Long-term effects of growth hormone replacement therapy in childhood-onset craniopharyngioma: results of the German Craniopharyngioma Registry (HIT-Endo)

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Abstract

Objective: Quality of survival, prognosis and long-term outcome are often severely impaired in childhood-onset craniopharyngioma (CP) patients. Identification of risk factors for sequelae such as growth hormone (GH) deficiency is important for appropriate treatment and rehabilitation.

Design: In a cross-sectional study, 79 CP patients recruited in HIT-Endo before 2000 were analyzed according to GH substitution: (a) CP never GH treated (noGH); (b) CP GH treated only during childhood (pedGH); (c) CP under GH, initiated at adulthood (adultGH); (d) CP under GH during childhood and continued during adulthood (contGH).

Methods: Progression-free (PFS) and overall survival (OS), height, BMI, psychosocial and neuropsychological status (EORTC QLQ-C30, MFI-20).

Results: OS and PFS rates were similar in all subgroups. ContGH and pedGH CP presented with increases in height ($P=0.002$; $P=0.0001$) during long-term follow-up when compared with baseline. In all subgroups except for pedGH, increases in BMI were observed when compared with BMI at diagnosis. For emotional functionality and physical fatigue, adultGH CP showed worse ($P=0.037$; $P=0.034$) response (mean: 61.4%; 12.5%) when compared with pedGH CP (mean: 83.5%; 7.7%). Observed differences were not related to irradiation and hypothalamic involvement. In terms of psychosocial status, no differences were observed between subgroups.

Conclusions: We conclude that GH substitution was safe with regard to risk of tumor progression/relapse in CP. Growth was improved by GH, whereas the development of obesity was not influenced by GH substitution. However, early initiation of GH substitution after CP diagnosis might have beneficial effects on weight development and neuropsychological outcome.

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Introduction

Childhood-onset craniopharyngioma (CP) is a rare embryonic tumor, arising from remnants of Rathke pouch (1, 2). Although the tumor typically presents with histological signs of low-grade malignancy (WHO

grade 1) and overall survival is high in CP patients, quality of survival (QoS) is frequently reduced due to considerable morbidity (3, 4). QoS and long-term outcome in survivors of CP are severely reduced due to hormonal deficits that

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typically result in obesity and stunted growth (5, 6). Furthermore, hypothalamic involvement (HI) and surgical lesions of hypothalamic structures cause considerable QoS impairments (7, 8, 9, 10). Growth hormone (GH) substitution has been safely and successfully used to treat and/or prevent short stature in childhood cancer survivors and CP patients (11, 12, 13, 14). The impact of GH substitution therapy on psychosocial status, QoS, weight and height, in long-term survivors of CP patients is not well characterized.

Because prospective studies analyzing impact of GH substitution on QoS in CP patients do not exist, QoS, weight development and growth of CP patients recruited in the German Craniopharyngioma Registry were evaluated with regard to age at initiation, dosage and duration of GH replacement therapy (15).

Subjects and methods

Patients

We analyzed history before CP diagnosis in 280 childhood-onset CP patients, diagnosed between 1966 and 2000, registered in the German Craniopharyngioma Registry (NCT00258453; NCT01272622) and recruited in our prospective multicenter trial HIT-Endo and KRANIOPHARYNGEOM 2000/2007 (16). HIT-Endo trial data include data on physical condition, auxiological parameters and an evaluation of the patient's records for history, clinical manifestations, imaging results, operative strategies, irradiation (dosage, age at initiation) and treatment period of GH substitution therapy. In all cases included in our cross-sectional study, the histological diagnosis of adamantinomatous CP was confirmed by neuropathological reference assessment. HI was reference assessed by a neuroradiologist blinded for clinical data-based CT, MRI and/or neurosurgical intraoperative inspection. HI was assumed when involvement of hypothalamic structures either by CP growth into hypothalamus or displacement of hypothalamic structures by CP. Tumor size was calculated using maximal tumor diameters in two dimensions based on reference assessment of neuroradiological imaging.

In our cross-sectional study, we were able to analyze prognoses in 261 of 280 (93%) long-term survivors of CP with a minimum of 10-year follow-up (16). Four questionnaires were mailed to 93 patients for whom current postal addresses were available, to collect data on current height and body weight, GH substitution, psychosocial and neuropsychological status, and physical

and mental fatigue. Seventy-nine of 93 (85%) patients answered the questionnaires. Long-term survivors after CP, eligible for study participation, were analyzed according to GH substitution in four subgroups: (a) patients, who never received GH substitution (noGH), (b) patients, who received GH substitution only during childhood and did not continue during adulthood (pedGH), (c) patients, who started GH substitution at adulthood after not having received GH substitution therapy during childhood (adultGH), and (d) patients, who started GH substitution during childhood and continued after reaching adult age i.e. these patients presented under GH substitution at time of study (contGH). All CP showed clinical symptoms (reduced growth velocity and/or short stature) and laboratory findings indicative for GH deficiency after CP diagnosis i.e. pathological findings (GH <8.0 ng/mL) in two stimulating tests. Time point of initiation and duration of GH substitution therapy were based on decision of local treating physicians.

The study was approved by the local standing-committee on ethical practice of Medizinische Fakultät, Julius-Maximilians-Universität Würzburg, Germany (approval: 94/06), and written parental and/or patient consent was obtained in all cases. All procedures performed in our study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Auxiological data

Height and weight were analyzed based on measurements performed by clinicians participating in HIT-Endo at three time points: at CP diagnosis, 8–12 years after CP diagnosis, and during long-term follow-up i.e. >12 years after CP diagnosis. Height was evaluated by calculating height SDS according to references of Prader *et al.* (17). The degree of obesity was analyzed by calculating the BMI SDS according to references of Rolland-Cachera *et al.* (18).

Questionnaires

The EORTC QLQ-C30 questionnaire measures health-related QoS in cancer survivors and consists of single-item measures and multi-item scales, including three symptom scales, five functional scales, a global QoS/health status scale and six single items (19). The scores of the single items and scales are assessed as percentages. A 100% score refers to the highest item response; a 0% score of represents no response. Global health status and functional scales

are scored positively; the higher the percentage, the better global health status and functioning. Symptom scales are scored negatively; the higher the percentage, the more symptoms are observed (19).

The MFI-20 questionnaire quantifies fatigue in five dimensions: general fatigue, mental fatigue, reduced activity, physical fatigue and reduced motivation. MFI-20 domains are assessed by 20 questions, which are scored on a likert scale ranging from 1 to 5. Each of the five MFI-20 domains represent a score ranging from 4 to 20; the higher the score, the more response for the respective domain and the more fatigue the patient is observed to experience (20).

In adult long-term CP survivors aged >20 years at the time of study, a newly designed questionnaire was used to assess psychosocial status (10).

Statistical analyses

Statistical analysis was performed using SPSS 19.0 (SPSS, Inc.). Mann–Whitney *U* test was used for comparison of continuous variables between two independent groups and Wilcoxon signed-rank test was used for comparison of two related groups for continuous variables. Chi-square test was used for comparison of different groups for categorical variables. Progression-free survival (PFS) and overall survival (OS) rates were estimated by Kaplan–Meier analyses. Events for estimation of PFS were defined as neuroradiologically confirmed >20% progression of residual tumor, reference-confirmed tumor recurrence after reference-confirmed complete surgical resection and death. Inferential statistics are intended to be exploratory (hypotheses generating), not confirmatory, and are interpreted accordingly. The local significance level is set to 0.05, i.e. *P* values of ≤ 0.05 were considered statistically significant. No adjustment for multiple testing was applied.

Results

Long-term outcome and survival rates

Childhood-onset CP patients ($n=280$) diagnosed between 1966 and 2000 were registered in the German Craniopharyngioma Registry and analyzed prospectively in the multicenter studies HIT-Endo and KRANIOPHARYNGEOM 2000/2007 (16). Long-term outcome with regard to GH substitution could be analyzed in 79 (28%) of these patients. The questionnaires used to analyze GH substitution therapy in patient history and the current height and body weight, QoS and psychosocial status of long-term survivors recruited in HIT-Endo were mailed at least 9.8 years after CP diagnosis

to 93 of 280 patients (33%); 79 CP patients (85%) responded and 14 CP patients (15%) did not. No differences in terms of gender, age at CP diagnosis, BMI SDS, follow-up interval, degree of surgical resection and HI were observed between the participating group of CP patients and the group of CP patients not responding to the mailing and therefore not participating in our study (data not shown).

Patient characteristics and auxiological data of 79 participating CP patients (36 males, 43 females) are depicted in Table 1. Median age at the time of diagnosis was 9.2 years. Median time interval between CP diagnosis and study was 15.9 years, ranging from 9.8 to 33.8 years. Median age at evaluation was 31 years, ranging from 20 to 48 years. The median BMI SDS at CP diagnosis was +0.68 s.d. (range: -2.7 to $+7.0$ s.d.). The median BMI SDS at study was +3.14 s.d. (range: -0.79 to $+10.90$ s.d.) ($P<0.001$). All CP patients underwent surgery. In 30 CP patients (38%), a total resection was achieved, in 43 (54%) patients an incomplete resection, and for 6 (8%) patients the degree of surgical resection was not specified. A total of 39 CP patients (49%) presented with reference-confirmed HI and 38 (48%) without HI at the time of primary diagnosis. Because of limited quality of MRI diagnostics, HI status could not be specified in two patients (3%).

We compared characteristics of GH subgroups and observed no differences with regard to gender, age at diagnosis, symptoms in patient history and follow-up period. Tumor size, location and HI were similar in each subgroup. No differences between GH subgroups were detectable in terms of degree of surgical resection and the rate of performed radio oncological treatments (external photon irradiation, median dose: 54 Gy) (Table 1).

OS rates were similar for all analyzed subgroups. Two fatal events occurred, one in the nonGH and one in the contGH subgroup. In 65 of 79 CP patients, data for estimation of PFS by Kaplan–Meier analyses were available. PFS rates were comparable between the contGH, pedGH, adultGH, noGH patient subgroups ($P=0.0893$) (Fig. 1).

Height development

We compared height development in our GH subgroups for the time points (a) at the time of CP diagnosis, (b) during 8–12 years of follow-up and (c) after >12-year follow-up after CP diagnosis. Patients substituted with GH during growth phase (contGH and pedGH subgroups) presented with significant increases in height SDS (contGH: $P=0.002$; pedGH: $P=0.0001$) during long-term follow-up when compared with height at diagnosis. In patients without GH substitution (noGH)

Table 1 Patient characteristics of childhood-onset craniopharyngioma patients (CP) recruited in HIT-Endo who did not participate in the current cross-sectional study (NP) and characteristics of participating HIT-Endo patients included in the study (SC) with regard to growth hormone (GH) substitution therapy.

	NP	SC	P (NP vs SC)		noGH	contGH	pedGH	adultGH	P GH-sub- groups
Patients, n (%)	205 (100)	79 (100)			8 (10)	34 (43)	26 (33)	11 (14)	
Gender, male/female, n (%)	110 (54)/95 (46)	36 (46)/43 (54)	0.965		3 (37)/5 (63)	18 (53)/16 (47)	11 (42)/15 (58)	4 (36)/7 (64)	0.741
Age at diagnosis (years)	9.3 (0.05–27)	9.2 (2–18)	0.271		8.7 (4–17)	8.1 (3–18)	8.1 (3–17)	11.9 (2–18)	0.439
Age at last visit/study (years)	23.1 (1.5–56.4)	31.0 (20–48)	0.168		29.5 (26–43)	31.5 (21–46)	28.0 (20–48)	35.0 (26–48)	0.214
Follow-up time (years)	14.1 (0.1–38.9)	15.9 (9.8–33.8)	0.303		15.8 (13.9–25.2)	16.6 (9.9–27.6)	13.5 (9.8–33.8)	16.2 (10.3–27.4)	0.556
Tumor location, n (%)									
Extrasellar	7 (3)	9 (11)	0.532		/	4 (12)	4 (15)	1 (9)	1.000
Intra and extrasellar	4 (2)	30 (38)			/	14 (41)	11 (42)	5 (45)	
Intrasellar	32 (16)	/			/	/	/	/	
n.a.	162 (79)	40 (50)			8 (100)	16 (47)	11 (42)	5 (45)	
Tumor size (cm ²)	9.0 (1.0–36)	8.0 (1.5–64)	0.117		13.5 (3–64)	7.8 (1.5–30)	6.9 (4–13)	13.0 (6–25)	0.424
Hypothalamic involvement, n (%)									
Confirmed involvement	101 (49)	39 (49)	0.100		2 (25)	15 (44)	13 (50)	9 (82)	0.083
No involvement	58 (28)	38 (48)			6 (75)	18 (53)	12 (46)	2 (18)	
n.a.	46 (22)	2 (2)			/	1 (3)	1 (4)	/	
Degree of resection, n (%)									
Complete resection	63 (31)	30 (38)	0.531		4 (50)	15 (44)	8 (31)	3 (27)	0.709
Incomplete resection	93 (45)	43 (54)			4 (50)	17 (50)	16 (61)	6 (54)	
n.a.	49* (23)	6 (8)			/	2 (6)	2 (8)	2 (18)	
Irradiation, n (%)									
Irradiation	66 (32)	27 (34)	0.256		1 (12)	9 (26)	14 (54)	3 (27)	0.258
No irradiation	94 (46)	44 (56)			6 (75)	21 (62)	10 (38)	7 (64)	
n.a.	45 (22)	8 (10)			1 (12)	4 (12)	2 (7)	1 (9)	
Growth hormone substitution									
Age at initiation (years)	/	12 (1–38)			/	11 (1–16)	11 (3–17)	21 (19–38)	
Age at end/ongoing (years)	/	23 (11–43)			/	28 (20–43)	17 (11–23)	28 (22–43)	
Duration (years)	/	11 (0–31)			/	17 (10–31)	6 (1–17)	6 (0–16)	

*Including three CP patients without surgery.
adultGH, CP under GH started at adulthood age; contGH, CP with GH started during childhood and continued during adult age; n.a., data not available; noGH, CP never GH treated; pedGH, CP GH treated only during childhood.

Figure 1

Kaplan-Meier analysis of progression-free survival (PFS) of patients with childhood-onset craniopharyngioma (CP) recruited in HIT-Endo with regard to growth hormone (GH) substitution therapy. noGH, CP never GH-treated; pedGH, CP GH-treated only during childhood; adultGH, CP under GH started at adulthood age; contGH, CP with GH started during childhood and continued during adult age.

and patients treated only at adult age (adultGH), long-term increases of height SDS were not detectable when compared with respective height SDS at the time of CP diagnosis (Fig. 2).

Weight development

We compared weight development in our GH subgroups for the time points (a) at CP diagnosis, (b) during 8–12 years of follow-up and (c) after >12-year follow-up after CP diagnosis. BMI SDS was similar at CP diagnosis for all GH subgroups. At the time of the study, in all patient subgroups except for the pedGH subgroup, significant increases in BMI SDS were detectable when compared with BMI SDS at time of CP diagnosis. However, it has to be pointed out that patients with GH substitution during childhood continuing at adult age (contGH) also experienced significant increases in BMI SDS between the time of CP diagnosis and 8–12 years of follow-up ($P=0.01$) and >12-year follow-up ($P=0.001$). Differences between BMI SDS at 8–12 years of follow-up vs >12-year follow-up were not observed in any of the subgroups (Fig. 3). Long-term BMI SDS at >12-year

Figure 2

Height development in childhood-onset craniopharyngioma patients (CP) recruited in HIT-Endo with regard to growth hormone (GH) substitution therapy. noGH, CP never GH-treated; pedGH, CP GH-treated only during childhood; adultGH, CP under GH started at adulthood age; contGH, CP with GH started during childhood and continued during adult age. Height SDS (17) is shown at time of diagnosis and at two intervals after diagnosis (8–12 years and >12 years). Black boxes: height SDS at diagnosis; gray boxes: height SDS at 8–12 years follow-up; white boxes: height SDS at >12 years follow-up. The horizontal line in the middle of the box depicts the median. The top and bottom edges of the box respectively mark the 25th and 75th percentiles. Whiskers indicate the range of values that fall within 1.5 box-lengths.

follow-up reached similar high plateaus when compared between subgroups ($P=0.087$).

Neuropsychological status and QoS

QoS and neuropsychological status were assessed >10 years after CP diagnosis using EORTC QLQ-C30 and MFI-20 questionnaires in 77 CP patients. Analyzing EORTC QLQ-C30 functioning domains, differences between GH subgroups were detectable only in terms of emotional functioning (Fig. 4A). AdultGH CP patients presented with a worse response ($P=0.037$) in this domain (mean percentage: 61.4%) when compared with pedGH CP patients (mean percentage: 83.5%). For EORTC QLQ-C30

Figure 3

Weight development in childhood-onset craniopharyngioma patients (CP) recruited in HIT-Endo with regard to growth hormone (GH) substitution therapy. noGH, CP never GH treated; pedGH, CP GH treated only during childhood; adultGH, CP under GH started at adulthood age; contGH, CP with GH started during childhood and continued during adult age. BMI SDS (18) is shown at time of diagnosis and at two intervals after diagnosis (8–12 years and >12 years). Black boxes: BMI SDS at diagnosis; gray boxes: BMI SDS at 8–12 years follow-up; white boxes: BMI SDS at >12 years follow-up. The horizontal line in the middle of the box depicts the median. The top and bottom edges of the box respectively mark the 25th and 75th percentiles. Whiskers indicate the range of values that fall within 1.5 box-lengths.

symptom scales, no differences were detectable between GH subgroups (Fig. 4B).

In the MFI-20 questionnaire, CP patients of the adultGH subgroup were observed with a higher score in the domain physical fatigue (mean score: 12.5) when compared with pedGH CP patients (mean score: 7.7) (Fig. 4C). Differences between GH subgroups with regard to the other MFI-20 domains (general fatigue, reduced activity, reduced motivation and mental fatigue) did not reach statistical significance.

Furthermore, we compared neuropsychological status, QoS and fatigue between 27 CP patients who were treated with external photon irradiation (XRT) and 42 non-irradiated CP patients. Differences between irradiated and non-irradiated CP patients were not detectable for

Figure 4

EORTC QLQ-C30 functioning domains (A) and symptom scales (B) and MFI-20 fatigue domains (C) in childhood-onset craniopharyngioma patients (CP) recruited in HIT-Endo with regard to growth hormone (GH) substitution therapy. Black boxes: CP with GH started during childhood and continued during adult age (contGH); dark grey boxes: CP patients GH-treated only during childhood (pedGH); hatched boxes: CP under GH started at adulthood age (adultGH); white boxes: CP patients never GH-treated (noGH). The horizontal line in the middle of the box depicts the median. The top and bottom edges of the box respectively mark the 25th and 75th percentiles. Whiskers indicate the range of values that fall within 1.5 box-lengths.

any of the EORTC QLQ-C30 and MFI-20 domains (data not shown).

Psychosocial status

To assess previously not analyzed long-term outcome in CP patients, we evaluated psychosocial status with regard to parameters such as married/partner, offspring, employment, professional education and having a driver license in adult CP patients (age at study >20 years). Only 2 of the 79 adult CP patients (2.5%) reported having (healthy) offspring. These two CP patients belonged to the contGH subgroup. However, no differences between GH subgroups could be detected for all parameters assessed in the psychosocial questionnaire (Table 2).

Discussion

Overall survival after childhood-onset CP is high. The 10-year survival rates range from 62 to 100% after radical complete surgical resection (10, 21, 22, 23, 24, 25, 26, 27), 27–86% after incomplete surgical resection (10, 21, 22, 23, 24, 25), 74–100% after incomplete surgical resection followed by irradiation (21, 25) and 81–100% after radiooncological treatment alone (26, 27). Adult-onset CP patients are reported to have up to fivefold higher mortality and morbidity rates when compared to general population (28, 29) and to patient cohorts with different origin of pituitary insufficiency. Many published reports on long-term follow-up after childhood-onset CP are focused on survival rates and lack information on specific sequelae (22, 25, 26, 27, 30). However, QoS is frequently impaired in the pediatric age group due to treatment and/or disease-associated factors such as HI, neuropsychological (31, 32) and neuroendocrine deficits (16, 21, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42) including GH

deficiency being the most frequent pituitary deficiency (54–100%) (1, 37, 39).

Our study is the first report in the literature, which analyzed not only long-term survival but also psychosocial status and QoS with special regard to timing and duration of GH substitution therapy. In our study cohort, we observed an OS rate 100% as no fatal events occurred. We have previously reported on impairments in terms of psychosocial status, such as living in partner relationship/marriage, having offspring and holding of a driver license, as well as severe QoS-compromising sequelae such as reduced motivation and physical functioning in long-term survivors of childhood-onset CP with HI. Physical fatigue, obesity, dyspnea and diarrhea were major sequelae in these patients. However, associations with GH substitution were not analyzed in that study (10).

It is well known that GH substitution therapy improves growth in childhood-onset CP patients (43, 44, 45). However, long-term effects of GH substitution therapy on height, weight, QoS and psychosocial status have not been investigated prospectively in childhood-onset CP patients. Accordingly, we analyzed for CP patients recruited before 2000 and observed prospectively in the HIT-Endo trial whether (1) GH substitution therapy was associated with changes in height, BMI, QoS and psychosocial and neuropsychological status during long-term follow-up of >10 years after CP diagnosis and (2) whether these changes were related to age at initiation and duration of GH substitution therapy.

Differences between the analyzed subgroups of GH-substituted and non-substituted CP patients with regard to age at CP diagnosis and study, gender, follow-up interval, tumor location and size, HI, degree of surgical resection and irradiation were not detectable (Table 1). Our results support previous findings (11) that GH substitution was not associated with decreased OS and EFS rates. However, it has to be pointed out that regardless of

Table 2 Psychosocial status of childhood-onset craniopharyngioma patients (CP) recruited in HIT-Endo with regard to growth hormone (GH) substitution therapy. Data are presented as *n* (%).

	Total	noGH	contGH	pedGH	adultGH	P
<i>n</i>	79	8	34	26	11	
Married/partner	11 (13.9)	1 (12.5)	4 (11.8)	5 (19.2)	1 (9.1)	0.857
Children/pregnant	2 (2.5)	0 (0.0)	2 (5.9)	0 (0.0)	0 (0.0)	0.713
Social functionality/friends	50 (63.3)	4 (50.0)	21 (61.8)	17 (65.4)	8 (72.7)	0.766
Professional education	38 (48.1)	3 (37.5)	18 (53.0)	14 (53.8)	3 (27.3)	0.442
Employed	52 (65.8)	5 (62.5)	20 (58.8)	21 (80.8)	6 (54.5)	0.251
Driver's license	42 (53.2)	4 (50.0)	17 (50.0)	14 (53.8)	7 (63.6)	0.886
Psychological treatment	33 (41.8)	4 (50.0)	13 (38.2)	14 (53.8)	2 (18.2)	0.219

adultGH, CP under GH started at adulthood age; contGH, CP with GH started during childhood and continued during adult age; noGH, CP never GH treated; pedGH, CP GH treated only during childhood.

GH substitution frequent events in terms of progression and relapses occurred during long-term follow-up in all analyzed subgroups (11, 46).

We recently reported on short-term effects of GH substitution on growth during the first 3 years after CP diagnosis (6). Whereas significant improvements of growth could not be observed under GH substitution therapy at 3 years after CP diagnosis (6), in this study, we report on significantly improved growth in all GH-substituted subgroups (contGH and pedGH). Non-GH-substituted patients and CP patients with GH substitution confined to adult age (adultGH) presented with similar height SD at diagnosis and during long-term follow-up.

Severe hypothalamic obesity is a major well-described sequelae after childhood-onset CP, occurring in 40–66% of CP patients (47, 48). Hypothalamic obesity represents a significant risk factor for chronic diseases resulting in increased risk for cardiovascular disease and metabolic syndrome (49, 50). HI and/or treatment-related hypothalamic lesions are major risk factors for the development of hypothalamic syndrome (16, 51, 52). Especially long-term CP survivors with hypothalamic lesions present with morbidity including severe obesity and impaired QoS (15, 36, 37, 38, 39, 40, 41, 49, 53). Previous follow-up studies reported on the prevalence of hypothalamic obesity but did not include detailed analyses of weight development during long-term follow-up (25, 28, 54). In the present study, we analyzed BMI SDS after follow-up of >12 years. The rate of HI and the degree of treatment-related hypothalamic damage were similar in all analyzed subgroups. Significant weight gain resulting in obesity was observed in all patient subgroups. We also could demonstrate for all subgroups that no further BMI SDS increase could be observed after >12 years of follow-up.

Several studies (45, 55, 56, 57, 58) report on protective effects of GH substitution therapy on body composition and weight development in adult-onset CP survivors. However, similar to previous reports in our study GH substitution did not prevent the development of severe obesity after childhood-onset CP. However, it should be pointed out, that in our pedGH subgroup increases in BMI SDS during follow-up did not reach statistical significance. Using the least invasive, hypothalamus-sparing surgical techniques is currently considered to be the most appropriate option to handle hypothalamic obesity, since effective treatment of hypothalamic obesity is still not available.

Childhood patients treated early on with GH (pedGH) presented with an overall better long-term outcome in terms of height, weight and neuropsychological findings

when compared with patients in whom GH substitution was initiated later on during adulthood (adultGH) or patients who did not receive any GH substitution at all (noGH). Patients of the pedGH subgroup developed no relevant BMI SDS increase when compared with all other subgroups. Interestingly, this observation is not supported by our findings in the subgroup receiving GH substitution during childhood and adult age (contGH). We speculate that GH substitution was continued in this subgroup due to persisting problems concerning previous weight gain. Furthermore, pedGH patients showed better scores for emotional functioning and a lower level of physical fatigue when compared with GH patients with adult-onset GH substitution. This might indicate that early onset of GH substitution after CP diagnosis provides advantages in terms of follow-up prognosis. Furthermore, diarrhea and pulmonary complaints observed as major long-term sequelae after CP by Sterkenburg *et al.* (10) were no predominant findings in any of our GH subgroups.

Due to retrospective analysis, the results of our study are limited. Some observations are speculative at this point. The decision on indication and time of initiation of GH substitution was made by treating physicians and not based on randomization. A specific grading of HI as performed in recent prospective studies (15, 59, 60) was not possible due to missing data and minor quality of neuroradiological imaging in our retrospective analysis. We have chosen to express BMI SDS according to standards reported by Rolland-Cachera *et al.* (18) because these allow the calculation of BMI SDS for a wide age range from early childhood to adult age. A further limitation of our study is the lack of specific data on body composition. We were not able to analyze fat mass and lean mass by dual-energy X-ray absorptiometry (DEXA) or other comparable techniques. These parameters on body composition will be part of future planned studies on this cohort of long-term CP survivors.

We conclude that GH substitution was safe with regard to long-term risk of tumor progression and relapse in CP patients. Growth was improved by GH substitution, whereas weight development leading to severe obesity was not influenced by GH substitution. Early initiation of GH substitution after CP diagnosis might have beneficial effects on weight development and neuropsychological outcome.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement

S B researched the data and wrote the manuscript. A B participated in data analyses and reviewed/edited the manuscript. A S S conducted and supervised multicenter data collecting and reviewed/edited the manuscript. M E did statistical analyses and discussion and reviewed/edited the manuscript. H L M initiated and conducted the multicenter trials HIT-Endo and KRANIOPHARYNGEOM 2000/2007, contributed to the analytical plan and discussion and reviewed/edited the manuscript.

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