Diagnosis and complications of Cushing’s disease: gender-related differences

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Abstract

Objective Cushing’s disease (CD) presents a remarkable preponderance in female gender, with a female-to-male ratio of 3–8:1. The aim of this study was to evaluate gender-related differences in the presentation of CD, as regards: biochemical indices of hypercortisolism; sensitivity of diagnostic tests; clinical features and complications of disease.

Methods We retrospectively studied 84 adult patients with CD, 67 women and 17 men, evaluated at diagnosis. We compared the features of the disease between the sexes and analysed the effect of gender on CD complications, adjusted for potential confounders (age, gonadal status, BMI, urinary free cortisol values).

Results We observed no differences between males and females as regards age at diagnosis, disease duration and BMI. Men, compared with women, presented higher urinary free cortisol values (P < 0.001) and ACTH values (P < 0.05). As regards diagnostic tests, men presented a lower ACTH response to DDAVP stimulation (P < 0.05). The pituitary tumour itself was less easily visualized by pituitary MRI in males compared with females (P < 0.05). Furthermore, some complications of disease were more frequent or more severe in men, in particular hypokalaemia (P < 0.05), hypercoagulable state and osteoporosis at lumbar spine (P < 0.01), with consequent higher risk of vertebral fractures. Male gender was found to be an independent risk factor for dyslipidaemia, severity of hypertension, lumbar osteoporosis and fractures.

Conclusions Although CD is less frequent in male patients, in this gender, it presents with more florid clinical manifestations and may imply more diagnostic difficulties.

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attending the Endocrinology Unit of Padova between 2002 and 2010 and were evaluated at diagnosis. No patient was taking therapy to reduce ACTH or cortisol secretion. We considered only patients with pituitary-dependent ACTH hypersecretion – confirmed by histology, or by bilateral inferior petrosal sinus sampling (BIPSS, performed in 15 patients with discordant results of noninvasive diagnostic tests), or by remission of disease (retrospectively assessed) after pituitary surgery and/or radiotherapy.

Diagnostic evaluation

The diagnosis of cortisol excess, suspected on clinical ground, was confirmed by biochemical evaluation: increased 24-h urinary free cortisol (UFC) levels (median of 3 samples), failure of serum cortisol decrease <50 nmol/l after 1-mg dexamethasone suppression test and loss of circadian rhythm in cortisol secretion (assessed by 0800 and 2300 h serum cortisol and, since 2006, also salivary cortisol levels).\(^1\)–\(^7\) Plasma and urinary cortisol levels were determined in all patients by RIA (Diagnostic Product Corp., Los Angeles, CA, USA). Urinary free cortisol was expressed as the ratio between the measured value and the upper limit of normality. Salivary cortisol was determined by RIA (Radim, Pomezia, Italy) in 30 patients.

The diagnosis of ACTH-dependent Cushing’s syndrome was based on the presence of detectable plasma ACTH concentrations (>10 ng/l),\(^1\)–\(^3\) measured by IRMA (Nichol Institute Diagnostics, San Juan Capistrano, CA, USA). The source of ACTH secretion was investigated by dynamic endocrine assessment and by pituitary magnetic resonance imaging (MRI).\(^1\)–\(^3\) Endocrine assessment included overnight 8-mg dexamethasone suppression test (8 mg-DST), CRH stimulation test (100 \(\mu\)g i.v. ovine CRH) and DDAVP test (10 \(\mu\)g i.v.). Criteria considered indicative of pituitary ACTH secretion were a decrease of morning plasma cortisol levels \(\geq 80\%\) after 8 mg-DST, a rise above baseline of ACTH levels \(\geq 50\%\) and/or of cortisol levels \(\geq 20\%\) after CRH and DDAVP stimulation.

Pituitary MRI was performed in all patients with superconducting magnet scanner (TESLA 1-5), before and after gadolinium injection. MRI response was defined ‘negative’ if no pituitary adenoma was visible, ‘positive for microadenoma’ if a pituitary adenoma <10 mm of diameter was evident, or ‘positive for macroadenoma’ if tumour diameter was \(\geq 10\) mm.

Clinical and biochemical evaluation

For all patients, we collected medical charts reporting clinical history and physical examination at diagnosis.

Disease duration was estimated by the time elapsed from the appearance of the first signs and symptoms of hypercortisolism to diagnosis.

BMI, systolic and diastolic blood pressures, serum potassium levels, glucose metabolism and lipid profile were evaluated at diagnosis in all patients, using standard methods.

BMI was measured as the ratio between the weight and the square of the height. BMI between 25 and 30 kg/m\(^2\) is defined as overweight, BMI above 30 kg/m\(^2\) as obesity. Data about waist and hip circumference were missing in many patients, due to the retrospective condition of the study, so we could not consider visceral obesity in our analysis.

Patients were considered affected by arterial hypertension when their blood pressure values were \(\geq 140/90\) or they were already taking antihypertensive therapy. To estimate the severity of hypertension, we considered the number of antihypertensive drugs (0, 1 or \(\geq 2\)) required to control blood pressure.

Hypokalaemia was defined as the presence of serum potassium values <3.4 mEq/l.

Diabetes mellitus, impaired fasting glucose and impaired glucose tolerance were diagnosed in accordance with the commonly accepted guidelines.\(^8\) For the purposes of our study, we did not distinguish the three conditions, but we expressed alterations of glucose metabolism as a dichotomous variable (‘presence’ or ‘absence’ of alterations).

Hypercholesterolaemia was defined as total cholesterol levels \(\geq 6.2\) mmol/l with LDL-cholesterol \(\geq 4.1\) mmol/l. HDL-cholesterol was considered low if \(< 1\) mmol/l in men and \(< 1.28\) mmol/l in women. Hypertriglyceridaemia was defined as triglyceride levels \(\geq 1.7\) mmol/l.\(^9\) We defined patients as dyslipidaemic if they presented alterations in one or more of these parameters, or were in treatment with hypolipidaemic drugs.

Gonadal status was evaluated on the basis of clinical history and of serum levels of FSH, LH and sex hormones. Premenopausal women were considered hypogonadal when presented amenorrhea or serum 17\(\beta\)-estradiol levels below the normal range for early follicular phase. Men were considered hypogonadal when serum total testosterone levels were \(< 8\) nmol/l and/or free testosterone levels (calculated by total testosterone and serum SHBG, using the Vermeulen equation\(^10\)) were \(< 180\) pmol/l.

Coagulation and fibrinolysis evaluation

To study the hypercoagulable state which affects patients with CD, the following clotting and fibrinolysis indexes were evaluated: PT; aPTT; factor VIII coagulant activity (FVIII:C); von Willebrand factor antigen (VWF:Ag) and collagen-binding activity (VWF:CBA); PAI-1 antigen and activity (PAI-1:Ag and PAI-1:act). PT and aPTT were measured by standard methods. FVIII:C was determined using a one-stage method, with copheloplastin as activated cephalin. VWF:Ag was measured with a home-made ELISA method, using a horseradish peroxidase–conjugated anti-VWF antibody (Dako, Glostrup, Denmark). As VWF concentrations are regulated by AB0 blood group,\(^11\) measured VWF:Ag values were corrected according to patients’ group, with 62–116 U/dl taken as the normal range for 0 blood group, and 67–171 U/dl for non-0 groups. These reference ranges were calculated in 160 normal individuals.\(^12\) VWF:CBA was assessed by ELISA, using type I and type III collagen diluted in acetic acid solution. PAI-1:Ag was measured by ELISA and PAI-1:act by chromogenic substrate method (Biopool, Umeå,
Sweden). At the time of haemostatic analysis, no patient was taking drugs influencing clotting tests.

We also retrospectively recorded any venous thromboembolic event occurred during active phase of disease or just after neurosurgery. Diagnoses of deep-vein thrombosis and of pulmonary embolism were performed in accordance with the commonly accepted guidelines.

Vascular study

We evaluated the prevalence of carotid atherosclerotic plaques in 64 of our patients, 50 women and 14 men, by echo-colour Doppler ultrasonography of the right and left common carotid arteries, carotid bulbs, internal carotid arteries and external carotid arteries. Ultrasonography was performed using an ATL Apogee 800 plus instrument (Advanced Technology Laboratories, USA) with an 8.5 MHz probe for B-mode echography and 6 MHz probe for pulsed-waved Doppler.

Evaluation of bone mineral density and prevalence of clinical fractures

In 81 of our patients (64 women and 17 men), bone mineral density (BMD) at lumbar spine (L1–L4), femoral neck (FN) and total femur (TF) were determined by dual energy X-ray absorptiometry (DEXA), using Hologic QDR 4500 C densitometer (Hologic Inc., Waltham, MA, USA). Individual BMD values were expressed both as absolute values (BMD, g/cm²) and as T-scores and Z-scores. According to the WHO criteria, osteopaenia was defined as a T-score between –1 and –2.5, and osteoporosis as a T-score < –2.5. At the time of the evaluation, no patient was taking drugs or had other medical conditions known to affect bone metabolism.

In all patients, a detailed documentation about previous fractures was obtained. In each patient with clinical symptoms of vertebral fractures (such as dorsal or lumbar back pain, or height decrease), spinal radiographs of the vertebrae T1–L5 were obtained. Vertebral fractures were diagnosed on visual inspection using the semiquantitative method described by Genant et al.33 According to this technique, fractures assessed on lateral thoracolumbar spine radiographs were defined as reductions of more than 20% in anterior, middle or posterior vertebral height. As a spinal X-ray examination was not systematically performed in all patients, we did not investigate potential asymptomatic vertebral fractures but only clinically evident ones.

Statistical analysis

Data were analysed using the statistical software SAS System (SAS Institute Inc., Cary, NC, USA). Quantitative data were reported as median and range (minimum and maximum values) and compared between groups using the nonparametric Mann–Whitney U-test. Categorical data were summarized as counts and percentage of subjects in each category, and compared with chi-square or Fisher’s exact test, as appropriate.

The associations between quantitative variables were tested by either Pearson product-moment correlation or Spearman correlation, as appropriate.

Multivariate logistic regression analysis was applied to evaluate the effect of gender on CD complications, adjusted for potential confounders (age, BMI, gonadal status, UFC values). The effect of gender on clotting factors and on lumbar and femoral BMD was evaluated by analysis of covariance, considering the potential confounders (age, BMI, gonadal status, UFC values) as covariates. Statistical significance was considered as a P value < 0.05.

Results

Patients’ characteristics according to gender are shown in Table 1. A greater frequency of presentation of CD was observed in females (67/84 – 80%) than in males (17/84 – 20%), with a F/M ratio of 4:1. Age at diagnosis, disease duration and BMI were similar between sexes. A total of 44 women were pre- and 23 postmenopausal. Among premenopausal women, 17 (39%) were hypo- and 27 eugonadal. A total of 8 (47%) of the 17 men were hypo- and 9 eugonadal. The prevalence of hypogonadism did not significantly differ between sexes.

Diagnostic evaluation

Biochemical indices of hypercortisolism in our patients are shown in Table 1. Men presented higher UFC (P < 0.001) and ACTH (P < 0.05) levels compared with women. 0800 and 2300 h serum cortisol and late-night salivary cortisol were also slightly higher in males, although this did not reach statistical significance. As regards dynamic endocrine tests performed to establish the diagnosis of CD, men presented a lower, but not significantly, response to 8 mg-DST in terms of percentage of patients with adequate cortisol suppression (65% in M vs 75% in F). No difference between sexes was found in ACTH and cortisol response to CRH test (responsive patients 82% vs 84% for ACTH, 94% vs 85% for cortisol, in M and F, respectively, NS). For DDAVP test, instead, we recorded a significantly lower ACTH response in men compared with women (percentage of responsive patients: 47% vs 76%, p < 0.05). A similar trend was also seen for cortisol response to DDAVP, but this did not reach statistical significance (percentage of responsive patients: 65% vs 85% in M and F).

Pituitary MRI findings are shown in Fig. 1. The prevalence of macroadenomas was higher, although not significantly, in men compared with women (24% vs 7.5%, P = 0.07). Moreover, men had a higher prevalence of negative MRI, as their microadenomas were less frequently visualized (6/13, 46%) than those of women (49/62, 79%), P < 0.05.

It was necessary to perform a BIPSS to rule out the suspicion of an ectopic origin of ACTH production in 30% of male and in 15% of female patients (NS).

Complications of cortisol excess

Figure 2 illustrates the prevalence of CD complications in male and female patients. Figure 3 represents the odds ratios for the
Table 1. Patients’ characteristics and biochemical parameters of hypocortisolism according to gender.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Females</th>
<th>Males</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.0 (15.0–70.0)</td>
<td>40.0 (16.0–62.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>24.0 (6.0–108.0)</td>
<td>30.0 (12.0–72.0)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>27.5 (18.3–45.3)</td>
<td>29.3 (20.3–37.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Gonadal status</td>
<td>E:27%(40%)/H:17(26%)/P:23(34%)</td>
<td>E:9(33%)/H:8(47%)/P:23(34%)</td>
<td>NS</td>
</tr>
<tr>
<td>UFC (nmol/l)</td>
<td>2.35 (0.34–11.20)</td>
<td>4.27 (1.50–21.90)</td>
<td>0.0008</td>
</tr>
<tr>
<td>ACTH (ng/l)</td>
<td>43.2 (15.0–145.0)</td>
<td>66.8 (18.0–133.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>F8 (nmol/l)</td>
<td>599.0 (264.9–1407.6)</td>
<td>631.0 (369.8–1460.0)</td>
<td>NS</td>
</tr>
<tr>
<td>F23 (nmol/l)</td>
<td>459.4 (160.0–1268.0)</td>
<td>532.7 (157.0–949.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Morning salivary cortisol (ng/ml)</td>
<td>13.70 (5.80–33.82)</td>
<td>10.22 (7.69–30.70)</td>
<td>NS</td>
</tr>
<tr>
<td>Late-night salivary cortisol (ng/ml)</td>
<td>8.15 (4.33–25.93)</td>
<td>13.58 (6.43–21.10)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are expressed as median and range. E, eugonadal; H, hypogonadal; P, postmenopausal; UFC, urinary free cortisol, reported as the ratio between the measured value and the upper limit of normality; ACTH = 0800 h plasma adrenocorticotropic hormone (normal range 10–50 pg/ml); F8 = 0800 h plasma cortisol (n.r. 198–695 nmol/l); F23 = 2300 h plasma cortisol (n.r. 69–345 nmol/l); morning salivary cortisol = 0800 h salivary cortisol (n.r. 6–13 ng/ml); late-night salivary cortisol = 2300 h salivary cortisol (n.r. <3 ng/ml); NS, not significant.

Fig. 1 Pituitary MRI findings in patients with CD according to gender.

The effect of male gender on CD complications, adjusted for potential confounders (age, BMI, hypogonadism, UFC values).

Hypokalaemia. The prevalence of hypokalaemia at diagnosis was significantly higher in males than in females (41% vs 12%, P < 0.05) and patients with hypokalaemia presented higher UFC values than those without (median: 5.4 vs 2.35 times the upper limit of normality, P < 0.01). At logistic regression analysis, hypokalaemia was independently associated with UFC levels (OR = 1.28, P < 0.01) but not with gender, age, BMI or hypogonadism.

Cardiovascular risk factors. The prevalence of alterations of glucose metabolism was similar in men and women (47 vs 42%, NS); patients with glucose intolerance were older (median age: 48.5 vs 36 years, P < 0.05) than those without. At logistic regression analysis, age (OR = 1.04, P < 0.05) and BMI (OR = 1.096, P < 0.05) showed significant association with impaired glucose metabolism, whereas sex, hypogonadism and UFC values did not.

The frequency of dyslipidaemia (considered as a whole) did not significantly differ between sexes (59 vs 38%, NS). Hypercholesterolaemia was the most frequent alteration, with similar distribution in men and women (41 vs 34%, NS). Instead, a higher male prevalence was reported for hypertriglyceridaemia (41 vs 12%, P < 0.05) and for HDL reduction (29 vs 9%, P < 0.05). Dyslipidaemic patients were older (median age 50 vs 36 years, P < 0.05) than subjects without this complication. When age, sex, BMI, hypogonadism and UFC values were included in logistic regression model, both age (OR = 1.056, P < 0.01) and male gender (OR = 5.38, P < 0.05) appeared to be associated with dyslipidaemia. In particular, age was predictive of hypercholesterolaemia (OR = 1.062, P < 0.01), whereas male gender was associated with hypertriglyceridaemia (OR = 9.02, P < 0.01) and low HDL (OR = 9.48, P < 0.01).

Arterial hypertension was slightly more frequent in males, although not significantly (P = 0.06). Hypertensive patients were older (median age 46.5 vs 32 years, P < 0.05) than normotensive ones. At logistic regression analysis, only age was significantly associated with hypertension (OR = 1.122, P < 0.001), whereas the number of antihypertensive drugs required to control blood pressure was predicted both by age (OR = 1.111, P < 0.001) and by male gender (OR = 4.28, P < 0.05).

Hypercoagulability. Among clotting and fibrinolysis indices, VWF:Ag, FVIII:C and PAI-1:Ag values tended to be higher in men, without reaching statistical significance (Table 2). Age correlated negatively with aPTT values (R = −0.272, P < 0.05) and positively with FVIII:C (R = 0.262, P < 0.05) and VWF:Ag (R = 0.418, P < 0.01) values. PAI-1:Ag and PAI-1:act correlated positively with BMI (R = 0.483, P < 0.05 for PAI-1:Ag; R = 0.632, P < 0.001 for PAI-1:act). At analysis of covariance, after inclusion of gender, age, BMI, UFC values and hypogonadism in the model, VWF:Ag was significantly associated with age (P < 0.05), whereas PAI-1:Ag was independently predicted by BMI (P < 0.01) and male gender (P < 0.01).

The prevalence of venous thromboembolic events (VTE) was double in males compared with females: deep-vein thrombosis and/or pulmonary embolism events, in fact, occurred in 9% of women and in 18% of men during active phase of disease or just after remission (NS). Patients who developed VTE were older (P < 0.01), presented shorter aPTT (P < 0.01) and higher vWF (P < 0.01) and UFC values (P < 0.05) than those who did not. Age (OR = 1.112, P < 0.05) and UFC levels (OR = 1.28, P < 0.01).
were found to be predictive of thromboembolic events at logistic regression analysis, whereas gender, BMI and hypogonadism were not.

Vascular study. Carotid echo-colour Doppler ultrasonography revealed the presence of atherosclerotic plaques (causing a degree of stenosis between 10% and 40%), in 22% of female and 28% of male patients; therefore, the prevalence of plaques did not differ by gender. At logistic regression analysis, age resulted the only factor significantly associated with atherosclerotic plaques (OR = 1.24, *P < 0.01).

Bone mineral density and prevalence of clinical fractures. Lumbar osteoporosis was found at DEXA with higher frequency in males compared with females (59% vs 20%, *P < 0.01), whereas no difference was reported between sexes at femoral site.

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Table 2. Clotting and fibrinolysis indices according to gender.

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<th>Females</th>
<th>Males</th>
<th>P value</th>
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<tbody>
<tr>
<td>PT (%)</td>
<td>105-10</td>
<td>102-45</td>
<td>(75-20–110-00)</td>
</tr>
<tr>
<td>aPTT(s)</td>
<td>24-50</td>
<td>24-30</td>
<td>(19-30–30-00)</td>
</tr>
<tr>
<td>FVIII:C (%)</td>
<td>155-70</td>
<td>176-00</td>
<td>(77-00–279-70)</td>
</tr>
<tr>
<td>vWF:Ag after ABO blood group correction (U/dl)</td>
<td>168-65</td>
<td>218-30</td>
<td>(98-40–386-80)</td>
</tr>
<tr>
<td>Patients with increased vWF:Ag levels</td>
<td>22 (50%)</td>
<td>8 (67%)</td>
<td>NS</td>
</tr>
<tr>
<td>vWF:CBA (%)</td>
<td>139-00</td>
<td>147-30</td>
<td>(67-80–338-90)</td>
</tr>
<tr>
<td>PAI-1:Ag (ng/ml)</td>
<td>10-50</td>
<td>23-05</td>
<td>(4-00–245-50)</td>
</tr>
<tr>
<td>PAI-1:att (U/ml)</td>
<td>3-50</td>
<td>6-30</td>
<td>(0-10–24-30)</td>
</tr>
</tbody>
</table>

Data are expressed as median and range. PT, prothrombin time, expressed as prothrombin activity (n.r. = 70–100%); aPTT, activated partial thromboplastin time; n.r. = 24–36,5 s; FVIII:C, factor VIII coagulant activity (n.r. = 60–160%); vWF:Ag, von Willebrand factor antigen (n.r. = 62–116 U/dl in individuals with 0 blood group and 67–171 U/dl in individuals with non-0 group); vWF:CBA, VWF collagen-binding activity (n.r. = 60–150%); PAI-1:Ag, plasminogen activator inhibitor-1 antigen (n.r. = 3–10 ng/ml); PAI-1:att, plasminogen activator inhibitor-1 activity (n.r. = 0–10 U/ml); NS, not significant.

L1–L4 BMD, both expressed as absolute value and as T- and Z-score, was significantly lower in men than in women with CD (P < 0.05 for absolute values, P < 0.01 for T-scores, P < 0.001 for Z-scores). We found a significant inverse correlation between L1–L4 Z-score and 2300 h serum cortisol levels (R = -0.270, P < 0.05). At femoral site, BMD values did not differ between genders (Fig. 4).

When age, sex, BMI, hypogonadism and UFC values were included in logistic regression model, male gender (OR = 13-2 P < 0.001), age (OR = 1.033, P < 0.05) and hypogonadism (OR = 4.75, P < 0.01) were all found to be associated with lumbar osteoporosis, whereas age (OR = 1.054, P < 0.01), hypogonadism (OR = 2.0, P < 0.05) and BMI (OR = 0.87, P < 0.01) were predictive of femoral osteoporosis. At analysis of covariance, L1–L4 Z-score was predicted by age (P < 0.01), male gender (P < 0.0001) and hypogonadism (P < 0.01). FN Z-score was predicted only by BMI (P < 0.05) and TF Z-score by BMI (P < 0.001) and the presence of hypogonadism (P < 0.05).

Clinically evident fractures occurred with higher frequency in male gender than in women (29% vs 9%, P < 0.05). Male sex (OR = 23-5, P < 0.01) and age (OR = 1.123, P < 0.01) were both independently associated with risk of symptomatic fractures, whereas BMI, hypogonadism and UFC values were not.

Discussion

It’s well known that ACTH-secreting pituitary tumours in adult patients occur more frequently in female gender, with a F/M ratio of 3-8:1. A similar epidemiology is also seen for other kinds of pituitary adenomas – in particular prolactinomas – and may be linked to the expression, in these tumours, of oestrogen receptors. In fact, oestrogen receptors ERβ were detected in the majority of ACTH-secreting pituitary adenomas. The potential influence of sex steroids in the development of CD is also suggested by the different epidemiology of the pathology in paediatric population, as observed in a study by Storr et al.15 which reported a higher prevalence of CD in males among prepubertal patients; the percentage of female patients gradually increased during and after puberty, reaching a preponderance in postpubertal age; this may be in relation with the hormonal change, with increased production of oestrogens during and after puberty in females.

Gender differences in the presentation and course of Cushing’s disease were first investigated by Pecori Giraldi et al., in 2003. These authors evaluated 280 patients with CD (233 females and 47 males) collected by the Italian multicentre study on Cushing’s syndrome. Compared with this survey, our study was conducted on a smaller population, as we only considered patients attending the Endocrinology Unit of Padova. On the other hand, all patients were evaluated with similar diagnostic (biochemical and instrumental) techniques, both for the confirmation of hypercortisolism and of its aetiology, and for the study of its complications. A point of strength of our study lies in the clinical details provided (e.g. BMD, severity of hypertension, coagulation parameters). We also investigated the influence of possible confounding factors (age, gonadal status, obesity, severity of hypercorticism) on the development of CD complications, to analyse the real impact of gender on them.

Our results seem to corroborate the previous findings, indicating a more severe disease in male gender, both in terms of hormonal levels and of prevalence and gravity of some complications. Unlike Pecori Giraldi et al., we did not find differences between sexes for age at diagnosis. We confirmed, instead, that men with CD present higher UFC and plasma ACTH levels than women at the time of diagnosis. This fact suggests a more pronounced secretory activity of the pituitary adenoma in males.

The estimated disease duration appeared similar between sexes.

As regards diagnostic tests performed to investigate the source of ACTH secretion, male patients suppressed less than females after 24 h-DST, but this difference was not significant in our sample, unlike in Pecori Giraldi study. Instead, for DDAVP stimulation test, which had not been previously evaluated, we observed a significantly lower response in male gender: this fact may contribute to pitfalls in the diagnosis of Cushing’s syndrome in men, due to the role of this test in the differential diagnosis of pseudo-Cushing’s states from endogenous hypercortisolism, but also to its complementary role in the diagnosis of ACTH-dependent CS and moreover to its usefulness in the follow-up of patients in remission from CD, in order to identify those at major risk for recurrence of disease.17–19 We have to
consider that its information may be less efficacious in male gender. Another finding of our study was the evidence that microadenomas in male patients with CD are less frequently visualized at pituitary MRI. This fact, together with the lower sensitivity of endocrine tests, may contribute to diagnostic difficulties, and this is particularly relevant as ectopic ACTH hypersecretion, the other cause of ACTH-dependent Cushing’s syndrome which must be considered in the differential diagnosis with CD, is relatively more frequent in male gender. Actually, our male patients underwent more frequently invasive procedures such as BIPSS to get a definitive diagnosis.

As regards clinical manifestations of the disease, the higher UFC levels observed in men went hand in hand with an increased prevalence of hypokalaemia: this electrolytic disorder, in fact, is generally associated with severe hypercortisolism, as high cortisol levels may saturate the cortisol-inactivating enzyme 11β-hydroxysteroid dehydrogenase type 2 at the renal tubule, thereby allowing access of intact cortisol to the mineralocorticoid receptors.20

The frequency of arterial hypertension did not significantly differ between genders. However, males seemed to be more severely affected than females, as we could deduce from the analysis of the number of antihypertensive drugs required to control blood pressure. Impaired glucose metabolism appeared to be strictly related to patient’s age, rather than to gender. As regards dyslipidaemia, instead, male sex was found to be an independent risk factor, with major influence on triglycerides and HDL levels. We also found a tendency to higher levels of clotting factors in male patients, although age and UFC values were the most important factors influencing the development of thromboembolic events.

Finally, important differences between genders were found when evaluating bone complications; in fact, male patients were found to be affected by more severe bone damage than women at lumbar spine. Conversely, at femoral site, we reported no differences between sexes, despite the higher hormonal values of male patients. L1–L4 Z-score correlated significantly with 2300 h serum cortisol levels, whereas no correlation was found between femoral BMD and biochemical indices of hypercorticism. This is consistent with a major influence of cortisol excess at sites rich in trabecular bone (such as lumbar spine)21, as already observed in other studies.22–24

Male gender per se was found to be an important risk factor for lumbar osteoporosis and fractures in CD. Another interesting observation was the significant influence of hypogonadism on BMD values, both at lumbar spine and at
Conclusions

Cushing’s disease in male patients, although less frequent, has a more florid clinical presentation, with higher hormonal levels and greater prevalence and severity of some complications.

Male patients with CD, besides, present additional diagnostic difficulties, due to the lower sensitivity of some endocrine tests used to confirm the aetiology of the disease and to the less frequent identification of the lesion at the pituitary MRI.

Cushing’s disease is a rare but severe condition, which requires carefulness and caution in all patients, because of the complexity of differential diagnosis, therapy and management of complications. However, this seems to be even more true in case of male patients, who need a very prompt diagnosis and therapy, in order to reduce cortisol levels and prevent or limit disease complications.

Disclosure

The authors have nothing to disclose. The study was not supported financially in any way.

References