Clinical features of GH deficiency and effects of 3 years of GH replacement in adults with controlled Cushing’s disease

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Abstract

Objective: Patients in remission from Cushing’s disease (CD) have many clinical features that are difficult to distinguish from those of concomitant GH deficiency (GHD). In this study, we evaluated the features of GHD in a large cohort of controlled CD patients, and assessed the effect of GH treatment. Design and methods: Data were obtained from KIMS, the Pfizer International Metabolic Database. A retrospective cross-sectional comparison of background characteristics in unmatched cohorts of patients with CD (n = 684, 74% women) and nonfunctioning pituitary adenoma (NFP A; n = 2990, 39% women) was conducted. In addition, a longitudinal evaluation of 3 years of GH replacement in a subset of patients with controlled CD (n = 322) and NFP A (n = 748) matched for age and gender was performed. Results: The cross-sectional study showed a significant delay in GHD diagnosis in the CD group, who had a higher prevalence of hypertension, fractures, and diabetes mellitus. In the longitudinal, matched study, the CD group had a better metabolic profile but a poorer quality of life (QoL) at baseline, which was assessed with the disease-specific questionnaire QoL-assessment of GHD in adults. After 3 years of GH treatment (mean dose at 3 years 0.39 mg/day in CD and 0.37 mg/day in NFP A), total and low-density lipoprotein cholesterol decreased, while glucose and HbAlc increased. Improvement in QoL was observed, which was greater in the CD group (KCD group versus KNFP A group, P < 0.01).

Conclusion: In untreated GHD, co-morbidities, including impairment of QoL, were more prevalent in controlled CD. Overall, both the groups responded similarly to GH replacement, suggesting that patients with GHD due to CD benefit from GH to the same extent as those with GHD due to NFP A.

Introduction

Cushing’s disease (CD) is a rare disorder with high pre- and post-operative morbidity and mortality, including increased risk of metabolic derangements, fractures, thromboembolism, and hemorrhage (1). Many clinical features in CD overlap those in GH deficiency (GHD) (1–3). In both diseases, visceral obesity, decreased lean body mass, decreased bone mineral density, reduced physical capacity, dyslipidemia, glucose intolerance, and reduced quality of life (QoL) are seen. It is well established that GH replacement reverses most of the features of adult GHD (4, 5). There are many underlying disorders that may result in GHD, with the most common etiology of GHD in adults being non-functioning pituitary adenoma (NFP A) (2, 3). In KIMS (Pfizer International Metabolic Database, a surveillance study of adult patients with GHD), GH was reported to be related to NFP A in 23.8% of the patients and to CD in 5.8% of the patients.

Despite long-term remission of CD, patients may experience considerable impairment in QoL with physical and psychosocial dysfunction (6), particularly if surgical or radiation treatment is associated with hypopituitarism. In these patients, the role of long-term consequences of CD may be difficult to distinguish from the role of those of concomitant GHD. Feldt-Rasmussen et al. (7), Johannsson et al. (8), and Colson et al. (9) have focused on the effect of GH treatment in GHD adults with previous CD. These studies, which included 135, 15, and 39 patients respectively, showed similar effects of GH treatment on metabolic parameters and body composition as compared to GHD of other etiologies, although improvement in QoL was not significant in the only study that addressed this parameter (7).

Our study evaluated the features of untreated GHD in patients with controlled CD by comparing clinical characteristics of large cohorts of patients with
controlled CD and those with NFPA prior to the commencement of GH therapy as well as by assessing reversibility of impairments in both groups after 3 years of GH replacement.

Subjects and methods

Patients

Data regarding patients with controlled CD and NFPA were obtained from KIMS (Pfizer International Metabolic Database) – the largest pharmaco-epidemiological surveillance study on GH therapy in adults with GHD (10). After approval of the protocol by Institutional Review Boards, informed consent for registration in the database was obtained from all patients. Patients were enrolled between 1994 and 2008. Information about enrolled patients is dependent on the clinical practice and is reported by investigators. As detailed information on the status of CD, including criteria for its full cure, is not included in the database, patients with CD are here referred to as ‘controlled CD’. CD patients enrolled into KIMS between 1994 and 1999 \((n = 135)\) were reported previously (7), constituting 21% of the total cohort of CD patients in this study \((n = 684)\).

The current paper consists of two separate analyses:

i) Analysis A: a cross-sectional comparison of background characteristics in unmatched cohorts of patients with controlled CD \((n = 684)\) and NFPA \((n = 2990)\) to determine whether demographics and phenotype differ in these two groups of patients diagnosed with GHD.

ii) Analysis B: a longitudinal evaluation of 3 years of GH replacement in the subsets of patients with controlled CD \((n = 322)\) and NFPA \((n = 748)\) matched for age and gender and naive or semi-naive (off GH for at least 6 months prior to entry into KIMS) to GH treatment at KIMS entry.

Out of the CD patients who were included in Analysis A, but not in Analysis B \((n = 362)\), 191 patients had already been treated with GH upon entry into KIMS, and thus were not eligible for longitudinal analysis of GH replacement effects, and 171 patients either were followed for shorter than 3 years or were not having data at the 3-year visit (90th percentile of follow-up in KIMS was 1.9 years).

Background and baseline characteristics

Analysis A Information regarding gender, age at diagnosis, age at GHD diagnosis, and age at start of GH treatment as well as medical history was obtained with special emphasis on hypertension, coronary disease, stroke, diabetes mellitus, and fracture rate.

GHD was diagnosed locally based on recommended GH stimulation tests and clinical manifestations. Approximately 60% of the patients in both the groups were diagnosed with an insulin hypoglycemia stimulation test (ITT). The remaining patients were diagnosed by arginine test or glucagon test, and test profiles were similar in each group.

The number and type of other pituitary deficiencies at baseline were assessed by local measurements.

Patient-reported outcomes such as information about personal situation and social functioning were self-reported in the KIMS Patient Life Situation Form (10).

Analysis B The following parameters were assessed before and after 3 years of GH treatment: insulin-like growth factor 1 (IGF1), body mass index (BMI), waist circumference, blood pressure, blood lipids, glucose, HbA1c, and QoL.

Serum IGF1 concentrations were measured at a central facility first by RIA after acid/ethanol precipitation of IGF-binding proteins (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA), and then by chemiluminescence immunoassays (Nichols Advantage System followed by Immulite 2500, DPC Siemens, Los Angeles, CA, USA). For each assay, age- and gender-specific reference ranges were used to determine IGF1 SDS. Reference ranges and consistency of IGF1 SDS values between assays were validated internally.

Normal blood pressure was defined as 130/85 mmHg or below. Measurements of serum total cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride concentrations were performed centrally, and serum concentrations of low-density lipoprotein (LDL)-cholesterol were calculated using Friedewald’s formula (11). A total cholesterol concentration >5.20 mmol/l (201 mg/dl), HDL-cholesterol concentration <1.04 mmol/l (40 mg/dl) in males and 1.30 mmol/l (50 mg/dl) in females. LDL-cholesterol concentration >3.38 mmol/l (131 mg/dl), and triglyceride concentration >1.65 mmol/l (146 mg/dl) were considered abnormal.

Plasma glucose and HbA1c were reported as analyzed locally.

QoL was assessed by the QoL-assessment of GHD in adults (QoL-AGHDA) questionnaire (12). Higher numerical scores, to a maximum of 25, denote poorer QoL.

GH dosing was at the discretion of treating physicians, and was reported to the KIMS database. GH dose was analyzed as a starting dose, i.e. dose reported at the entry into KIMS visit, and as a dose reported at the visit after 3 years of treatment.

Statistical analysis

Data analyses were performed using SAS 8.2 (SAS Institute, Cary, NC, USA). Data are presented as mean ± S.D. unless otherwise specified. The significance of effects between groups was determined by unpaired
t-tests for normally distributed data and by the Wilcoxon rank-sum tests for non-normally distributed data. For within-group comparisons, signed rank test was used. For proportions, Fisher’s chi² test was used.

The matching for age in Analysis B was performed by arbitrarily excluding NFPA patients with ages above the mean age of the CD patients until the mean age was roughly the same, i.e. no statistical difference. In this age-matched group, gender turned out to be the same.

A P value < 0.05 was considered to be statistically significant.

Results

Analysis A

Background characteristics Patients with CD were in remission (controlled CD) according to the reporting physician. Approximately 94% of the patients came from Europe, and 98% were of Caucasian origin. The proportion of women in the CD group was almost twice as high as that in the NFPA group (Table 1). Of CD patients, 360/684 were treated with surgery alone, 236/684 were treated with both surgery and radiation, and 56/684 were treated with radiation alone (the treatment breakdown was similar in patients with NFPA). In 5% (32/684) of the patients with CD and in 7% (200/2990) of the patients with NFPA, neither surgery nor radiotherapy was reported. Additionally, in 27 patients with CD, bilateral adrenalectomy was reported, and in 28 patients previous treatment with ketoconazole and in 16 patients previous treatment with metyrapone were reported. Both ketoconazole and metyrapone had been stopped before inclusion.

The majority of the patients in both the groups had multiple pituitary insufficiencies: 30% in the CD group and 45% in the NFPA group had panhypopituitarism, whereas 9% in the CD group and 7% in the NFPA group had an isolated GHD. Glucocorticoid therapy was reported in ~60% of patients in both the groups, of whom 70% were treated with hydrocortisone, 26% with cortisone acetate, and the remaining patients with prednisolone or dexamethasone. Glucocorticoid dosing, expressed as hydrocortisone equivalent dose (13), was similar in both the groups (CD: 22.3 ± 9.9 mg/day and NFPA: 22.6 ± 8.1 mg/day). Seventy percent of the patients in both the groups were naive to GH treatment at KIMS entry, whereas 30% had taken it in the past, but had been off GH for at least 6 months before study entry.

A history of hypertension, diabetes mellitus, and fractures were reported more frequently in the controlled CD group than in the NFPA group. The frequency of coronary heart disease and stroke was similar in both the groups, despite the significant difference in mean age. In the subset of patients in whom visual status was reported (CD = 444 and NFPA = 2081), visual field defects and ophthalmoplegia were found in 14 and 3% respectively in the CD group compared with the 61 and 12% in the NFPA group (P < 0.0001 and P < 0.0001 respectively).

The patients with controlled CD were 8 years younger than the patients in NFPA group at the time of diagnosis of the pituitary disease. 6 years younger when GHD was confirmed, and 6 years younger when they started on GH. The mean lag time between onset of pituitary disease and diagnosis of GHD was longer in the CD group than in the NFPA group (8 ± 8.0 vs 5 ± 6.3 years respectively, P < 0.001). However, a similar time had elapsed from GHD diagnosis and initiation of GH treatment in both the groups (3 ± 2.8 vs 3 ± 3.1 years respectively, NS).

Personal situation and social functioning The proportion of unmarried (never married) patients was higher in the CD group (15%) than in the NFPA group (9%; P < 0.01). There was no difference in other marital status (widower and divorced), and about 75% in both the groups were married. Eighty-two percent of CD patients had more than 10 years of education compared with 70% in the NFPA group (P < 0.0001). The type of employment (office or manual) was similar in both the groups. Twenty-one percent in the CD group received sick leave or disability benefits compared with 14% in the NFPA group (P < 0.0001). Despite their younger age, one-third of the CD patients reported a need for

Table 1 Background characteristics of patients with Cushing’s disease and non-functioning pituitary adenomas. Data are presented as proportions and mean ± 2 s.d.

<table>
<thead>
<tr>
<th></th>
<th>Cushing’s disease group (n=684)</th>
<th>Non-functioning pituitary adenoma group (n=2990)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender – female (%)</td>
<td>74‡</td>
<td>39</td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery (%)</td>
<td>53</td>
<td>56</td>
</tr>
<tr>
<td>Irradiation (%)</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Both (%)</td>
<td>34</td>
<td>36</td>
</tr>
<tr>
<td>Pituitary insufficiencies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH (%)</td>
<td>71</td>
<td>73</td>
</tr>
<tr>
<td>TSH (%)</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>FSH/LH (%)</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>ADH (%)</td>
<td>28‡</td>
<td>18</td>
</tr>
<tr>
<td>Abnormal prolactin (%)</td>
<td>6*</td>
<td>7</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>35§</td>
<td>22</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>5.7</td>
<td>6.3</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13.5§</td>
<td>5.1</td>
</tr>
<tr>
<td>Fractures</td>
<td>28*</td>
<td>18</td>
</tr>
<tr>
<td>Age at onset of pituitary disease (years)</td>
<td>38 (±11.9)‡</td>
<td>46 (±12.8)</td>
</tr>
<tr>
<td>Age at GHD diagnosis</td>
<td>45 (±11.8)‡</td>
<td>51 (±12.1)</td>
</tr>
<tr>
<td>Age at start of GH</td>
<td>48 (±11.8)‡</td>
<td>54 (±11.6)</td>
</tr>
</tbody>
</table>

*P < 0.05, †P < 0.001, §P < 0.000.

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assistance with daily life activities compared with 17% of the NFPA patients (P<0.0001), of which assistance with errands and housekeeping were most commonly required in both the groups. In both the groups, ~80% of the patients had children.

**Analysis B**

**Baseline characteristics and 3-year GH treatment effects** Patients with CD and NFPA who had data entered into the KIMS database at baseline and after 3 years of GH were selected. A total of 322 patients with GHD associated with successful treatment for CD were matched for gender and age to 748 patients with NFPA (Table 2). The majority of the patients were from Europe (93%), and were of Caucasian origin (97%). According to the reporting physician, patients with CD were in remission (controlled CD). Ninety-three percent of the patients in the CD group were treated for ACTH deficiency compared with 92% in the NFPA group. The corresponding proportions for treatment of TSH deficiency were 89% in both the groups, and those for treatment of FSH/LH deficiency were 84 and 83% respectively in women and 92 and 89% respectively in men. Thus, no differences in hormonal treatment were seen between the groups. Mean GH peaks on ITT and arginine and glucagon tests were similar in both the groups. IGFI SDS was −1.7 ± 1.6 in the CD group and −1.6 ± 1.5 in the NFPA group. Patients in the CD group had a significantly lower systolic blood pressure (P<0.05), and levels of total and LDL-cholesterol at baseline as well as fasting glucose. Mean QoL-AGHDA score was higher in patients with CD, indicating a poorer QoL than in patients with NFPA.

At baseline, 24% of the CD patients and 16% of the NFPA patients were on antihypertensive therapy (P<0.001). Of the patients who were not on antihypertensive treatment, 32% in the CD group and 38% in the NFPA group had systolic blood pressure above 130 (P<0.05), while 27% in the CD group and 28% in the NFPA group had diastolic blood pressure above 85 (NS). Sixteen percent of the CD patients and 11% of the NFPA patients were on lipid-lowering drugs (P<0.001), and in patients who were not on lipid-lowering therapy, total cholesterol and LDL-cholesterol were lower in the CD group than in the NFPA group (P<0.05 and P<0.01 respectively). Five percent of the CD patients and 4% of the NFPA patients were receiving antidiabetic treatment (NS), and in patients who were not receiving antidiabetic treatment, fasting glucose was lower in the CD group (4.50 mmol/l) than in the NFPA group (4.66 mmol/l; P<0.01).

The GH dose was similar: the mean starting dose was 0.22 mg/day in both the groups, and the mean dose at 3 years was 0.39 mg/day in the CD group and 0.37 mg/day in the NFPA group (NS). On these doses, IGFI SDS increased significantly in both the groups, with an increment of 2.2 ± 1.9 and 2.1 ± 1.7 in the CD group and NFPA group respectively (P<0.001 for both).

BMI increased significantly in the CD group but not in the NFPA group. Waist circumference and systolic blood pressure decreased significantly only in the NFPA group. A reduction in total and LDL-cholesterol was seen in both the groups compared with baseline, and improvement in QoL as measured by a decrease in the mean QoL-AGHDA scores was observed in both the groups.

The changes after 3 years of GH treatment were not significantly different between the groups, except for change in QoL-AGHDA score where patients with CD showed greater improvement (P<0.01). However, the mean QoL-AGHDA score in the CD group did not reach as low a score as in the NFPA group (8.3 vs 6.6 P<0.01; Fig. 1).

Controlling for treatment with lipid-lowering drugs, the decrease in total cholesterol in the patients not treated with lipid-lowering drugs was −0.5 ± 1.0 mmol/l (P<0.0001) in the CD group and −0.4 ± 0.9 mmol/l (P<0.0001) in the NFPA group. LDL-cholesterol decreased by −0.5 ± 0.8 mmol/l (P<0.0001) in the CD group and by −0.4 ± 0.9 mmol/l (P<0.0001) in the NFPA group. The changes in

**Table 2** Clinical and metabolic parameters at baseline and the change after 3 years of GH replacement in patients with Cushing's disease and non-functioning pituitary adenomas. Data are expressed as mean ± s.d. score. The patients were matched for gender and age.

<table>
<thead>
<tr>
<th></th>
<th>Cushing’s disease group (n=322)</th>
<th>Non-functioning adenomas group (n=748)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.5±5.6</td>
<td>0.3±3.9</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>96.9±14.8</td>
<td>−1.1±8.2</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>127/80±18/11</td>
<td>−0.7/−0.9±17/12</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.7±1.2</td>
<td>−0.6±1.2</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.3±0.4</td>
<td>0.0±0.3</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>3.5±1.0</td>
<td>−0.6±1.0</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>2.0±1.1</td>
<td>−0.1±1.2</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>4.7±1.2</td>
<td>0.5±1.2</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.2±0.8</td>
<td>0.2±0.8</td>
</tr>
<tr>
<td>QoL-AGHDA</td>
<td>14.8±6.8</td>
<td>−6.0±8.4</td>
</tr>
</tbody>
</table>

Significant differences between the groups *P<0.05, †P<0.01, ‡P<0.001. Significant differences for change (within the groups) §P<0.05, ††P<0.01, ‡‡P<0.001.
HDL-cholesterol and triglycerides were not significant in either of the groups. In addition, an increment in glucose and HbA1c was observed in both the groups; in the CD group controlling for antidiabetic treatment, patients who were not on antidiabetic treatment, fasting glucose increased by 0.4 ± 1.0 mmol/l (P < 0.0001), and in the NFP A group, it increased by 0.2 ± 1.3 mmol/l (P < 0.0001). Four patients in the CD group and 13 patients in the NFP A group developed diabetes mellitus (NS).

Recurrences in CD The total number of recurrences reported in cohort A was 16 (2.3%), and it did not constitute a reason for excluding the patients from longitudinal analysis.

Discussion

In this study, we evaluated the features of untreated GHD in controlled CD in comparison to patients with NFP A prior to the commencement of GH therapy, and assessed the reversibility of symptoms after 3 years of GH treatment in age- and gender-matched subsets. The cross-sectional study showed a significant delay in GHD diagnosis in the CD group, with a 3-year delay compared with those in the NFP A group between the diagnosis and the commencement of GH therapy. As expected, there was also a higher prevalence of hypertension and diabetes mellitus as well as fracture rate in patients with CD. Personal situation and social functioning were worse in the CD group, with more individuals being unmarried, requiring assistance with daily activities, and on sick leave. At baseline in the longitudinal, matched study CD patients had a better metabolic profile but poorer QoL. After 3 years of GH treatment, similar metabolic benefits were seen in both the groups, except for a greater increment in glucose in CD patients not treated with antidiabetic medication. Although QoL still remained worse in the NFP A group, it improved to a larger extent in the CD group.

Analysis A

Epidemiology and disease-specific patterns of the CD and NFP A groups were confirmed, with CD patients most typically being younger and females. Of note, the lag time for diagnosis of GHD was significantly longer, by 3 years in the CD group. This may be caused by an overlap of non-specific symptoms of both CD and GHD, so that the latter possibility was not initially considered. Alternatively, it is possible that clinicians intentionally waited for several years after CD is in remission to explore the possibility of GHD (1, 14, 15) as spontaneous restoration of somatotroph function in CD is often observed, and evaluation of GH secretion was postponed to at least 12 months following remission of CD (14–16). In the present study, 11 patients started on GH within 12 months after the CD diagnosis (data not shown), but on average, GHD was diagnosed 8 years after the CD diagnosis, so the probability of spontaneous restoration of GH secretion is low. The observations of a longer time needed to diagnose GHD and the higher proportion of co-morbidities in patients with CD than in patients with NFP A confirm the complexity of illness in CD, which may be predominantly attributable to the primary disease, rather than to GHD. However, once CD patients were diagnosed with GHD, they initiated GH replacement after the same interval as patients with NFP A.

Analysis B

Surprisingly, but likely related to the fact that patients with active CD were not included in the database when both the groups were matched for gender and age, we found that before GH treatment, patients with CD had lower systolic blood pressure, better lipid profile, and lower fasting glucose levels and did not differ in BMI and waist circumference compared with the NFP A patients. However, in both the groups, mean total cholesterol and LDL-cholesterol as well as triglycerides were above the reference values, possibly as a result of GHD. Controlling for the effect of treatment with antihypertensive,
lupid-lowering, and antidiabetic medication by separate subgroup analysis, total cholesterol and LDL-cholesterol remained significantly lower in the CD group. Only a minority of patients in the two groups were treated with these medications, although a significant larger proportion of the patients in the CD group received antihypertensive medication and lipid-lowering drugs. In the unmatched study, 13.3% of the CD group had diabetes, while in the matched study 5% of the CD patients were treated with antidiabetic medication.

There are only a few studies addressing GH replacement in CD, with fewer than 200 total patients (7–9), and only one study explored the effect on QoL (7). A major strength of our study is that it comprises the largest series of GH-deficient patients associated with CD reported to date.

In the current study, we found that in patients with CD, BMI increased and no change in waist circumference was observed, whereas the opposite was found in patients with NFP A. The results from dual energy x-ray absorptiometry (DEXA) scans, unfortunately reported only in a few patients, showed a greater increase in lean body mass in the CD group than in the NFP A group (data not shown). Unchanged absolute value of waist circumference in light of an increased BMI indicates its proportional decrease, which may be related to the increase in lean body mass. Based on our findings, it could be speculated that patients with CD in comparison with patients with NFP A showed a better response with regard to a change in lean body mass but not fat mass. The effect of GH replacement on blood lipids and glucose levels was similar to that observed in previous studies. Separating patients who were not on antihypertensive, lipid-lowering and antidiabetic medication showed a more pronounced reduction in total and LDL-cholesterol, whereas glucose increased more in the CD group than in the NFP A group, but without a difference between the groups in the proportion of patients who developed diabetes mellitus. Thus, the CD patients seem to be more sensitive to GH effects on both lipid and glucose metabolism.

QoL has previously been shown to be impaired in patients with controlled Cushing’s disease (6, 7, 17, 18). However, only two studies have taken the possible role of GHD into account (6, 7). In the present study, a significant improvement in QoL was observed after 3 years of GH treatment. Although a greater improvement was seen in the CD group, QoL remained worse compared with the NFP A group, which may be a consequence of more prevalent co-morbidities in the CD group (19). The larger cohort and longer treatment time in our study most likely explain the greater effects on QoL in patients with controlled CD compared with the previously published studies.

The risk of recurrence in CD during GH treatment is an important issue. As recently reviewed by Blevins et al. (20), the recurrence rate after pituitary microsurgery for ACTH-producing microadenomas is ~10%, while the recurrence rate after surgery for ACTH-producing macroadenomas increases to as much as 30%. Furthermore, most recurrences occur within 5 years of surgery (20). This means that there is a fairly high natural recurrence rate in patients who are not on GH treatment. However, in the present study, fewer patients (2.3%) than expected were reported to have recurrences in CD. The reason for this is unclear, but it could be due to the selection of successfully treated patients for treatment with GH as well as the observation that GH treatment was started on average 10 years after CD onset.

Increased mortality ratio is observed in both CD (1) and hypopituitary patients without GH replacement (21–25), most often related to cardio- and cerebrovascular risk factors. GH replacement has been shown to improve the adverse body composition, cardiovascular risk factors (25, 26), and poor QoL associated with GHD (27, 28). In CD, markers of cardiovascular risk remain abnormal for up to 5 years after surgery (29). Therefore, patients with CD and untreated GHD would be expected to have a considerably increased risk of cardiovascular diseases for several years after surgery. In the current study, patients in the CD group had a better metabolic profile than the patients in the NFP A group, perhaps because of the longer time between diagnosis of CD and diagnosis of GHD. In addition, the metabolic effects of GH treatment were similar in the two groups.

There are limitations of our study. KIMS is an international observational database with a continuous enrollment of patients, and therefore, the length of the follow-up varies. The patients in the cross-sectional study were selected from the KIMS database based on the CD and NFP A diagnosis. For the longitudinal study, we chose an arbitrary 3-year follow-up to ensure that effects of GH replacement were seen, and at the same time, to be able to include a sufficient number of patients. Thus, patients who were not reported at the 3-year visit were not included in the analysis. Additionally, as KIMS reflects daily clinical practice and patients’ eligibility for treatment, the diagnostic and therapeutic information included in our study depend on study physicians and possibly vary between different countries. In addition, recruitment of patients for GH treatment could be biased by the physicians’ desire to correct QoL rather than metabolic parameters. However, the fact that IGF1 and lipids were analyzed centrally strengthens our results.

In conclusion, this study shows, in controlled CD patients in remission, a higher prevalence of co-morbidities, a better lipid profile and a poorer QoL compared with the NFP A patients. CD patients were not diagnosed with GHD on average for 8 years after the onset of pituitary disease, representing a 3-year lag in comparison to the NFP A patients. However, once diagnosed, both the groups commenced GH replacement after the same interval and experienced similar improvements in clinical parameters after 3 years. Notably, the beneficial effects on QoL were greater in the CD group. Because of the overall, and particularly
the QoL, benefits of GH treatment in patients with CD, we recommend confirmation of GHD when the CD is controlled and initiation of GH replacement in the absence of contraindications.

Declaration of interest

P Jönsson and M Koltowska-Häggström are employed by Pfizer Health AB. All other authors are KIMS investigators, and have received lecture fees from Pfizer, and U Feldt-Rasmussen and B M K Biller from NovoNordisk. C Höybye, P Trainer, U Feldt-Rasmussen, and B M K Biller are members of Pfizer advisory boards.

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