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Gender-Related Differences in the Presentation and Course of Cushing's Disease

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Cushing's disease (CD) presents a marked female preponderance, but whether this skewed gender distribution has any relevance to the presentation and outcome of CD is not known. The aim of the present study was the comparison of clinical features, biochemical indices of hypercortisolism, and surgical outcome among male and female patients with CD. The study population comprised 280 patients with CD (233 females, 47 males) collected by the Italian multicentre study. Epidemiological data, frequency of clinical signs and symptoms, urinary free cortisol (UFC), plasma ACTH and cortisol levels, responses to dynamic testing, and surgical outcome were compared in female and male patients. Male patients with CD presented at a younger age, compared with females (30.5 ± 1.93 *vs.* 37.1 ± 0.86 yr, $P < 0.01$), with higher UFC and ACTH levels (434.1 ± 51.96 *vs.* 342.1 ± 21.01% upper limit of the normal range for UFC, $P < 0.05$; 163.9 ± 22.92 *vs.* 117.7 ± 9.59% upper limit of the normal range for ACTH, $P < 0.05$). No difference in ACTH and cortisol responses to CRH, gradient at inferior petrosal sinus sampling, and cortisol inhibition after low-dose dexamethasone was recorded between sexes. In contrast, the sensitivity of the high-dose dexamethasone test was significantly lower in male than in female patients. Of particular interest, symptoms indicative of hypercatabolic state were more frequent in male patients; indeed, males presented a higher prevalence of osteoporosis, muscle wasting, striae, and nephrolitiasis. Conversely, no symptom was more frequent in female patients with CD. Patients with myopathy, hypokalemia, and purple striae presented significantly higher UFC levels, compared with patients without these symptoms. Lastly, in male patients, pituitary imaging was more frequently negative and immediate and late surgical outcome less favorable. In conclusion, CD appeared at a younger age and with a more severe clinical presentation in males, compared with females, together with more pronounced elevation of cortisol and ACTH levels. Furthermore, high-dose dexamethasone suppression test and pituitary imaging were less reliable in detecting the adenoma in male patients, further burdening the differential diagnosis with ectopic ACTH secretion. Lastly, the postsurgical course of the disease carried a worse prognosis in males. Altogether, these findings depict a different pattern for CD in males and females. (*J Clin Endocrinol Metab* 88: 1554–1558, 2003)

CUSHING'S DISEASE (CD), like many other endocrine disorders, presents a marked female preponderance. Indeed, the first description of an ACTH-secreting pituitary adenoma by Harvey Cushing was formulated (not serendipitously) in a woman, Minnie (1). Since then, the pathophysiology of CD has been studied from multiple approaches but, apart from epidemiological considerations, the possible influences of this skewed gender ratio went unremarked. Indeed, little is known on the distribution of clinical manifestations and laboratory findings in the two sexes, because most large series of patients with CD refer to the patient population as a whole. Clues from the physiology of the hypothalamo-pituitary-adrenal (HPA) axis, however, point toward a gender-dependent difference in pituitary and adrenal secretions (2–5). It seemed, therefore, of interest to investigate the distribution of clinical features and biochemical indices of hypercortisolism in male and female patients with CD.

Subjects and Methods

The study population comprised 280 patients with CD (233 females and 47 males) collected by the Italian multicentre study on Cushing's syndrome. Participating centers were asked to fill out a detailed questionnaire comprising clinical features, laboratory data, results of imaging studies, outcome of surgery, and follow-up of single patients (for detailed description, see Ref. 6). For the purpose of this study, the following findings were evaluated: sex, age, time elapsed from the appearance of first signs of hypercortisolism to diagnosis, weight, height, appearance of purple striae, plethoric face, buffalo hump, acne, ecchymoses, and thinning of the extremities. Furthermore, the occurrence of osteoporosis, hypertension, hypokalemia, nephrolitiasis, psychiatric disturbances, and impaired glucose tolerance and/or diabetes was registered. The results of basal and dynamic evaluation of the HPA axis, *i.e.* urinary free cortisol (UFC), plasma ACTH and cortisol levels, cortisol circadian rhythm and suppressibility (with 1 mg and 8 mg dexamethasone), ACTH and cortisol response to CRH stimulation using recommended cut-offs (6), inferior petrosal sinus sampling (IPSS), pituitary radiology, transsphenoidal surgery, and subsequent cure/recurrence were also included in the analysis.

Statistical evaluation

Continuous data were analyzed using the Mann-Whitney test, whereas qualitative differences were evaluated with χ^2 statistics or Fisher's exact test, as appropriate. Linear regression analysis was used to test for trends between variables. ACTH and UFC are reported as percentage excess of the normal range adopted by each laboratory, with the upper normal value set at 100%. This was not necessary for plasma cortisol because normal ranges were superimposable across laboratories. Values are stated as mean ± SEM.

Results

CD presented at a younger age in men, compared with women (30.5 ± 1.93 *vs.* 37.0 ± 0.86 yr, $P < 0.01$); indeed, over

Abbreviations: CD, Cushing's disease; ES, ectopic ACTH secretion; HPA, hypothalamo-pituitary-adrenal; IPSS, inferior petrosal sinus sampling; NS, not significant; UFC, urinary free cortisol.

half of male patients were diagnosed before the age of 30, whereas less than 25% of females were diagnosed in the same age range. Males presented with higher ACTH levels (163.9 ± 22.92 *vs.* 117.7 ± 9.59% upper limit of the normal range, $P < 0.05$) and UFC (434.1 ± 51.96 *vs.* 342.1 ± 21.01% upper limit of the normal range, $P < 0.05$). Plasma cortisol also was slightly higher in males, although this did not reach statistical significance [30.1 ± 1.71 *vs.* 28.5 ± 1.33 μg/dl (830.5 ± 47.18 *vs.* 786.3 ± 36.69 nM), $P = 0.058$; Fig. 1]. No correlation was found between age at diagnosis and UFC, cortisol and ACTH plasma levels.

The time interval elapsed between appearance of first symptoms of hypercortisolism and diagnosis seemed to be similar in men and women [26.2 ± 3.41 *vs.* 29.8 ± 1.95 months, not significant (NS)]. UFC was negatively correlated with time-to-diagnosis ($r = -0.2$, $P < 0.005$), and the correlation was maintained even when patients were subdivided according to sex. No correlation was detected with circulating ACTH and cortisol levels.

As regards clinical features, the prevalence of osteoporosis (47% *vs.* 32%, $P < 0.05$), muscle wasting (64% *vs.* 45%, $P < 0.05$), purple striae (72% *vs.* 51%, $P < 0.01$), and nephrolitiasis (21% *vs.* 6%, $P < 0.01$) was greater in male compared with female patients; conversely, no differences between sexes were recorded in the occurrence of acne, moon facies, ecchymoses, hypokalemia, psychiatric disorders, glucose intolerance or diabetes, hypertension, buffalo hump, and obesity (Table 1). Body mass index was similar in male and female patients (28.2 ± 0.68 *vs.* 29.4 ± 0.46 kg/m^2, NS). Male patients with striae presented a younger age, compared with men without this sign (27.9 ± 1.94 *vs.* 37.1 ± 3.45 yr, $P < 0.05$), whereas male patients with muscle atrophy or hypertension were older than their counterparts without these features (33.7 ± 2.50 *vs.* 24.8 ± 2.56 yr, $P < 0.05$; and 34.3 ± 2.25 *vs.* 22.4 ± 2.79 yr, $P < 0.005$, respectively). Likewise, among female patients with CD, striae were present in younger patients (33.3 ± 1.18 *vs.* 40.9 ± 1.13 yr, $P < 0.001$), as was acne (27.9 ± 1.12 *vs.* 40.5 ± 1.12 yr, $P < 0.001$); conversely, the age of female patients with muscle atrophy, hypertension, and osteoporosis was significantly greater than in females without such signs (38.9 ± 1.38 *vs.* 35.4 ± 1.05 yr, $P < 0.05$; 39.9 ± 0.98 *vs.* 31.0 ± 1.42 yr, $P < 0.001$; and 40.6 ± 1.49 *vs.* 35.4 ± 1.02 yr, $P < 0.005$, respectively). No age differences were observed as regards the other features of hypercortisolism.

Of interest, independently from gender, patients with muscle atrophy, purple striae, hypokalemia, ecchimoses, moon facies, and hypertension presented significantly higher UFC and/or plasma cortisol levels, compared with patients without these signs (Fig. 2). Furthermore, ACTH levels were significantly higher in patients with psychiatric disturbances (Fig. 2).

As regards the tests performed to establish the diagnosis of CD, no differences between sexes were recorded in ACTH and cortisol responses to CRH stimulation, both in terms of maximal increase over baseline (304.5 ± 75.86 *vs.* 213.8 ± 18.9% ACTH increase, NS; and 74.4 ± 13.03 *vs.* 78.6 ± 6.32% cortisol increase, NS, in male and female patients, respectively) and number of patients responsive to the test (77% *vs.* 89% sensitivity for ACTH, NS; and 57% *vs.* 61% sensitivity for cortisol, NS, in males and females, respectively). Low-dose dexamethasone testing was equally diagnostic in men and women (93% and 92% sensitivity, NS). Interestingly, the sensitivity of the high-dose dexamethasone suppression test was lower in males than in females (57% *vs.* 82%, $P < 0.05$), although the mean decrease from baseline was quite superimposable (55.1 ± 7.94 *vs.* 69.3 ± 3.15% decrease, NS, in males and females, respectively). There was no difference in the basal and post-CRH ACTH gradient at IPSS between male and female patients, nor did sensitivity of the test differ among sexes (basal and post-CRH center:periphery gradient 72% *vs.* 84% and 74% *vs.* 89% in males and females, respectively; both NS).

Pituitary adenomas were visualized more frequently in women, compared with men (64% *vs.* 45%, $P < 0.05$), whereas the prevalence of macroadenomas was similar in the

TABLE 1. Prevalence of signs/symptoms of CD according to gender

Sign/symptom	Women	Men
Obesity	86.2	85.1
Moon facies	81.1	89.4
Hypertension	67.4	68.1
Buffalo hump	53.6	51.1
Purple striae	50.6	72.3[a]
Impaired glucose tolerance/diabetes	45.4	42.8
Muscle atrophy	45.5	63.8[a]
Psychiatric disturbances	34.3	25.5
Osteoporosis	31.6	46.8[a]
Ecchymoses	32.2	21.3
Acne	27.5	19.1
Hypokalemia	21.8	32.6
Nephrolitiasis	6.4	21.3[a]

Data are expressed as percentage of whole female or male patient population.

[a] $P < 0.05$ *vs.* females.

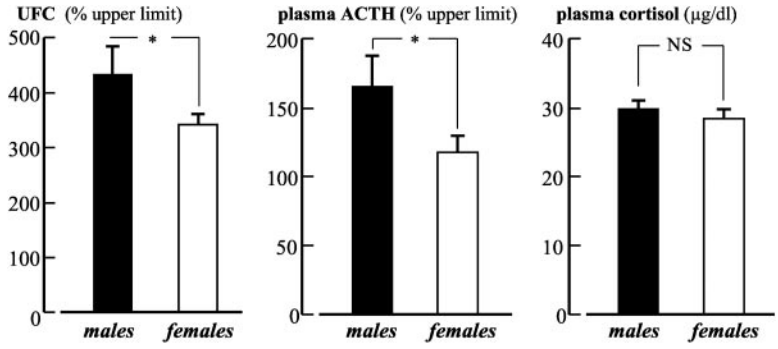

FIG. 1. Mean UFC, plasma ACTH, and cortisol levels in male and female patients with CD. UFC and ACTH levels are expressed as percentage excess of the normal range adopted by each laboratory, with the upper normal value set at 100%. *, $P < 0.05$.

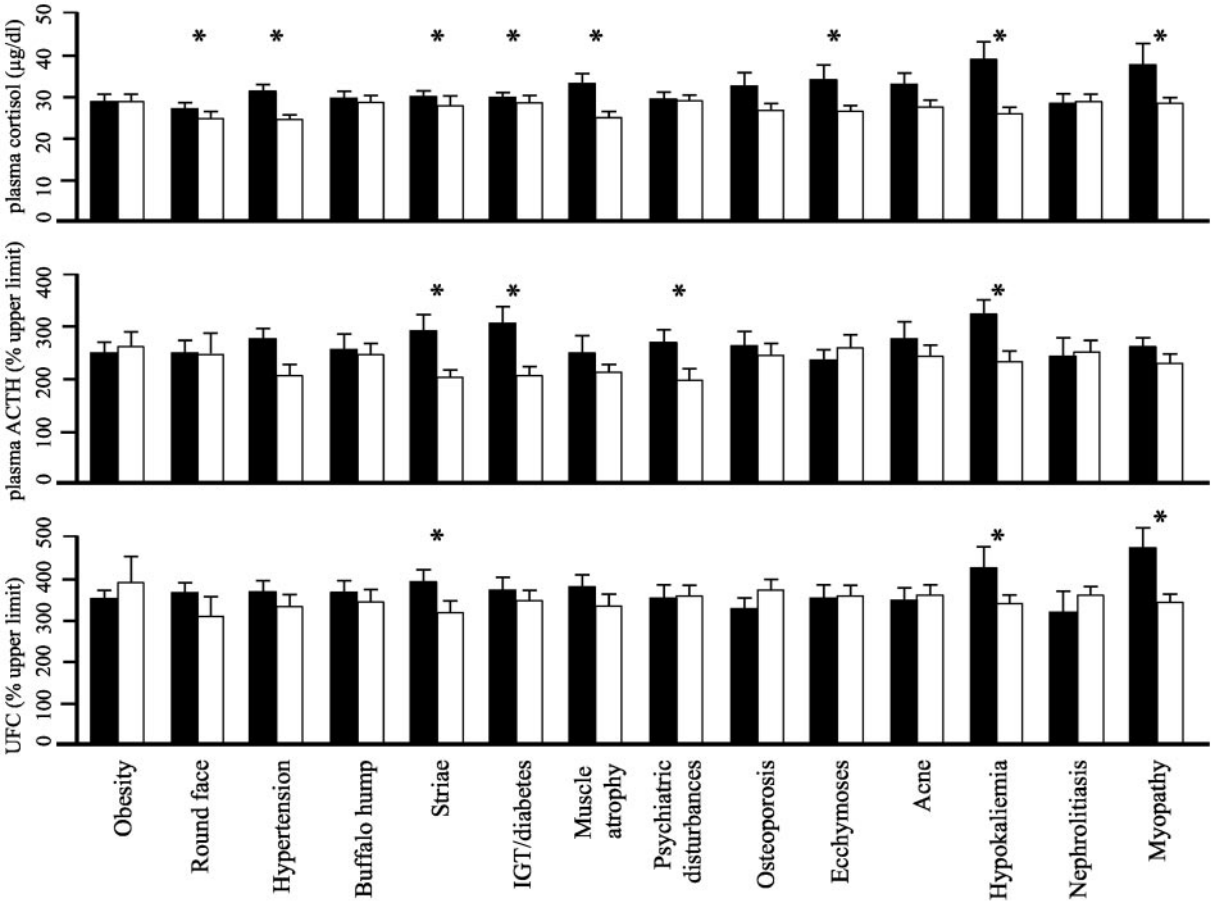

FIG. 2. Mean UFC, plasma ACTH, and cortisol levels according to the presence (■) or absence (□) of signs/symptoms in patients with CD. UFC and ACTH levels are expressed as percentage excess of the normal range adopted by each laboratory, with the upper normal value set at 100%. IGT, Impaired glucose tolerance. *, $P < 0.05$.

two groups (14% *vs.* 10%, NS, in men *vs.* women) and did not correlate with age, or ACTH, cortisol, and UFC levels (data not shown). An adenoma was detected at transsphenoidal surgery with equal frequency in male and female patients (74% and 80%, NS, respectively). Male patients incurred in a somewhat lower surgical success rate (58% *vs.* 70%, NS) and seemed to recur more frequently (32% *vs.* 15%, $P < 0.05$).

Discussion

Ever since Minnie, Harvey Cushing's first patient with CD, endocrinologists have come to appreciate that ACTH-secreting pituitary adenomas occur more frequently in women than in men. This is not unique to CD, given that many other endocrine disorders present a marked female preponderance (7), but whether this sexual dimorphism carries over into the clinical features of the disease has never been evaluated.

Our study now revealed that male patients with CD present at a younger age with a more florid clinical presentation. Indeed, some of manifestations of excess cortisol production were more frequent in men (in particular, osteoporosis, muscle atrophy, and purple striae, which represent the proteocatabolic effects of hypercortisolism). Comparison of the age of patients with or without these features confirmed the greater incidence of striae in younger men and women and muscle atrophy in older patients (8, 9). The increased prevalence of osteoporosis in men with CD has been a matter of debate, because some authors report parallel data (8), whereas others disagree (9). Our large series now confirms the higher incidence of osteoporosis in male patients with CD. Conversely, no single symptom was more frequently found in female patients, except for a slight (and not significant) higher incidence of psychiatric disturbances and ecchymoses. The possibility that females presented with a less severe clinical presentation as a result of an early seeking of medical advice for symptoms, such as menstrual irregularities or changes in the physical appearance, can be excluded by the similar time-to-diagnosis recorded between the two sexes. The increased symptom prevalence of hypercatabolic signs went hand in hand with higher UFC, plasma ACTH and cortisol concentrations at the time of diagnosis in males with CD, indicating a more pronounced secretory activity by the pituitary tumor and adrenal gland. As regards the tests used for the differential diagnosis of ACTH-dependent Cushing's syndrome, males with CD suppressed less than females after 8 mg dexamethasone, whereas no sexual dimorphism was observed in the responses and sensitivity of CRH testing and IPSS. Furthermore, the pituitary tumor itself was less easily visualized by imaging techniques and re-

curred more frequently after pituitary surgery in male patients, suggesting that not only has the tumor a greater secretory drive combined with a smaller size but also a more aggressive nature in men. In this context, it is of interest to recall that incidental pituitary abnormalities were detected with equal frequency in male and female normal subjects (10).

Irrespecive of gender, cortisol levels in plasma and urine were higher in patients presenting with the more severe symptoms of hypercortisolism, such as muscle atrophy, hypokalemia, ecchymoses, and hypertension. Very high cortisol levels are known to be associated with severe clinical manifestations, such as psychosis (11), peritonitis (12), and opportunistic infections (13). Our findings indicate that the degree of hypercortisolism might account also for the progressive appearance of more common symptoms of Cushing's syndrome. Indeed, there have been recent reports linking cortisol levels with features such as hypoalbuminemia (14) and amenorrhea (15) in patients with Cushing's syndrome. The fact that other symptoms of severe hypercortisolism, such as steroid-induced diabetes and osteoporosis, were not associated with higher cortisol levels suggests the contribution of factors other than cortisol to the development of these features.

Interestingly, higher plasma ACTH levels were recorded in patients with psychiatric disturbances, whereas no association with cortisol levels in plasma or urine was detected. This finding is in keeping with the known effects of ACTH on behavioral or cognitive functions (16, 17) and with the direct link between ACTH and psychiatric symptoms suspected by Ross and Linch (9) in the exemplary review of symptoms of hypercortisolism and confirmed by Starkman *et al.* (18).

Our observation that some clinical and biochemical features of CD are gender-related bears particular relevance for the diagnostic work-up of Cushing's syndrome. In fact, whereas CD favors the female sex, ectopic ACTH secretion (ES, a rarer cause of ACTH-dependent Cushing's syndrome) presents the opposite gender ratio (6, 19), possibly a consequence of the higher incidence of oat cell tumors in men. In addition to this inverted gender ratio, ES is mostly characterized by a more severe clinical presentation and profound disruption of HPA function. In the past, a man presenting with ACTH-dependent Cushing's syndrome of recent appearance and striking clinical presentation engendered a high degree of suspicion for ES. Our data now indicate that males with CD, like their counterparts with ES, often present with pronounced stigmata of hypercortisolism, absent cortisol suppression after high-dose dexamethasone, and negative pituitary imaging and may thus be easily misdiagnosed, especially in centers where CRH testing and IPSS are not available.

One last gender-related issue of a more oncological nature is worth mentioning. ACTH-secreting pituitary adenomas stand out as one of the few tumors with higher incidence in females, together with thyroid carcinomas, PRL secreting pituitary tumors, meningiomas, and adenocarcinomas of the gallbladder and of the salivary gland (7, 20). Conversely, the vast majority of neoplasms occur in males, even excluding sex- and occupation-related tumors. The higher prevalence of tumors in females may be linked to the presence of estrogen receptors, which have, in fact, been detected in thyroid carcinomas, meningiomas, and ACTH-secreting pituitary tumors (21–23); the progesterone receptor has been less extensively studied. The importance of sex steroids as a contributing factor to the development of ACTH-secreting pituitary tumors is also suggested by the observation that CD occurs with equal prevalence in prepubertal girls and boys (24, 25). Male gender, *per se*, seems to be associated with a worse prognosis in patients with CD, and this holds true also for thyroid carcinomas (26).

In conclusion, CD in male patients is characterized by a more severe clinical presentation, higher ACTH and cortisol levels, and a reduced suppression after 8 mg dexamethasone, compared with female patients. This dimorphic pattern calls for a novel clinical awareness during the diagnostic work-up, given the risk of overlap with ES. Lastly, male patients with CD seem to be burdened by a worse prognosis after surgery.

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