History before diagnosis in childhood craniopharyngioma: associations with initial presentation and long-term prognosis

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Abstract

Objective: Childhood craniopharyngiomas (CP) are often diagnosed after a long duration of history (DOH). Tumor size, hypothalamic involvement (HI), and obesity are associated with reduced overall survival (OS) and functional capacity (FC). The effect of DOH and specific symptoms in history on presentation at initial diagnosis and long-term prognosis are unknown.

Design: Retrospective analysis of patients' records and prospective longitudinal follow-up.

Methods: Histories of 411 CP patients recruited in HIT Endo, KRANIOPHARYNGEOM 2000 were retrospectively evaluated for DOH, symptoms, and characteristics. The effect of specific manifestations and DOH on clinical presentation and tumor characteristics at time of initial CP diagnosis and long-term outcome were analyzed. Main outcome measures were 10-year OS and progression-free survival (PFS), FC, and BMI during longitudinal follow-up.

Results: Median DOH was 6 months (range: 0.1–108 months) and correlated with age at diagnosis. Tumor size, HI, degree of resection, and BMI at diagnosis were not related to DOH. In multivariate analysis adjusted for age at diagnosis, only hydrocephalus was found to have a relevant influence on DOH. Visual and neurological deficits were associated with larger initial tumor size and impaired 10-year OS. Weight gain and growth failure were observed with longest DOH. PFS and FC were not related to any specific symptom. Endocrine deficits at diagnosis were associated with long DOH.

Conclusions: CP is frequently diagnosed after long DOH, especially in older children. However, DOH was not associated with tumor size, HI, survival, or FC. Visual and neurological deficits necessitate rapid diagnostic workup.

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Introduction

Childhood-onset craniopharyngioma (CP) are rare intracranial embryonal malformations of the sellar region arising from remnants of Rathke's pouch (1, 2). They show low-grade histological malignancy (WHO I) and frequently affect hypothalamic and pituitary regions due to their location. Hypothalamic involvement (HI) of CP, resulting in pathological patterns of eating behavior and obesity, is the most serious risk factor – its aforementioned manifestations impairing prognosis and quality of life in surviving patients (1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15).

The diagnosis of childhood-onset CP is often made late – sometimes years after the initial appearance of symptoms (1, 5) – with a clinical picture at the time of diagnosis often dominated by nonspecific manifestations of intracranial pressure. Further primary manifestations are visual impairment, namely losses of visual acuity and visual field (62–84%) and endocrine deficits (52–87%). The recent literature has documented that any clinical combination of headache, visual impairment, growth failure, and/or polydipsia/polyuria should arouse

suspicion of childhood CP in the differential diagnosis process (5). The prognostic relevance of specific symptoms and duration of history (DOH) on clinical presentation at the time of initial CP diagnosis and long-term outcome had not yet been analyzed, leading to the focus of this study. The major clinical rationale for our study relates to a frequent concern of patients and their families and whether potential delays in the individual diagnostic process might have caused limitations in terms of successful treatment and long-term prognosis.

Accordingly, we analyzed the effect of specific complaints in history and DOH on clinical presentation, tumor, and patient characteristics at the time of initial diagnosis, as well as their impact on prognostic outcome, in a large cohort of 411 long-term survivors of childhood-onset CP recruited in the German Craniopharyngioma Registry before 2007 and monitored longitudinally in HIT Endo and KRANIOPHARYNGEOM 2000 respectively.

Subjects and methods

Patients

For this study, 411 patients with childhood-onset CP, recruited in the German CP registry and prospectively evaluated in the multicenter trials HIT Endo and KRANIOPHARYNGEOM 2000 (Clinical Trial No.: NCT00258453), were analyzed for history, DOH, and the presentation of initial manifestations and influence of these factors on prognosis during long-term follow-up of more than 11 years (range: 11–38) (16). Furthermore, the first symptoms in history as documented in patients' records were identified and analyzed for any association with initial clinical manifestation and outcome. The HIT Endo/KRANIOPHARYNGEOM 2000 data include results of physical examination and anthropometric measurements at the time of diagnosis and an evaluation of the patient's records for imaging results, clinical manifestations, history, and operative strategies. The histological diagnosis of a CP was confirmed by reference assessment in all cases. HI was assessed by magnetic resonance imaging (MRI), computed tomography (CT), and/or microscopic inspection during surgery. HI was defined as the involvement of hypothalamic structures either by tumor growth into the hypothalamus or displacement of hypothalamic structures by the tumor. Tumor size was calculated using the maximal tumor diameters (A, B) in two dimensions ($A \times B/2$) based on the results of CT or MRI. For long-term survival rates (10-year overall

survival (OS) and progression-free survival (PFS)), we were able to analyze 10-year OS in 391 patients (95%) and PFS in 305 patients (74%) (16).

The study was approved by the local standing committee on ethical practice, and written parental and/or patient consent was obtained in all cases.

BMI

Body composition and the degree of obesity were evaluated by calculating the BMI SDS according to the references of Rolland-Cachera *et al.* (17).

Questionnaires

The German daily life ability scale Fertigkeitenskala Münster-Heidelberg (FMH) was used for self-assessment of functional capacity (FC) (18). A total 274 of the 411 (67%) patients answered the FMH questionnaire. The FMH measures the capability for routine actions, with 56 items such as 'can walk without aid' or 'earns money.' It was normalized with 971 persons (45.5% female), ages between 0 and 102 years, resulting in age-dependent percentiles (18). The retest-reliability-coefficient was 0.99. The validity was tested in ten brain tumor patients; there was good agreement with IQ ($r=0.7$) and semi-quantitative assessments performed by a physician ($P<0.001$). The average time for answering the FMH questionnaire was 4.5 min in first-time users (19).

Statistical analysis

Statistical analysis were performed using SPSS 19.0 (SPSS, Inc.). For comparison of two independent groups for a continuous variable, the Mann–Whitney *U*-test was used. For comparison of different groups for categorical variables, the χ^2 -test was used. Correlation between two variables was analyzed using the Spearman correlation coefficient. OS and PFS rates were estimated by the Kaplan–Meier method. Groups were compared concerning OS and PFS using the Log-rank test. DOH was analyzed by multivariable linear regression using forward as well as backward selection methods excluding factors with $P>0.1$. Because DOH was highly skewed, a log-transformation was applied. Model assumptions were verified by residual analysis. *P* values of ≤ 0.05 were chosen as being statistically significant. Inferential statistics are intended to be exploratory (hypotheses generating), not confirmatory, and are interpreted accordingly.

Results

We analyzed history, DOH, the presentation of initial manifestations, and the prognostic effect of these factors on outcome during long-term follow-up of more than 11 years (range: 11–38) in 411 patients with childhood-onset CP. Initial gross-total resection of CP was achieved in 136 of 349 CP patients (47%) with known degree of resection; 326 of 411 CP patients (79%) received a single surgical intervention, 32 patients (8%) received two operations, 19 patients (5%) three operations, and 21 patients (5%) were treated by more than four operations (range: 4–9). Of the 411 CP patients 68 (16%) received irradiation (13% external photon irradiation, 2% γ -knife, 0.5% proton beam therapy, 1.2% stereotactic seed implantation).

The most frequent symptom in the histories of the 411 patients before initial diagnosis of childhood CP was headache (50%) (Table 1). Neurological deficits and symptoms as documented before diagnosis and treatment in 70 patients (17%) included seizures, cranial nerves palsy, ataxia/unsteadiness, and decreased consciousness.

Initial symptoms were not documented in 16% of the patients' records. Two of 411 patients presented without relevant symptoms and were diagnosed based on imaging due to a history of an accident (head trauma). The combination of headache and growth failure (18%) was the most frequently reported coupling in their histories, followed by headache and neurological deficits (15%), headache plus neurological and visual deficits (9%), and headache plus visual impairment plus growth failure (8%). A combination of headache, visual impairment, and polydipsia/polyuria was reported in the histories of only 2% of all patients.

The DOH before initial diagnosis of childhood-onset CP (median DOH: 6 months, range: 0.1–108 months) was not related to hypothalamic tumor involvement, visual impairment, or the degree of surgical resection at the time of initial diagnosis (Table 2). Figure 1A shows that DOH did not correlate with tumor size at the time of CP diagnosis (Spearman correlation coefficient: -0.07 ; $P=0.32$). Frequently, patients were diagnosed with large tumors after short DOH and with small tumors after long DOH (Fig. 1A). Patients with hydrocephalus were diagnosed after a shorter DOH when compared to patients without hydrocephalus at the time of initial diagnosis. The development of obesity during postoperative follow-up was not related to DOH (Table 2).

Data on endocrine deficits as initial clinical pre-surgical manifestations could be analyzed based on records in 325 of 411 patients (79%). A total 142 CP

Table 1 Characteristics of 411 patients with childhood-onset CP recruited in HIT Endo and KRANIOPHARYNGIOMA 2000 at the time of diagnosis and symptoms in patients' history before initial diagnosis of childhood craniopharyngioma. BMI SDS according to the references of Rolland-Cachera *et al.* (17).

Symptom in history	n (y/n)	Tumor size at diagnosis (cm ³)		Tumor location at diagnosis (%)			Hypothalamic involvement at diagnosis (%)		BMI at diagnosis (SDS)		
		Yes	No	Intra-sellar	Supra-sellar	Intra- and supra-sellar	Yes	No	Yes	No	P
Headache	206/96	9.2 (1.1–0.6)	9.0 (0.4–128.7)	1.3	25.9	72.8	67.8	73.4	0.8 (–7.92–8.80)	0.4 (–5.00–9.90)	0.17
Nausea	42/80	14.0 (2.2–0.6)	8.7 (0.4–28.7)	0.0	20.5	79.5	88.9	78.2	0.58 (–3.23–8.80)	1.27 (–5.00–9.90)	0.01
Visual impairment	161/130	12.3 (2.9–128.7)	6.0 (0.4–101.5)	1.5	28.5	70.0	79.4	61.4	0.93 (–5.00–8.27)	0.5 (–3.81–9.90)	0.16
Neurological deficits	68/224	14.9 (1.6–101.5)	7.5 (0.4–128.7)	2.0	20.0	78.0	78.6	68	0.91 (–5.00–9.90)	0.59 (–3.81–8.27)	0.52
Weight gain	49/251	9.0 (1.7–35.8)	9.0 (0.4–128.7)	4.9	29.3	65.9	79.5	69.1	2.95 (–0.11–9.90)	0.4 (–5.00–7.55)	<0.01
Growth failure	110/191	8.5 (0.4–70.6)	10.2 (1.1–128.7)	3.2	24.5	72.3	68.3	72.6	0.12 (–5.00–6.08)	1.10 (–2.67–9.90)	<0.01
Polydipsia/Polyuria	23/97	6.6 (0.4–67.5)	10.6 (1.6–128.7)	0.0	17.4	82.6	69.6	85.4	1.51 (–2.60–9.90)	0.82 (–5.00–6.83)	0.36

y/n, yes/no; bold values and ranges indicate significant differences.

Clinical Study	A Hoffmann and others	History before craniopharyngioma diagnosis	173:6	856
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Table 2 Duration of history (DOH) before initial diagnosis of childhood-onset CP in 411 patients recruited in HIT Endo and KRANIOPHARYNGEOM 2000 in regard to patients' characteristics at the time of initial diagnosis and at last visit. BMI SDS according to the references of Rolland-Cachera *et al.* (17).

Clinical criteria	n (y/n)	DOH in patients (months)		P
		With criteria	Without criteria	
Visual impairment at diagnosis	161/130	6 (0.0–108.0)	10 (0.0–108.0)	0.14
Hydrocephalus at diagnosis	136/126	6 (0.0–108.0)	12 (0.3–96.0)	0.01
Hypothalamic involvement	23/99	6 (0.3–108.0)	5 (0.3–108.0)	0.33
Tumor location				0.278
Intrasellar	5	4 (0.0–12.0)		
Suprasellar	61	9 (0.0–84.0)		
Intra + Supra	169	6 (0.0–96.0)		
Tumor size (cm ²) at initial diagnosis				0.66
≤20	172		6 (0.0–96.0)	
>20	32	6 (0.5–72.0)		
Endocrine deficits at diagnosis	123/167	9 (0.0–108.0)	6 (0.0–96.0)	0.01
Degree of initial tumor resection				0.07
Incomplete	213		6 (0.0–108.0)	
Complete	136	10 (0.0–108.0)		
BMI >3 s.d. at last visit				0.35
≤3 s.d.	179		6 (0.0–108.0)	
>3 s.d.	175	6 (0.0–84.0)		
BMI >4 s.d. at last visit				0.28
≤4 s.d.	220		7 (0.0–108.0)	
>4 s.d.	134	6 (0.0–84.0)		

Bold values and ranges indicate significant differences.

patients (44%) presented with endocrine deficits at the time of CP diagnosis. In 184 patients (56%) no endocrine deficits were noted in the records on initial manifestations. Patients with endocrine deficiencies were diagnosed after a longer DOH ($P=0.01$).

We analyzed whether specific symptoms in a patient's history were associated with clinical presentation and imaging tumor characteristics at the time of initial diagnosis. Patients with histories of nausea and growth failure presented with a lower BMI SDS at diagnosis, whereas patients with histories of weight gain showed higher BMI SDS when compared with patients without complaints about weight gain (Table 1). The rates of HI and tumor size were higher in patients with visual impairment. Tumor size was also significantly larger in patients with neurological deficits at diagnosis.

Specific symptoms in history before CP diagnosis were negatively associated with prognosis during long-term follow-up. Ten-year OS rates were lower in patients with nausea, visual impairment, and neurological deficits in history before diagnosis, whereas 10-year PFS rates were not related to a specific initial symptom (Table 3). Development of obesity during long-term follow-up was associated with visual impairment and weight gain in

history before diagnosis. Patients suffering from growth failure during history before diagnosis developed a lower BMI at last visit.

We also analyzed the time course of each patient's history by evaluating their first symptom and the interval between its initial appearance and time of CP diagnosis. The most frequent first symptom in our CP patients was headache (38%). DOH before diagnosis was shorter in patients with nausea, visual impairment, and neurological deficits as first symptoms. Patients with weight gain and growth failure as first symptoms were diagnosed after longer DOH before diagnosis (Table 4). In addition, the relation between DOH and four symptoms (hydrocephalus, headache, visual impairment, and neurological deficits) was analyzed applying multivariable linear regression models. Only hydrocephalus was found to have a significant influence on DOH ($P=0.01$). This was confirmed when adjusting for age at diagnosis: hydrocephalus was the only relevant factor ($P=0.1$).

The first symptom in history was often associated with specific clinical features in long-term outcome. Weight gain as the first symptom resulted in a higher BMI; growth failure as the first symptom resulted in a lower BMI after long-term follow-up. All four patients

Figure 1

(A) For the whole craniopharyngioma patient group, no significant correlation was detected between tumor size at initial craniopharyngioma diagnosis and duration of history before initial craniopharyngioma diagnosis (Spearman

correlation coefficient: -0.07 ; $P = 0.32$). (B) Duration of history before initial craniopharyngioma diagnosis was positively correlated with patients' age at initial craniopharyngioma diagnosis (Spearman correlation coefficient: 0.32 ; $P < 0.01$).

with nausea as the first symptom experienced relapses or tumor progressions and showed lower scores for FC after long-term follow-up (Table 5).

DOH correlated positively with age at diagnosis (Spearman correlation coefficient: 0.32 ; $P < 0.001$) (Fig. 1B). Infants and young children (age < 7 year at diagnosis) presented more frequently with neurological deficits (13%) and nausea (4%) as a first symptom and after a shorter DOH, when compared with older children (age ≥ 7 year at diagnosis) and adolescents (neurological deficits: 5%; nausea: 0%). Growth failure as a first symptom was more frequently observed in these older children and adolescents ($P < 0.001$).

Discussion

The diagnosis of childhood-onset CP is often made late, in many cases years after the initial appearance of symptoms (20). HI of CP has been reported as a major risk factor to impairment of long-term survival (7, 8, 14) and quality of life (8, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30) in CP patients. The question of whether DOH before diagnosis – specifically whether prolonged interval between the first appearance of symptoms and the time of diagnosis –

contributes to adverse sequelae and impaired survival had not been answered before this study.

We therefore analyzed the largest (to our knowledge) published cohort of childhood-onset CP patients for DOH before diagnosis. A major observation of our study is the great variability of DOH among pediatric CP patients. This result must be interpreted with respect to the huge heterogeneity regarding location, shape, speed of growth, formation of cysts, and compliance of brain tissue to progressive displacements observed in CP. The classic division in pediatric and adult subgroups of lesions should be reconsidered in favor of the concept of 'individual' lesion, based on clinical and pathological objective data.

The two clinically most important results of our study are the recognition of some 'first' symptoms, which definitely shortened the DOH and forced a prompt diagnosis and surgical treatment of children with CP (nausea, visual impairment, and neurological deficits); and the observation that within the population of childhood-onset CP a stratification of patients can be made according to the DOH (shown in Fig. 1B) – that is, among the 'oldest' group of patients (10–20 years old), cases with the 'longest' DOH are dominant. This finding is fundamental for two reasons. First, it supports the 'embryological' theory about CP pathogenesis, according

Table 3 Patients characteristics and outcome in terms of 10-year overall survival, 10-year progression-free survival, degree of obesity (BMI SDS (17)), and functional capacity at last visit with regards to symptoms in history documented in records of 411 patients with childhood-onset CP, recruited in the German Craniopharyngioma Registry and analyzed after longitudinal follow-up in the trials HIT Endo and KRANIOPHARYNGEOM 2000. BMI SDS according to the references of Rolland-Cachera et al. (17).

Symptom in history	n (y/n)	Overall survival (10 years)			Progression-free survival (10 years)			BMI (SDS) at last visit			Functional capacity at last visit (FMH %)		
		Yes	No	P	Yes	No	P	Yes	No	P	Yes	No	P
Headache	206/96	0.96 ± 0.02	0.99 ± 0.02	0.32	0.56 ± 0.05	0.49 ± 0.07	0.28	3.05 (−1.79–13.55)	2.3 (−1.85–13.90)	0.15	50 (4–95)	47.5 (6–95)	0.22
Nausea	42/80	0.89 ± 0.05	0.99 ± 0.01	0.04	0.16 ± 0.09	0.36 ± 0.08	0.95	3.23 (−1.79–2.73)	2.81 (−1.74–10.89)	0.54	45 (4–95)	50 (12–95)	0.05
Visual impairment	161/130	0.94 ± 0.02	0.99 ± 0.01	0.02	0.49 ± 0.05	0.55 ± 0.07	0.44	2.97 (−1.85–13.55)	1.92 (−1.79–13.90)	0.03	47 (4–95)	50 (7–95)	0.07
Neurological deficits	68/224	0.92 ± 0.03	0.97 ± 0.01	0.01	0.35 ± 0.08	0.60 ± 0.05	0.06	2.85 (−1.74–12.73)	2.42 (−1.79–13.55)	0.38	44.5 (1–95)	50 (4–95)	0.00
Weight gain	49/251	0.92 ± 0.05	0.97 ± 0.01	0.30	0.44 ± 0.10	0.56 ± 0.04	0.17	4.97 (−1.15–13.90)	2.15 (−1.85–10.12)	<0.01	50 (4–95)	48 (4–95)	0.81
Growth failure	110/191	0.93 ± 0.03	0.97 ± 0.01	0.60	0.46 ± 0.76	0.57 ± 0.04	0.91	1.34 (−1.85–13.90)	3.13 (−1.52–13.55)	<0.01	48 (4–95)	50 (4–95)	0.87
Polydipsia/ Polyuria	23/97	1.00	0.94 ± 0.03	0.14	0.37 ± 0.13	0.28 ± 0.69	0.75	3.05 (−0.35–10.51)	2.83 (−1.79–12.73)	0.84	48 (12–95)	49.5 (4–95)	0.76

y/n, yes/no; bold values and ranges indicate significant differences.

to Erdheim's concepts, as many tumors diagnosed in teenagers were already present at early ages, although for specific topographic or biological reasons, they did not cause acute severe symptoms leading to a prompt diagnosis. Second, it suggests the existence of different kinds of lesions according to their biological behavior ('rapid' vs 'slow' growing tumors), a concept first pointed out by Bartlett (31).

DOH before diagnosis was not related to HI, tumor size, or visual impairment at the time of initial CP diagnosis. These findings support the clinical relevant speculation that potential delays in making the CP diagnosis do not directly lead to larger tumors with increased rates of HI and visual impairment. This speculation is supported by the study's observation that CP patients with long-term development of severe obesity had similar durations of history before diagnosis when compared with normal weight survivors. The degree of initial tumor resection was not related to DOH before diagnosis. We conclude that long DOH before diagnosis is not a relevant risk factor leading to a worse outcome in terms of visual impairment, hypothalamic obesity, or tumor characteristics associated with neuroendocrine deficiencies and limited neurosurgical approaches.

However, the lack of correlation between severity of symptoms, CP topography, and surgical outcome seems to be counterintuitive, as one should expect worse outcomes with large lesions involving the hypothalamus and causing acute high intracranial pressure. Postoperative results, however, depend mainly on the surgical goal pursued by the surgeon, and in our multicenter study, a radical total gross removal was reported in less than 50% of cases. Although the surgical 'experience' factor is generally considered as a fundamental variable to increase the rate of 'safe' radical CP removal, the main bias in scientific literature is that only excellent series including 'radical removals' are reported, whereas 'older' necropsy studies prove that a large amount of lesions show intimate adhesions to the hypothalamus, optic chiasm, and perforant vessels, without any possible safe plane of dissection (32, 33). Accordingly, it can be speculated that a conservative surgical 'philosophy' in the cohort determined the good outcome in terms of functionality, and consequently the lack of correlation between CP features and postoperative outcome.

DOH was not correlated with CP topography in our study. Hydrocephalus at initial CP diagnosis has been recently reported as a clinical manifestation not associated with impaired outcome in terms of survival and FC (8). However, hydrocephalus did influence

Table 4 Duration of history, tumor characteristics, and BMI at the time of diagnosis in regard to different first initial symptoms in history documented in the records of 411 patients with childhood-onset CP, recruited in the German Craniopharyngioma Registry and analyzed longitudinally in the trials HIT Endo and KRANIOPHARYNGEOM 2000. BMI SDS according to the references of Rolland-Cachera *et al.* (17).

First symptom in history	n (y/n)	Duration of history (months)			Hypothalamic involvement at diagnosis (%)			BMI (SDS) at diagnosis			Tumor size at diagnosis (cm ²)		
		Yes		P	Yes		P	Yes		P	Yes		P
		No	No		No	No		No	No		No	No	
Headache	158/138	6.0 (0.5–108.0)	9.5 (0.0–108.0)	0.22	80.0	70.7	0.48	0.75 (–7.92–7.00)	0.50 (–5.00–9.90)	0.27	8.8 (1.1–70.6)	10.4 (0.4–128.7)	0.18
Nausea	4/292	1.0 (0.3–2.0)	6.0 (0.0–108.0)	0.01	100.0	71.2	0.37	–0.39 (–2.00–0.58)	0.70 (–7.92–9.90)	0.11	20.5 (12.0–29.0)	9.1 (0.4–128.7)	0.20
Visual impairment	45/251	2.8 (0.3–96.0)	8.0 (0.0–108.0)	0.03	75.0	70.8	0.59	0.94 (–5.00–5.95)	0.58 (–7.92–9.90)	0.20	12.3 (3.7–128.7)	9.0 (0.4–98.8)	0.04
Neurological deficits	23/273	2.0 (0.3–48.0)	8.0 (0.0–108.0)	<0.01	80.0	70.7	0.39	0.38 (–2.67–1.60)	0.70 (–7.92–9.90)	0.16	15.6 (2.9–98.8)	9.0 (0.4–128.7)	0.07
Weight gain	12/284	24.0 (6.0–60.0)	6.0 (0.0–108.0)	<0.01	72.7	71.4	0.92	6.85 (1.40–9.90)	0.58 (–7.92–7.00)	<0.01	12.9 (3.8–22.6)	9.0 (0.4–128.7)	0.25
Growth failure	41/255	24.0 (3.0–108.0)	6.0 (0.0–108.0)	<0.01	58.9	73.6	0.06	–0.38 (–3.23–4.25)	0.89 (–7.92–9.90)	<0.01	8.2 (1.5–36.0)	9.9 (0.4–128.7)	0.31
Polydipsia/Polyuria	11/285	6.0 (1.0–60.0)	6.0 (0.0–108.0)	0.42	63.6	71.8	0.56	0.74 (–2.60–2.35)	0.67 (–7.92–9.90)	0.75	3.9 (0.4–19.7)	9.8 (1.1–128.7)	0.02

y/n, yes/no; bold values and ranges indicate significant differences.

Table 5 Ten-year overall survival, 10-year progression-free survival, functional capacity (percentiles for FMH ability score), and degree of obesity (BMI SDS (17)) at last visit with regards to different first initial symptoms in history documented in the records of 411 patients with childhood-onset CP, recruited in the German Craniopharyngioma Registry and analyzed after longitudinal follow-up in the trials Hit Endo and KRANIOPHARYNGEOM 2000. BMI SDS according to the references of Rolland-Cachera *et al.* (17).

First symptom in history	n (y/n)	Overall survival (10 years)			Progression-free survival (10 years)			BMI (SDS) at last visit			Functional capacity at last visit (FMH %)		
		Yes		P	Yes		P	Yes		P	Yes		P
		No	No		No	No		No	No		No	No	
Headache	158/138	0.96±0.02	0.96±0.02	0.96	0.58±0.05	0.48±0.06	0.36	3.47 (–1.79–3.55)	2.15 (–1.85–13.90)	0.10	50 (4–95)	48 (1–95)	0.20
Nausea	4/292	1.00	0.96±0.01	0.70	0.00	0.54±0.04	0.04	3.03 (2.59–4.56)	2.67 (–1.85–13.90)	0.67	27 (4–33)	50 (1–95)	0.00
Visual impairment	45/251	1.00	0.95±0.02	0.64	0.49±0.09	0.54±0.05	0.52	1.79 (–1.85–3.90)	3.00 (–1.79–13.55)	0.44	49 (25–95)	49 (1–95)	0.75
Neurological deficits	23/273	0.90±0.07	0.96±0.01	0.57	0.56±0.16	0.53±0.04	0.96	2.23 (–1.52–7.72)	2.83 (–1.85–13.90)	0.46	45 (1–95)	50 (4–95)	0.35
Weight gain	12/284	0.92±0.08	0.96±0.01	0.05	0.34±0.18	0.54±0.04	0.19	7.74 (3.10–10.89)	2.58 (–1.85–13.90)	<0.01	41 (4–95)	49 (1–95)	0.53
Growth failure	41/255	0.93±0.05	0.97±0.01	0.99	0.48±0.12	0.54±0.04	0.67	1.19 (–1.74–0.12)	3.11 (–1.85–13.90)	<0.01	50 (6–95)	48 (1–95)	0.18
Polydipsia/Polyuria	11/285	1.00	0.96±0.01	0.32	0.6±0.18	0.53±0.04	0.99	3.43 (–0.60–9.12)	2.66 (–1.85–13.90)	0.97	48 (27–90)	49 (–95)	0.52

y/n, yes/no; bold values and ranges indicate significant differences.

significantly the DOH, and CPs causing hydrocephalus are those occupying the third ventricle and expanding toward the Monro foramina. The lack of a significant relationship between the patterns of symptoms and the topography of the lesion in our study could be due to an inadequate topographical scheme of classification, which does not take into account the involvement of the third ventricle compartment or, alternatively, the primary infundibulo-tuberal development of the lesion (34, 35, 36, 37, 38). An accurate discrimination of vital structures such as the infundibulum, the third ventricle floor (tuber cinereum), the third ventricle cavity, and the type and degree of optic chiasm distortion (39) could not be performed due to missing imaging data not available in our retrospective multicenter study.

Accordingly, the development of acute hydrocephalus seems to be the critical factor that shortened the diagnosis of the lesion and forced a prompt surgical treatment. It is important to emphasize the possible cause of symptoms: headache may occur without hydrocephalus, because of stretching of the dura mater, as in the case of intrasellar lesions. However, nausea/vomiting is indicative of hydrocephalus.

The fact that HI was not related significantly to any specific symptom may also be influenced by our neuroradiological classification of HI. Hypothalamic dysfunction is directly related to Fröhlich syndrome, sleepiness, diabetes insipidus, memory defects, behavioral disturbances, gait defects, and autonomic system alterations (40). Importantly, growth failure is inversely related to HI and therefore a useful clinical marker to differentiate anatomical/functional levels of damage. The differentiation between anterior (grade I) and anterior and posterior (grade II) HI on preoperative sagittal MRIs (41, 42) does not seem to be adequate to discriminate a real infiltration/invasion of the tuber cinereum from the displacement of the third ventricle floor (43). Simple compression of the hypothalamus by a pure suprasellar CP, probably without functional effects, must be differentiated from invasion of such a structure, almost invariably associated with a progressive weight gain and other neuroendocrine, autonomic, and behavioral alterations.

The clinical combination of headache, visual impairment, decreased growth rate, and polydipsia/polyuria should arouse suspicion of childhood CP in the differential diagnosis (1, 5, 14, 16, 29, 42, 44, 45, 46, 47, 48, 49, 50, 51, 52). In our study, the combination of headache and growth failure (18%) was most frequent. This finding is supported by a previous report (53) on reduced growth rate as an early clinical manifestation in childhood CP. The

most specific combination of symptoms (1, 5) indicating CP (headache, visual impairment, and polydipsia/polyuria) was observed in only 2% of all cases.

Visual impairment before diagnosis was associated with HI and tumor size and therefore might serve as a potential risk factor in case of suprasellar tumor extension. Acute visual disturbances may be related also to papilledema initially, which is followed by optic atrophy (irreversible damage), so the effect of a late diagnosis of visual deficits on postoperative visual function may depend on the early identification of situations of acute intracranial pressure, either from clinical signs (papilledema) or neuroradiological ones (hydrocephalus, brain swelling).

We also examined the association of specific symptoms in history with long-term prognosis. Weight gain in history before diagnosis was a risk factor for increased BMI both at diagnosis and during long-term follow-up. This finding is supported by previous reports confirming an increased BMI at initial diagnosis as a risk factor for long-term obesity (16, 53, 54). On the other hand, growth failure before diagnosis indicated a lower risk of obesity both at diagnosis and during long-term follow-up. This could be explained by the observation that growth failure was also associated with smaller tumors, more confined to the sellar and pituitary area and therefore without HI.

The results of our study are limited due to its retrospective analysis of history based on patients' records, and as indicated, some observations are speculative at this point. A specific grading of HI, as performed in recent prospective studies (41, 42), would have been helpful but was not possible due to the quality of the neuroradiological imaging in our retrospective analysis.

We conclude that childhood-onset CP is frequently diagnosed after very long DOH, especially in older children and adolescents. However, long DOH before diagnosis is not a risk factor for large tumor size or impaired outcome in terms of survival or FC. However, this may certainly not be true for some individual patients who would have benefitted from minimizing diagnostic delay. Visual impairment and neurological deficits in history should be considered as symptoms necessitating rapid diagnostic workup. Weight gain and growth failure are very early symptoms in history, which should lead to early consideration of CP in differential diagnosis.

Declaration of interest

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Author contribution statement

A Hoffmann designed the retrospective analyses of patients' records and longitudinal follow-up data, participated in statistical analyses, and wrote and reviewed the manuscript. S Boekhoff evaluated patients' records and participated in writing and reviewing the manuscript. U Gebhardt supervised statistical analyses, completed the graphical work on figures, and reviewed the manuscript. A M M Daubenbüchel participated in data evaluation, performed plausibility controls, and participated in writing and reviewing the manuscript. A S Sterkenburg participated in designing the study, evaluating patients' records, and writing and reviewing the manuscript. M Eveslage performed the statistical analyses and reviewed the manuscript. H L Müller initiated the study, participated in the evaluation of patients' records, supervised plausibility controls and statistical analyses, and reviewed the manuscript. H L Müller is the coordinator of the German Craniopharyngioma Registry and chairman of the HIT Endo / KRANIOPHARYNGEOM 2000/2007 trials.

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References

- Muller HL. Craniopharyngioma. *Endocrine Reviews* 2014 **35** 513–543. (doi:10.1210/er.2013-1115)
- Muller HL. Craniopharyngioma. *Handbook of Clinical Neurology* 2014 **124** 235–253. (doi:10.1016/B978-0-444-59602-4.00016-2)
- Muller HL. Consequences of craniopharyngioma surgery in children. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 1981–1991. (doi:10.1210/jc.2011-0174)
- Muller HL. Paediatrics: surgical strategy and quality of life in craniopharyngioma. *Nature Reviews. Endocrinology* 2013 **9** 447–449. (doi:10.1038/nrendo.2013.125)
- Muller HL. Childhood craniopharyngioma – current concepts in diagnosis, therapy and follow-up. *Nature Reviews. Endocrinology* 2010 **6** 609–618. (doi:10.1038/nrendo.2010.168)
- Hoffmann A, Postma FP, Sterkenburg AS, Gebhardt U & Muller HL. Eating behavior, weight problems and eating disorders in 101 long-term survivors of childhood-onset craniopharyngioma. *Journal of Pediatric Endocrinology & Metabolism* 2015 **28** 35–43. (doi:10.1515/jpem-2014-0415)
- Sterkenburg AS, Hoffmann A, Gebhardt U, Warmuth-Metz M, Daubenbüchel AM & Muller HL. Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. *Neuro-Oncology* 2015 **17** 1029–1038. (doi:10.1093/neuonc/nov044)
- Daubenbüchel AM, Hoffmann A, Gebhardt U, Warmuth-Metz M, Sterkenburg AS & Muller HL. Hydrocephalus and hypothalamic involvement in pediatric patients with craniopharyngioma or cysts of Rathke's pouch: impact on long-term prognosis. *European Journal of Endocrinology* 2015 **172** 561–569. (doi:10.1530/EJE-14-1029)
- Fahlbusch R, Honegger J, Paulus W, Huk W & Buchfelder M. Surgical treatment of craniopharyngiomas: experience with 168 patients. *Journal of Neurosurgery* 1999 **90** 237–250. (doi:10.3171/jns.1999.90.2.0237)
- Caldarelli M, Massimi L, Tamburrini G, Cappa M & Di Rocco C. Long-term results of the surgical treatment of craniopharyngioma: the experience at the Policlinico Gemelli, Catholic University, Rome. *Child's Nervous System* 2005 **21** 747–757. (doi:10.1007/s00381-005-1186-5)
- Muller HL. Childhood craniopharyngioma. Recent advances in diagnosis, treatment and follow-up. *Hormone Research* 2008 **69** 193–202. (doi:10.1159/000113019)
- Hoffman HJ, De Silva M, Humphreys RP, Drake JM, Smith ML & Blaser SI. Aggressive surgical management of craniopharyngiomas in children. *Journal of Neurosurgery* 1992 **76** 47–52. (doi:10.3171/jns.1992.76.1.0047)
- Elliott RE, Jane JA Jr & Wisoff JH. Surgical management of craniopharyngiomas in children: meta-analysis and comparison of transcranial and transphenoidal approaches. *Neurosurgery* 2011 **69** 630–643; discussion 643. (doi:10.1227/NEU.0b013e31821a872d)
- Daubenbüchel AM & Muller HL. Neuroendocrine disorders in pediatric craniopharyngioma patients. *Journal of Clinical Medicine* 2015 **4** 389–413. (doi:10.3390/jcm4030389)
- Hoffmann A, Warmuth-Metz M, Gebhardt U, Pietsch T, Pohl F, Kortmann RD, Calaminus G & Muller HL. Childhood craniopharyngioma – changes of treatment strategies in the trials KRANIOPHARYNGEOM 2000/2007. *Klinische Pädiatrie* 2014 **226** 161–168. (doi:10.1055/s-0034-1368785)
- Muller HL, Bueb K, Bartels U, Roth C, Harz K, Graf N, Korinthenberg R, Bettendorf M, Kuhl J, Gutjahr P *et al.* Obesity after childhood craniopharyngioma – German multicenter study on pre-operative risk factors and quality of life. *Klinische Pädiatrie* 2001 **213** 244–249.
- Rolland-Cachera MF, Cole TJ, Sempe M, Tichet J, Rossignol C & Charraud A. Body mass index variations: centiles from birth to 87 years. *European Journal of Clinical Nutrition* 1991 **45** 13–21.
- Wolff JE, Daumling E, Dirksen A, Dabrock A, Hartmann M & Jurgens H. Munster Heidelberg abilities scale – a measuring instrument for global comparison of illness sequelae. *Klinische Pädiatrie* 1996 **208** 294–298.
- Muller HL, Gebhardt U, Faldum A, Emser A, Etavard-Gorris N, Kolb R & Sorensen N. Functional capacity and body mass index in patients with sellar masses – cross-sectional study on 403 patients diagnosed during childhood and adolescence. *Child's Nervous System* 2005 **21** 539–545. (doi:10.1007/s00381-005-1166-9)
- Muller HL. Childhood craniopharyngioma. *Pituitary* 2013 **16** 56–67. (doi:10.1007/s11102-012-0401-0)
- Bereket A, Kiess W, Lustig RH, Muller HL, Goldstone AP, Weiss R, Yavuz Y & Hochberg Z. Hypothalamic obesity in children. *Obesity Reviews* 2012 **13** 780–798. (doi:10.1111/j.1467-789X.2012.01004.x)
- Gautier A, Godbout A, Groshen C, Tejedor I, Coudert M, Courtillot C, Jublanc C, De Kerdanet M, Poirier JY, Riffaud L *et al.* Markers of recurrence and long-term morbidity in craniopharyngioma: a systematic analysis of 171 patients. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 1258–1267. (doi:10.1210/jc.2011-2817)
- Cohen M, Bartels U, Branson H, Kulkarni AV & Hamilton J. Trends in treatment and outcomes of pediatric craniopharyngioma, 1975–2011. *Neuro-Oncology* 2013 **15** 767–774. (doi:10.1093/neuonc/not026)
- Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, Zerah M, Bezerra M, Renier D, Pierre-Kahn A *et al.* Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. *Journal of Neurosurgery* 2007 **106** 3–12.
- Elowe-Gruau E, Beltrand J, Brauner R, Pinto G, Samara-Boustani D, Thalassinou C, Busiah K, Laborde K, Bodaert N, Zerah M *et al.* Childhood craniopharyngioma: hypothalamus-sparing surgery decreases the risk of obesity. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 2376–2382. (doi:10.1210/jc.2012-3928)
- Fjalldal S, Holmer H, Rylander L, Elfving M, Ekman B, Osterberg K & Erfurth EM. Hypothalamic involvement predicts cognitive performance and psychosocial health in long-term survivors of childhood craniopharyngioma. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 3253–3262. (doi:10.1210/jc.2013-2000)

- 27 Erfurth EM, Holmer H & Fjalldal SB. Mortality and morbidity in adult craniopharyngioma. *Pituitary* 2013 **16** 46–55. (doi:10.1007/s11102-012-0428-2)
- 28 Haliloglu B & Bereket A. Hypothalamic obesity in children: pathophysiology to clinical management. *Journal of Pediatric Endocrinology & Metabolism* 2015 **28** 503–513. (doi:10.1515/jpem-2014-0512)
- 29 de Vile CJ, Grant DB, Hayward RD, Kendall BE, Neville BG & Stanhope R. Obesity in childhood craniopharyngioma: relation to post-operative hypothalamic damage shown by magnetic resonance imaging. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 2734–2737.
- 30 Hoffmann A, Bootsvelde K, Gebhardt U, Daubenbuchel AM, Sterkenburg AS & Muller HL. Nonalcoholic fatty liver disease and fatigue in long-term survivors of childhood-onset craniopharyngioma. *European Journal of Endocrinology* 2015 **173** 389–397. (doi:10.1530/EJE-15-0422)
- 31 Bartlett JR. Craniopharyngiomas – a summary of 85 cases. *Journal of Neurology, Neurosurgery, and Psychiatry* 1971 **34** 37–41. (doi:10.1136/jnnp.34.1.37)
- 32 Steno J. Microsurgical topography of craniopharyngiomas. *Acta Neurochirurgica. Supplement* 1985 **35** 94–100.
- 33 Pascual JM, Prieto R & Carrasco R. Infundibulo-tuberal or not strictly intraventricular craniopharyngioma: evidence for a major topographical category. *Acta Neurochirurgica* 2011 **153** 2403–2425; discussion 2426. (doi:10.1007/s00701-011-1149-4)
- 34 Kassam AB, Gardner PA, Snyderman CH, Carrau RL, Mintz AH & Prevedello DM. Expanded endonasal approach, a fully endoscopic transnasal approach for the resection of midline suprasellar craniopharyngiomas: a new classification based on the infundibulum. *Journal of Neurosurgery* 2008 **108** 715–728. (doi:10.3171/JNS/2008/108/4/0715)
- 35 Pascual JM, Carrasco R, Prieto R, Gonzalez-Llanos F, Alvarez F & Roda JM. Craniopharyngioma classification. *Journal of Neurosurgery* 2008 **109** 1180–1182; author reply 1182–1183. (doi:10.3171/JNS.2008.109.12.1180)
- 36 Pascual JM, Gonzalez-Llanos F, Barrios L & Roda JM. Intraventricular craniopharyngiomas: topographical classification and surgical approach selection based on an extensive overview. *Acta Neurochirurgica* 2004 **146** 785–802. (doi:10.1007/s00701-004-0295-3)
- 37 Pan J, Qi S, Lu Y, Fan J, Zhang X, Zhou J & Peng J. Intraventricular craniopharyngioma: morphological analysis and outcome evaluation of 17 cases. *Acta Neurochirurgica* 2011 **153** 773–784. (doi:10.1007/s00701-010-0938-5)
- 38 Qi S, Peng J, Pan J, Zhang X, Lu Y, Fan J & Huang G. Growth and weight of children with craniopharyngiomas based on the tumour location and growth pattern. *Journal of Clinical Neuroscience* 2013 **20** 1702–1708. (doi:10.1016/j.jocn.2012.12.030)
- 39 Prieto R, Pascual JM & Barrios L. Optic chiasm distortions caused by craniopharyngiomas: clinical and magnetic resonance imaging correlation and influence on visual outcome. *World Neurosurgery* 2015 **83** 500–529. (doi:10.1016/j.wneu.2014.10.002)
- 40 Castro-Dufourny I, Carrasco R, Prieto R, Barrios L & Pascual JM. The infundibulo-tuberal syndrome caused by craniopharyngiomas: clinicopathological evidence from an historical French cohort (1705–1973). *Pituitary* 2015 **18** 642–657. (doi:10.1007/s11102-014-0623-4)
- 41 Muller HL, Gebhardt U, Teske C, Faldum A, Zwiener I, Warmuth-Metz M, Pietsch T, Pohl F, Sorensen N & Calaminus G. Post-operative hypothalamic lesions and obesity in childhood craniopharyngioma: results of the multinational prospective trial KRANIOPHARYNGEOM 2000 after 3-year follow-up. *European Journal of Endocrinology* 2011 **165** 17–24. (doi:10.1530/EJE-11-0158)
- 42 Muller HL, Gebhardt U, Faldum A, Warmuth-Metz M, Pietsch T, Pohl F, Calaminus G & Sorensen N. Xanthogranuloma, Rathke's cyst, and childhood craniopharyngioma: results of prospective multinational studies of children and adolescents with rare sellar malformations. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 3935–3943. (doi:10.1210/jc.2012-2069)
- 43 Pascual JM, Prieto R, Carrasco R & Barrios L. Displacement of mammillary bodies by craniopharyngiomas involving the third ventricle: surgical-MRI correlation and use in topographical diagnosis. *Journal of Neurosurgery* 2013 **119** 381–405. (doi:10.3171/2013.1.JNS111722)
- 44 Matson DD & Crigler JF Jr. Management of craniopharyngioma in childhood. *Journal of Neurosurgery* 1969 **30** 377–390. (doi:10.3171/jns.1969.30.4.0377)
- 45 Petito CK, DeGirolami U & Earle KM. Craniopharyngiomas: a clinical and pathological review. *Cancer* 1976 **37** 1944–1952. (doi:10.1002/1097-0142(197604)37:4<1944::AID-CNCR2820370446>3.0.CO;2-)
- 46 Weiner HL, Wisoff JH, Rosenberg ME, Kupersmith MJ, Cohen H, Zagzag D, Shiminski-Maher T, Flamm ES, Epstein FJ & Miller DC. Craniopharyngiomas: a clinicopathological analysis of factors predictive of recurrence and functional outcome. *Neurosurgery* 1994 **35** 1001–1010; discussion 1010–1001. (doi:10.1227/00006123-199412000-00001)
- 47 Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, Ansorge O, Shine B, Turner HE & Wass JA. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. *Clinical Endocrinology* 2005 **62** 397–409. (doi:10.1111/j.1365-2265.2005.02231.x)
- 48 Baskin DS & Wilson CB. Surgical management of craniopharyngiomas. A review of 74 cases. *Journal of Neurosurgery* 1986 **65** 22–27. (doi:10.3171/jns.1986.65.1.0022)
- 49 Duff J, Meyer FB, Ilstrup DM, Laws ER Jr, Schleck CD & Scheithauer BW. Long-term outcomes for surgically resected craniopharyngiomas. *Neurosurgery* 2000 **46** 291–302; discussion 302–295. (doi:10.1097/00006123-200002000-00007)
- 50 Van Effenterre R & Boch AL. Craniopharyngioma in adults and children: a study of 122 surgical cases. *Journal of Neurosurgery* 2002 **97** 3–11. (doi:10.3171/jns.2002.97.1.0003)
- 51 Banna M, Hoare RD, Stanley P & Till K. Craniopharyngioma in children. *Journal of Pediatrics* 1973 **83** 781–785. (doi:10.1016/S0022-3476(73)80369-5)
- 52 Hetelekidis S, Barnes PD, Tao ML, Fischer EG, Schneider L, Scott RM & Tarbell NJ. 20-year experience in childhood craniopharyngioma. *International Journal of Radiation Oncology, Biology, Physics* 1993 **27** 189–195. (doi:10.1016/0360-3016(93)90227-M)
- 53 Muller HL, Emser A, Faldum A, Bruhnken G, Etavard-Gorris N, Gebhardt U, Oeverink R, Kolb R & Sorensen N. Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 3298–3305. (doi:10.1210/jc.2003-031751)
- 54 Hoffmann A, Gebhardt U, Sterkenburg AS, Warmuth-Metz M & Muller HL. Diencephalic syndrome in childhood craniopharyngioma – results of German Multicenter Studies on 485 long-term survivors of childhood craniopharyngioma. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 3972–3977. (doi:10.1210/jc.2014-1680)

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