CLINICAL STUDY

The European Registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics

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Abstract

Objective: The European Registry on Cushing's syndrome (ERCUSYN) is designed to collect prospective and follow-up data at EU level on Cushing's syndrome (CS).

Design and methods: Baseline data on 481 CS patients (390 females, 91 males; mean age ($\pm$s.d.): 44 $\pm$ 14 years) collected from 36 centres in 23 countries, including new patients from 2008 and retrospective cases since 2000. Patients were divided into four major aetiologic groups: pituitary-dependent CS (PIT-CS) (66%), adrenal-dependent CS (ADR-CS) (27%), CS from an ectopic source (ECT-CS) (5%) and CS from other aetiologies (2%).

Results: Proportion of men in the ECT-CS group was higher than in the other groups ($P < 0.05$). The ADR-CS group was older than the PIT-CS ($P < 0.05$). Prevalence of hirsutism (92%) and diabetes (74%) in ECT-CS was higher than in the other groups ($P < 0.05$ and $P < 0.01$ respectively). PIT-CS had more skin alterations, menstrual irregularities and hirsutism than ADR-CS ($P < 0.01$). Reduced libido was more prevalent in men than women ($P < 0.01$). Prevalence of spine osteoporosis was higher in men than women ($P < 0.05$), and males had more vertebral and rib fractures than females (52 vs 18% for vertebrae; $P < 0.001$ and 34 vs 23% for ribs; $P < 0.05$). ECT-CS consulted a diabetologist more frequently than ADR-CS ($P < 0.05$), while a gynaecologist was consulted more often by women with PIT-CS or ADR-CS than with ECT-CS ($P < 0.05$). Overall, weight gain was more common in women than men ($P < 0.01$). CushingQoL and EuroQoL visual analogue scale scores did not differ between the groups.

Conclusions: The ERCUSYN project demonstrates a heterogeneous clinical presentation of CS at a European level, depending on gender and aetiology.

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Introduction

Cushing's syndrome (CS) is a rare disease with an incidence ranging from 0.7 to 2.4 per million people per year (1). Such a low incidence makes it cumbersome to obtain exhaustive data on many aspects of this potentially lethal disorder, including clinical presentation and management. Indeed, many controversial issues of CS still wait to be clarified from large-scale studies (2, 3).

The European Registry on Cushing's syndrome (ERCUSYN) is a project supported by the European Commission Public Health Programme aimed at gathering data at EU level on clinical features, diagnostic procedures and therapeutic strategies in CS patients. The creation of this large European database is expected to provide comprehensive information on all stages of the disease from the first diagnosis to long-term follow-up. This ultimately should result in earlier recognition of CS and all its comorbidities, and assist

clinicians in considering and treating all possible manifestations of the disease, thus improving long-term prognosis.

This first report from the ERCUSYN project describes the baseline characteristics of CS patients, including epidemiology, comorbidities, health-related quality of life (HRQoL) and bone status. This study also allows an analysis of the heterogeneous clinical presentation of CS at a European level.

Materials and methods

ERCUSYN is a web-based, multicentre, observational study that enrolled 508 CS patients from 36 centres in 23 European countries diagnosed after January 1st, 2000 to October 31st, 2010. Because 27 patients were excluded from the study due to lack of definitive diagnosis, a total of 481 patients were included in the final analysis. The entire study comprised of a prospective cohort of 398 CS patients who were recruited from October 1st 2008 (when the database was opened) to October 31st 2010, and a retrospectively collected cohort of 83 patients diagnosed of CS since January 1st 2000, with yearly updates. All participants were asked to fill every blank of the ERCUSYN database with information on any consecutive patient who received diagnosis of CS in their centres, during the time period established for the study. Patients were classified in the following four major groups depending on the diagnosis: pituitary-dependent CS (PIT-CS), adrenal-dependent CS (ADR-CS), such as CS from an adrenal adenoma, CS from an ectopic source (ECT-CS) and CS from other aetiologies (OTH-CS), including cyclic CS, primary pigmented nodular adrenocortical disease (PPNAD) and ACTH-independent macronodular adrenocortical hyperplasia (AIMAH).

Aetiologic classification was based on histologic documentation of ACTH-secreting or adrenal tumor. In case histological reports were not available, biochemical and clinical resolution of hypercortisolism after surgical resection were used as a diagnostic confirmation. In patients with ECT-CS or OTH-CS who were not operated on, diagnosis was based on biochemical test results and/or imaging, as confirmed by the managing physician.

Patients with adrenal cancer were excluded from the database.

The ERCUSYN database comprises of three major sections. The first contained information on patients at diagnosis, such as baseline demographic and anthropometric characteristics, aetiology of CS and diagnosis date, the time frame between onset of symptoms and final diagnosis of CS, other specialists consulted for Cushing's symptoms before establishing correct diagnosis, clinical features, comorbidities and bone status. Moreover, two questionnaires on QoL (the disease-generated CushingQoL and the generic

EuroQoL-5D) were included (4, 5). This study is aimed at analysing these data. The first section also contained an accurate description of all the tests that were performed to diagnose CS and define its aetiology; it comprised of basal and stimulated hormonal values, imaging (computed tomography (CT), magnetic resonance imaging (MRI), ultrasounds) and bilateral, inferior petrosal sinus sampling (IPSS) results, if available.

The second section was about therapy. Participants were asked to provide specific information on any treatment (medical, surgical and radiation therapy) given to patients not only after the first diagnosis, but also in case of any relapse of the disease. Subsections on post-surgical histology confirmation, and clinical/biochemical outcome in the immediate, postoperative period were also included.

The third major section, which contained information on each follow-up visit, resembled the layout of the first section. In particular, it focused on the long-term outcome of treatment, based on biochemistry and imaging parameters and comprised a subsection on post-treatment hormone replacement therapies, pituitary deficiencies, clinical features, QoL and bone status, as assessed during each follow-up visit. In case of patient's death, participants were asked to indicate the cause.

All the participants were asked to fill in all the blanks of the database with any required information. If a specific item was not available, they were asked to choose one of the following options: 'not answered' (i.e. when information was completely missing) or 'not known' (i.e. when a test or clinical evaluation had been performed but results were not available for any reason).

Due to the wide interlaboratory variability of the assays used in the participating centres throughout Europe, participants were requested to provide basal and stimulated hormone levels together with the description of whether each test was 'supporting' or 'not supporting' the diagnosis, based on the reference limit applied in each centre. Similarly, the results of IPSS were qualitatively described as 'supporting' or 'not supporting' the pituitary origin of CS. Clinical features and diagnostic interpretation of tests were based on international consensus and guidelines.

Results of dual-energy X-ray absorptiometry (DXA) at spine and hip were qualitatively described as 'normal' (T score $= \geq -1$ s.d.), 'indicative of osteopenia' (T score between -1 and -2.5 s.d.) or 'indicative of osteoporosis' (T score < -2.5 s.d.).

The same description was required in case a bone CT scan was performed. Because only three bone CT results were available, they were not included in the final analysis of data. Participants were also asked to describe whether fractures were documented on plain radiography at the following sites: vertebrae, hip, rib, wrist metatarsal or 'other'.

Specific questionnaires were used in CS patients to assess QoL. The CushingQoL questionnaire had a time frame refering to the preceding 4 weeks, and contained 12 questions that were completed in under 5 min. Answers were based on Likert scales and had five response categories: 'Always', 'Often', 'Sometimes', 'Rarely' and 'Never' or 'Very much', 'Quite a bit', 'Somewhat', 'Very little' and 'Not at all'. Rated on a scale of 1–5, 1 corresponds to 'Always' or 'Very much' and 5 to 'Never' or 'Not at all'. Therefore, a lower score indicates greater impact on HRQoL. The score is the sum of the all item responses and can range from 12 (worst HRQoL) to 60 points (best HRQoL), which is standardised on a scale from 0 (worst HRQoL) to 100 (best HRQoL) (4). The EuroQoL-5D is a self-completion questionnaire that comprises of questions on problems encountered in five dimensions and a EuroQoL visual analogue scale (EQ-VAS). In this study, we report results of the EQ-VAS by which subjects used to rate their own health, where 0 is the 'worst' and 100 is the 'best' imaginable health state (5).

The ERCUSYN study was approved by the ethics committee of the Hospital Sant Pau, Barcelona, Spain, which is the coordinating centre of the project. In addition, the local ethics committee approval was obtained for each participating institution and all patients gave their written or verbal informed consent, depending on national legal requirements.

All the data inserted into the system were carefully monitored for inconsistencies and validated before starting statistical analysis.

Statistical analysis

SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA) was used to perform data analysis. All the data were normally distributed except delay to diagnosis. Data were expressed as mean$\pm$S.D. Delay to diagnosis was expressed as median with interquartile range.

Statistical significance was defined as a two-tailed P value ≤ 0.05.

Comparisons between the aetiologic groups were performed by ANOVA followed by Bonferroni test as a *post hoc* test or a Kruskal–Wallis H test, depending on the data distribution. Comparison between genders was performed by Student's *t*-test, while Mann–Whitney's *U* test was used to compare the delay to diagnosis between two groups. A χ^2 test was performed for categorical variables. Bivariate correlations (Pearson) were analysed between either CushingQoL or EQ-VAS and gender, age at diagnosis, delay to diagnosis, body mass index (BMI), depression, diabetes and hypertension. Multivariate regression analyses using standard least square modelling was performed to assess the contribution of gender, age, diagnosis, delay to diagnosis, BMI, depression, diabetes and hypertension to either the CushingQoL or EQ-VAS score.

Results

Patient characteristics

In this study, 481 patients were analysed. Three hundred and seventeen (66%) of them had PIT-CS, 130 (27%) had ADR-CS and 24 (5%) had ECT-CS. Ten patients (2%) were classified as having OTH-CS, including 5 PPNAD, 4 AIMAH and 1 cyclical CS.

Of the 296 patients with PIT-CS having baseline pituitary CT or MRI described in the database, 177 (60%) had documented microadenoma and 63 (21%) a macroadenoma (29 intrasellar and 34 extrasellar). Imaging failed to visualise the pituitary source of ACTH hypersecretion in 56 patients with PIT-CS (19%).

Of the 13 patients with ECT-CS having histology reports available in the database, six had bronchial carcinoid tumors (one atypical), three a small-cell lung carcinoma, two a pancreatic neuroendocrine tumor, one a seminoma and another a neuroendocrine thymic carcinoma. Of the 11 patients without histology reports, two underwent a CT which documented a lung mass.

General characteristics of the entire series and each aetiologic group are described in Table 1. The female to male ratio overall was 4:1. Percent of men in the ECT-CS group was significantly higher than in the other aetiologic groups ($P < 0.05$).

Patients in the ADR-CS group were significantly older than those in the PIT-CS group ($P < 0.05$). In the overall series, mean age at diagnosis was 47 ± 14 years (range: 15–75 years) in men and 44 ± 14 years (range: 15–84 years) in women. Inter-gender difference in the age at diagnosis was at the limit of significance ($P = 0.055$). Mean BMI was 31 ± 6 kg/m^2 (range: 22–48 kg/m^2) in men and 31 ± 7 kg/m^2 (range: 17–56 kg/m^2) in women ($P = NS$). Mean waist in men (112 ± 17 cm (range: 92–152 cm)) was significantly higher ($P < 0.05$) than that measured in women (104 ± 17 cm range: 70–170 cm).

Of the 382 patients with data on smoking habits available, 118 (31%) were smokers. Prevalence of patients with smoking habits was significantly higher in patients with ADR-CS compared with patients in the OTH-CS group (49 vs 13%; $P < 0.05$).

Of the 347 patients with data available on working status, 163 (47%) were actively employed, 18 (5%) homemakers, 19 (5%) students, 68 (20%) retired, 32 (9%) were on sick leave and 47 (14%) were unemployed.

Symptoms

Information on time elapsed between onset of symptoms and final diagnosis of CS was available in 430 patients overall (PIT-CS, 291; ADR-CS, 107; ECT-CS, 22; OTH-CS, 10).

The median of the delay to diagnosis was 2 years (interquartile range: 3 years) in the overall series.

Table 1 General characteristics of the overall population of patients with Cushing's syndrome and of each aetiologic group. Data are presented as mean±s.d. (range). Data on age and gender were available for the whole series. Data on BMI were available for 411 patients (PIT-CS, 274; ADR-CS, 108; ECT-CS, 21; OTH-CS, 8). Data on waist circumference (WC) were available for 115 patients (PIT-CS, 78; ADR-CS, 28; ECT-CS, 6; OTH-CS, 3). Data on blood pressure were available for 435 patients (PIT-CS, 286; ADR-CS, 116; ECT-CS, 23; OTH-CS, 10).

	PIT-CS	ADR-CS	ECT-CS	OTH-CS	Total
n (%)	317 (66)	130 (27)	24 (5)	10 (2)	481
Gender (F/M)	257/60	112/18	13/11	8/2	390/91
% Males	19%*	14%*	46%	20%	19%
Age at diagnosis (y)	42.7±13.5 (15–84)	46.9±13.6[†] (19–71)	46.8±14.2 (22–68)	47.6±17 (19–69)	44.2±13.7 (15–84)
BMI	30.9±7.1 (18.6–55.7)	30.4±6.2 (17–48)	29.2±6.1 (21.4–44.8)	30.7±5.8 (20.7–39.5)	30.7±6.8 (17–55.7)
WC (cm)	105.8±17.8 (73–152)	103.9±16.6 (70–150)	102.3±11.9 (89–120)	99.3±8.1 (90–105)	105±17 (70–152)
SP	140±19.8 (91–230)	145.6±23.8 (100–225)	143.9±24.8 (100–200)	145±24.7 (110–180)	142±21 (100–230)
DP	86.3±14 (90–130)	90±13.3 (90–140)	89.8±13.4 (60–110)	87.4±10.7 (77–110)	87.2±13.7 (60–140)

PIT-CS, pituitary-dependent CS; ADR-CS, adrenal-dependent CS; ECT-CS, CS from an ectopic source; OTH-CS, CS from other aetiologies including five primary pigmented nodular adrenocortical disease (PPNAD), four ACTH-independent macronodular adrenocortical hyperplasia (AIMAH) and one cyclical CS. BMI, body mass index (kg/m^2); SP, systolic blood pressure (mmHg); DP, diastolic blood pressure (mmHg). *$P<0.05$ versus ectopic; [†]$P<0.05$ versus pituitary.

In particular, the median of the delay to diagnosis was 2 years (interquartile range: 3 years) in the PIT-CS group, 2 years (interquartile range: 2 years) in the ADR-CS group, 0.5 years (interquartile range: 0.95) in the ECT-CS group and 1 year (interquartile range: 6.8 years) in the OTH-group. Median of time elapsed to diagnosis was significantly lower in the ECT group compared with either the PIT-CS or the ADR-CS group ($P<0.01$ for both comparisons).

The baseline clinical presentation is described in Table 2 and Fig. 1. Of all patients with data available, the most common features at diagnosis were weight gain (81%), hypertension (78%), skin alterations (73%) and myopathy (67%). Weight gain was the most frequent clinical finding in patients with PIT-CS (82%), ADR-CS (82%) and OTH-CS (80%), while among those with ECT-CS it was hypertension (88%). Hirsutism was found in 92% of women with ECT-CS and its prevalence was significantly higher compared with that in the other groups (63% in the PIT-CS and 50% in the OTH-CS; $P<0.05$ for both comparisons; 37% in the ADR-CS; $P<0.01$). Prevalence of diabetes mellitus was significantly higher in the ECT-CS group (74%) than in the other aetiologic groups (33% in the PIT-CS, 34% in the ADR-CS and 20% in the OTH-CS; $P<0.01$ for all comparisons). Patients with PIT-CS had significantly more skin alterations, menstrual irregularities and hirsutism compared with those with ADR-CS (78 vs 64% for skin alterations, 63 vs 43% for menstrual irregularities and 63 vs 37% for hirsutism; $P<0.01$ for all comparisons). No significant differences between the groups were observed in the prevalence of any other reported symptoms or signs.

The most prevalent features at diagnosis in female patients were weight gain (86%), hypertension (77%) and myopathy (66%). In men, hypertension (83%), myopathy (71%) and reduced libido (69%) were more commonly found.

When inter-gender differences in the prevalence of any CS clinical finding were evaluated, weight gain

Table 2 Baseline clinical presentation in the overall population of patients with Cushing's syndrome and of each aetiologic group. Data for each aetiologic group and the overall series are expressed as number of patients with a sign or symptom/total number of patients with records available for that sign or symptom. Percentages are shown in parenthesis.

	PIT-CS	ADR-CS	ECT-CS	OTH-CS	Overall
Weight gain	240/294 (82)	93/113 (82)	16/23 (70)	8/10 (80)	357/440 (81)
Hypertension	233/306 (76)	103/126 (82)	21/24 (88)	6/10 (60)	363/466 (78)
Skin alterations	227/292 (78)*	78/122 (64)	18/24 (75)	6/10 (60)	329/448 (73)
Myopathy	181/272 (67)	69/107 (64)	20/24 (83)	6/8 (75)	276/411 (67)
Hirsutism[a]	145/232 (63)*,[‡]	37/100 (37)[†]	12/13 (92)	4/8 (50)[‡]	198/353 (56)
Menstrual irregularities[a]	123/195 (63)*	35/82 (43)	4/9 (44)	3/8 (38)	165/294 (56)
Reduced libido	61/123 (50)	15/43 (35)	5/10 (50)	3/4 (75)	84/180 (47)
Depression	93/243 (38)	31/106 (29)	9/22 (41)	4/10 (40)	137/381 (36)
Diabetes mellitus	96/294 (33)[†]	43/127 (34)[†]	17/23 (74)	2/10 (20)[†]	158/454 (35)
Hair loss	76/224 (34)	29/98 (30)	4/19 (21)	1/10 (10)	110/351 (31)
Fractures	55/263 (21)	21/114 (18)	7/22 (32)	2/9 (22)	85/408 (21)

PIT-CS, pituitary-dependent CS; ADR-CS, adrenal-dependent CS; ECT-CS, CS from an ectopic source; OTH-CS, CS from other aetiologies. *$P<0.01$ versus adrenal; [†]$P<0.01$ versus ectopic; [‡]$P<0.05$ versus ectopic.
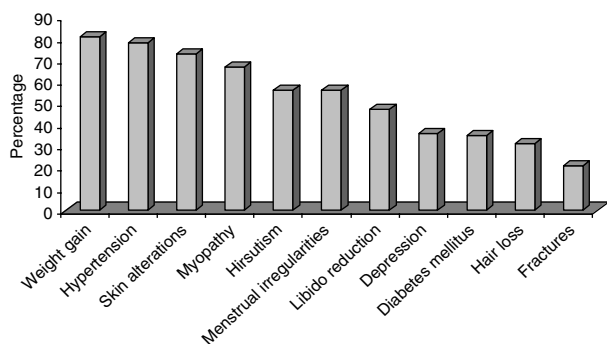[a]Data refer to female patients.

Figure 1 Distribution of symptoms in the overall population of patients with Cushing's syndrome.

resulted significantly more common in women compared with men (86 vs 62%; $P < 0.01$). Fractures and reduced libido were more frequently reported in men than in women (33 vs 18% and 69 vs 40%, respectively; $P < 0.01$ for both comparisons).

Bone status

Data on DXA and radiographic assessment in the overall series and each aetiologic group are described in Table 3. Vertebral fractures were more prevalent in ECT-CS compared with PIT-CS (44 vs 25%; $P < 0.05$).

Bone characteristics in both sexes are described in Table 4. Osteopenia at the spine, as measured by DXA, was reported in 43% of men and 41% of women. Prevalence of osteoporosis at the spine was significantly higher in men compared with women (40 vs 20%; $P < 0.05$). Men had significantly more vertebral and rib fractures compared with women (52 vs 18% for vertebrae; $P < 0.001$ and 34 vs 23% for ribs; $P < 0.05$).

Bone fractures occurred in 39 of the 63 (62%) patients with osteoporosis and in 44 of 105 (42%) patients with osteopenia at any sites. Nineteen of the 77 (25%) patients with normal bone mineral density (BMD)

experienced a bone fracture. Osteoporosis was significantly more prevalent in patients with bone fracture compared with those without a bone fracture ($P < 0.05$).

Other specialists consulted before reaching the correct diagnosis of CS

Data on specialists consulted before establishing correct diagnosis of CS are shown in Table 5. Overall, 77% of patients with data available were referred to their general practitioner. Diabetologists were consulted by 24% of patients and gynaecologists were observed by 24% of female patients. A diabetologist was consulted more frequently by patients with ECT-CS than those with ADR-CS (41% ECT-CS versus 19% ADR-CS; $P < 0.05$), while a gynaecologist was consulted more frequently by women with either PIT-CS or ADR-CS than those with ECT-CS (24% PIT-CS, 25% ADR-CS versus 9% ECT-CS; $P < 0.05$).

No inter-gender difference in the specialists consulted (other than gynaecologists) was observed between males and females.

Quality of life

Baseline HRQoL evaluated by a generic EQ-VAS and a new disease-generated (CushingQoL) questionnaire were available for 122 (25%) and 132 patients (27%) respectively. Results are shown in Table 6. Mean CushingQoL score was 39 ± 17 (range: 0–83) overall. Specifically, mean CushingQoL score was 40 ± 17 (range: 4–83) in the PIT-CS group, 39 ± 14 (range: 0–77) in the ADR-CS, 27 ± 13 (range: 6–44) in the ECT-CS and 23 ± 2 in the OTH-CS group. No significant difference in the CushingQoL score was observed between the groups.

Mean EQ-VAS score was 52 ± 19 (range: 1–90) overall. Mean EQ-VAS was 54 ± 19 (range: 1–90) in the PIT-CS group, 53 ± 15 (range: 1–80) in the ADR-CS, 37 ± 23 (range: 10–70) in the ECT-CS and 28 ± 18

Table 3 Bone status in the overall population of patients with Cushing's syndrome and of each aetiologic group. Data are expressed as percentage of patients with records available for each assessment. DXA of the spine was available in 211 patients (PIT-CS, 136; ADR-CS, 57; ECT-CS, 11; OTH-CS, 7). DXA of the hip was available in 206 patients (PIT-CS, 134; ADR-CS, 55; ECT-CS, 10; OTH-CS, 7). Radiographic assessment was available in 97 patients of the overall series (PIT-CS, 57; ADR-CS, 29; ECT-CS, 9; OTH-CS, 2).

	PIT-CS	ADR-CS	ECT-CS	OTH-CS	Overall
DXA spine osteopenia	40	46	36	43	41
DXA spine osteoporosis	22	25	27	29	23
DXA hip osteopenia	46	64	40	43	50
DXA hip osteoporosis	12	11	10	14	12
X-ray vertebral fracture	25	31	44*	0	41
X-ray hip fracture	2	7	0	0	5
X-ray rib fracture	28	28	0	0	39
X-ray wrist fracture	7	3	0	0	8
X-ray metatarsal fracture	7	0	11	0	8

DXA, dual-energy X-ray absorptiometry; PIT-CS, pituitary-dependent CS; ADR-CS, adrenal-dependent CS; ECT-CS, CS from an ectopic source; OTH-CS, CS from other aetiologies. *$P < 0.05$ versus PIT-CS.

Table 4 Bone status in men and women with Cushing's syndrome. Data are expressed as percentage of patients with records available for each assessment. DXA at the spine was available in 176 women and 35 men. DXA at the hip was available in 160 women and 29 men. Radiographic assessment was available in 68 women and 29 men.

	Men	**Women**	***P* value**
DXA			
Spine osteopenia	43	41	NS
Spine osteoporosis	40	20	<0.05
Hip osteopenia	53	49	NS
Hip osteoporosis	12	12	NS
X-ray			
Vertebral fracture	52	18	<0.001
Hip fracture	3	3	NS
Rib fracture	34	23	<0.05
Wrist fracture	3	6	NS
Metatarsal fracture	7	4	NS

NS, not significant; DXA, dual-energy X-ray absorptiometry.

(range: 15–40) in the OTH-CS group. No significant difference in the EQ-VAS score was observed between the groups.

CushingQoL score was available for 16 men and 116 women. EQ-VAS was available for 15 men and 107 women. Mean CushingQoL score was 40 ± 15 (range: 15–58) in men and it was not significantly different from the mean score of 38 ± 17 (range: 0–83) reported in women. Similarly, mean EQ-VAS was not significantly different between the sexes (52 ± 12 (range: 30–71) in men versus 52 ± 20 (range: 1–90) in women).

Analysis of the prospective data

We also repeated all the analysis after excluding the 83 retrospective cases to determine if they might bias the results. Most of the results obtained in the prospective population were concordant with those from the overall (prospective + retrospective) series. However, prevalence of myopathy was significantly higher in the ECT-CS group than in the ADR-CS group (86 vs 61%; $P < 0.05$), when only prospective data were analysed. Moreover, a diabetologist was visited more frequently by patients

with PIT-CS compared with those in the ADR-CS group (26 vs 19%; $P < 0.05$) in the prospective series. These differences were the only ones not observed in the overall (prospective + retrospective) population.

Predictors of response

Multivariate regression analyses for either the CushingQoL or the EQ-VAS score were performed. Gender, age, diagnosis, delay to diagnosis, BMI, depression, diabetes and hypertension were included in the model as independent variables.

Depression was the only independent determinant of a lower CushingQoL score.

None of the variables included significantly predicted the EQ-VAS score.

Discussion

This study presents baseline demographic and clinical characteristics of a cohort of 481 patients with CS of different aetiologies, which have been collected from 36 centres in 23 European countries participating in the ERCUSYN project. Overall, 66% of CS patients had a pituitary adenoma, 27% an adrenal adenoma, 5% CS from an ectopic ACTH source and 2% OTH-CS, including cyclical CS and nodular adrenal hyperplasia, consistent with previous reports (2, 6–9). However, the proportion of adrenal adenomas was higher in our cohort than in previous studies, which reported diagnosis of adrenal adenoma in 5–22.3% of all cases (7, 8, 10). Moreover, patients with adrenal adenoma were significantly older than those with PIT-CS, in contrast to a previous study on 426 CS patients (288 with PIT-CS, 80 with adrenal adenoma, 24 with adrenal carcinoma, 25 with ectopic ACTH/CRH secretion and 9 with ACTH-independent nodular adrenal hyperplasia) which did not show any difference in the age at diagnosis between the aetiologic groups (8).

Prevalence of CS symptoms in our cohort was not different from that described in other studies (1, 11, 12). However, muscle weakness was somewhat more

Table 5 Other specialists consulted before reaching the correct diagnosis of Cushing's syndrome. Data for each aetiologic group and the overall series are expressed as number of patients visiting a specialist/total number of patients with records available for each specialist. Percentages are shown in parenthesis. For gynaecologist only the females were considered.

	PIT-CS	**ADR-CS**	**ECT-CS**	**OTH-CS**	**Overall**
General practitioner	198/260 (76)	90/114 (79)	18/22 (82)	5/10 (50)	311/406 (77)
Diabetologist	58/236 (25)	19/98 (19)	9/22 (41)[†]	2/9 (22)	88/365 (24)
Gynaecologist	47/193 (24)*	21/85 (25)*	1/11 (9)	2/8 (25)	71/297 (24)
Psychiatrist/psychologist	28/226 (12)	10/97 (10)	2/22 (9)	2/10 (20)	42/355 (12)
Rheumatologist/orthopaedist	25/224 (11)	10/96 (10)	2/22 (9)	2/10 (20)	39/352 (11)
Dermatologist	18/227 (8)	5/97 (5)	1/22 (5)	2/10 (20)	26/356 (7)
Other[a]	121/229 (53)	47/90 (52)	10/18 (56)	6/9 (67)	184/346 (53)

PIT-CS, pituitary-dependent CS; ADR-CS, adrenal-dependent CS; ECT-CS, CS from an ectopic source; OTH-CS, CS from other aetiologies. *$P < 0.05$ versus ECT-CS; [†]$P < 0.05$ versus ADR-CS.
[a]Includes 'other endocrinologists', 'cardiologists', 'gastroenterologists' and 'neurologists'.

Table 6 Mean quality of life (QoL) scores in the entire series of patients with Cushing's syndrome and each aetiologic group. Cushing QoL score was available in 132 patients (PIT-CS, 94; ADR-CS, 30; ECT-CS, 6; OTH-CS, 2). EuroQoL score was available in 122 patients (PIT-CS, 84; ADR-CS, 30; ECT-CS, 6; OTH-CS, 2). No significant differences in both QoL assessments were observed between the groups.

	PIT-CS	ADR-CS	ECT-CS	OTH-CS	Overall
CushingQoL score	40 ± 17 (4–83)	39 ± 14 (0–77)	27 ± 13 (6–44)	23 ± 21 (2–38)	39 ± 17 (0–83)
EuroQoL scale	54 ± 19 (1–90)	53 ± 15 (10–80)	37 ± 23 (10–70)	28 ± 18 (15–40)	52 ± 19 (1–90)

PIT-CS, pituitary-dependent CS; ADR-CS, adrenal-dependent CS; ECT-CS, CS from an ectopic source; OTH-CS, CS from other aetiologies.

frequent in our series (73%) than in others (56–60%) (1, 11). In contrast, reduced libido and depression were documented in our patients less commonly than in other reports (1). Interestingly, when only men were considered, prevalence of low libido increased and it was significantly higher than in women, suggesting that this symptom is often overlooked and underreported in female patients. In our study, diabetes mellitus and hirsutism occurred more frequently in patients with ectopic CS compared with the other major aetiologic groups. In this study by Ilias *et al.* (13), hirsutism was described in 75% of patients with ectopic CS, and it was among the most common clinical findings in this aetiologic group. As for diabetes mellitus, previous large studies have shown a lower prevalence in patients with an ectopic source of ACTH (9, 13). In particular, Ilias *et al.* (13) documented diabetes in half of 90 patients with ectopic CS, while Isidori *et al.* (9) described 37.5% prevalence in a series of 40 patients. However, two other smaller studies on patients with ectopic CS recently described diabetes mellitus in 75–80% of cases (14, 15), consistent with our results in a larger cohort. Accordingly, in our study, a diabetologist was consulted more often by patients who were subsequently diagnosed with ectopic CS than those with other aetiologies. It should be underlined that the use of different diagnostic criteria for diabetes mellitus may partly explain the reported discrepancies in the prevalence of this disease among the studies.

Because hypokalemia was not listed in the database among the possible signs of CS at presentation, we could not evaluate its prevalence and diagnostic role in our study.

We confirm previous reports that documented a more rapid onset of symptoms in many cases of ectopic syndrome from a pulmonary source (1, 7). We observed a significantly lower median of time elapsed to diagnosis in these patients compared with those in either the pituitary or adrenal group, although a bias from a survival factor cannot be excluded when analysing patients with ectopic ACTH secretion. Invitti *et al.* (8) described a mean time to diagnosis of 18 ± 4.7 months in Italian patients with ectopic syndrome, which was shorter, although not significantly, than that found in the other diagnostic groups. Importantly, in our series, the median of the delay to diagnosis was remarkable, 2 years overall.

More than 80% of patients included in our study consulted a general practitioner for complaints associated with underlying CS. Although from our database it was not possible to infer how many patients have been directly addressed to an endocrinologist by their general practitioners and how many have consulted one or more specialist(s) by their own initiative, we could demonstrate that a large proportion of subjects saw at least one doctor other than the endocrinologist before CS was diagnosed and a large number of specialists missed the correct diagnosis. This likely contributed to the described large time frame between the appearance of first symptoms of hypercortisolism and the recognition of CS. The negative consequences of such a delay to diagnosis on patient's health, disease outcome and care expenses are evident. These findings highlight the need for increasing the awareness on CS and its broad spectrum of clinical manifestations among all the clinicians, including general practitioners, to promote earlier recognition of symptoms and shorten the time to correct diagnosis.

It should be emphasised that our database comprises of patients who have been evaluated in 36 referral centres of 23 European countries. Quality and organisation of health care systems, as well as specialisation degree and experience level of peripheral providers who first saw undiagnosed patients broadly varied across Europe and, sometimes, even within the same country. These differences should be taken into account to interpret the data from the ERCUSYN study, including the delay to diagnosis. At the same time, health authorities and planners should be aware of the cost of this delay and implement policies to improve this situation.

The deleterious effects of glucocorticoid excess on bone are well documented (16, 17). In our large series of 97 patients with bone X-ray assessment available, we observed an elevated prevalence of bone fractures, mainly localised at the spine and ribs.

Men were significantly more susceptible to fractures at the spine and hip than women, and also showed a higher prevalence of vertebral osteoporosis, as previously observed by others (12, 18). Causes of this sexual dimorphism are not known but a role of CS-associated hypogonadism cannot be ruled out. Sex steroids have positive actions on bone density and trophic effects on skeletal development (19). Testosterone production rate is subnormal in men with CS (20) and low bioavailable testosterone has been recently shown to be associated with a high fracture risk, especially the nontraumatic, in community-dwelling

men (21). Moreover, low testosterone levels might also negatively impact extraskeletal functions, such as muscle strength, resulting in increased fall risk (22). A gender-related difference in bone susceptibility to the hypercatabolic effects of cortisol should be also considered (23).

Previous studies showed that adrenal (24) or ectopic (25) aetiology of CS may be associated with higher prevalence of vertebral osteoporosis. This topic is still controversial (26) and we, like others (18), did not find any differences in BMD between the aetiologic groups.

Patients with CS have poor QoL as assessed by generic (10, 27–29) and disease-specific questionnaires (4). We used for the first time the EQ-VAS in the evaluation of self-perceived health status in CS. It disclosed a mean score of 52 ± 19, which was lower than reference values from The Netherlands (80.7 ± 17.2) and Spain (74 ± 24.9) (30).

Our patients also showed a significant impairment of QoL, as measured by the disease-generated CushingQoL questionnaire. We found a global mean score of 39, while Webb *et al.* (4) documented a mean score of 53 in both active and 'cured' CS patients from five European countries, and a score of 46 in those with current hypercortisolism. Thus, our European-wide study demonstrates that QoL in patients with active CS is even worse than what was observed in previous smaller studies (4, 31). Both EQ-VAS and CushingQoL did not reveal any aetiology-related difference in QoL. However, both QoL scores resulted lower, although not significantly, in patients with ectopic CS in comparison to those with PIT-CS or ADR-CS, consistent with their higher prevalence of some comorbidities and the negative effects of the commonly found underlying malignancy. Of note, depression was the only negative predictor of the CushingQoL score, whereas other variables, including delay to diagnosis, diabetes or hypertension, did not significantly influence the QoL measurements used in our study. Factors which have not been included in the current analysis, such as cortisol levels, or concomitant multiple pituitary hormone deficiency might also influence QoL (31).

Inclusion of a relatively small set of retrospective data is a limitation of the study. However, the results obtained after analysing only the prospective data were substantially concordant with those from the analysis of the overall population. The multicentre design is another limitation of the study because there were differences in the diagnostic approach and management among the participating centres across Europe. However, the entire database has been thoroughly reviewed for data quality control applying rigorous criteria of validation. We think that this careful review allowed us to obtain reliable and complete information, and attenuated potential 'centre effect'.

In conclusion, these first data from the ERCUSYN, the largest collaboration of endocrine centres in Europe and in the world, demonstrated an elevated morbidity at diagnosis in CS patients, with low bone mass, especially in men, and impaired QoL. It illustrated differences in clinical presentation of CS depending on gender and aetiology, and confirmed a long delay between onset of symptoms and diagnosis of CS, with a high number of specialists consulted who often missed the correct diagnosis. Thus, there is great potential for improvements in the time to diagnosis that would have obvious consequences for patients and for the health care systems, which must meet the long-term sequelae of delayed diagnosis. Further analyses from the ERCUSYN project are expected to provide new insights into the diagnostic and therapeutic challenges of CS.

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