CLINICAL STUDY

Comorbidity and cardiovascular risk factors in adult GH deficiency following treatment for Cushing's disease or non-functioning pituitary adenomas during childhood

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Abstract

Objective: Cushing's disease (CD) and non-functioning pituitary adenoma (NFPA) are rare in paediatric patients. The aim of this study was to describe long-term consequences in adults with GH deficiency (GHD) treated for CD or NFPA during childhood.

Design, patients and methods: This was a retrospective analysis of data from KIMS (Pfizer International Metabolic Database). Background characteristics, anthropometry and comorbidity were studied in 47 patients diagnosed with childhood-onset (CO)-CD and 62 patients with CO-NFPA. Data from 100 ACTH-sufficient patients with CO-idiopathic hypopituitarism (CO-Idio) were used for comparison. Cardiovascular risk profile was analysed at baseline and at 1 year on GH treatment in a subgroup of patients (17 CO-CD, 24 CO-NFPA and 55 CO-Idio) not receiving GH treatment at study entry.

Results: The median age at diagnosis of pituitary tumour was 14.0 years (range 10–17) in patients with CO-CD and 13.7 years (range 8–17) in CO-NFPA. In addition to GHD, 41% of patients with CO-CD had three or four other pituitary hormone deficiencies compared with 78% of patients with CO-NFPA ($P < 0.001$). Eighty-nine per cent of patients with CO-CD had height SDS lower than 0 compared with 61% of patients with CO-NFPA ($P = 0.002$). Hypertension was more common in CO-CD compared with CO-Idio (23 vs 9%, $P = 0.018$). At 1 year on GH treatment, total- and low-density lipoprotein-cholesterol decreased significantly in CO-CD but not in CO-NFPA.

Conclusion: Adult patients with GHD following treatment for paediatric CD and NFPA have long-term adverse consequences. Despite more severe hypopituitarism in CO-NFPA, patients with CO-CD have more frequently compromised final stature.

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Introduction

Pituitary neoplasms are rare in children and adolescents. Of these, the most commonly occurring are craniopharyngiomas (1) and prolactinomas (2, 3). Although no accurate data on prevalence exist, both ACTH-producing pituitary adenomas (Cushing's disease (CD)) and non-functioning pituitary adenomas (NFPAs) are considered extraordinarily rare in childhood (1, 3, 4, 5, 6, 7).

Symptoms and signs in adults with pituitary tumours differ from those in children and adolescents where decreased growth rate, inappropriate weight gain and pubertal delay are early manifestations (1, 5, 8). Paediatric CD may also present with typical Cushingoid features. As ACTH-secreting adenomas are usually small (<5 mm in diameter), symptoms such as

headache and visual field defects due to tumour growth rarely occur (9), in contrast to NFPA which are typically larger (5, 10). As in adults, transsphenoidal surgery is the treatment of choice in children with CD, as well as in those with NFPA requiring treatment due to local symptoms (11). In patients where transsphenoidal surgery is judged to be inappropriate or has been unsuccessful, second-line treatment may become necessary; some of these treatments, such as additional neurosurgical intervention or pituitary radiation, may further compromise pituitary function.

Long-term consequences after cure of paediatric CD have been reported in few studies. Final height and bone mineral density are frequently compromised (12, 13, 14, 15). Anterior pituitary function is also affected in a substantial number of patients (16, 17), especially in those treated with pituitary radiotherapy (17).

Metabolic status after cure is poorly studied in paediatric patients with CD; there are no studies on glucose and lipid metabolism. Only one study addressed blood pressure and demonstrated that 16% of patients had systolic and 4% had diastolic hypertension 1 year post-operatively (18). Long-term outcome in children and adolescents with NFPA has not been systematically studied.

The aim of this study was to analyse the baseline characteristics, anthropometry, comorbidity and cardiovascular risk profile, before and after 1 year of GH replacement therapy, in GH deficiency (GHD) adults treated for childhood-onset CD (CO-CD) and CO-NFPA. The primary comparison was between CO-CD and CO-NFPA. In addition, to distinguish between the impact of adenoma subtype and associated treatment and the effects of GHD, a control group of patients with CO-idiopathic hypopituitarism (CO-Idio) was also studied.

Materials and methods

Patients and study design

Data on patients in this study were obtained from KIMS (Pfizer International Metabolic Database) – a large pharmacoepidemiological surveillance study on GH therapy in adults with GHD (19). Patients who were younger than 18 years when diagnosed with CO-CD or CO-NFPA, and enrolled in KIMS between 1994 and 2009, were identified and compared with a control group of ACTH-sufficient patients with CO-Idio, matched for gender and age at pituitary disease onset. Individual patient data were thoroughly reviewed to exclude functioning pituitary adenomas and other sellar lesions from the NFPA category. For matching purposes, patients with CO-Idio younger than 9 years (as no patients with CO-CD and CO-NFPA were younger than 10 and 8 years respectively) and/or with unknown age at disease onset were excluded. Characteristics of matched CO-Idio and unmatched CO-Idio subjects ($n=919$) from which the 100 matched controls were drawn are shown in Table 1.

Two analyses were performed. The first was a cross-sectional study on background characteristics (gender, age at diagnosis of pituitary disease, age at GHD diagnosis, age at entry into KIMS, pituitary adenoma treatment, hormone deficiencies and previous GH treatment), anthropometry (height, weight and body mass index (BMI)) and comorbidity (hypertension/anti-hypertensive treatment, diabetes mellitus (DM) and anti-diabetic medication, lipid-lowering treatment, history of stroke or coronary artery disease) in all patients, irrespective of previous GH treatment. In this part of the analysis, 47 patients with CO-CD and 62 with CO-NFPA were identified and compared with 100 matched ACTH-sufficient patients with CO-Idio. All

patients were diagnosed with GHD as reported by individual participating centres.

The second was a longitudinal study in which the effect of GH treatment on metabolic risk profile (weight, BMI, waist circumference (WC), blood pressure, serum lipid levels, fasting plasma glucose and HbA1c) was analysed in a cohort with data available from visits at baseline and at 1 year on GH. Patients who had never received treatment with GH (true naïve) or received none during the 6 months before entry into KIMS (semi-naïve) were studied. To be eligible for the longitudinal analysis, GHD had to be confirmed with appropriate stimulation tests (as GH peak $< 3 \mu\text{g/l}$), or patients had to have serum levels of insulin-like growth factor 1 (IGF1) below -2 SDS in combination with panhypopituitarism, in accordance with international guidelines (20). Furthermore, patients with CO-CD were included only if they were tested for GHD at least 1 year after cure of CD. Data on 17 patients with CO-CD, 24 with CO-NFPA and 55 with CO-Idio were analysed in this part of the analysis.

Ethical considerations

The KIMS protocol was approved by the Institutional Review Boards, as required by local regulations in each participating country. Before registration in the database, written informed consent was obtained from patients according to country regulations. KIMS is conducted according to the Declaration of Helsinki.

Methods

Data on background characteristics, comorbidity, height, weight, WC and blood pressure were obtained from KIMS as reported by each participating clinical centre. BMI was calculated as weight/height^2 (kg/m^2). Height SDS was calculated from previously published normative data (21).

Serum IGF1 concentrations were measured at a central facility. Between 1994 and November 2002, serum IGF1 was measured with RIA after acid/ethanol precipitation of IGF-binding proteins (Nichols Institute, San Juan Capistrano, CA, USA). Thereafter, a chemiluminescence immunoassay was used (Nichols Advantage; Nichols Institute Diagnostics, San Clemente, CA, USA). The currently used method (since September 2006) is IMMULITE 2500 (Diagnostic Products Corp., Siemens, Deerfield, IL, USA). For each assay, age- and gender-specific reference ranges were used to determine IGF1 SDS.

Serum levels of total cholesterol (22), HDL-cholesterol (23) and triglycerides (TGs) (24) were measured centrally as described previously. Serum concentrations of LDL-cholesterol were calculated using Friedewald's formula (25). Plasma glucose and HbA1c were analysed locally by each participating centre.

Table 1 Background characteristics at baseline in GHD adults treated for CO-CD, CO-NFPA CO-Idio. Data are presented as mean $\pm$ s.d. (10th–90th percentile).

	CO-CD (n=47)	CO-NFPA (n=62)	CO-Idio matched group (n=100)	Overall CO-Idio unmatched group ^a (n=919)
Male/female (n)	22/25	32/30	50/50	586/333
Age at KIMS start (years)	29.7 $\pm$ 9.2 (20–45)	30.7 $\pm$ 10.5 (19–45)	29.0 $\pm$ 9.9 (18–42)	27.7 $\pm$ 10.0 (18–42)
Age at diagnosis of pituitary disease (years)	13.9 $\pm$ 2.6 (10–17)	13.3 $\pm$ 4.0 (8–17)	13.8 $\pm$ 2.4 (10–17)	8.6 $\pm$ 4.7 (2.5–17)
Age at GHD diagnosis (years)	24.0 $\pm$ 10.9 (12–38)	22.8 $\pm$ 11.9 (12–40)	18.7 $\pm$ 8.9 (11–34) ^{†,‡}	13.6 $\pm$ 11.1 (3.5–29)
Time from diagnosis of pituitary disease to diagnosis of GHD (years)	10.1 $\pm$ 10.6 (0–26)	9.6 $\pm$ 11.9 (0–30)	4.8 $\pm$ 9.3 (0–21) ^{‡,A}	5.0 $\pm$ 10.2 (0–20)
Time from diagnosis of pituitary disease to start of GH treatment in adulthood (years)	15.1 $\pm$ 9.2 (6–30)	16.5 $\pm$ 10.3 (5–31)	14.6 $\pm$ 9.9 (2–28)	18.4 $\pm$ 9.9 (7–31)
Treatment (%)				
Surgery	51	38	0	0
Radiotherapy	13	6	0	0
Surgery and radiotherapy	32	38	0	0
Hormone deficiencies (%)				
ACTH	70	82	0 ^{‡,A,b}	43
TSH	65	85 [§]	57 ^{*,A}	61
LH/FSH	67	89	68 [†]	63
ADH	20	44	12 ^A	6
GH treatment status (%) ^c				
Non-naïve	49	46	35	35
Semi-naïve	15	21	54	58
True naïve	36	33	11	7
Duration of GH treatment before entry into KIMS (semi- and non-naïve patients)	6.7 $\pm$ 4.3 (0.5–12)	6.2 $\pm$ 4.7 (0.7–13)	3.8 $\pm$ 3.7 (0.3–9.1)	4.6 $\pm$ 4.0 (0.3–10)

Significant differences between CO-CD and CO-Idio: * $P \leq 0.05$, [†] $P \leq 0.01$, [‡] $P \leq 0.001$; significant differences between CO-CD and CO-NFPA: [§] $P \leq 0.05$, ^{||} $P \leq 0.01$; significant differences between CO-NFPA and CO-Idio: [†] $P \leq 0.01$, ^A $P \leq 0.001$. ADH, anti-diuretic hormone; GHD, GH deficiency; TSH, thyroid-stimulating hormone.

^aNo statistical analyses were performed between the unmatched CO-Idio and the other three groups; they are shown in this table to indicate the overall CO-Idio data set from which the 100 matched patients were drawn.

^bAll matched CO-Idio patients were ACTH sufficient according to study design.

^cNon-naïve, patients on GH replacement treatment at study entry; semi-naïve, patients off GH replacement for at least 6 months before study entry; true naïve, patients who had never received GH before study entry.

The presence of DM was defined as any of the following:

- i) DM and/or use of anti-diabetic medication reported at entry; ii) fasting plasma glucose > 7 mmol/l; iii) non-fasting plasma glucose > 11.1 mmol/l; or iv) HbA1c $> 6.5\%$. When only fasting blood glucose was available, the values were multiplied by a factor of 1.1 for conversion to fasting plasma glucose. The presence of hypertension was defined as a history of hypertension and/or anti-hypertensive treatment at entry or blood pressure $> 130/85$ mmHg. Dyslipidemia was defined as use of lipid-lowering treatment at entry or any of the following: i) total cholesterol > 5.2 mmol/l; ii) HDL-cholesterol < 1.04 mmol/l in males and < 1.3 mmol/l in females; iii) LDL-cholesterol > 3.4 mmol/l; or iv) TG > 1.7 mmol/l.

For patients receiving treatment with cortisone acetate (CA) or prednisolone, the hydrocortisone (HC) equivalent (HCEq) dose was calculated. Thus, the equivalent dose of 20 mg HC was 25 and 5 mg for CA and prednisolone respectively, as described previously (26).

Statistical analysis

Values are expressed as mean $\pm$ s.d. or median (10–90 percentiles). The significance of effects between groups

was calculated by unpaired *t*-tests for normally distributed data and the Wilcoxon rank-sum tests for non-normally distributed data. The significance of effects within groups was calculated by the signed rank test. For proportions, Pearson's χ^2 or Fisher's exact test was used as appropriate. All statistical tests performed were pair-wise tests, and no adjustment for multiplicity was made. A *P* value of < 0.05 was considered statistically significant.

Results

Cross-sectional study

Background characteristics The mean age at diagnosis of CD ($n = 47$) was 13.9 ± 2.6 years (median 14.0, range 10–17) and of NFPA ($n = 62$) was 13.3 ± 4.0 years (median 13.7, range 8–17; $P = 0.340$). Gender distribution was similar between the groups: 25 (53%) women in the CO-CD group and 30 (48%) women in the CO-NFPA group ($P = 0.563$). Age at baseline (entry into KIMS) did not differ between the groups (Table 1). Time from diagnosis of pituitary disease onset to diagnosis of

GHD was longer in patients with CO-CD (10.1 ± 10.6 years, median 7.8, range 0–26) and CO-NFPA (9.6 ± 11.9 years, median 9.6, range 0–30) compared with patients with CO-Idio (4.8 ± 9.3 years, median 0.2, range 0–21; $P < 0.001$). Time from diagnosis of pituitary disease to beginning of GH treatment in adulthood did not differ between the groups (Table 1).

Patients with CO-CD had less severe hypopituitarism, expressed as the number of anterior pituitary hormone deficits, compared with CO-NFPA (Fig. 1). Of the CO-CD patients, 70% had ACTH insufficiency, 65% had TSH deficiency and 67% had hypogonadotrophic hypogonadism compared with 82% ($P = 0.133$), 85% ($P = 0.003$) and 89% ($P = 0.007$) of patients with CO-NFPA respectively (Table 1). In addition to GHD, 41% of patients with CO-CD had three or four other pituitary hormone deficiencies compared with 78% of patients with CO-NFPA ($P < 0.001$). The mean HCeQ dose for ACTH-insufficient patients was 23.6 ± 7.0 mg/day in CO-CD and 22.2 ± 8.1 mg/day in CO-NFPA ($P = 0.659$).

Information about the primary treatment for the pituitary adenoma was available in 45 of 47 patients with CO-CD and 51 of 62 patients with CO-NFPA ($P = 0.034$; Table 1). Of the CO-CD patients, 24 (51%) were treated with pituitary surgery alone, six (13%) with radiotherapy alone and 15 (32%) with both surgery and radiotherapy. Seven patients (15%) were receiving treatment with fludrocortisone, indicating previous bilateral adrenalectomy. Twenty-three (38%) patients with CO-NFPA were treated with pituitary surgery alone, four (6%) with radiotherapy alone and 24 (38%) with both surgery and radiotherapy.

Visual field defects were less frequently reported in patients with CO-CD (two of 23, 8.7%) compared with patients with CO-NFPA (14 of 29, 48%; $P = 0.002$). Ophthalmoplegia was reported in none of the

22 patients with CO-CD and in three of the 27 patients with CO-NFPA (11%; $P = 0.159$).

Anthropometry at baseline Patients with CO-CD were shorter (162 ± 9 cm, $P = 0.538$) compared with CO-NFPA (167 ± 12 cm, $P = 0.025$) but not compared with CO-Idio (161 ± 9 cm, $P = 0.002$). Mean height SDS was -1.3 ± 1.2 in CO-CD ($P = 0.423$), -0.7 ± 1.7 in CO-NFPA ($P = 0.037$) and -1.6 ± 1.8 in CO-Idio ($P = 0.003$). Forty (89%) patients with CO-CD ($P = 0.002$) had height SDS lower than 0 compared with 38 (61%) with CO-NFPA ($P = 0.002$) and 83 (83%) with CO-Idio ($P = 0.002$; Fig. 2). Comparable proportions of male and female patients had SDS below -2 in all the three groups (data not shown).

Weight and BMI did not differ between CO-CD (75 ± 23 kg and 28.8 ± 10.5 kg/cm² respectively) and CO-NFPA (75 ± 21 kg and 26.6 ± 5.9 kg/cm², $P = 0.929$ and 0.173 respectively). Patients with CO-CD tended to weigh more and have higher BMI compared with CO-Idio (68 ± 20 kg and 26.2 ± 7.4 kg/cm² respectively), although the difference did not reach statistical significance ($P = 0.088$ and 0.090 respectively). Fifteen (34%) patients with CO-CD ($P = 0.128$) had BMI above 30 kg/cm² compared with 13 (21%) CO-NFPA ($P = 0.151$) and 21 (21%) CO-Idio ($P = 0.944$; Fig. 3).

Patients with CO-CD who had never received treatment with GH before entering KIMS (true naïve, $n = 16$) showed a tendency towards shorter stature (median 157 cm, range 147–177) and higher BMI (median 30.1 kg/m², range 20.3–39.4) compared with semi- and non-naïve patients ($n = 29$; median height: 165 cm, range 153–174; median BMI 24.7 kg/m², range 19.6–37.6; $P = 0.068$ and 0.077 respectively).

Height, weight and BMI did not differ between ACTH-sufficient and -insufficient patients, neither in CO-CD nor in CO-NFPA (data not shown).

Figure 1 Number of additional pituitary hormone deficiencies (expressed in %) in adult patients treated for CO-CD, CO-NFPA and CO-Idio. Forty-one per cent of patients with CO-CD had three or four additional pituitary hormone deficiencies compared with 78% CO-NFPA ($P < 0.001$). Fifteen per cent of patients with CO-CD had four additional pituitary hormone deficiencies compared with 44% CO-NFPA ($P < 0.01$). No patient with CO-Idio had four other pituitary hormone deficiencies as all were ACTH sufficient according to study design.

Co-morbidities at baseline At baseline, 11 (23%) patients with CO-CD and 11 (14%) with CO-NFPA had hypertension ($P = 0.220$). The prevalence of hypertension was lower in CO-Idio ($n = 9$, 9%) compared with CO-CD ($P = 0.018$) but not with CO-NFPA ($P = 0.294$).

The prevalence of dyslipidemia did not differ between the groups: 23% in CO-CD, 20% in CO-NFPA and 17% in CO-Idio ($P = 0.814$). Only two patients had type 2 DM at baseline: one with CO-CD and one with CO-Idio. Two patients in CO-NFPA group and two in CO-Idio group were reported to have coronary artery disease. No patient was reported to have cerebrovascular disease.

Longitudinal study

Metabolic risk profile at baseline and treatment effects of GH at 1 year Data from 17 patients with CO-CD, 24 with CO-NFPA and 55 with CO-Idio were analysed.

Figure 2 Height SDS (expressed in %) in adult patients treated for CO-CD, CO-NFPA and CO-Idio. Eighty-nine per cent of patients with CO-CD ($P=0.349$) had height SDS lower than 0 compared with 61% of patients with CO-NFPA ($P=0.002$) and 83% of patients with CO-Idio ($P=0.002$). Twenty-four per cent of patients with CO-CD ($P=0.127$) had height SDS lower than -2 compared with 19% of patients with CO-NFPA ($P=0.527$) and 37% of patients with CO-Idio ($P=0.016$).

At baseline, weight, BMI, WC, blood pressure, serum lipid levels, fasting plasma glucose and HbA1c did not differ between patients with CO-CD and CO-NFPA (Table 2). CO-Idio had lower body weight, BMI, total cholesterol and LDL-cholesterol compared with CO-CD and higher fasting plasma glucose than CO-NFPA.

The mean GH dose at 1 year on treatment was comparable in the following groups: 0.43 ± 0.23 mg/day in CO-CD, 0.49 ± 0.21 mg/day in CO-NFPA and 0.40 ± 0.26 mg/day in CO-Idio. IGF1 SDS increased significantly to comparable levels in all the groups, from -3.2 ± 2.2 to -0.8 ± 2.2 in CO-CD, from -3.1 ± 2.3 to -0.4 ± 1.9 in CO-NFPA and from -4.1 ± 2.1 to -1.3 ± 1.7 in CO-Idio (Table 2). Weight, BMI and WC did not change significantly at 1 year in patients with CO-CD and CO-Idio (Table 2). In CO-NFPA group, WC and weight increased significantly but not BMI. Total- and LDL-cholesterol decreased in both CO-CD and CO-Idio groups but not in CO-NFPA group. Blood pressure, HDL-cholesterol, TG, fasting plasma glucose and HbA1c levels did not change significantly in any of the groups.

Discussion

CD and NFPA are extremely rare in the paediatric population. The current study is one of the largest series on CO-CD and to our knowledge the first to describe patients who had CO-NFPA. The study, which focused on those with GHD on replacement in adulthood, demonstrates that paediatric onset of both CD and NFPA may have serious consequences for adult health. In both the groups, adult height was lower than expected, more than half of the patients were overweight or obese and pituitary deficiencies in addition to GHD were common.

Pituitary hormone deficiencies in patients in remission after treatment for CO-CD have been reported in smaller studies. In a study of 40 surgically treated patients, only 25% had hypopituitarism, of whom the majority had isolated GHD (12). In another study, the prevalence of hypopituitarism was 10% after the primary operation and 45% after a subsequent operation (16). In patients treated with pituitary radiotherapy following unsuccessful transsphenoidal surgery, GHD was reported in five out of six patients 1 year later (17). On retesting at a mean of 9.3 years after radiotherapy, three out of four patients were GH sufficient and other anterior pituitary functions were normal in five out of six patients. In the current study, 32% of CO-CD patients were treated with both transsphenoidal surgery and radiotherapy and presumably a further 15% with bilateral adrenalectomy. Reporting of bilateral adrenalectomy is not mandatory in KIMS, so this conclusion is based on the assumption that patients receiving fludrocortisone had been treated with adrenalectomy. The differences seen between this study and the previous reports may be due to the fact that all patients in the KIMS database per definition have GHD and often other pituitary dysfunction and therefore represent patients at one end of a spectrum of long-term consequences of the disease and its treatment, whereas other studies may have included more unselected patient groups. Nevertheless, the current report highlights the high rate of pituitary deficiencies in a large cohort of adults who had received treatment during childhood for two pituitary adenoma subtypes that are rare in paediatrics.

The majority of patients with adult-onset CD are women (27). In the paediatric population on the other hand, the gender distribution has been reported as equal and our results were in agreement with previous studies (4). In our study, the mean age at diagnosis also did not differ between boys and girls, in contrast to

Figure 3 BMI categories (expressed in %) in adult patients treated for CO-CD, CO-NFPA and CO-Idio. Fifteen (34%) patients with CO-CD ($P=0.128$) had BMI more than 30 compared with 13 (21%) patients with CO-NFPA ($P=0.151$) and 21 (21%) patients with CO-Idio ($P=0.944$).

Table 2 Anthropometry and cardiovascular risk profile at baseline and change at 1 year on GH replacement in GH deficiency adults, treated for CO-CD, CO-NFPA and CO-Idio. Data are presented as mean $\pm$ s.d.

	CO-CD (n=17)		CO-NFPA (n=24)		CO-Idio (n=55)	
	Baseline	Change	Baseline	Change	Baseline	Change
Height (cm)	162 $\pm$ 7	0.3 $\pm$ 0.6	165 $\pm$ 11	0.3 $\pm$ 0.6	161 $\pm$ 11	0.3 $\pm$ 1.0
Weight (kg)	80 $\pm$ 25	-0.6 $\pm$ 4.1	72 $\pm$ 22	1.5 $\pm$ 5.3	68 $\pm$ 17*	1.1 $\pm$ 5.1
BMI (kg/cm ²)	31.1 $\pm$ 11.5	-0.4 $\pm$ 1.6	26.0 $\pm$ 6.7	0.3 $\pm$ 2.1	26.0 $\pm$ 6.1*	0.32 $\pm$ 1.9
WC (cm)	92 $\pm$ 15	-2.5 $\pm$ 6.1	88 $\pm$ 15	1.6 $\pm$ 3.0 ^{†,}	86 $\pm$ 15	-0.1 $\pm$ 6.9
SBP (mmHg)	117 $\pm$ 14	0.8 $\pm$ 10	115 $\pm$ 14	1.2 $\pm$ 13	116 $\pm$ 13	-4.3 $\pm$ 13
DBP (mmHg)	76 $\pm$ 10	-3.8 $\pm$ 10	74 $\pm$ 11	-1.4 $\pm$ 9	72 $\pm$ 9	1.1 $\pm$ 9
IGF1 SDS	-3.2 $\pm$ 2.2	2.9 $\pm$ 1.5 [§]	-3.1 $\pm$ 2.3	3.1 $\pm$ 2.2	-4.1 $\pm$ 2.1	3.1 $\pm$ 2.3
Cholesterol (mmol/l)	6.5 $\pm$ 1.4	-0.9 $\pm$ 0.7 [§]	5.5 $\pm$ 1.2	-0.3 $\pm$ 0.5 [†]	5.6 $\pm$ 1.4*	-0.4 $\pm$ 0.6
LDL-cholesterol (mmol/l)	4.2 $\pm$ 1.0	-0.9 $\pm$ 0.7 [§]	3.6 $\pm$ 1.0	-0.4 $\pm$ 0.8	3.6 $\pm$ 1.4*	-0.5 $\pm$ 0.5
HDL-cholesterol (mmol/l)	1.2 $\pm$ 0.3	-0.1 $\pm$ 0.1	1.1 $\pm$ 0.2	0.1 $\pm$ 0.2	1.3 $\pm$ 0.5	0.0 $\pm$ 0.3
TG (mmol/l)	1.8 $\pm$ 1.2	0.5 $\pm$ 1.1	1.7 $\pm$ 0.8	0.1 $\pm$ 1.0	1.7 $\pm$ 1.3	-0.2 $\pm$ 1.1
Fasting plasma glucose (mmol/l)	4.6 $\pm$ 0.7	-0.2 $\pm$ 0.5	4.3 $\pm$ 0.4	-0.1 $\pm$ 0.9	4.7 $\pm$ 0.7 [‡]	0.2 $\pm$ 0.7
HbA1c (%)	4.7 $\pm$ 0.7	0.1 $\pm$ 0.4	4.7 $\pm$ 0.6	0.2 $\pm$ 0.4	5.0 $\pm$ 0.8	0.0 $\pm$ 0.4

Significant differences between CO-CD and CO-Idio: * P <0.05; significant differences between CO-CD and CO-NFPA: † P <0.05; significant differences between CO-NFPA and CO-Idio: ‡ P <0.05; significant differences for change (within the groups) CO-CD: § P <0.05, CO-NFPA: || P <0.05, CO-Idio: || P <0.05. BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

another study indicating that boys were diagnosed at a younger age than girls (28).

NFPA is exceptionally rare in children and adolescents. In a group of children requiring surgical treatment for pituitary adenoma, 4–6% have NFPA (6, 7). To our knowledge, no long-term follow-up studies have been conducted in patients with paediatric NFPA. Although pituitary insufficiency was common in the CO-CD group in this study, thyrotrophin and gonadotrophin deficiency as well as diabetes insipidus were even more common in patients with CO-NFPA. Patients with CO-NFPA also had more frequently reported visual field defects than the CO-CD group, which is most likely due to a larger tumour size in the CO-NFPA patients.

Growth retardation is one of the cardinal features of paediatric CD (12, 13, 14, 15). The main mechanisms thought to be involved are glucocorticoid-induced impairment of GH secretion and peripheral IGF1 resistance (29). In our study, 89% had height SDS below 0 and one-fourth had SDS below -2. Patients with CO-CD had shorter stature compared with CO-NFPA, despite more severe hypopituitarism in the latter group supporting the concept that the hypercortisolism associated with CD is most likely a key mechanism behind their short stature. To evaluate the potential effect of hypercortisolism and/or glucocorticoid replacement treatment on height, we included a comparison group of ACTH-sufficient patients with CO-Idio. Interestingly, patients with CO-Idio had final height comparable to CO-CD in contradiction with the above supposition. It is important to note that the adult CO-Idio patients may not be typical of the overall paediatric population with this disorder. Many of the patients in our cohort were first diagnosed with GHD in adulthood, demonstrated by the mean diagnostic delay of 5 years. Furthermore, as many had other pituitary hormone deficiencies, it is likely that the GHD *per se* was

not the dominating clinical problem at the time when pituitary disease was first diagnosed in some of the patients. However, the short median time from pituitary disease onset to GHD diagnosis confirms that at least 50% of patients were diagnosed with GHD in connection with diagnosis of pituitary disease.

Twenty-three per cent of adult patients with a history of treated CO-CD had hypertension, which was significantly more prevalent compared with CO-Idio, confirming the results from a previous study (18). Even though our study lacked data from healthy controls, the prevalence of hypertension seemed high for a group of individuals with a mean age of 30 years (30). In a recent study on adult-onset GHD patients from HypoCCS, another surveillance database, adult patients with GHD, previously treated for CD, had greater prevalence of cardiovascular and cerebrovascular disease compared with patients treated for NFPA (31). Prevalence of DM and the metabolic syndrome did not differ between the groups. It is important to note that patients in that study were older (mean age of 38 years in the CD group and 48 years in the NFPA group), and none had CO disease. In this study, which focuses on CO patients, the prevalence of DM, stroke and coronary artery disease was low in all the three groups. Owing to the different age of onset of GHD and the relatively young age at entry in the current study, it is difficult to compare the cohorts reported from the two databases.

In CD, GH secretion can be impaired for at least 12 months after surgical treatment (29, 32). Patients with CO-CD were, therefore, only included in the longitudinal analysis if they were tested for GHD at least 1 year after cure of CD. While some authors recommend early evaluation and commencement of GH administration in order to accelerate linear growth and ensure optimal height achievement after treatment of CD in children (33), others had a more conservative approach (18). In

our study, although not statistically significant, height tended to be lower in patients who had never received GH treatment before entry compared with those who had received GH treatment. Our results, therefore, lend support for the former approach, although we emphasise that individual judgment is needed depending on factors such as age and pubertal stage.

The small number of patients limits interpretation of the results from the longitudinal analysis. Response to 1 year of GH treatment was similar in all the groups. Although weight, BMI and WC decreased in CO-CD patients, the change did not reach statistical difference. A surprising finding was that weight and WC increased in CO-NFPA patients while BMI did not. The most reasonable explanation for this discrepancy is the slight, but significant, increase in height that was also observed. Total cholesterol decreased in all the three groups and, in the CO-CD and CO-Idio groups, a decrease in LDL-cholesterol was also seen. The beneficial effect on cholesterol levels is thus comparable to that in patients with adult-onset disease (34). The decrease in total cholesterol was greater in CO-CD compared with CO-NFPA. Whether this is due to different mechanisms of GH action in these two patient groups or simply because CD patients lost weight (although not significantly) while NFPA gained weight remains unclear.

The study has several limitations such as the retrospective analysis on prospectively collected data, the lack of a normal control group and selection of the study population from a group of patients diagnosed with GHD, and thus not representing patients with CO-CD and NFPA at large. Furthermore, information on pituitary histology is not available in KIMS, which raises the question of misclassification of patients with NFPA, i.e. whether some of these patients might have other types of pituitary tumours such as craniopharyngiomas or prolactinomas. Although this cannot be ruled out, it is highly unlikely as the clinical, laboratory and radiological characteristics of NFPA, prolactinomas and craniopharyngiomas are usually quite different as is the post-operative management. Furthermore, all the available data, such as medical history, were thoroughly reviewed in order to minimise the risk of misclassification.

In conclusion, in this group of selected patients with adult GHD following treatment for rare paediatric pituitary adenomas, CD and NFPA, a high frequency of pituitary hormone deficiencies was seen and adult height was lower than expected, particularly in CO-CD. Further studies of the long-term impact of childhood CD and NFPA on adult health are important.

Declaration of interest

O Ragnarsson is a KIMS investigator and has received lecture fees from Pfizer. C Höybye is a KIMS investigator and member of Pfizer's Swedish study advisory board, has received lecture fees from Pfizer and Novo Nordisk and Otsuka and research grants from Pfizer, Novo Nordisk

and Ipsen. P J Jönsson and M Koltowska-Häggström are permanent employees of Pfizer Health AB. U Feldt-Rasmussen is a KIMS investigator and member of KIMS Strategic advisory board, has received lecture fees from Pfizer, Novo Nordisk, Merck Serono and Otsuka and research grants from Pfizer, Novo Nordisk, Novartis and Ipsen. G Johannsson owns stock in DuoCort AB and has received lecture fees from Novo Nordisk, Eli Lilly, Merck Serono and Pfizer. B M K Biller has received research grants from Eli Lilly, Novartis, Novo Nordisk and Pfizer and consulting honoraria from DuoCort, Novo Nordisk, Novartis and Pfizer.

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