapper [4] that the sex-specific difference is of clinical relevance in patients with hypercortisolism. Finally, concerning the hormone levels, both preoperative cortisol and postoperative cortisol in men were higher than those in women. Furthermore, their postoperative hormone levels in six months showed that the cortisol normalization rate was significantly lower in men than in women. This is in agreement with previous studies [16] that adenomas secreting ACTH occurred more frequently in women.

At present, contemporary treatment options of CD are limited and may pose additional risks. In our study, the recurrence rate in patients, 13.79%, was lower than that reported by others [17] with recurrence rates for males 30.43% and females 7.81%. Our results also indicated that men not only have greater but also have more invasive tumours with a possibility of lower recurrence rate reflecting long-term remission. We feel that the elevated rate of recurrence in male patients is an important finding, suggesting that careful long-term follow-up be needed in this subset of patients even if surgery is considered successful.

Finally, reduced HRQoL is a common complaint of patients suffering from pituitary tumours. HRQoL assessment gives clinician important information on patients' everyday life. Recently, the CushingQoL questionnaire was deemed reliable and valid for Cushing's syndrome [3]. From the results of our study, CushingQoL scores in male and female patients were 55.98 ± 17.88 and 57.00 ± 15.32 , respectively, which were similar to those reported in recent research [18]. Furthermore, there was no significant difference in the scores between genders. However, male patients scored lower on physical symptoms such as tendency to bruise and taking a long time to heal wounds than females, while females scored lower on the somniphathy and psychiatric symptoms (such as becoming more irritable, less like going out). These results were in accordance with those reported by Pecori et al. [7] that somniphathy and psychiatric symptoms were more common and more easily impaired in women than in men. Hirsch [13] also reported that patients often feel fatigue, emotional instability, depression, and sleeping difficulties.

Previously reported data appear to corroborate the findings that CD is more common in women than in men [19]. However, despite the abundance of published data concerning various aspects of the clinical course and treatment of CD, few investigations have paid attention to the clinical features, laboratory findings and HRQoL assessment between genders. In an attempt to distinguish such differences, our study investigated 87 patients who underwent surgery for a period of five years to conclude a gender-dependent difference in presentation and postoperative outcomes in CD patients. Our findings suggested that longer-term follow-up, increased awareness and earlier diagnosis in men could be helpful in improving the treatment of CD. It is our hope that our research will provide innovative insights in this important field.

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