From first symptoms to final diagnosis of Cushing’s disease: experiences of 176 patients

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Abstract

Objective: To obtain structured information on the diagnostic delay in patients with Cushing’s disease (CD) from the patients perspective to provide leverage points for earlier diagnosis.

Design: The study includes 176 patients with ACTH-dependent CD who had received pituitary surgery completed a self-developed questionnaire on their symptomatology before the illness was diagnosed, the course and length of the diagnostic process, and the role of the involved health care professionals.

Methods: Data were analyzed statistically. Answers in free text options were categorized and counted.

Results: The overall diagnostic process took 3.8 ± 4.8 years (median 2 years), during which 4.6 ± 3.8 (1–30) physicians were consulted, most frequently the family physician (FP; 83.0%). The presented symptoms were various and often vague, e.g. ‘poor general condition’ at FPs, or very common in the field of the visited specialist (i.e. ‘skin changes’ at dermatologists). Women recognized the first CD symptoms themselves significantly more frequently than men, whereas physicians recognized CD symptoms significantly more frequently in males.

Conclusion: A clear difficulty of diagnosing CD seems that patients describe isolated symptoms to the FP or the respective specialists according to their fields of specialization. As FPs are contacted most frequently, they should be trained to recognize the broad spectrum of CD symptoms, especially in female patients with weight gain, and initiate endocrinological referral.

Introduction

Endogenous adrenocorticotropic hormone (ACTH)-dependent Cushing’s disease (CD) is a life-threatening illness caused by chronic glucocorticoid excess caused by an ACTH-secreting pituitary adenoma (1). Clinical symptoms include weight gain, central obesity, plethora, hirsutism, and proximal muscle atrophy, in addition to hypertension, osteoporosis, and diabetes mellitus (2). The published estimates of disease incidence and prevalence range between 1.2 and 2.4 per million and 39 per million inhabitants respectively (3, 4).

Because of the insidious nature of the disease and the overlap with common symptoms of the general population such as overweight and hypertension, definite diagnosis is usually made years after disease-onset. The diagnostic latency of Cushing’s syndrome (CS) in general is reported with a median of 2 years in two recent studies, but studies which focus exclusively on the latency between symptom occurrence and diagnosis of pituitary-dependent CD are lacking so far (5, 6). Also, no data exist which elucidate the reasons for the long diagnostic process of patients with CD or CS.
The reasons for delayed diagnosis, suboptimal illness surveillance, or loss to follow-up may be accounted for by factors such as different availability of health care resources in rural or urban areas of a country and patient parameters such as sex and age. That these factors are important for the utilization of health care in general as has been shown by a study of Thode et al. (7) who found that residence, region, age, and sex significant influence the use of ambulatory primary health care.

Because of the significant burden of undiagnosed or undertreated CD on patients in terms of partially irreversible physical illness sequelae and impaired quality of life (2), the aim of this study was to systematically assess the course of the diagnostic process from symptom onset to the time of diagnosis and the role of the involved physicians from the patients’ perspective in order to obtain leverage points for earlier diagnosis.

Subjects and methods

The study was conducted at three large German Neurosurgical University referral centers (Erlangen-Nuremberg, Tuebingen, and Essen-Duisburg) between January 2013 and April 2014. Medical records from the year 2005 onward were screened for eligible patients who had received pituitary neurosurgery for biochemically proven central CD. Patients with all other forms of CS, patients under the age of 18 years, and patients with known active psychotic illnesses and known insufficient fluency of the German language were excluded from participation. All patients received an information letter explaining the purpose of the study, a consent form and a self-developed questionnaire. Next to covering sociodemographic data (i.e. level of education, marital, and occupational status), the medical history part of the questionnaire contained questions on weight, height, smoking status, initial CD-related symptoms, kind and number of medical professionals visited from the onset of CD-associated symptoms until diagnosis of CD (and who made it) as well as the specific complaints brought forward by the patient at the particular visit. For comparison between rural and urban areas of living, the population density of the patient’s place of residence was determined using data provided by the German Federal Statistical Office. A population density of ≥500 inhabitants/km² was considered as an urban and of <500 inhabitants/km² a rural place of living. The study was conducted in accordance with the Declaration of Helsinki and the Guideline for Good Clinical Practice (8, 9). The study protocol was approved by the local ethic committees of the Universities of Erlangen-Nuremberg, Tuebingen, and Essen-Duisburg. The patients were included if the signed consent form was returned with the filled-in questionnaire.

Statistical analyses

Database was generated by Microsoft Access 2010 (Microsoft Office 2010, Microsoft). Statistical analyses were conducted using IBM SPSS Statistics 22 (Statistical Package of the Social Sciences (SPSS, Inc.)). Descriptive statistics of interval-scaled data were expressed as mean and s.d. unless otherwise mentioned. Data were tested for normal distribution by conducting a Shapiro–Wilk test, in addition to histograms and Q-Q-Plots for every parameter. If data were not normally distributed, nonparametric tests were conducted. Data were analyzed separately for urban and rural areas and for sex. For group comparison Student’s t or Mann–Whitney U tests for unpaired variables were used. Nominal data were analyzed by χ² test or, if expected frequencies were below five, Fisher’s exact test. Group comparison between place of residence and sex were conducted for all variables. For variables containing free text options (i.e. ‘What were the symptoms you saw this medical specialist for?’), the answers were categorized and counted. Where applicable, a P value of ≤0.05 was considered to be statistically significant.

Results

Study population

The data of 176/318 mailed out questionnaires could be included in the study (of 144 females and 32 males), which corresponds to a 55.3% inclusion rate. Of the 176 participants, 86 lived in urban and 89 in rural areas. The subjects answered the questionnaire 7.6 ± 7.5 years after diagnosis of CD, at a mean age of 46.1 ± 13.7 years. Time delay between surgery and this study was 6.8 ± 6.7 years and 29 patients underwent surgery 1 year or less ago. Height (168.7 ± 8.8 cm for urban vs 167.1 ± 8.7 cm for rural regions) and weight (75.5 ± 19.3 kg for urban vs 78.6 ± 17.7 kg for rural regions) were similar in both groups and a higher BMI was observed in patients living in rural areas (28.1 ± 5.9 kg/m²) compared with participants in urban areas (26.5 ± 6.6 kg/m², P ≤ 0.05). Smoking status was 20.5% with no significant differences between rural and urban regions and sexes. Also, no differences between the age of women (45.2 ± 13.1 years) and men (49.7 ± 15.6 years, P = 0.097) were observed, but women were smaller in height than men (165.9 ± 7.4 cm vs 177.1 ± 8.7 cm for men, P < 0.05). No other sex-related differences were observed.
Sociodemographic data

Marital status was not different between groups before and after the diagnosis of CD, with most of the patients currently living together with their life partner (52.3% for urban regions and 59.6% for rural regions, \(P = 0.363\)). For level of education, there was an overall difference between rural and urban regions with regard to the level of secondary school degree \((P < 0.05)\), and with patients in rural areas having significantly less likely a university degree (13.5% vs 26.7%; \(P < 0.05\)). Also, no significant difference could be observed between the groups for occupational status, with presently 19.9% of all subjects working full-time and 27.2% working part-time.

Patient symptoms and diagnostic process

Men and women experienced a variety of symptoms which they attributed retrospectively to the onset of CD. The most frequent symptom categories and the medical specialist to whom they were presented are shown in Fig. 1.

Family physicians (FPs) were consulted most frequently (83.0%), in addition to internists (33.0%), orthopedists (31.3%), and dermatologists (26.1%). The presented symptoms were various and often vague, e.g. ‘poor general condition’ (at FPs), or very common in the field of specialty visited (e.g. ‘general skin changes’ in dermatology, ‘joint and muscle pain’ in orthopedics, ‘high blood pressure’ in cardiology). The most frequently and uniformly mentioned symptom was weight gain (30.0%). In the majority of cases, symptom onset was recognized by the patient themself, significantly more frequently by women (81.3%) than by men (59.4%, \(P = 0.011\)). In contrast, the physician was the first to recognize CD symptoms in 37.5% of the male, but only in 13.2% of the female participants \((P = 0.002)\).

After symptom onset, patients waited on average 0.9 ± 2.0 years until seeking medical advice (men 1.4 ± 3.1 years, females 0.8 ± 1.6 years, \(P = 0.417\)), also with no significant difference between urban and rural regions \((P = 0.212)\). The subjects consulted 4.6 ± 3.8 different physicians (range 1–30) before diagnosis of CD, with a significant difference between urban and rural areas (4.2 ± 4.0 vs 5.1 ± 3.5, \(P < 0.05\)) but not between men and women. Another 3.0 ± 4.5 years (median 1 year) elapsed until diagnosis of CD was established, leading to an overall diagnostic process of 3.8 ± 4.8 years (median 2 years), with no significant differences between place of residence and sexes. The patients reported that in the majority of cases, diagnosis of CD was verified by an endocrinologist (69.9%). Table 1 lists the different medical specialties named by our study participants as the ones who confirmed the diagnosis of CD.

Discussion

In this study, we assessed the diagnostic process in patients with pituitary-dependent CD in rural and urban environments in Germany from the patient’s perspective. The large sample size and the insights provided by the patient’s perspective are clear advantages of this study, yet a potential limitation that must be born in mind for the interpretation of the results is a certain degree of uncertainty in patients’ ability to remember the time points of symptom onset and the further diagnostic course exactly (10).

The overall diagnostic process from first symptoms to definite diagnosis of CD took 3.8 years (median of 2.0 years) on average in our study and patients waited almost a year from symptom-onset before seeking medical advice. Interestingly, significant differences between the number of consulted physicians between rural and urban places of living were observed, where the higher number of consulted doctors in rural areas may indicate a less dense net of medical specialists familiar with the diagnostic features of CD. Yet, the lacking difference between overall diagnostic latency between rural and urban areas in...
Germany indicates a relatively uniform availability and quality of the health care system in this densely populated and well-infrastructured country.

The median of 2 years from symptom-onset to diagnosis found in our study is identical to that reported in a recent study from the European Registry on Cushing’s Syndrome (ERCUSYN) (6) and another retrospective study on CS by Bolland et al. (5), but in these studies symptom-onset was rated by physicians on the basis of chart records. The fact that more than half of the patients of this study were diagnosed within 1 year from first physician contact (median of 1 year from first doctor visit to diagnosis) speaks for an improved awareness of this disease entity within the last years. Nevertheless, a broad variation of the diagnostic process ranging from 0 to 27 years was observed in our study, pointing to a need for further efforts to come to a speedier diagnosis.

Already in 1964, Nugent et al. suggested probability calculations with clinical symptoms and nonsteroid laboratory data in order to improve the diagnostic certainty of CS, using Bayes’ theorem (11, 12). This mathematical rule, ascribed to the 18th century minister Thomas Bayes and frequently used in modern evidence-based medicine, relates current to previous probabilities, taking into account new pieces of evidence. When interpreting the clinical symptoms of patients with CS, which are often overlapping with symptoms common in today’s population (e.g. overweight and insulin resistance), Bayes’ theorem shows how the initially very low previous probability of a true diagnosis of CS (because of the rarity of the disease) is influenced, when a new symptom or test result is added to the diagnostic process (12, 13). In this context, the studies by Nugent and other authors demonstrated how the probability of an overweight patient being correctly diagnosed with CS increases considerably when the specific symptoms of muscle weakness and ecchymosis or certain laboratory results are included in the statistical approach (12, 13, 14). Next to the use of specific symptom combinations, it might also be helpful to include the speed of symptom-onset and progression in clinical reasoning. As mentioned by Kreisberg (15), overweight and insulin resistance might develop over the course of years, while in CS symptom-onset is often abrupt.

Also, the experience of the physician plays an important role in the diagnostic process of CS. A FP’s lifetime experience of CS is likely to be relatively low, due to the low incidence of the disease in addition to the variety of the disorder (10). This underlines the importance of the endocrinologist who is familiar with the clinical features of the disease. In our study, the diagnosis of CD was made in 69.9% of cases by an endocrinologist and even attendants of endocrinology meetings rated their ability to clinically diagnose CS as dependent on their years of clinical practice (14).

An interesting gender difference in the diagnostic process was that in our study, women reported to have observed the onset of CD-related symptoms themselves significantly more frequently than males, where in turn the physician was more often the one recognizing changes significantly associated with CD first. Whether this difference is due to gender-specific aspects in symptom presentation or a better awareness of women for disease-related bodily changes remains a matter of speculation. There is also the possibility of an implicit physician bias in that women’s symptoms are possibly dismissed or belittled, especially when they relate to the outer appearance, such as weight gain, or mood swings (16). In our survey, this difference between self- and proxy-observed symptoms did not result in different diagnostic latencies between males and females. Nevertheless, the matter deserves clarification in further research.

In contrast to all other studies on the diagnostic process in patients with CD or CS, the patient’s perspective in the present investigation allows eye-opening insights of what might be the involuntary patient’s share in prolonging the way to diagnosis of CD: patients in our study reported to see the FP for very unspecific symptoms such as ‘general discomfort’ or weight gain. A further clear difficulty in the diagnostic process seems to be that patients consult specialists, and then describe isolated symptoms which are common in the respective field of specialization and, moreover, use unspecific laymen’s terminology (i.e. ‘skin changes’, ‘trouble with joints’). From our database, we were unable to infer whether specialists had been consulted on the FP’s or the patient’s own initiative. However, the rarity of the disease and the presentation of only a selection of symptoms predefined by the patient serve to explain why many specialists miss the correct diagnosis. The results highlight the need to increase awareness for the symptom

**Table 1** Different medical specialties named by the study participants as the ones who made the definite diagnosis of CD.

<table>
<thead>
<tr>
<th>Physician</th>
<th>Number of subjects (n)</th>
<th>Percentage of subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrinologist</td>
<td>123</td>
<td>69.9</td>
</tr>
<tr>
<td>Internist</td>
<td>18</td>
<td>10.2</td>
</tr>
<tr>
<td>Family physician</td>
<td>11</td>
<td>6.3</td>
</tr>
<tr>
<td>Neurologist</td>
<td>5</td>
<td>2.8</td>
</tr>
<tr>
<td>Gynecologist</td>
<td>4</td>
<td>2.3</td>
</tr>
<tr>
<td>Orthopedist</td>
<td>1</td>
<td>0.6</td>
</tr>
</tbody>
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spectrum of CD. Our own data and also data from ERCUSYN (6) demonstrate that more than 80% of patients with CD or CS see the FP, probably not only at the beginning of the diagnostic process but also at later stages. This implies a central role of the FP or general practitioner in the diagnostic process of CD. Based on our findings and the Bayesian reasoning described earlier, we therefore suggest to specifically train FPs and general practitioners to look for rare or not age-appropriate symptom combinations like buffalo hump, plethora, striae, proximal muscle weakness, and signs of osteoporosis in patients with weight gain. Early referral of such patients to an endocrinologist is then mandatory to facilitate timelier diagnosis.

Declaration of interest
I Kreitschmann-Andermahr, T Psaras, M Tsiogetka, S Siegel, M Milian, D Führer-Sakel, J Honegger, and M Buchfelder have received research and/or travel grants and/or speakers honoraria from Novartis, Germany. The other authors report no conflict of interest.

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Author contribution statement
I Kreitschmann-Andermahr, T Psaras, M Milian, S Siegel, D Starz, M Buchfelder performed study conception and development of the questionnaire. S Siegel, B Kleist, I Kreitschmann-Andermahr carried out. All co-authors performed data acquisition and discussion of results. All co-authors carried out preparation and revision of the manuscript.

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