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CUSHING'S SYNDROME IN THE ELDERLY: DATA FROM THE EUROPEAN REGISTRY ON CUSHING'S SYNDROME

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ABSTRACT

Objective: To evaluate whether age-related differences exist in clinical characteristics, diagnostic approach and management strategies in patients with Cushing's syndrome included in the European Registry on Cushing's Syndrome (ERCUSYN).

Design: Cohort study.

Methods: We analyzed 1791 patients with CS, of whom 1234 (69%) had pituitary-dependent CS (PIT-CS), 450 (25%) adrenal-dependent CS (ADR-CS) and 107 (6%) had an ectopic source (ECT-CS). According to the WHO criteria, 1616 patients (90.2%) were classified as younger (<65 years) and 175 (9.8%) as older (≥65 years).

Results:

Older patients were more frequently males and had a lower BMI and waist circumference as compared with the younger. Older patients also had a lower prevalence of skin alterations, depression, hair loss, hirsutism and reduced libido, but a higher prevalence of muscle weakness, diabetes, hypertension, cardiovascular disease, venous thromboembolism and bone fractures than younger patients, regardless of sex ($p<0.01$ for all comparisons). Measurement of UFC supported the diagnosis of CS less frequently in older patients as

compared with the younger (p<0.05). An extra-sellar macroadenoma (macrocorticotropinoma with extrasellar extension) was more common in older PIT-CS patients than in the younger (p<0.01). Older PIT-CS patients more frequently received cortisol-lowering medications and radiotherapy as a first-line treatment, whereas surgery was the preferred approach in the younger (p<0.01 for all comparisons). When transsphenoidal surgery was performed, the remission rate was lower in the elderly as compared with their younger counterpart (p<0.05).

Conclusions:

Older CS patients lack several typical symptoms of hypercortisolism, present with more comorbidities regardless of sex, and are more often conservatively treated.

SIGNIFICANCE STATEMENT

Clinical presentation of Cushing's syndrome (CS) was different in older patients as compared with that in the younger, with the former lacking some of the typical features of cortisol excess while presenting with a greater burden of comorbidities and an elevated prevalence of muscle weakness. Levels of urinary free cortisol were often within the normal range in the elderly, and a conservative treatment was frequently chosen in them. Our data emphasize the need of maintaining a high clinical suspicion of hypercortisolism in the general population, while taking into account specific age-related differences in the presentation of symptoms. Our data may contribute to reduce the delay to diagnosis in CS, which has been associated with increased morbidity and mortality.

INTRODUCTION

Cushing's syndrome (CS) is usually caused by excessive ACTH release from a pituitary corticotrope adenoma (Cushing's disease, CD) and, less frequently, by ectopic ACTH or (very rarely) CRH production. CS can also be ACTH-independent when caused by cortisol-secreting adrenocortical tumors or hyperplasia (1). CS is most frequently diagnosed in women (female to male ratio, 3-5:1) aged 40-50 years and is associated with a constellation of symptoms and signs, including, among others, weight gain, centripetal fat deposition, purple striae, skin thinning, muscle wasting and fatigue. Hypercortisolism is also related to several comorbidities, such as type 2 diabetes mellitus, arterial hypertension, cardiovascular disease, venous thromboembolism, mood disorders and osteoporosis which result in poor quality of life (QoL) and elevated mortality (2, 3, 4).

Life expectancy has increased during the last decades and the general population is progressively growing older, especially in Western countries (5). Consequently, the number of elderly people with endocrine diseases rising and mean age of patients regularly followed in referral centers for low-prevalence diseases, such as CS, is older than in the past.

Advanced age at diagnosis of CS is associated with an elevated mortality, both perioperatively and following long-term after remission (6, 7). Moreover, data from the European registry on Cushing's Syndrome (ERCUSYN) showed that older age at diagnosis predicted worse self-reported QoL more than one year after treatment (8).

Data on clinical presentation and management of CS in older patients are scarce. Some authors have reported individual cases of older patients with CS (9, 10, 11, 12) but have not focused on specific age-related differences in clinical presentation. Minniti et al. suggested that the clinical picture of CD in older patients may be milder than in younger patients (13).

Conversely, in a recent study, Qiao et al. showed that 45 CD patients older than 60 more commonly presented with a catabolic phenotype and cardiometabolic comorbidities as compared with younger patients (14).

Our study aimed to describe the age-related differences in clinical characteristics, diagnostic approach, management strategies, treatment outcome and mortality in patients with CS included in the European Registry on Cushing's Syndrome (ERCUSYN) the largest database existing to date on this condition.

METHODS

Description of the database

ERCUSYN is a web-based, multicenter, observational study that enrolled 1972 patients from 57 centers in 26 European countries at the time of the study (between January 1st, 2000 and January 31st, 2021). Patients were classified into four major etiologic groups: pituitary-dependent CS (PIT-CS), adrenal-dependent CS (ADR-CS; adrenal adenoma), CS from ectopic source (ECT-CS) and CS from other etiologies (OTH-CS), mainly including cyclic hypercortisolism. Etiologic classification was based on histologic documentation of ACTH-secreting or adrenal tumors. In case histological reports were not available, expert centers involved confirmed diagnosis in their local multidisciplinary team meetings, based on biochemical and clinical resolution of hypercortisolism after surgical resection, or, in patients who were not operated on, based on biochemical test results and/or imaging.

A detailed description of the database layout has been provided elsewhere (7). Briefly, the "diagnosis" section contains information at diagnosis: baseline demographics and anthropometric characteristics, etiology of CS and diagnosis date, delay between onset of

symptoms and final diagnosis of CS, clinical features, concomitant pituitary hormone deficiencies, menopausal status, comorbidities, such as cardiovascular disease (defined as a history of coronary heart disease or cerebrovascular accidents) and quality of life (QoL), the latter being assessed using both the generic EuroQoL and the disease-generated CushingQoL questionnaires. In this study, only EuroQoL measures will be shown, due to the low number of CushingQoL questionnaires administered to older people across Europe. The "imaging" subsection contains information on pituitary MRI ("microadenoma", "extrasellar macroadenoma", "intrasellar macroadenoma", and "no visible adenoma"). The "treatment" section contains information on surgery (type, date, number), RT (type, date), and medical treatment (date, dose, duration, number). The "follow-up" section resembles the layout of the "Diagnosis" section and contains information on clinical and hormonal status, including concomitant pituitary hormone deficiencies and menopausal status on each follow-up visit. The "death" section comprises information on the age of the deceased patients and the cause of death. Diagnosis of autonomous cortisol secretion and adrenal carcinoma were exclusion criteria of the ERCUSYN database.

Patients were grouped depending on their age at the time of diagnosis. Patients aged $\geq$ 65 were considered "elderly" and were compared with "younger" patients, aged <65 years. This classification was in accordance with the WHO definition (15). Data on MRI findings and remission rate in PIT-CS patients were also stratified, in women, based on the estrogen status and menopausal status. In particular, estrogen-sufficient women (premenopausal without gonadotropin deficiency) were compared with postmenopausal women or women with unreplaced gonadotropin deficiency.

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 informed consent, according to the EU *General Data Protection Regulation* (*GDPR*). This research complies with the Declaration Of Helsinki. All the data inserted into the system were carefully monitored for inconsistencies and validated before starting statistical analysis.

Statistical analysis

For statistical analysis, GraphPad Prism® version 9 (Graph-Pad Software, San Diego, Calif., USA) was used. Continuous data are presented as mean ± SD, while categorical variables are presented as absolute/relative frequencies. We performed statistical comparisons of quantitative data with Student's *t* test or ANOVA. When variables were not normally distributed, we used the Mann-Whitney U test. For statistical comparisons of dichotomous data, we used the χ^2 test and, when the sample size was < 10 we used the exact Fisher test. Comparison of remission rates depending on age were evaluated using Kaplan-Meier analysis and compared using the log-rank test. All statistical tests were two sided with p values of <0.05 considered to be significant.

RESULTS

1- CHARACTERISTICS OF THE OVERALL POPULATION

At the time of the analysis, 1972 patients with CS were included in the database. One hundred and eighty-one patients were excluded because the cause of CS was classified as "not known", "other" or related to "illicit receptor expression". Finally, we analyzed 1791 CS

patients classified as PIT-CS (n=1234), ADR-CS (n=450) or ECT-CS (n=107). The mean age of the whole population was 44.7±14.1 years and 1397 (78%) were females. One-thousand six hundred and sixteen patients (90.2%) were classified as younger (<65 years) and 175 (9.8%) were classified as elderly patients (≥ 65 years).

2- AGE-RELATED DIFFERENCES IN CLINICAL FEATURES AT DIAGNOSIS

The clinical presentation at diagnosis, depending on age, is shown in Table 1. There was a female preponderance in younger patients as compared with older [1289 (79.7%) vs. 107 (61.1%); p<0.01]. Elderly patients had lower BMI (26.7±5.7kg/m^2 vs. 29.7±7.1kg/m^2; p<0.01), lower waist circumference (97.1±10.8 vs. 103.1±16.5; p<0.01), lower prevalence of weight gain [87 patients (49.7%) vs. 1184 patients (73.2%); p<0.01], higher prevalence of hypertension [156 patients (89.1%) vs. 1084 patients (67.1%); p<0.01] and higher prevalence of diabetes mellitus [84 patients (48%) vs. 446 patients (27.6%); p<0.01], in comparison to younger patients. Elderly patients were less frequently depressed than younger ones [35 (20%) vs. 538 (33.3%); p<0.01] and were less frequently followed by a psychiatrist [9 (5.1%) vs. 170 patients (10.5%); p=0.02]. Elderly patients had lower prevalence of skin symptoms [103 patients (58.8%) vs. 1123 (69.4%); p<0.01], hirsutism in females [23 (22%) vs. 668 (52%); p<0.01], hair loss in females [22 (21%) vs. 351 (27%); p=0.03], and loss of libido [14 (8%) vs. 325 (20.1%); p<0.01] in comparison to younger patients. Prevalence of fractures was higher in the elderly [38 (21.7%) vs. 217 (13.4%); p<0.01] in comparison to younger patients.

3- AGE-RELATED DIFFERENCES IN CLINICAL FEATURES OF HYPERCORTISOLISM AT DIAGNOSIS BASED ON THE ETIOLOGY

3a- PIT-CS

Age-related clinical presentation in PIT-CS is shown in Figure 1 and Table 2. Of 1234 PIT-CS patients with data available, 103 patients (8.3%) were older, and 1131 (91.7%) were younger. Fifty-six older and 889 younger patients were females (54% vs. 72%; p<0.01). The commonest metabolic features in elderly patients as compared with their younger counterparts were lower BMI, lower waist circumference, lower prevalence of weight gain, higher prevalence of hypertension and higher prevalence of diabetes mellitus (p<0.01 for all comparisons). Prevalence of muscle weakness in the older was greater as compared with that in younger patients (p<0.01). Concerning psychiatric complications of PIT-CS, elderly patients were less depressed and, accordingly, less frequently followed by a psychiatrist (p<0.01 and p=0.03 respectively). Older females had lower prevalence of hirsutism and hair loss, while low libido and higher prevalence of fractures were observed in the overall older population as compared with younger (p<0.01 for all comparisons).

Data on cardiovascular morbidity were available in all 103 older and 1131 younger patients. Prevalence of cardiovascular disease at diagnosis was higher in the older as compared with the younger ([24/103 (23%) vs. 25/1131 (2%); p<0.01]. Ischemic heart disease was more frequently reported in the older as compared with the younger [19/103 (18.4%) vs. 20/1131 (1.5%); p<0.01]. Thrombosis was more frequently reported in the older as compared with the younger [26/103 (25.2%) vs. 59/1131 (5.2%); p<0.01)].

3b- ADR-CS

Age-related clinical presentation in ADR-CS is shown in Table 3.

Of 450 ADR-CS patients with available data, 52 (11.6%) were older and 398 (88.4%) younger. Thirty-eight older patients and 352 younger patients were females (73% vs. 88%; $p<0.01$). Prevalence of hypertension and type 2 diabetes was greater in the older as compared with the younger ($p<0.01$ for all comparisons). Older females had lower prevalence of hirsutism and hair loss ($p<0.05$). The differences in the prevalence of other clinical features between the two groups were not statistically significant, most probably due to the small number of patients included.

In the younger group, the proportion of women was lower in PIT-CS patients as compared with ADR-CS patients [889 (72%) vs. 352 female patients (88%), respectively; $p=0.04$]. Prevalence of hypertension was lower in PIT-CS as compared with ADR-CS [724 (64%) vs. 291 (73%); $p<0.01$]. Prevalence of hirsutism was higher in PIT-CS women as compared with ADR-CS women [526 (46%) vs. 116 (29%), respectively; $p<0.01$]. The prevalence of skin symptoms was higher in PIT-CS as compared with ADR-CS patients [818 (72%) vs. 238 (60%). The prevalence of weight gain was higher in PIT-CS as compared with ADR-CS patients (904 (80%) vs. 226 (57%). respectively, $p<0.01$].

Among elderly patients (>65 years old), the mean waist circumference was lower in PIT-CS as compared with ADR-CS patients (95 cm vs. 103 cm, respectively; $p=0.03$). The mean BMI was lower in PIT-CS as compared with ADR-CS patients (24 Kg/m^2 vs. 30 Kg/m^2, respectively; $p=0.01$).

3c- ECT-CS

Of 107 ECT-CS patients with data available, 20 (18.7%) were older and 87 (81.3%) were younger patients. Prevalence of hypertension and type 2 diabetes was greater in the older as compared with the younger [18 (90%) vs. 69 (79%) for hypertension and 18 (90%) vs. 33 (38%) for type 2 diabetes; p<0.01 for both comparisons]. The differences in the prevalence of other clinical features between the two groups were not statistically significant, most probably due to a smaller numbers of patients.

4- SEX-RELATED DIFFERENCES IN OLDER PATIENTS AT DIAGNOSIS

Of 175 elderly patients with data available, 68 were males (38.8%) and 107 (61.2%) were females. At diagnosis, female elderly patients had a significantly higher systolic blood pressure as compared with their male counterparts (152±15 mmHg vs. 140±6; p<0.01) and loss of libido was significantly less prevalent in elderly females in comparison with elderly males [4 (4%) vs. 14 (21%); p<0.01] (Table 4). Older males had a significantly lower BMI (26±9 kg/m^2 vs. 29.6±6 kg/m^2; p=0.02), higher prevalence of diabetes mellitus [36 (53%) vs. 112 (34%); p<0.01] and a lower prevalence of depression [9 (19%) vs. 130 (40%); p<0.01] as compared with their younger counterpart (Table 4). Older females had a significantly higher prevalence of hypertension [96 (90%) vs. 830 (64%); p<0.01], higher prevalence of muscle weakness [63 (59%) vs. 615 (48%); p=0.01], higher prevalence of diabetes mellitus [56 (52%) vs. 354 (27%); p<0.01], lower prevalence of depression [23 (22%) vs. 408 (32%); p=0.02], lower prevalence of weight gain [56 (53%) vs. 1019 (79%); p<0.01], and higher prevalence of fractures [26 (24%) vs. 145 (11%); p=0.01] (Table 4).

5- HEALTH-RELATED QUALITY OF LIFE AT DIAGNOSIS

Of 437 patients (24.4%) with EuroQoL data available, 34 (7.8%) were older and 403 (92.2%) were younger. Older patients scored worse on several items of EuroQoL as compared with younger patients, including mobility issues and self-care issues but they scored better on anxiety/depression issues ($p<0.05$ for all comparisons).

6- AGE-RELATED DIFFERENCES IN DIAGNOSIS AND MANAGEMENT STRATEGIES IN PATIENTS WITH PIT-CS

6a- Diagnosis in elderly patients with PIT-CS

We also separately analyzed PIT-CS patients, who represented the largest etiologic group in the ERCUSYN database.

Hormone assessment

Of the 943 patients with biochemical data available, 75 (8%) were older and 868 (92%) were younger. In older patients with PIT-CS, UFC measurements supported the diagnosis of hypercortisolism PIT-CS less frequently than in younger patients [(65/75 (87%) vs. 828/868 (95%); $p<0.01$]. The rest of hormone assessments were similar between younger and older patients with PIT-CS.

Imaging

We had available information on pituitary MRI in 1113 patients (90%) of whom 1021 were younger (90%) and 92 older (89%). The prevalence of a microadenoma was lower in the

older in comparison to the younger [36(39%) vs. 574 (56%); p<0.01]. Prevalence of an extra-sellar macroadenoma was higher in older patients in comparison to the younger with PIT-CS [16 (17.4%) vs. 103 (10.1%); p=0.02]. Corticotropinomas were not visualized on MRI in 219 younger patients (21.5%) vs. 23 older patients (25%); p=0.4.

Of 1113 patients with pituitary MRI data available, 810 patients were females (72.7%), of whom 563 (69.5%) were estrogen-sufficient/premenopausal and 247 (30.5%) were estrogen-deficient/ postmenopausal. Extrasellar macroadenomas were less prevalent in estrogen sufficient/premenopausal women as compared with estrogen deficient/postmenopausal women [37/563 (6.5%) vs. 39/247 (15.8%); p<0.01].

6b- Choice of treatment in elderly patients with PIT-CS

Differences in management strategy in patient with PIT-CS, depending on age, are shown in Table 5.

Of the 1234 PIT-CS patients with data on first-line treatment available, 1082 (87.7%) underwent pituitary surgery, of whom 71 were older (68.9%) and 1011 younger (89.3%) (p<0.01). The rate of older patients who never received transsphenoidal surgery was higher as compared with the younger [32 (31.1%) vs. 120 (10.6%); p<0.01)].

Cortisol-lowering medications were more frequently chosen as a first-line treatment in the older as compared with the younger (41 (39.8%) vs. 307 (27.1%); p<0.01).

A total of 137 patients with PIT-CS were treated with radiotherapy (RT), of whom 120 younger (10.6%) and 17 older (13.6%) (p=0.06). Use of radiotherapy as a first line therapy

was more frequent in elderly patients as compared with younger patients (6 (35.3%) vs. 8 (6.6%); p<0.01).

The prevalence of an extrasellar adenoma was greater in patients who were conservatively treated with first-line medical therapy as compared with that in the group of patients who underwent first-line surgery [13/41 (31%) vs. 3/71 (4%), respectively; p<0.001].

Thirty-eight (37%) older patients were diagnosed before 2010 and 65 (63%) after 2010. We did not find any differences in the frequency of any modalities of first-line treatment in patients who received diagnosis of CD before 2010 as compared with those diagnosed after 2010 (p=0.8 for TSS; p=0.7 for both radiotherapy and medical treatment). However, more CD patients with persistent/recurrent disease included after 2010 received medical therapy as compared with those included before 2010 [52/65 (80%) vs. (12/37) (32%), respectively; p<0.01].

6c- Age-related differences in remission and relapse rate in PIT-CS patients

Of 1047 patients with PIT-CS who underwent transsphenoidal surgery with data available, 71 (6.8%) were older and 976 (93.2%) were younger. Remission rate was lower in the older as compared with the younger [37 (52%) vs. 636 (65%); p=0.03]. Relapse rates after successful pituitary surgery were not different in the older as compared with the younger (p=0.8). In elderly patients, remission rates were 48%, 51%, 51% and 51% at 1 year, 5 years, 10 years and 15 years respectively vs. 60%, 65.5%, 66.3% and 66.3% at 1 year, 5 years, 10 years and 15 years respectively in younger patients (p=0.04) (Figure 2).

When only female patients without gonadotropin deficiency were analyzed and stratified according to their reproductive status, estrogen-sufficient/premenopausal patients had higher remission rate after the first transsphenoidal surgery as compared with that in estrogen deficient/postmenopausal women [358/586 (61%) vs. 142/291 (48%); p<0.01)]. Relapse rate was also higher in estrogen-sufficient as compared with that in estrogen-deficient patients [73/358 (20%) vs. 18/142 (12%); p=0.04].

7- AGE-RELATED DIFFERENCES IN MORTALITY

Among the 1791 patients included in the study, 67 (3.7%) died during the follow-up period. As expected, a larger proportion of older patients had died at last follow-up as compared with the younger [21/175 (12%) vs. 46/1616 (3%); p<0.01]. The causes of death were the following: tumor progression (n=21; 31.3%), infections (n=12; 17.9%), cardiovascular disease (n=5; 7.5%), cerebrovascular disease (n=5; 7.5%), thromboembolism (n=2; 3%) or other causes (n=12; 17.9%). There were no age-related differences in the causes of death. Active disease predicted mortality in the elderly [HR, 3.3 (95% CI, 1.2-8.4)].

In patients with PIT-CS and ADR-CS, proportion of older patients who died was higher than that of the younger [14/103 (13%) vs. 22/1131 (2%); p<0.01 for PIT-CS; 3/52 (6%) vs. 4/398 (1%); p=0.04 for ADR-CS). In patients with ECT-CS, there were no age-related differences in mortality rate between the groups.

Of 67 deceased patients, 29 (43.2%) died within 90 days from start of treatment. The proportion of elderly who died within 90 days from treatment did not differ from the proportion in younger patients [11/21 (52.4%) vs. 18/46 (39.1%); p=0.3].

DISCUSSION

Our data from ERCUSYN demonstrated that the proportion of CS in patients older than 65 years was 9.8%, and there were age-specific differences in the clinical presentation of endogenous hypercortisolism. Several typical symptoms of hypercortisolism were less frequent in the older patients as compared with the younger, including weight gain, skin alterations, hair loss, hirsutism, low libido and depression. On the contrary, the prevalence of muscle weakness, hypertension, type 2 diabetes, cardiovascular disease, thromboembolism and bone fractures was higher in the elderly. In the second part we only analyzed PIT-CS patients because they represented the largest etiologic group which provided the most significant results. Indeed, focusing on PIT-CS, older patients often had a macroadenoma but less frequently underwent transsphenoidal surgery (TSS) as compared with the younger. Instead, cortisol-lowering agents and radiotherapy were more often chosen as a first-line therapeutic options in the former.

Our data also showed that aging attenuates the well-known female preponderance in the prevalence of PIT-CS observed in adult population (14, 16). In fact, slightly more than half of the elderly patients were females, whereas women represented almost three-quarters of the younger patients. Because estrogens enhance corticotrope proliferation *in vitro,* and the expression of the estrogen receptor beta (ERβ) has been detected in the majority of ACTH-secreting adenomas, the reduction of the "gender-gap" we have found in aged patients with PIT-CS may be due to the lack of estrogens in older women, and resembles that reported in childhood (17, 18, 19). Accordingly, we have shown that estrogen-sufficient women with PIT-CS presented with a higher relapse rate after the first TSS as compared with

postmenopausal patients, suggesting that corticotropinomas may have a more aggressive biological behavior in the former. However, remission rate was also greater in estrogen-sufficient women as compared with their estrogen-deficient counterparts, likely due to the fact that the former more frequently had a microadenoma as compared with the latter. In fact, older PIT-CS patients of both sexes more commonly had a macroadenoma and less frequently experienced remission after TSS as compared with the younger population. These data are novel and in contrast with those by Qiao et al. who showed a tendency towards a lower female to male ratio in the older as compared with the younger, but did not document any age-related differences in both the adenoma size at diagnosis and the remission rate after surgery in 45 patients older than 60, as compared with 90 younger patients (14).

Higher prevalence of an extrasellar macroadenoma in our larger population of elderly patients is an interesting finding. Although the time elapsed from the appearance of symptoms to diagnosis, as reported by the patients, was similar between the older and the younger population, a certain delay in the recognition of symptoms and consequent later detection of the underlying pituitary lesion in this group of patients cannot be excluded. This is in accordance with our results demonstrating that “red-flag symptoms” of CS, such as facial plethora, purple striae, easy bruising and central obesity, are often lacking in older patients, making the early diagnosis of hypercortisolism more difficult in them than in the younger. Even the appearance of less specific symptoms of CS, such as weight gain, was not as frequent in the older as it was in the younger, further contributing to reduce the probability that an aged patient seeks medical advice to treat or prevent them. Furthermore, it is intuitive that some of the most frequently reported symptoms or comorbidities in the elderly, such as muscle weakness, hypertension, type 2 diabetes and bone fractures, might have been

erroneously attributed to the aging process itself by clinicians, who may overlook other important clinical signs suggestive of cortisol excess and, therefore, exclude *a priori* other diagnoses.

Our data emphasize the need of maintaining a high clinical suspicion of hypercortisolism in the general population, while taking into account specific age-related differences in the presentation of symptoms.

Surprisingly, we found a lower prevalence of depression in the elderly with PIT-CS in comparison to the younger. Several mechanisms associated with both aging and hypercortisolism contribute to the development of depressive symptoms (20). Indeed, depression was documented in 36% of Ercusyn patients overall, whereas Qiao et al. showed that prevalence of mood disorders was around 29% in both younger and older patients. We showed that depression was diagnosed in 18% of older PIT-CS patients vs. 35% of the younger. A possible explanation for these discrepant results may be that severity of mood disorders may be underestimated in the elderly due to their tendency to underreport depressive symptoms (21). Indeed, affective symptoms in CS patients are often underecognized by the clinicians, which may lead to an inaccurate estimation of the real prevalence of depression in this condition (22). Moreover, major depression has been demonstrated to occur less frequently in older subjects, thus further complicating the recognition of symptoms (23). Additionally, younger patients perceiving Cushing-related symptoms may be more impacted emotionally due to their physical and psychological limitations, than older patients who would conform more, considering them part of their aging process.

We have shown that muscle weakness and myopathy were more common in older patients as compared with the younger, whereas the latter more frequently presented with central obesity, hirsutism/hair loss and skin alterations including easy bruising, purple striae and thin skin. Of note, a physiological skin thinning usually occurs with aging and, therefore, it may be underestimated as a potential manifestation of cortisol excess during physical examination. On the contrary, Qiao et al. reported more central obesity in the elderly along with more muscle wasting and did not find any age-related differences in the prevalence of other typical signs and symptoms of hypercortisolism, such as fatigue and skin abnormalities (14). Both cortisol excess and aging are known to cause sarcopenia, defined as low muscle mass, impaired muscle quality and poor functionality (24, 25). While both conditions may have concurred to increase the prevalence of muscle weakness observed in our population, there may be age-related differences in the glucocorticoid receptor sensitivity in peripheral tissues, making the elderly more prone to develop muscle impairment, as well as other comorbidities, in the presence of excessive cortisol, as compared with the younger (26, 27, 28, 29). While studies in humans are needed to investigate this hypothesis, additional mechanisms for muscle weakness and sarcopenia in CS might be lower sex hormone levels due to cortisol suppression of the hypothalamic-pituitary-gonadal axis and suppression of GH and IGF-1 secretion by excess cortisol, in addition to lower levels of IGF-1 in elderly due to physiological decline by aging. Indeed, the rate of muscle wasting, as well as that of type 2 diabetes and hypertension, was higher in older CS patients as compared with that in patients with non-functioning pituitary adenomas of the same age, suggesting that the negative, multisystemic effect of hypercortisolism could prevails on that caused by aging alone (14). Moreover, a detrimental effect of concomitant low IGF-I levels on muscle health cannot be excluded, although we did

not find any differences in the prevalence of GH deficiency between older and younger patients (30). The paradoxical results on the lack libido-related complain in elderly patients with CS may be explained by the fact that elderly patients under-report libido-related issues and physicians probably also under-assess these issues. Indeed, although it is not fully understood, the aging-related decrease in libido correlates with the physiological decrease in sex hormone levels (31).

We have also described for the first time that there are differences in the management of PIT-CS between elderly patients and their younger counterparts throughout Europe. Although the surgical resection of the corticotropinoma remains the first-line treatment of PIT-CS, elderly patients were treated in a more conservative manner, undergoing surgery less frequently than the younger whereas receiving more cortisol-lowering drugs and radiotherapy as first line treatments (32). When focusing on patients with micro adenomas, the proportion of patients treated more conservatively remained higher in older patients as compared with their younger counterparts. A more conservative approach relying on medical therapy or radiotherapy instead of surgery may be advisable in the elderly with an elevated comorbidity load, which may increase the risk of death or major postoperative complications. Accordingly, in a recent study focusing on the outcomes of transsphenoidal surgery in 123 elderly patients with pituitary adenomas, Thakur et al. showed that this procedure is effective and safe in carefully selected subjects, being followed by a low complication rate and a postoperative readmission rate of 11%, mostly for delayed hyponatremia (33). As a matter of fact, older patients had more thromboembolism, cardiovascular diseases, hypertension and type 2 diabetes at diagnosis as compared with the younger, which may potentially increase peri- and postoperative morbidity and mortality (7, 34, 35). However, longitudinal studies comparing

the long-term efficacy and safety of either approach are needed, especially in view of the growing proportion of elderly patients referred to endocrine units in the recent years.

Missing or incomplete information is a potential shortcoming of a multicenter registry like the Ercusyn, but the proportion of patients with complete data was high and allowed creating the largest dataset available to date. The database was also carefully reviewed for data quality prior to data analysis, which guaranteed a satisfactory reliability of our results.

Another limitation is the lack of both quantitative data and standardized methods to evaluate hormone levels. Indeed, we have shown that UFC measurements supported the diagnosis of CS in the elderly less frequently than in the younger, suggesting that a milder hormone elevation may develop in the former. This finding may be due to a milder hormone elevation in the former, although a concomitant renal impairment in the elderly may also play a role To establish some hormone cut-offs potentially associated with a more suggestive clinical picture in older patients would be helpful, to develop a diagnostic algorithm for early recognition of hypercortisolism in this category of subjects. Yet, Ercusyn data cannot currently address this point.

In conclusion, our study showed that clinical presentation of CS is different in older patients as compared with that in the younger, with the former lacking some of the typical features of cortisol excess while presenting with a greater burden of comorbidities and an elevated prevalence of muscle weakness along with levels of UFC which are often within the normal range. Moreover, although older patients frequently have a macroadenoma at diagnosis, a conservative, non-surgical management is more often chosen likely in the attempt to avoid postoperative complications. Future studies are needed to evaluate the long-term effects of each treatment in the elderly, and establish the safest strategy within an individualized approach.

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LEGENDS

Figure 1. Common clinical presentation of patients with PIT-CS, depending on age. This picture represents some age-related differences in clinical presentation. A detailed description of all the features found is provided in the text

Figure 2. Disease free survival of younger and older patients after successful transsphenoidal surgery (Kaplan-Meier analysis).

Table 1. Comparison of clinical presentations at diagnosis in elderly patients (≥65 years old) with CS versus younger patients (<65 years old) with CS.

Table 2. Comparison of clinical presentations at diagnosis in elderly patients (≥65 years old) with PIT-CS versus younger patients (<65 years old) with PIT-CS.

Table 3. Comparison of clinical presentations at diagnosis in elderly patients (≥65 years old) with ADR-CS versus younger patients (<65 years old) with ADR-CS.

Table 4. Comparison of clinical presentations at diagnosis in elderly patients (≥65 years old) with CS versus younger patients (<65 years old) with CS, depending on age.

p value[a]: Comparison of initial clinical presentation between males and females among younger patients (<65 years old) with CS.

p value[b]: Comparison of initial clinical presentation between males and females among older patients (≥65 years old) with CS.

Table 5. Comparison of management strategies in elderly patients (≥65 years old) with PIT-CS versus younger patients (<65 years old) with PIT-CS.

1

	< 65 years old	≥ 65 years old	p value
Number of patients, n(%)	1616 (90.2)	175 (9.8)	-
PIT-CS, n(%)	1131 (70)	103 (58.8)	**<0.01**
ADR-CS, n(%)	398 (24.6)	52 (29.7)	0.1
ECT-CS, n(%)	87 (5.4)	20 (11.5)	**<0.01**
Age (year), mean+/-SD	42+/-12	69.6+/-4.7	**<0.01**
Female, n(%)	1289 (79.7)	107 (61.1)	**<0.01**
Onset of symptoms (year), mean+/-SD	2.9+/-3.3	3.1+/-4.8	0.5
ON DEX cortisol (nmol/L), mean+/-SD	496+/-375	436+/-317	0.3
BMI, mean+/-SD	29.7+/-7.1	26.7+/-5.7	**<0.01**
Waist circumference (cm), mean+/-SD	103.1+/-16.5	97.1+/- 10.8	**<0.01**
Hypertension, n(%)	1084 (67.1)	156 (89.1)	**<0.01**
SBP (mmHg), mean+/-SD	140+/-21	149+/-22	**<0.01**
DBP (mmHg), mean+/-SD	88+/-14	84+/-12	**<0.01**
Muscle weakness, n(%)	821 (50.9)	101 (57.7)	0.09
Diabetes mellitus, n(%)	446 (27.6)	84 (48)	**<0.01**
Depression, n(%)	538 (33.3)	35 (20)	**<0.01**
Loss of libido, n(%)	325 (20.1)	14 (8)	**<0.01**
Hair loss (only for females), n(%)	351 (27.2)	22 (20.7)	**0.03**
Hirsutism (only for females), n(%)	668 (51.8)	23 (21.5)	**<0.01**
Skin symptoms, n(%)	1123 (69.4)	103 (58.8)	**<0.01**
Weight gain, n(%)	1184 (73.2)	87 (49.7)	**<0.01**
Fractures, n(%)	217 (13.4)	38 (21.7)	**<0.01**

Followed by a psychiatrist, n(%)	170 (10.5)	9 (5.1)	**0.02**

Table 1. Comparison of clinical presentations at diagnosis in elderly patients (≥65 years old) with CS versus younger patients (<65 years old) with CS.

	< 65 years old	**≥ 65 years old**	**p value**
Number of patients, n(%)	1131 (91.7)	103 (8.3)	-
Age (year), mean+/-SD	40.9+/-12.2	70.2+/-4.7	**<0.01**
Female, n(%)	889 (72)	56 (54.3)	**<0.01**
Onset of symptoms (year), mean+/-SD	3+/-3.2	2.6+/-3.6	0.5
UFC/24h, mean+/-SD	898+/-1219	900+/-899	0.6
ON DEX cortisol (nmol/L), mean+/-SD	496+/-375	436+/-317	0.3
BMI, mean+/-SD	29.7+/-20.6	24.2+/-12.7	**<0.01**
Waist circumference (cm), mean+/-SD	103.9+/-16.7	95+/- 10.4	**<0.01**
Hypertension, n(%)	724 (64)	93 (90.2)	**<0.01**
SBP (mmHg), mean+/-SD	138+/-20.2	149+/-22	**<0.01**
DBP (mmHg), mean+/-SD	87+/-13.7	86+/-14.1	0.7
Muscle weakness, n(%)	551 (48.7)	61 (59.2)	**0.04**
Diabetes mellitus, n(%)	307 (23.1)	42 (40.7)	**<0.01**
Depression, n(%)	394 (34.8)	19 (18.4)	**<0.01**
Loss of libido, n(%)	241 (21.3)	5 (4.8)	**<0.01**
Hair loss (only for females), n(%)	242 (27.2)	13 (26.5)	0.2
Hirsutism (only for females), n(%)	524 (58.9)	13 (26.5)	**<0.01**
Skin symptoms, n(%)	818 (72.3)	67 (65)	0.1
Weight gain, n(%)	904 (79.9)	53 (51.4)	**<0.01**
Fractures, n(%)	154 (13.6)	26 (25.2)	**<0.01**
Followed by a psychiatrist, n(%)	119 (10.5)	4 (3.8)	**0.03**

Table 2. Comparison of clinical presentations at diagnosis in elderly patients (≥65 years old) with PIT-CS versus younger patients (<65 years old) with PIT-CS.

	< 65 years old	≥ 65 years old	p value
Number of patients, n(%)	398 (88.4)	52 (11.6)	-
Age (year), mean+/-SD	44.6+/-11.3	67.8+/-3.1	**<0.01**
Female, n(%)	352 (88.4)	38 (73.1)	**<0.01**
Onset of symptoms (year), mean+/-SD	2.7+/-3.5	3.7+/-5.3	0.9
BMI, mean+/-SD	29.9+/-6.7	30.2+/-5.4	0.5
Waist circumference (cm), mean+/-SD	102.4+/-16.6	103.4+/-11.8	0.5
Hypertension, n(%)	291 (73.1)	45 (86.5)	**0.03**
SBP (mmHg), mean+/-SD	142+/-19	144+/-20	0.7
DBP (mmHg), mean+/-SD	89+/-13	82+/-8	0.3
Muscle weakness, n(%)	202 (50.7)	24 (46.1)	0.5
Diabetes mellitus, n(%)	112 (28.1)	26 (50)	**<0.01**
Depression, n(%)	118 (29.6)	10 (19.2)	0.5
Loss of libido, n(%)	67 (16.8)	6 (11.5)	0.4
Hair loss (only for females), n(%)	97 (27.5)	6 (17.1)	**0.03**
Hirsutism (only for females), n(%)	116 (32.9)	8 (21)	**0.02**
Skin symptoms, n(%)	238 (59.7)	23 (44.2)	**0.03**
Weight gain, n(%)	226 (56.7)	26 (50)	0.3
Fractures, n(%)	49 (12.3)	9 (17.3)	0.3
Followed by a psychiatrist, n(%)	46 (11.5)	4 (7.7)	0.5

Table 3. Comparison of clinical presentations at diagnosis in elderly patients (≥65 years old) with ADR-CS versus younger patients (<65 years old) with ADR-CS.

	< 65 years old FEMALES	< 65 years old MALES	≥ 65 years old FEMALES	≥ 65 years old MALES	p value[a]	p value[b]
Number of patients, n(%)	1291	325	107	68	-	-
Age (year), mean±SD	42±11	42±12	68±4	69±4	0.9	0,8
Onset of symptoms (year), mean±SD	2±2	2±2	3±4	2±5	0.7	0.07
BMI, mean+/-SD	28±16.4	29.6±6	26.8±8.8	26±9*	0.1	0.8
Waist circumference (cm), mean±SD	102±17	105±11	96±10	97±10	0.09	0.6
Weight gain, n(%)	1019 (79)	252 (78)	56 (53)**	34 (50)	0.5	0.7
Muscle weakness, n(%)	615 (48)	206 (63)	63 (59)**	41 (60)	**<0,01**	0.8
SBP (mmHg), mean+/-SD	139±21	147±20	152±15	140±6	**<0,01**	**<0.01**
DBP (mmHg), mean+/-SD	87±13	91±15	83±20	84±11	**0,02**	0.7
Hypertension, n(%)	830 (64)	254 (78)	96 (90)**	60 (88)	**<0.01**	0.7
Diabetes mellitus, n(%)	354 (27)	112 (34)	56 (52)**	36 (53)*	**0.01**	0.9
Fractures, n(%)	145 (11)	81 (25)	26 (24)**	13 (19)	**<0.01**	0.4
Depression, n(%)	408 (32)	130 (40)	23 (22)**	9 (19)*	**<0.01**	0.2
Loss of libido, n(%)	214 (17)	112 (35)	4 (4)	14 (21)	**<0.01**	**<0.01**

Table 4. Comparison of clinical presentations at diagnosis in older (≥65 years old) versus younger (<65 years old) CS patients, depending on gender.

p value[a]: Male vs. female younger patients

p value[b]: Male vs. female older patients

*p<0.05 vs. younger male patients
**p<0.05 vs. younger female patients

	<65 years old	≥65 years old	p value
No pituitary surgery, n(%)	120 (10)	32 (31)	**<0.01**
1 pituitary surgery, n(%)	804 (71)	60 (58)	**<0.01**
2 or more pituitary surgeries, n(%)	207 (18)	11 (10)	0.05
Medical therapy as first line, n(%)	307 (27)	41 (39)	**<0.01**
Bilateral adrenalectomy, n(%)	56 (4)	5 (4)	1
RT, n(%)	120 (10)	17 (13)	0.06
RT as first line therapy, n(%)	8 (7)	6 (35)	**<0.01**
RT as second line therapy, (%)	112 (93)	11 (65)	**<0.01**

Table 5. Comparison of management strategies in elderly patients (≥65 years old) with PIT- CS versus younger patients (<65 years old) with PIT-CS.

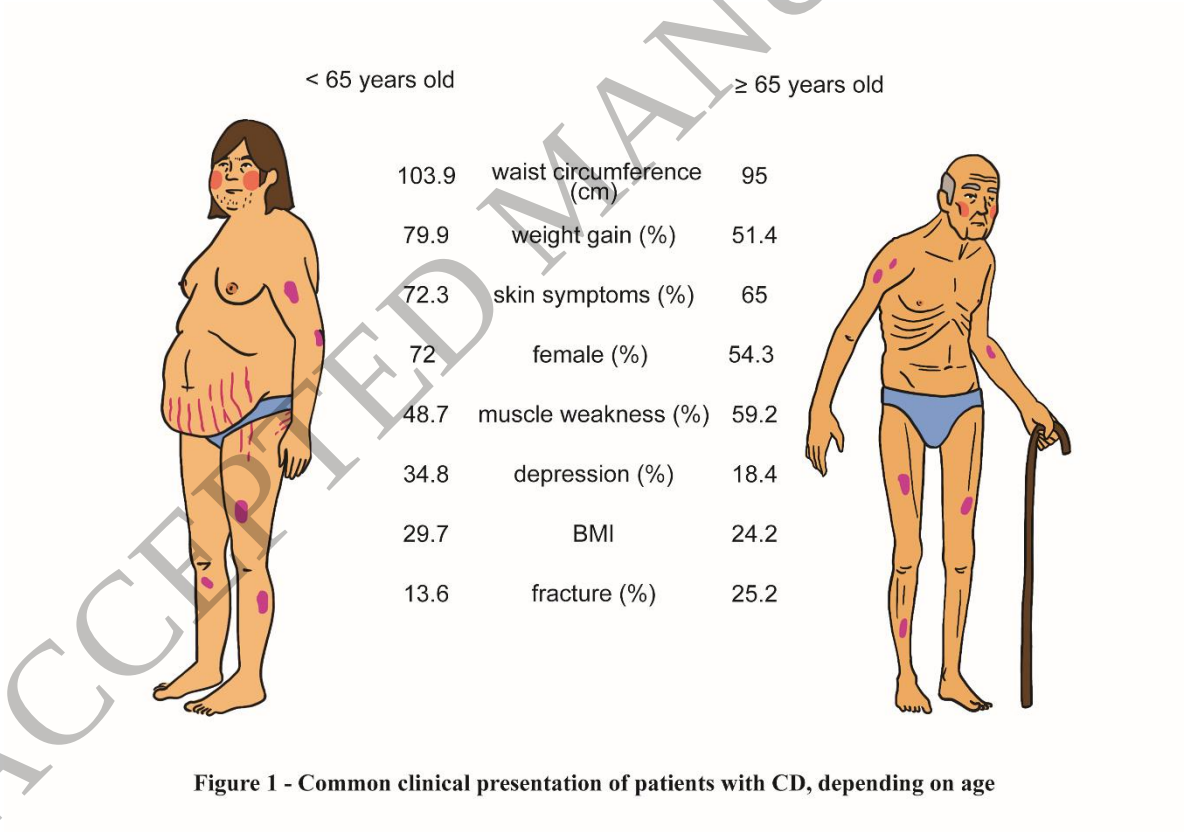
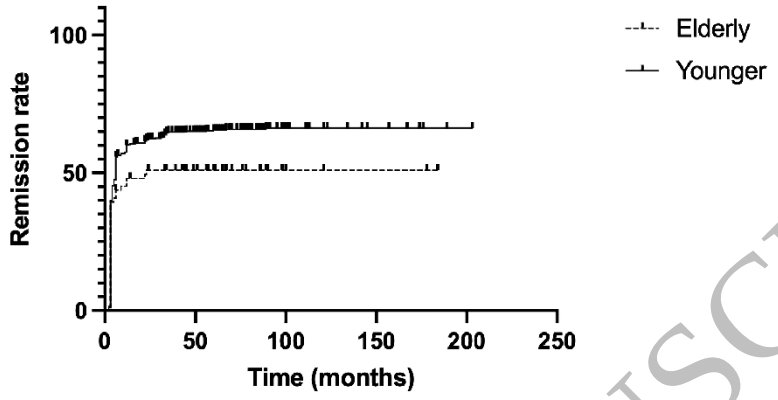


Figure 1 - Common clinical presentation of patients with CD, depending on age

Figure 1
210x148 mm (x DPI)

Figure 2. Disease free survival of younger and older patients after successful transsphenoidal surgery.



1

2 *Figure 2*
3 *559x314 mm (x DPI)*