

RESEARCH

Unmet needs in Cushing's syndrome: the patients' perspective

Elena Valassi^{1,2,3}, Iacopo Chiodini^{4,5}, Richard A Feelders⁶, Cornelia D Andela⁷, Margueritta Abou-Hanna⁸, Sarah Idres⁸ and Antoine Tabarin⁹

¹Endocrinology Department, Germans Trias i Pujol Hospital and Research Institute, Badalona, Barcelona, Spain

²Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain

³Universitat Internacional de Catalunya (UIC), Barcelona, Spain

⁴IRCCS, Istituto Auxologico Italiano, Milan, Italy

⁵Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy

⁶Division of Endocrinology, Erasmus Medical Centre, Rotterdam, Netherlands

⁷Division of Endocrinology and Centre for Endocrine Tumours, Leiden University Medical Centre, Leiden, Netherlands

⁸HRA Pharma Rare Diseases, Châtillon, France

⁹Department of Endocrinology and INSERM U862 University and CHU of Bordeaux, Pessac, France

Correspondence should be addressed to E Valassi: evalassi.germanstrias@gencat.cat

Abstract

Background: Cushing's syndrome (CS) is a rare condition of chronically elevated cortisol levels resulting in diverse comorbidities, many of which endure beyond successful treatment affecting the quality of life. Few data are available concerning patients' experiences of diagnosis, care and persistent comorbidities.

Objective: To assess CS patients' perspectives on the diagnostic and care journey to identify unmet therapeutic needs.

Methods: A 12-item questionnaire was circulated in 2019 by the World Association for Pituitary Organisations. A parallel, 13-item questionnaire assessing physician perceptions on CS patient experiences was performed.

Results: Three hundred twenty CS patients from 30 countries completed the questionnaire; 54% were aged 35–54 and 88% were female; 41% were in disease remission. The most burdensome symptom was obesity/weight gain (75%). For 49% of patients, time to diagnosis was over 2 years. Following treatment, 88.4% of patients reported ongoing symptoms including, fatigue (66.3%), muscle weakness (48.8%) and obesity/weight gain (41.9%). Comparisons with delay in diagnosis were significant for weight gain ($P = 0.008$) and decreased libido ($P = 0.03$). Forty physicians completed the parallel questionnaire which showed that generally, physicians poorly estimated the prevalence of comorbidities, particularly initial and persistent cognitive impairment. Only a minority of persistent comorbidities (occurrence in 1.3–66.3%; specialist treatment in 1.3–29.4%) were managed by specialists other than endocrinologists. 63% of patients were satisfied with treatment.

Conclusion: This study confirms the delay in diagnosing CS. The high prevalence of persistent comorbidities following remission and differences in perceptions of health between patients and physicians highlight a probable deficiency in effective multidisciplinary management for CS comorbidities.

Key Words

- ▶ Cushing's syndrome
- ▶ management
- ▶ patient experience
- ▶ patient survey
- ▶ quality of life

Endocrine Connections
(2022) 11, e220027

Introduction

Cushing's syndrome (CS) is a morbid endocrine condition due to prolonged exposure to high circulating cortisol levels (1, 2, 3). Hypercortisolism may cause irreversible physical and psychological changes in several tissues, leading to debilitating morbidities which persist over the long term after the resolution of excessive hormone levels, such as cardiovascular complications, metabolic and skeletal disorders, infections and neuropsychiatric disturbances (3, 4). Even patients who have been biochemically 'cured' for over 10 years have a residual overall higher risk of mortality, mostly from circulatory disease and diabetes (5). Moreover, people with a history of CS suffer from impaired quality of life (QoL) (6). Several studies suggest that the prevalence of persistent comorbidities is correlated with the duration of exposure to cortisol excess (7, 8). However, as the signs and symptoms of CS overlap with common diseases such as the metabolic syndrome and depression, the time taken to diagnose CS is often long, resulting in a significant number of patients with persistent sequelae and impairments in QoL (6, 9).

Given the burden of the disease, ideal CS treatment would include early diagnosis, curative surgery and multidisciplinary care of comorbidities both pre- and post-cure of CS, including the psychological dimension of the patient's disease experience (10). Few data are available about patients' perceptions of the medical journey from first symptoms to diagnosis, treatment and follow-up. The aim of this study was, therefore, to explore CS patients' experiences of symptoms, diagnosis, care and treatment satisfaction around the world and to compare patients' perceptions of CS with those of physicians.

Methods

Patient questionnaire design

A 12-item patient questionnaire was developed based on the generally understood clinical characteristics and symptomology of CS, aiming to assess patients' experiences of symptoms, diagnosis, care and treatment satisfaction (1, 2) (Supplementary File 1, see section on [supplementary materials](#) given at the end of this article). The questionnaire was initially offered in English and made available via the SurveyMonkey online platform from March to May 2019. The survey was completed anonymously and required no specific participant identification or any details that could be used to identify individual participants. In addition to basic demographics (i.e. country of residence, sex, age and highest educational level attained), the questionnaire asked

ten multiple-choice and two open questions. The survey was shared by the World Association for Pituitary Organisations (WAPO), Adrenal Net, Cushing's Support & Research Foundation and the Pituitary Foundation, as well as being distributed to local patient associations. As a second step, the questionnaire was translated into eight additional languages (French, Dutch, Spanish, Chinese, Portuguese, Italian and German) and was recirculated by the WAPO, Adrenal Net and China Hypercortisolism Patient Alliance to the different local patient associations for distribution in November 2019. As this was a non-interventional, anonymous patient survey, distributed by the patient associations themselves, and not initiated or funded by a research or educational institution, no ethical review was required. Written consent was obtained from each respondent after full explanation of the purpose and nature of the survey.

Comparative physician survey

In addition, a 13-item physician questionnaire was developed to assess physicians' perspectives on CS symptoms and comorbidities. This physician questionnaire was conducted by HRA Pharma Rare Diseases at the 2019 European Congress of Endocrinology, in Lyon, France. This anonymous questionnaire was completed by 40 qualified physicians. The responses from the patient survey were compared for context with the physicians' estimates of the prevalence of CS symptoms and comorbidities. Although the physician questionnaire was conducted independently of the patient questionnaire, and used a different question structure, the comparison with the current patient questionnaire is included to further enrich and contextualise the patient responses.

Data analysis

All responses and answers were collected, coded and analysed using Microsoft Excel. Data preparation involved removing duplicate answers, or where possible analysing and reclassifying qualitative responses reported as 'other', based on the accompanying details to new or existing response options.

Statistical methodology

Complementary statistical analyses using SAS software were performed using the chi-square and Fisher tests, depending on the cell counts, to compare (i) the time between first symptoms and diagnosis and the persistence of symptoms and (ii) persistence of symptoms, with the specialities of the

physicians currently treating the respondents. Frequency distribution of a particular variable was displayed and compared with the frequency distribution of the comparator variable. A significance level of 0.05 was applied.

Results

Demographic characteristics

Three hundred twenty patients from 30 countries completed the patient questionnaire, with 27% ($n=87$) coming from the United Kingdom and 14% ($n=44$) from the United States of America. More than half (53.7%, $n=172$) of the patients were aged between 35 and 54 years, and 88.4% ($n=283$) were female. The

majority of patients (53.1%, $n=170$) had undergraduate or postgraduate qualifications (Table 1).

Time to diagnosis

The time to diagnosis from first reporting of CS symptoms was declared to be within 2 years for 48.4% ($n=155$) (Table 1) and was over 2 years in 48.7% ($n=156$) and over 3 years in 30.3% ($n=97$).

Initial symptoms

A broad range of signs and symptoms were initially noticed by patients, with weight gain, hirsutism or acne, fatigue, sleep disturbances, depressive symptoms, muscle weakness, anxiety and hypertension all being reported in over 50% of

Table 1 Patient demographics.

Sex	$N = 319^a$
Female	283 (88.4%)
Male	36 (11.3%)
Age group	$N = 320$
18–24 years	16
25–34 years	49
35–44 years	71
45–54 years	101
55–64 years	54
65–74 years	24
≥75 years	5
Region ^b	$N = 320$
Western Europe	222
North America	60
China	16
Australasia	14
South America	5
Africa	3
Education	$N = 320$
High school graduate/secondary education diploma	35%
Undergraduate degree	25.6%
Post-graduate degree	27.5%
Prefer not to say	10.6%
Time from first symptoms to diagnosis	$N = 320$
0–6 months	18.4%
6–12 months	15.6%
1–2 years	14.4%
2–3 years	18.4%
3–5 years	11.6%
5–10 years	8.4%
10–15 years	7.5%
15–20 years	0.9%
20+ years	1.9%
Unknown	2.8%

^aOne patient responded 'non-binary'. ^bWestern Europe: United Kingdom ($n = 87$), the Netherlands ($n = 38$), France ($n = 37$), Spain ($n = 12$), Denmark ($n = 10$), Norway ($n = 9$), Germany ($n = 6$), Italy ($n = 5$), Ireland ($n = 4$), Belgium ($n = 4$), Poland ($n = 4$), Sweden ($n = 2$), Malta ($n = 2$), Switzerland ($n = 1$), Czech Republic ($n = 1$); Africa: South Africa ($n = 1$), Gabon ($n = 1$), Zimbabwe ($n = 1$); Australasia: Australia ($n = 8$), New Zealand ($n = 6$); South America: Colombia ($n = 2$), Bolivia ($n = 1$), Argentina ($n = 1$), Brazil ($n = 1$); North America: United States of America ($n = 44$), Canada ($n = 13$), Costa Rica ($n = 1$), Mexico ($n = 1$), Dominican Republic ($n = 1$).

patients (Table 2). Obesity/weight gain was most commonly cited (75%, $n=240$) as being burdensome. Fatigue, feelings of depression or mood problems, sleep disturbances, muscle weakness and hirsutism were also very commonly (>40%) mentioned as being burdensome. Burdensome symptoms classified as ‘other’ were rare (<1%) and included issues such as hormonal problems and dental problems.

Person who made the initial CS diagnosis

In 53.8% ($n=172$) of cases, an endocrinologist made the initial diagnosis of CS or prescribed the first screening tests, Table 3. General practitioners made 18.1% of diagnoses ($n=58$), in the remaining cases a diversity of other physicians directly or indirectly contributed to make the diagnosis, as indicated in Table 3. A small but noticeable number (5.6%, $n=18$) of patients self-diagnosed and then convinced their physician to order the diagnostic tests.

Response to treatment

At the time of answering the questionnaire, 55.8% ($n=178$) of patients were not in remission. 40.8% of patients ($n=130$) were in true biochemical remission (Fig. 1). This latter group was a composite including patients who responded: ‘In remission (no treatment)’ (16.3%, $n=52$), ‘Received an operation to remove adrenal glands’ (22.9%, $n=73$) and ‘Treated with hydrocortisone’ (1.6%, $n=5$). Thirteen percent of the patients ($n=41$) were on cortisol-lowering treatment

and 6.6% of the patients ($n=21$) had not had or were awaiting surgery. Following treatment for CS, 11.6% of the patients ($n=37$) reported having no further symptoms related to the condition, with 88.4% ($n=283$) still symptomatic. Of the total population ($n=320$), the most bothersome symptoms were fatigue (66.3%, $n=212$), muscle weakness (48.8%, $n=156$) and obesity/weight gain (41.9%, $n=134$) (Table 4).

Comparison of time to diagnosis and persistence of symptoms

To compare the time to diagnosis and the persistence of symptoms following treatment, an analysis of a number of variables was performed comparing the group with persistent symptoms after treatment ($n=283$) with those who did not ($n=37$) in terms of time to diagnosis. Patients with a longer time to diagnosis reported significantly more frequent weight gain ($P=0.008$), and more frequent reduced libido ($P=0.03$) after treatment. Although not statistically significant, there was a strong trend towards patients reporting a longer time to diagnosis and a greater frequency of persistent perceived bone issues after treatment ($P=0.053$), as well anxiety ($P=0.07$) and depression/mood concerns ($P=0.08$).

Physicians involved in follow-up

Once diagnosed, almost all patients (97.8%, $n=313$) were managed by an endocrinologist, followed by

Table 2 Patient-reported symptoms (multiple answers were possible).

	Symptoms first noticed (%)	Most burdensome perceived symptoms before diagnosis (%)
Weight gain	85.0	75.0
Hirsutism/acne	76.3	42.8
Fatigue	66.3	54.1
Sleep disturbances	64.4	41.9
Skin problems	64.7	21.3
Depression/mood problems	58.8	48.1
Muscle weakness	57.8	43.4
Anxiety	54.1	39.1
Hypertension	52.5	22.2
Loss of concentration	45.0	28.4
Memory problems	41.9	30.3
Menstrual disturbances	35.6	12.5
Decreased libido	32.5	12.5
Bone problems	23.1	14.4
Infections	23.8	10.3
Glucose intolerance	17.2	8.4
Blood clot	5.3	
Pain(s)	3.1	
Vision problems	2.8	
Headache	2.5	
Cravings	1.6	
Other	8.4	1.9

Table 3 Patient perception of physician specialty.

Specialty	Person who made the initial diagnosis or suspected Cushing's syndrome (%) (n = 320)	Physicians involved in the management of Cushing's syndrome (%) (n = 320)
Endocrinologist	53.8	97.8
General practitioner/family doctor	18.1	56.3
Self-diagnosed	5.6	-
Hospital/emergency doctor	3.8	-
Internist	2.5	0.9
Gynecologist	1.9	14.1
Cardiologist	1.9	13.4
Bone specialist	1.9	14.1
Dermatologist	1.6	11.6
Haematologist	0.9	3.8
Ophthalmologist	0.9	3.1
Nurse	0.9	2.5
Radiologist	0.9	0.6
Family or friend	0.9	-
Psychiatrist or psychologist	0.9	23.4
Healer	0.6	2.2
Surgeon	0.6	-
Oncologist	0.3	6.6
Gastroenterologist	0.3	1.3
Neurologist	0.3	4.1
Others	1.6	-
Physiotherapist	-	14.4
Dietician	-	9.7
Neurosurgeon	-	8.1
Social worker	-	4.1
Ear, nose and throat specialist	-	1.6
Sports physician	-	1.3
Sleep specialist	-	0.9
Urologist	-	0.6
Orthopaedic surgeon	-	0.3

a GP/family doctor (56.3%, n=180). A psychiatrist/psychologist was involved in 23.4% (n=75), followed by a physiotherapist (14.4%, n=46), rheumatologist (14.4%, n=46), gynecologist (14.1%, n=45), cardiologist (13.4%, n=43), dermatologist (11.6%, n=37) and a dietician (9.7%, n=31) (Table 3).

Treatment of persistent symptoms

Table 4 shows the prevalence of persistent symptoms after treatment, common ongoing comorbidities included fatigue, muscle weakness and weight gain. The percentage of patients who were treated for comorbidities is also

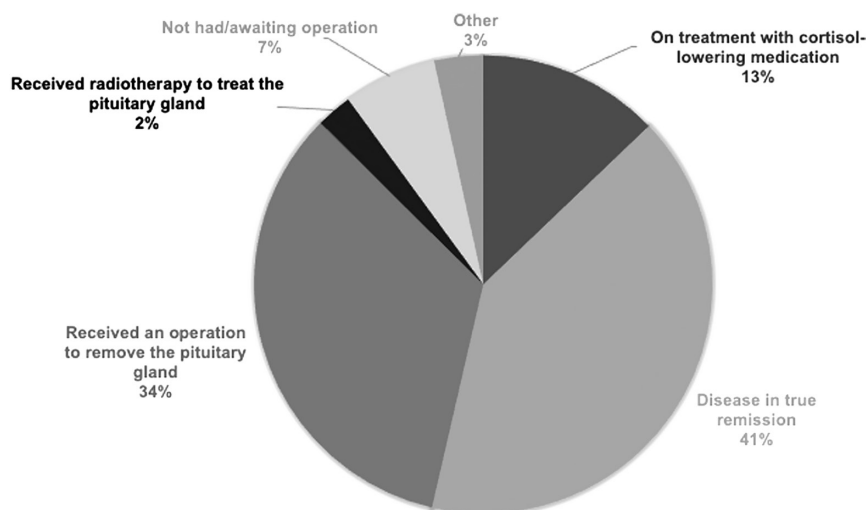


Figure 1 Patient description of their current clinical situation (n = 319). The category 'Disease in true remission' combines scores for 'In remission (no treatment)' (16.3%), 'Received an operation to remove adrenal glands' (22.9%) and 'Treated with hydrocortisone' (1.6%). One person did not complete the question.

Table 4 Persistent symptoms.

Symptom	Persistent bothersome symptoms ^a (%) (<i>n</i> = 320)	Treatment received for symptoms (%) (<i>n</i> = 320)
Fatigue	66.3	15.9
Muscle weakness	48.8	17.2
Weight gain	41.9	8.4
Depression, mood problems	36.9	28.8
Poor concentration	35.9	4.1
Memory problems	33.8	5.6
Sleep problems	33.1	14.1
Anxiety	30.6	14.7
Decreased libido	25.3	4.1
Bone problems	19.1	21.9
Hypertension	18.4	29.4
Hirsutism	17.5	4.1
Skin problems	16.6	6.9
Glucose intolerance	8.8	10
Menstrual problems	9.1	4.7
Infections	7.2	4.7
Blood clot	3.8	2.2
Acne	2.8	1.3
Other	4.4	5.3
No treatment	1.3	8.1
Only hydrocortisone	-	1.6

^aUp to five answers were possible.

shown. Noticeable undertreatment occurred for many symptoms, for example, fatigue was a consistent symptom for 66.3% (*n* = 212), whereas only 15.9% (*n* = 51) were receiving ongoing care for fatigue and persistent muscle weakness was reported in 48.8% (*n* = 156) with 17.2% (*n* = 55) of patients being treated for this (Table 4).

The high frequency of persistent symptoms suggests that patients were not followed-up by specific specialists, for example of the 212 patients with persistent fatigue, only 60 (28.2%) were seeing a psychiatrist/psychologist (Table 4). Enduring poor concentration and memory problems were relatively frequent (35.9%, 33.8%) but were rarely treated by a specialist (4.1 and 5.6%, respectively).

Three-quarters of patients reported that their work life had been affected (75%, *n* = 240). Social life (65.3%, *n* = 209), family life (57.8%, *n* = 185), interpersonal relationships (51.6%, *n* = 165), and sexual life (48.8%, *n* = 155) had also been significantly affected by their illness. Thirty-seven percent of the patients (*n* = 118) reported that their economic situation had been negatively affected. ‘Other’ responses for this question included reductions in self-esteem, self-image and self-confidence. Sixty-three percent of patients (193/305) were satisfied with their treatment and 36.7% (*n* = 112) were not.

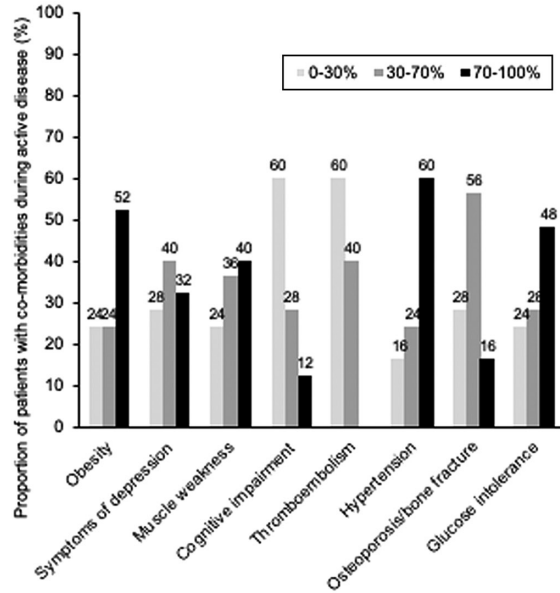
Comparative analysis physician questionnaire

In the complementary physician questionnaire (*n* = 40), unlike the patient questionnaire where most respondents

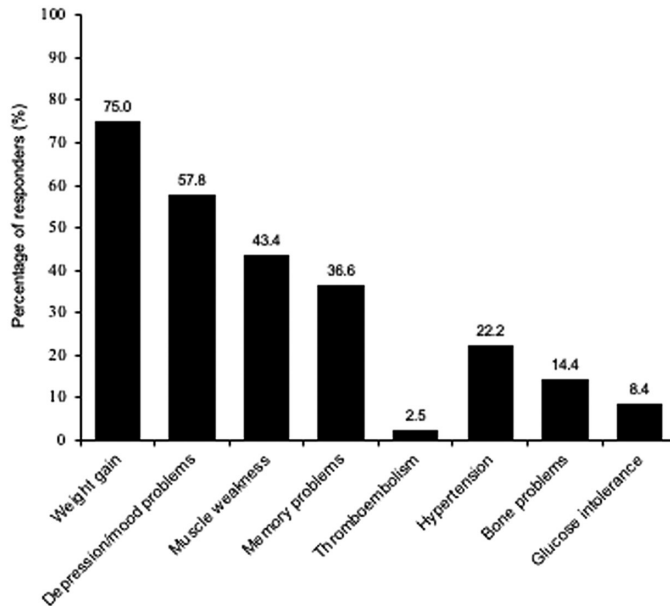
were from the United Kingdom, the United States of America, the Netherlands and France, most of the physicians surveyed were from Western Europe, although there were representatives from other parts of the world. In the physician questionnaire, 83% (*n* = 33) were endocrinologists, 13% (*n* = 5) internal medicine specialists and 5% (*n* = 2) other disciplines. Sixty percent (*n* = 24) had over 10 years clinical experience, and 93% (*n* = 37) were experienced in the treatment of CS, seeing an average of 10 patients per year. Of the specialties involved in the care of CS, 96% of physicians (*n* = 38) considered endocrinologists to be involved, 48% (*n* = 19) included family doctors/GPs, 20% (*n* = 8) cardiologists, 28% (*n* = 11) psychiatrists/psychologists and 28% (*n* = 11) included dietitians. These results are consistent with the patients’ perceptions, with the exception of dietitians, who only 10% of patients reported seeing (Table 3).

Figure 2A compares the frequency of common symptoms that patients found to be most burdensome during the active phase of the disease, with what physicians thought were the most common symptoms. Although for methodological reasons a statistical comparison was not possible and the comparisons are approximate, these findings suggest that physicians’ perceptions of the prevalence of symptoms were different from those reported by patients. A majority of physicians (Fig. 2A) inadequately estimated (both underestimated and overestimated) the presence of depression, muscle weakness, cognitive

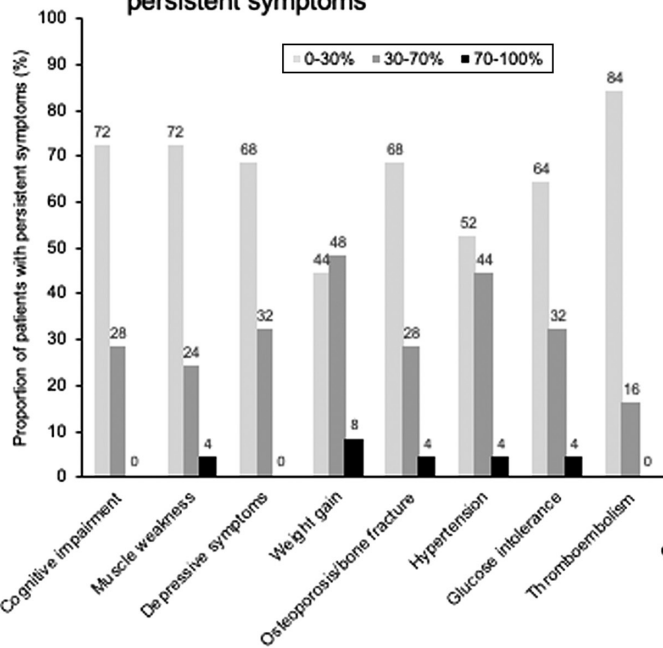
A Physician perception of co-morbidities during active CS



Patient perception of most burdensome symptoms during active CS



B Physician perception of persistent symptoms



Patient perception of persistent symptoms after treatment

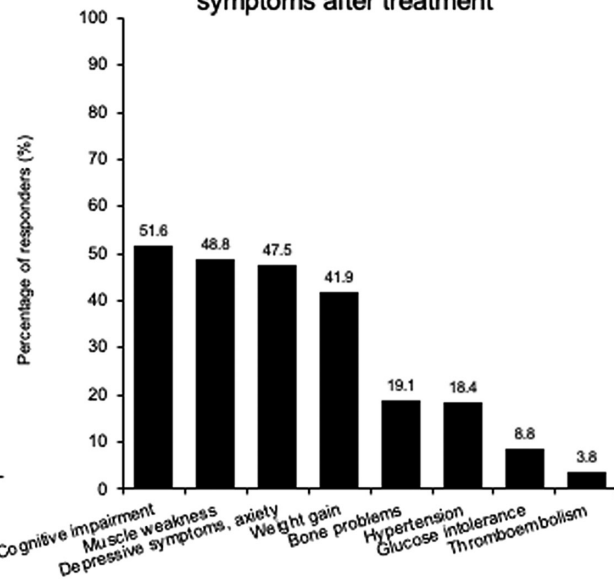


Figure 2

(A) Physician ($n = 40$) perception of patient comorbidities (left) and patient reports of the most burdensome symptoms during active CS (right). (B) Physician ($n = 40$) perception of CS symptoms after cure (right) and patient reports of persistent burdensome symptoms after treatment (left). Only the relevant common results from the physician and patient surveys are shown above. The physician survey included categories 'insulin resistance', 'dyslipidaemia', 'cardiovascular complications' and 'psychosis', which are not shown because these same categories were not reported in the patient survey. In the patient survey, responses for the categories: 'anxiety' were regrouped with 'depressive symptoms' and 'memory problems' and 'poor concentration' were regrouped into the 'cognitive impairment' category for easier comparison with the physician survey.

impairment, hypertension, bone problems and glucose intolerance. **Figure 2B** compares the physician's perception of the frequency of persistent symptoms with the patients' experience of persistent symptoms. A majority of physicians differently estimated the prevalence of persistent cognitive impairment, muscle weakness, depressive symptoms and weight gain.

Discussion

This large, international CS patient survey confirms previous findings that despite complaining of multiple symptoms, there is a mean 34-month delay in diagnosis (9). In addition, despite treatment resulting in biochemical remission, patients report persistent comorbidities with associated psychological and social impacts that negatively affect the QoL (11, 12). In the present survey a majority of patients reported that they are not being managed by the appropriate specialists, suggesting an absence in multidisciplinary care that may be secondary to an underestimation of the sequelae of CS by endocrinologists.

The present survey confirmed that no specific symptom initiated a diagnosis, but rather a range of burdensome symptoms occurring with similar frequency to those reported in previous surveys (1, 2), with the notable difference in that in a USA-German survey, cognitive and psychological symptoms were bothersome for 61% of US and 66% of German patients (13), whereas in the present survey 38% considered depression/mood problems burdensome. Such differences may be a result of different terms being used to describe depression or mood symptoms as well as cultural differences between populations.

The distribution of time to diagnosis, with around 50% diagnosed after 2 years of symptoms and approximately 30% still undiagnosed after 3 years is of a similar magnitude to previous surveys, where 67% of patients waited at least 3 years until diagnosis (14). In the CSFR study in 2014, patients waited a median of 5 years until diagnosis (15). Even though the estimated time to diagnosis may be similar to those in previous studies – 34 months a recent meta-analysis (9) and 2 years in the ERCUSYN database (16) – there is clearly still room for improvement, especially as delayed diagnosis is associated with persistent comorbidities (9, 17, 18, 19). Physicians should consider that in patients with diabetes, hypertension and osteoporosis hypercortisolism may be hidden (20). Due to the elevated incidence of mood and cognitive dysfunction at CS diagnosis, questioning the patient whether they feel that 'something unusual is happening' such as mood swings and sleeping disorders

may be helpful, as a not insignificant proportion of patients self-diagnose CS (15).

Awareness of the clinical presentation patterns of CS should be increased among general practitioners but also in specialists other than endocrinologists. In the current survey, the low proportions of physiotherapists, neurologists, orthopaedic surgeons and psychiatrists identifying CS represent an educational opportunity to improve early diagnosis. It is for instance not widely known that venous thromboembolic events or fragility fractures can be a presenting symptom of CS (20, 21). It is encouraging that rheumatologists already recommend excluding occult endogenous hypercortisolism as a first cause of muscle weakness (22).

Multidisciplinary care is recommended for the ongoing management of patients after biochemical cure, with a particular emphasis on the QoL, depressive symptoms and anxiety (11). Specialist care is recommended for specific comorbidities, for example physiotherapists are required to help revert musculoskeletal impairment and prevent further deterioration (23), and bone specialists are required to manage the individual patient fracture risk according to the patient's age and evolution of bone status after surgery (24). In the present survey, almost all patients were treated by endocrinologists and the role of specialists treating particular comorbidities was limited despite the ongoing complaints in patients. This is particularly evident in the high prevalence of muscle weakness, which was rarely managed by physiotherapists. This failure to provide multidisciplinary care may account for why nearly 40% of CS patients were dissatisfied with their treatment.

The exact number of patients with controlled hypercortisolism cannot be evaluated from the questionnaire. The degree of control of hypercortisolism remains debatable in patients treated with cortisol-lowering agents and may not be equivalent to remission following surgery (25, 26). In the present survey, the vast majority reported persistent and burdensome symptoms despite treatment, which is in line with previous reports of persistent low body satisfaction and high rates of depression and anxiety (27). When compared with longer time to diagnosis, the only comparisons that reached statistical significance were weight gain and decreased libido; whereas, there was a trend towards extended time to diagnosis and worsening of depressive symptoms and anxiety. These findings confirm the need for early diagnosis and treatment as the duration of exposure to hypercortisolism is a predictor of persistent morbidities and long-term impairments in the QoL (15).

Although the parallel physician perception questionnaire was limited by small size and methodological

differences in comparison to the patient survey, the results suggest that physicians' perceptions contrast with patients' experiences. Physicians tended to underestimate weight gain and cognitive impairment during the active phase of the disease, and underestimate the prevalence of cognitive impairment, depressive symptoms and muscle weakness following treatment. A recent survey on physician vs patient perspectives on postsurgical recovery also highlighted important differences in perceptions, suggestive of poor communication (28). However, these comparisons are limited in that physicians' estimations may be influenced by the clinical importance of certain symptoms, whereas for patients these may or may not be particularly onerous. Nevertheless, these findings do suggest that some symptoms do not receive enough attention, possibly due to insufficient awareness of these symptoms as real clinical problems.

The strength of this survey is that it includes a large and international population, whereas previous surveys tended to be carried out in individual countries. It informs the quantitative and qualitative understanding of CS patients' experiences with their treatment journeys and highlights some important lacunae in the management of CS, as well as identifying some differences in physician and patient perceptions about the burden of CS comorbidities.

A limitation in the study design was the inability of the questionnaire to clearly distinguish a subgroup who were biochemically cured and had ongoing symptoms. Indeed, remission was based on patients' declarations instead of an objective hormone assessment, which is an unavoidable limitation of online surveys. On the other hand, the survey was precisely designed to capture patients' perceptions about their health status, regardless of having received a diagnosis of "remission" or not from their endocrinologist. Patients who had pituitary surgery were not considered as being "in remission" in order to mitigate the impact of this limitation on the final analysis. The major limitations of this survey also include its cross-sectional design, depending upon an individual assessment at a single time point and relying on patients' memories. The comparison of the patient and doctor cohorts was limited by having different questionnaire methodologies and the lack of matching of patients and their endocrinologists. The questionnaire results could also not be corroborated against clinical records and no matched control group was assessed. Selection bias was another potential limitation, as patients were recruited through patient associations, which may have skewed the population towards patients with a higher disease burden; moreover, patients with chronic conditions who respond to questionnaires tend to have a low QoL (15).

Conclusion

This international cross-sectional study confirms that symptoms experienced by patients with CS are diverse, burdensome and endure beyond treatment (20). Delays in diagnosis may contribute to persistent symptoms after treatment. Care of patients with persistent comorbidities affecting the QoL (e.g. obesity, cognitive impairment, depression and muscle weakness) could be improved through more frequent multidisciplinary collaboration with healthcare professionals outside of endocrinology.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-22-0027>.

Declaration of interest

A T participated in research studies, received research grants and honorarium for talks at symposia and boards from HRA Pharma Rare Diseases, Pfizer, Novartis and Recordati Rare Diseases. C A participated in research studies and received honoraria for talks at symposia and participation in advisory boards from HRA Pharma Rare Diseases. E V participated in research studies and received honoraria for talks at symposia and participation in advisory boards from HRA Pharma Rare Diseases and Recordati Rare Diseases. I C is an investigator in studies using relacorilant (Corcept Therapeutics) in patients with hypercortisolism and has received consulting fees from Corcept Therapeutics and HRA Pharma Rare Diseases. R F has received research grants from Strongbridge and Recordati Rare Diseases and honoraria for talks at symposia and for participating in advisory boards from HRA Pharma Rare Diseases, Corcept, Ipsen, Novartis and Recordati Rare Diseases. M A H and S I are employees of HRA Pharma Rare Diseases. R A F is a member of the editorial board of Endocrine Connections. He was not involved in the editorial or review process of this paper, on which he is listed as an authors.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

The authors would like to thank all the patients involved who responded and the World Association for Pituitary Organisations (WAPO), Adrenal Net, China Hypercortisolism Patient Alliance, the Cushing's Support & Research Foundation (CSRF) and the Pituitary Foundation for assisting with the distribution of the patient questionnaires. The authors would also like to gratefully acknowledge the contribution of the ApotheCom communications agency for helping to conduct this survey.

References

- 1 Barbot M, Zilio M & Scaroni C. Cushing's syndrome: overview of clinical presentation, diagnostic tools and complications. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2020 **34** 101380. (<https://doi.org/10.1016/j.beem.2020.101380>)
- 2 Feelders RA, Newell-Price J, Pivonello R, Nieman LK, Hofland LJ & Lacroix A. Advances in the medical treatment of Cushing's syndrome. *Lancet: Diabetes and Endocrinology* 2019 **7** 300–312. ([https://doi.org/10.1016/S2213-8587\(18\)30155-4](https://doi.org/10.1016/S2213-8587(18)30155-4))

- 3 Lacroix A, Feelders RA, Stratakis CA & Nieman LK. Cushing's syndrome. *Lancet* 2015 **386** 913–927. ([https://doi.org/10.1016/S0140-6736\(14\)61375-1](https://doi.org/10.1016/S0140-6736(14)61375-1))
- 4 Pivonello R, De Martino MC, De Leo M, Simeoli C & Colao A. Cushing's disease: the burden of illness. *Endocrine* 2017 **56** 10–18. (<https://doi.org/10.1007/s12020-016-0984-8>)
- 5 Clayton RN, Jones PW, Reulen RC, Stewart PM, Hassan-Smith ZK, Ntali G, Karavitaki N, Dekkers OM, Pereira AM, Bolland M, *et al.* Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study. *Lancet: Diabetes and Endocrinology* 2016 **4** 569–576. ([https://doi.org/10.1016/S2213-8587\(16\)30005-5](https://doi.org/10.1016/S2213-8587(16)30005-5))
- 6 Feelders RA, Pulgar SJ, Kempel A & Pereira AM. The burden of Cushing's disease: clinical and health-related quality of life aspects. *European Journal of Endocrinology* 2012 **167** 311–326. (<https://doi.org/10.1530/EJE-11-1095>)
- 7 Scherthner-Reiter MH, Siess C, Gessl A, Scheuba C, Wolfsberger S, Riss P, Knosp E, Luger A & Vila G. Factors predicting long-term comorbidities in patients with Cushing's syndrome in remission. *Endocrine* 2019 **64** 157–168. (<https://doi.org/10.1007/s12020-018-1819-6>)
- 8 Ferrau F & Korbonits M. Metabolic comorbidities in Cushing's syndrome. *European Journal of Endocrinology* 2015 **173** M133–M157. (<https://doi.org/10.1530/EJE-15-0354>)
- 9 Rubinstein G, Osswald A, Hoster E, Losa M, Elenkova A, Zacharieva S, Machado MC, Hanzu FA, Zopp S, Ritzel K, *et al.* Time to diagnosis in Cushing's syndrome: a meta-analysis based on 5367 patients. *Journal of Clinical Endocrinology and Metabolism* 2020 **105** dgz136. (<https://doi.org/10.1210/clinem/dgz136>)
- 10 Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A & Endocrine Society. Treatment of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 2807–2831. (<https://doi.org/10.1210/jc.2015-1818>)
- 11 Webb SM, Santos A, Aulinas A, Resmini E, Martel L, Martínez-Momblán MA & Valassi E. Patient-centered outcomes with pituitary and parasellar disease. *Neuroendocrinology* 2020 **110** 882–888. (<https://doi.org/10.1159/000506809>)
- 12 Webb SM, Santos A, Resmini E, Martínez-Momblán MA, Martel L & Valassi E. Quality of life in Cushing's disease: a long term issue? *Annales d'Endocrinologie* 2018 **79** 132–137. (<https://doi.org/10.1016/j.ando.2018.03.007>)
- 13 Kreitschmann-Andermahr I, Siegel S, Gammel C, Campbell K, Edwin L, Grzywotz A, Kuhna V, Koltowska-Hägström M, Müller O, Buchfelder M, *et al.* Support needs of patients with Cushing's disease and Cushing's syndrome: results of a survey conducted in Germany and the USA. *International Journal of Endocrinology* 2018 **2018** 9014768. (<https://doi.org/10.1155/2018/9014768>)
- 14 Kreitschmann-Andermahr I, Psaras T, Tsiogka M, Starz D, Kleist B, Siegel S, Milian M, Kohlmann J, Menzel C, Führer-Sakel D, *et al.* From first symptoms to final diagnosis of Cushing's disease: experiences of 176 patients. *European Journal of Endocrinology* 2015 **172** 285–289. (<https://doi.org/10.1530/EJE-14-0766>)
- 15 Papoian V, Biller BM, Webb SM, Campbell KK, Hodin RA & Phitayakorn R. Patients' perception on clinical outcome and quality of life after a diagnosis of Cushing syndrome. *Endocrine Practice* 2016 **22** 51–67. (<https://doi.org/10.4158/EP15855.OR>)
- 16 Valassi E, Santos A, Yaneva M, Tóth M, Strasburger CJ, Chanson P, Wass JA, Chabre O, Pfeifer M, Feelders RA, *et al.* The European Registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics. *European Journal of Endocrinology* 2011 **165** 383–392. (<https://doi.org/10.1530/EJE-11-0272>)
- 17 Colao A, Pivonello R, Spiezia S, Faggiano A, Ferone D, Filippella M, Marzullo P, Cerbone G, Siciliani M & Lombardi G. Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 2664–2672. (<https://doi.org/10.1210/jcem.84.8.5896>)
- 18 Faggiano A, Pivonello R, Spiezia S, De Martino MC, Filippella M, Di Somma C, Lombardi G & Colao A. Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with Cushing's disease during active disease and 1 year after disease remission. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 2527–2533. (<https://doi.org/10.1210/jc.2002-021558>)
- 19 Lambert JK, Goldberg L, Fayngold S, Kostadinov J, Post KD & Geer EB. Predictors of mortality and long-term outcomes in treated Cushing's disease: a study of 346 patients. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 1022–1030. (<https://doi.org/10.1210/jc.2012-2893>)
- 20 Giovanelli L, Aresta C, Favero V, Bonomi M, Cangiano B, Eller-Vainicher C, Grassi G, Morelli V, Pugliese F, Falchetti A, *et al.* Hidden hypercortisolism: a too frequently neglected clinical condition. *Journal of Endocrinological Investigation* 2021 **44** 1581–1596. (<https://doi.org/10.1007/s40618-020-01484-2>)
- 21 van der Pas R, Leebeek FW, Hofland LJ, de Herder WW & Feelders RA. Hypercoagulability in Cushing's syndrome: prevalence, pathogenesis and treatment. *Clinical Endocrinology* 2013 **78** 481–488. (<https://doi.org/10.1111/cen.12094>)
- 22 Szczyński P, Świerkocka K & Olesińska M. Differential diagnosis of idiopathic inflammatory myopathies in adults – the first step when approaching a patient with muscle weakness. *Reumatologia* 2018 **56** 307–315. (<https://doi.org/10.5114/reum.2018.79502>)
- 23 Troy KL, Mancuso ME, Butler TA & Johnson JE. Exercise early and often: effects of physical activity and exercise on women's bone health. *International Journal of Environmental Research and Public Health* 2018 **15** 878. (<https://doi.org/10.3390/ijerph15050878>)
- 24 Kanis JA, Harvey NC, McCloskey E, Bruyère O, Veronese N, Lorentzon M, Cooper C, Rizzoli R, Adib G, Al-Daghri N, *et al.* Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. *Osteoporosis International* 2020 **31** 1–12. (<https://doi.org/10.1007/s00198-019-05176-3>)
- 25 Newell-Price J, Pivonello R, Tabarin A, Fleseriu M, Witek P, Gadelha MR, Petersenn S, Tauchmanova L, Ravichandran S, Gupta P, *et al.* Use of late-night salivary cortisol to monitor response to medical treatment in Cushing's disease. *European Journal of Endocrinology* 2020 **182** 207–217. (<https://doi.org/10.1530/EJE-19-0695>)
- 26 Ceccato F, Zilio M, Barbot M, Albiger N, Antonelli G, Plebani M, Watutantrige-Fernando S, Sabbadin C, Boscaro M & Scaroni C. Metyrapone treatment in Cushing's syndrome: a real-life study. *Endocrine* 2018 **62** 701–711. (<https://doi.org/10.1007/s12020-018-1675-4>)
- 27 Vermalle M, Alessandrini M, Graillon T, Paladino NC, Baumstarck K, Sebag F, Dufour H, Brue T & Castinetti F. Lack of functional remission in Cushing's syndrome. *Endocrine* 2018 **61** 518–525. (<https://doi.org/10.1007/s12020-018-1664-7>)
- 28 Acree R, Miller CM, Abel BS, Neary NM, Campbell K & Nieman LK. Patient and provider perspectives on postsurgical recovery of Cushing syndrome. *Journal of the Endocrine Society* 2021 **5** bvab109. (<https://doi.org/10.1210/jendso/bvab109>)

Received in final form 1 May 2022

Accepted 27 May 2022

Accepted Manuscript published online 27 May 2022