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Craniopharyngiomas presenting as incidentalomas: results of KRANIOPHARYNGEOM 2007

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Abstract

Purpose Childhood-onset craniopharyngiomas (CP) are diagnosed due to clinical symptoms (symCP) or incidentally (incCP). We investigated clinical manifestations and outcome in incCPs and symCPs.

Methods IncCP were discovered in 4 (3 m/1 f) and symCP in 214 (101 m/113 f) CP recruited 2007–2014 in KRANIOPHARYNGEOM 2007. Age, sex, height, body mass index (BMI), tumor volume, degree of resection, pre- and postsurgical hypothalamic involvement/lesions, pituitary function and outcome were compared between both subgroups.

Results Reasons for imaging in incCP were cerebral palsy, head trauma, nasal obstruction, and tethered-cord syndrome, whereas headache (44%), visual impairment (25%), and growth retardation (17%) lead to imaging in symCP. Tumor volume at diagnosis was smaller in incCP (median 2.39 cm^3; range 0.14–4.10 cm^3) when compared with symCP (15.86 cm^3; 0.002–286.34 cm^3). Age, gender, BMI, height, hydrocephalus, tumor location, and hypothalamic involvement at diagnosis of incCP were within the range of these parameters in symCP. Complete resections were achieved more frequently (3/4 patients) in incCP when compared with symCP (20%). Surgical hypothalamic lesions were distributed similar in incCP and symCP. Irradiation was performed only in symCP (33%). No noticeable differences were observed concerning survival rates, endocrine deficiencies, BMI, height, functional capacity and quality of life of the 4 incCP cases when compared with the symCP cohort.

Conclusions IncCP are rare (1.8%) and characterized by lack of endocrine deficiencies, resulting in normal height and BMI, no hydrocephalus, and smaller tumor volume at diagnosis when compared with symCPs. Outcome of the observed incCP is similar with symCP.

Clinical trial registration number: NCT01272622.

Keywords Craniopharyngioma · Incidentaloma · Hypothalamus · Pituitary · Quality of life

Introduction

Craniopharyngiomas are embryonic malformations with tumorous character located at the sellar region, originating from remnants of Rathke's pouch along the craniopharyngeal duct [1] and occurring with two peaks of incidence during childhood and adult age [2–4]. Treatment options include neurosurgical procedures for removal and radiation therapy [5, 6]. The close anatomical proximity and even involvement of optic structures and neuroendocrine hypothalamic-pituitary axes are a risk factor for severe disease and/or treatment-related sequelae [7–16]. In childhood-onset craniopharyngioma (CP), studies on history before CP diagnosis have revealed symptoms and complaints related to CP, which were documented in CP patients' records with a median duration of 5 months prior to CP diagnosis [17–19].

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We analyzed 218 CP patients recruited between 2007 and 2014 in the multinational trial KRANIOPHARYNGEOM 2007 for symptoms and complaints leading to MRI demonstrating the typical aspect of a CP. We observed a subgroup of 4 CP patients, who were diagnosed with CP as an incidental finding in MRI, without any symptoms or complaints clinically indicating CP (incCP). Histories, clinical presentation at the time of CP diagnosis, treatment and outcome were evaluated in these 4 incCP cases and compared with the group of 214 CP patients recruited in KRANIOPHARYNGEOM 2007 with CP diagnosed in MRI due to previous symptoms (symCP).

Patients and methods

218 (114 females/104 males) diagnosed with adamantinomatous CP (median age at diagnosis: 9.5 years, range 1.3–17.9 years) were recruited between 2007 and 2014 in the multinational trial KRANIOPHARYNGEOM 2007 (NCT01272622) [20] and observed prospectively with a median follow-up of 3.4 years (range 0.01–10.9 years). The histological diagnosis of adamantinomatous CP was confirmed by histopathological reference assessment in all cases. Four of these 218 patients (1.8%) were diagnosed as incCP and observed with a median follow-up of 5.9 years (range 2.1–8.0 years).

Neuroradiological diagnostics

Tumor volume and the degree of initial presurgical hypothalamic involvement and surgical hypothalamic lesions were reference-assessed in 207 of 218 (99.5%) CP patients. Cranial MRIs were performed according to the KRANIOPHARYNGEOM 2007 protocol [9, 10, 21] at the time of CP diagnosis and prospectively at 3-months intervals during follow-up. Neuroradiological assessment of CP tumor volume and location, degree of surgical resection, preoperative hypothalamic involvement (HI) and surgical hypothalamic lesions (HL) was performed on pre- and postoperative MRIs by a reference neuroradiologist blinded for clinical information. CP location was categorized according to the degree of HI: no HI detectable on presurgical MRIs; HI of anterior hypothalamic structures not involving mammillary bodies and hypothalamic structures dorsal of mammillary bodies; and HI of both anterior plus posterior hypothalamic areas, i.e. involving anterior hypothalamic structures, mammillary bodies and hypothalamic areas dorsal of mammillary bodies [9, 10]. Surgical HLs were graded based on postsurgical MRIs according to the same criteria in three categories: no HL: no HL detectable on postsurgical MRIs, anterior HL: HL of anterior hypothalamic structures not involving mammillary bodies, and anterior plus posterior HL: HL involving anterior hypothalamic structures, mammillary bodies and hypothalamic areas dorsal of mammillary bodies. Tumor size was calculated using the formula "½ (A × B × C)" (aligned to the ellipsoid model: 4/3 π [A × B × C]), where A, B and C are the maximum dimensions in the standard planes: axial (cranio-caudal, A), coronal (transverse, B) and sagittal (anteroposterior, C).

Clinical parameters

Auxiological and clinical parameters were collected in all patients based on the KRANIOPHARYNGEOM 2007 trial protocol. Body height (SDS) [22] and body weight were obtained at diagnosis and prospectively at 3-months intervals after CP diagnosis. BMI (w/h^2; w = weight/kilogram, h = height/meter) was calculated and depicted as SDS according to the references of Rolland-Cachera et al. [23] for each subject at CP diagnosis and at standardized time points (one and 3 years after CP diagnosis, and at last follow-up visit).

Quality of life questionnaires

In CP patients diagnosed at an age ≥ 5 years, the Pediatric Quality of Life (PEDQOL) [24, 25] questionnaire was used to analyze health-related quality of life (QoL) at standardized time points (3, 12 and 36 months after CP diagnosis). Additionally, parental assessment of patient QoL was obtained by PEDQOL in patients younger than 18 years at study. The PEDQOL questionnaire is defining health-related QoL within seven domains (autonomy, emotional stability, body image, cognition, physical function, social functionality in family, and social functionality among friends). A high score is equivalent to more negative self or parental QoL assessment [24].

The German daily life ability scale Fertigkeitenskala Münster-Heidelberg (FMH) was used to analyze functional capacity as a measure of QoL at the standardized time points 3 months, one and 3 years after CP diagnosis [26]. FMH assesses the capacity for routine actions in daily life with 56 items. It was normalized with 971 persons (45% female), aged between 0 and 102 years, resulting in age-dependent percentiles [27]. The average time for answering the FMH questionnaire is 4.5 min in first-time users [26].

Statistical methods

Statistical analyses were performed using SPSS 25 (SPSS, Inc.). Data are displayed as median (range) or frequency (percent). Progression-free survival (PFS) rates were assessed using the Kaplan–Meier estimator. Events for estimation of PFS were defined as neuroradiologically

confirmed > 25% increase of residual tumor, reference-confirmed tumor recurrence after reference-confirmed complete surgical resection, and death. Due to the small sample size in the incCP cohort, only descriptive analyses are presented. Rather than a statistical (inferential) conclusion, it is assessed if the measurements of parameters of incCP lie within the range of measurements in the symCP cohort.

Results

In 4 of 218 CP patients (1.8%) recruited in KRANIOPHARYNGEOM 2007, the CP diagnosis was made as incidental finding without any complaints directly referred to CP.

Incidentaloma cases of CP

Case 1 Three years old male patient, preterm born after 28 weeks of gestation with known retardation of mental and physical development and connatal cerebral palsy. MRI was performed with clinical suspected diagnosis of cerebral palsy and revealed an intrasellar mass (tumor volume: 0.89 cm^3) (Fig. 1a, b). Transsphenoidal resection. Normal findings for endocrine and ophthalmological status before and after complete surgical resection.

Case 2 An 8 years old boy suffered a moderate head trauma. The MRI showed an intra and suprasellar mass with imaging features typical for CP (cystic compartments, calcifications) compressing the 3rd ventricle and posterior hypothalamic structures (tumor volume: 3.88 cm^3) (Fig. 1c, d). History revealed no episodes of headache or visual impairment. Growth hormone deficiency was the only endocrine deficit detectable at the time of diagnosis. Anthropometric data at the time of CP diagnosis were not available. Complete surgical resection was achieved resulting in complete pituitary insufficiency.

Case 3 Due to complaints about chronic nasal obstruction, an MRI was performed in the 15 year old boy revealing an intra- and suprasellar partly solid, partly cystic mass

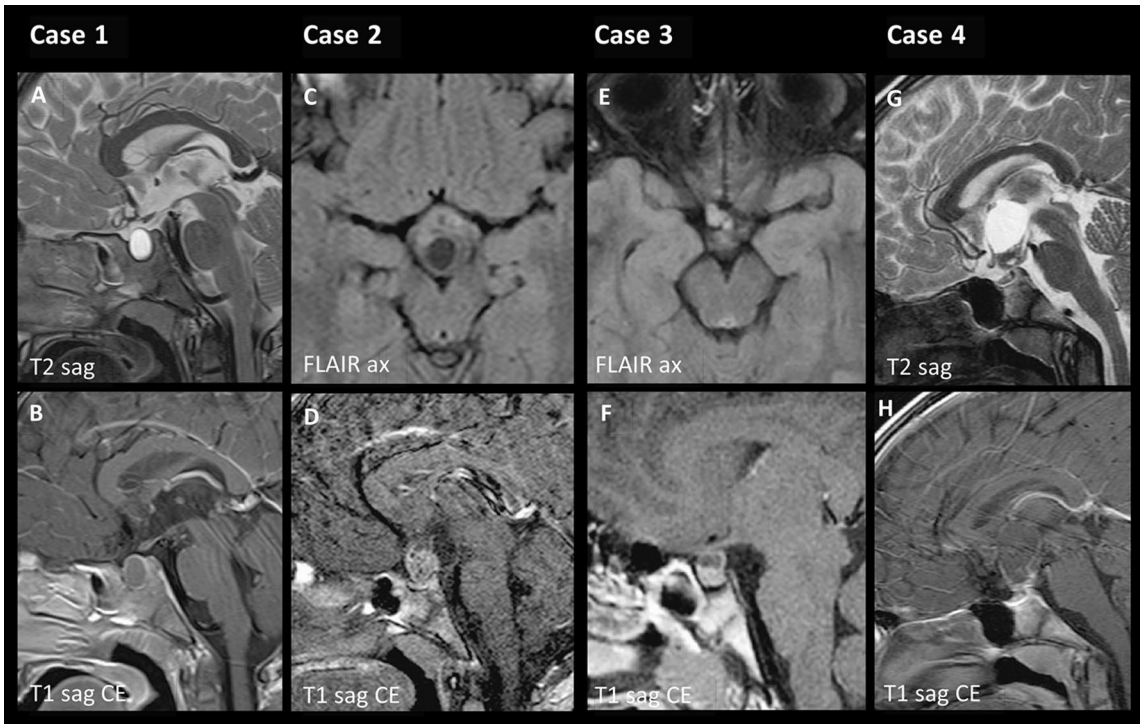

Fig. 1 Magnetic resonance imaging (MRI) at the time of diagnosis in 4 patients (Cases 1–4, **a**–**h**) diagnosed and recruited with incidentaloma craniopharyngioma (incCP) in the trial KRANIOPHARYNGEOM 2007 between 2007 and 2014. **a**, **b** (Case 1): Small, predominantly intrasellar and cystic lesion, displacing the sellar diaphragm upward, no contact to the optic system. **c**, **d** (Case 2): Medium sized, partly solid, partly cystic lesion compressing the optic chiasm as well as the anterior and posterior hypothalamus, primarily located in the suprasellar region, edema of the tractus opticus. **e**, **f** (Case 3): Small, partly solid, partly cystic lesion with an intra- and suprasellar location, displacing the optic chiasm slightly upward. **g**, **h** (Case 4): Medium sized, mostly suprasellar and cystic lesion with compression of the anterior and posterior hypothalamus. Additionally bleeding in a small Rathke's cleft cyst. In all cases, the solid parts and the cyst walls show some contrast enhancement and the cyst content some elevated signal on T1 due to protein-rich and colloid content. *T2* T2-weighted images, *FLAIR* fluid-attenuated inversion recovery, *T1* T1-weighted images, *sag* sagittal plane, *ax* axial plane, *CE* contrast enhanced

compressing the chiasm and the optic nerve on the right side (tumor volume: 0.14 cm^3) (Fig. 1e, f). No endocrine deficits. Impaired visual field on the right side. Complete surgical tumor removal.

Case 4 Seven-year-old girl with tethered cord surgery at age of 6 years. Follow-up monitoring by MRI revealed a predominantly suprasellar mass with progressive growth (Fig. 1g, h). No endocrine or ophthalmological deficiencies. Transcranial complete resection of the suprasellar mass (tumor volume: 4.10 cm^3) at 8 years of age. The patient developed complete pituitary deficiency and hypothalamic obesity due to surgical lesions located in anterior plus posterior hypothalamic areas (BMI at diagnosis: + 0.27 SD; BMI at last follow-up: + 7.29 SD).

At the time of CP diagnosis, 4 incCP patients presented with similar manifestations and clinical findings in terms of gender, age, height and BMI SDS when compared with 214 symCP. All incCP had extrasellar extension and no incCP was associated with primary hydrocephalus. IncCPs were smaller (median tumor volume: 2.39 cm^3; range 0.14–4.10 cm^3) when compared with symCP (median tumor volume: 15.86 cm^3; range 0.002–286.34 cm^3). The grades of presurgical hypothalamic involvement were distributed similarly in incCP and symCP (Table 1).

In symCP, the first symptoms in history were headache (44%), visual impairment (25%), growth retardation (17%), neurological symptoms (6%), polydypsia/polyuria (3%), nausea/vomiting (3%), weight gain (1%), and disturbances of pubertal development (1%). The longest intervals between first complaints and the time of symCP diagnosis were observed for reductions of growth rate (median interval between observation and CP diagnosis: 24 months) and weight gain (median interval between observation and CP diagnosis: 24 months) (Fig. 2).

Surgical approaches were similar in incCP and symCP. A high rate of complete surgical resections (75%) was observed in incCP. The rate of surgical HL and the distribution of different grades of HL were comparable between incCPs and symCPs (Table 2). Surgical HL were reference-confirmed in 3 of 4 incCP (anterior hypothalamic lesions in case 3 and anterior plus posterior hypothalamic lesions in cases 2 and 4). External irradiation was performed in 71 of 214 symCPs (33%). No patient with incCP was treated by irradiation. Overall survival rates (1.0 in both subgroups) were similar,

Table 1 Patient characteristics of childhood-onset craniopharyngioma (CP) patients recruited in KRANIOPHARYNGEOM 2007

	symCP	incCP	Case 1	Case 2	Case 3	Case 4
Patients, *n*	214	4	1	1	1	1
Gender, male/female, *n* (%)	101 (47)/113 (53)	3 (75)/1 (25)	m	m	m	f
Age at diagnosis (years)	9.6 (1.3–17.9)	8.1 (3.7–15.2)	3.7	8.3	15.2	7.9
Duration of history (months)	5 (0–108)	/	/	/	/	/
Follow-up time (years)	3.4 (0.0–10.9)	5.9 (2.1–8.0)	2.1	7.2	4.5	8.0
BMI-SDS (23) at diagnosis	0.48 (− 3.82 to 10.02)	1.54 (− 0.57 to 3.88)	− 0.57	3.88	2.80	0.27
Height-SDS (22) at diagnosis	− 1.01 (− 4.90 to 3.64)	0.38 (− 1.25 to 1.07)	1.07	− 1.25	0.11	0.65
BMI-SDS (23) at last visit	2.60 (− 2.89 to 13.22)	2.76 (2.08 to 8.00)	2.08	2.46	3.05	8.00
Height-SDS (22) at last visit	− 0.43 (− 4.94 to 3.09)	− 0.02 (− 1.49 to 2.79)	0.75	− 1.49	− 0.72	2.79
Hydrocephalus at diagnosis, *n* (%)	83 (38.8)	0 (0)				
Tumor location, *n* (%)						
Extrasellar location	44 (21)	2 (50)			x	x
Intra and extrasellar location	153 (72)	2 (50)	x	x		
Intrasellar location	3 (1)	0 (0)				
n.a.	14 (6)	0 (0)				
Tumor volume (cm^3)	15.86 (0.002–286.34)	2.39 (0.14–4.10)	0.89	3.88	0.14	4.10
Hypothalamic involvement (HI), *n* (%)						
No HI	11 (5)	1 (25)	x			
Anterior HI	55 (26)	1 (25)			x	
Anterior plus posterior HI	141 (66)	2 (50)		x		x
n.a.	7 (3)	0 (0)				

Characteristics in patients diagnosed and recruited with incidentaloma craniopharyngioma (incCP) and symptomatic craniopharyngioma (symCP) in the trial KRANIOPHARYNGEOM 2007 between 2007 and 2014

CP craniopharyngioma, *incCP* CP diagnosed as incidentaloma, *symCP* craniopharyngioma diagnosed due to clinical symptoms and complaints, *HI* presurgical hypothalamic involvement, *BMI* body mass index, *SDS* standard deviation score

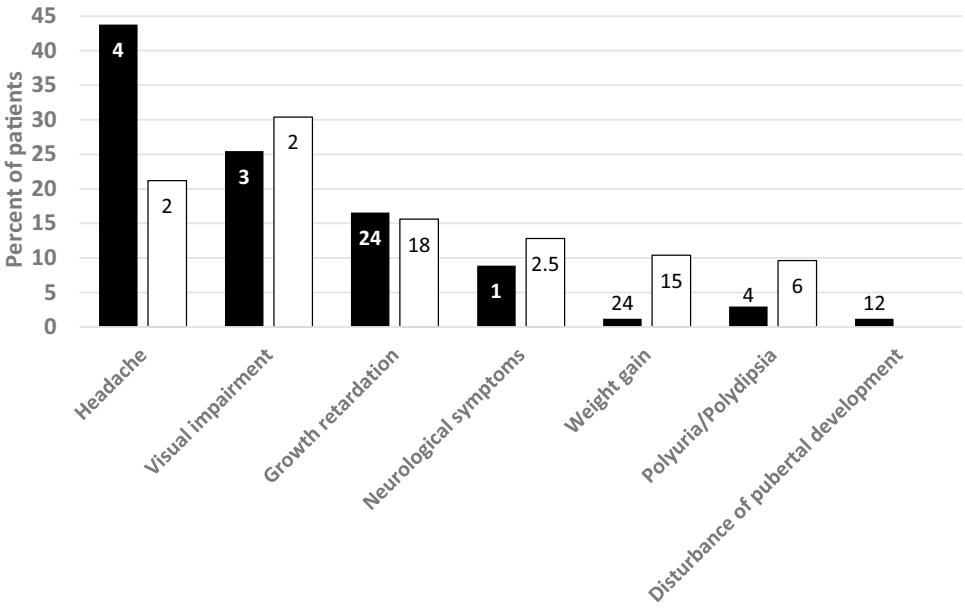

Fig. 2 Manifestations before diagnosis of symptomatic craniopharyngioma (symCP) in children and adolescents recruited in the trial KRANIOPHARYNGEOM 2007 between 2007 and 2014. Frequency of occurrence of each manifestation (%) before diagnosis (black) and frequency of occurrence as the initial manifestation (white). The median time (months) from the appearance of each initial manifestation until diagnosis is indicated as an insert or above each column. In the overall group, the median time interval between initial manifestation of disease and symCP diagnosis was 5 months, ranging from 0.01 to 108 months

i.e. no events were observed during follow-up. PFS rates were similar for incCP and symCP (Fig. 3).

After a median follow-up interval of 5.9 years in incCP and 3.4 years in symCP, height, BMI, endocrine deficiencies (Table 2, 3), and scores for health-related QoL (PEDQOL scores) both for self-assessment (Fig. 4a–g) and parental assessment of QoL (Supplementary Fig. 1a–g) by PEDQOL were similar in the subgroups of incCP and symCP. Furthermore, scores for functional capacity assessed by FMH questionnaire at the time points 3, 12, and 36 months after CP diagnosis were also similar for incCP and symCP (Fig. 5).

Table 2 Treatment characteristics

	symCP	incCP	Case 1	Case 2	Case 3	Case 4
Patients, n	214	4	1	1	1	1
Surgical approach, *n* (%)						
Transcranial approach	96 (45)	3 (75)		x	x	x
Transsphenoidal approach	32 (15)	1 (25)	x			
Other approach	13 (6)	0 (0)				
n.a.	73 (34)	0 (0)				
Degree of resection, *n* (%)						
Complete resection	42 (20)	3 (75)	x	x		x
Incomplete resection	134 (63)	1 (25)			x	
n.a.	38 (17)	0 (0)				
Hypothalamic lesion (HL), *n* (%)						
No HL	62 (29)	1 (25)	x			
Anterior HL	73 (34)	1 (25)			x	
Anterior plus posterior (HL)	70 (33)	2 (50)		x		x
n.a.	9 (4)	0 (0)				
Irradiation, *n* (%)						
Irradiation	71 (33)	0 (0)				

Treatment characteristics in patients diagnosed and recruited with incidentaloma craniopharyngioma (incCP) and symptomatic craniopharyngioma (symCP) in the trial KRANIOPHARYNGEOM 2007 between 2007 and 2014

CP craniopharyngioma, *incCP* CP diagnosed as incidentaloma, *symCP* symptomatic craniopharyngioma diagnosed due to clinical symptoms and complaints, *HL* surgical hypothalamic lesion, *n.a.* data not available

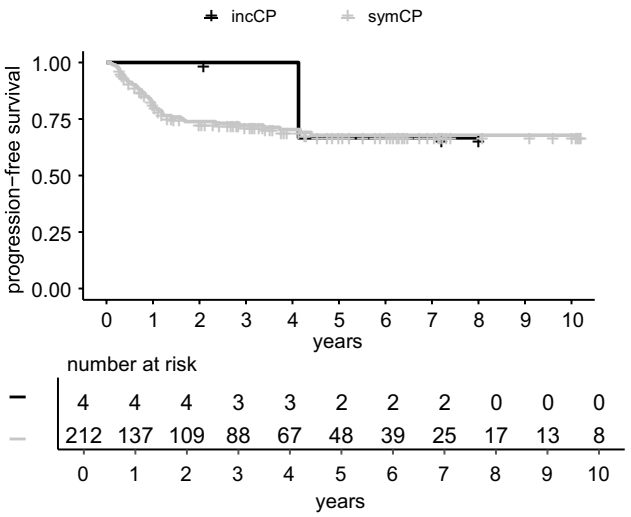

Fig. 3 Kaplan–Meier progression-free survival rate (PFS) in patients diagnosed and recruited with incidentaloma craniopharyngioma (incCP) and symptomatic craniopharyngioma (symCP) in the trial KRANIOPHARYNGEOM 2007 between 2007 and 2014

Table 3 Endocrine deficits in childhood-onset craniopharyngioma patients at the time of diagnosis and during follow-up

	symCP	incCP
Patients, *n*	214	4
Endocrine deficits at diagnosis, *n* (%)		
Growth hormone deficiency	41 (19)	0 (0)
Diabetes insipidus neurohormonalis	30 (14)	0 (0)
Hypothyroidism	37 (17)	0 (0)
Hypocortisolism	31 (15)	0 (0)
Hypogonadism	14 (7)	0 (0)
Endocrine deficits at last visit, *n* (%)		
Growth hormone deficiency	99 (46)	1 (25)
Diabetes insipidus neurohormonalis	130 (61)	2 (50)
Hypothyroidism	135 (63)	3 (75)
Hypocortisolism	134 (63)	3 (75)
Hypogonadism	47 (22)	0 (0)
No endocrine deficits detectable	6 (3)	1 (25)

Endocrine deficiencies at the time of diagnosis and at last visit in patients diagnosed and recruited with incidentaloma craniopharyngioma (incCP) and symptomatic craniopharyngioma (symCP) in the trial KRANIOPHARYNGEOM 2007 between 2007 and 2014

CP craniopharyngioma, *incCP* CP diagnosed as incidentaloma, *symCP* symptomatic craniopharyngioma diagnosed due to clinical symptoms and complaints

Discussion

Childhood-onset CPs are rare embryonic tumorous malformations originating in the sellar and parasellar area along the craniopharyngeal duct. Close anatomical proximity to hypothalamic-pituitary and visual structures results in severe tumor and/or treatment associated sequelae. Accordingly, hypothalamus-sparing strategies are the current recommendation for risk-appropriate treatment in CP [2, 5, 6, 28–30].

Headache, visual impairments, growth retardation, and polyuria/polydipsia are major clinical manifestations leading to CP diagnosis [2, 31–35]. Symptoms and complaints are known to occur years before diagnosis, which frequently leads to a long duration of history [17, 19]. Our analysis of complaints and clinical manifestations before diagnosis of CP and duration of history confirms these previous observations [17].

However, there are also CP cases, in which imaging is performed not due to symptoms related to CP, resulting in incidental CP diagnosis. We analyzed rate, clinical presentation and prognosis in 4 patients diagnosed and recruited with incCP in KRANIOPHARYNGEOM 2007 from 2007 to 2014.

Typical characteristics in incCP were the lack of endocrine deficiencies at diagnosis, resulting in normal height and BMI, no signs of increased intracranial pressure, i.e. no hydrocephalus, and smaller tumor volume at diagnosis when compared with symCPs. We have previously shown that reduced growth rate is a frequent and early symptom of CP occurring years before CP diagnosis [19]. It has to be pointed out, that in incCP height SDS at the time of diagnosis was within the normal range of height SDS. Unfortunately, data on growth rates before CP diagnosis were not available for incCP patients. Accordingly, it cannot be excluded that due to missing measurements, reduced growth rates at the time of CP diagnosis were not recognized in incCP. However, no incCP presented with short stature (height < -2 SDS) at the time of CP diagnosis.

It is known from previous reports [18] that hydrocephalus and clinical manifestations due to increased intracranial pressure such as headache and vomiting are major symptoms leading to CP diagnosis and influencing long-term outcome. In our incCP cohort, no case presented at diagnosis with hydrocephalus. Smaller tumor volume of incCP could explain this difference between incCP and symCP.

Presurgical hypothalamic involvement is a known risk factor for impaired long-term prognosis in terms of hypothalamic syndrome [10–14]. The similar rate and grades of presurgical HI in both subgroups were unexpected. Three of the 4 incCP cases presented with HI at the time of diagnosis. Based on these findings, we speculate that primary hypothalamic tumor involvement associated with potential symptoms of hypothalamic dysregulation has less impact on initial clinical presentation when compared with endocrine deficiencies associated with pituitary involvement.

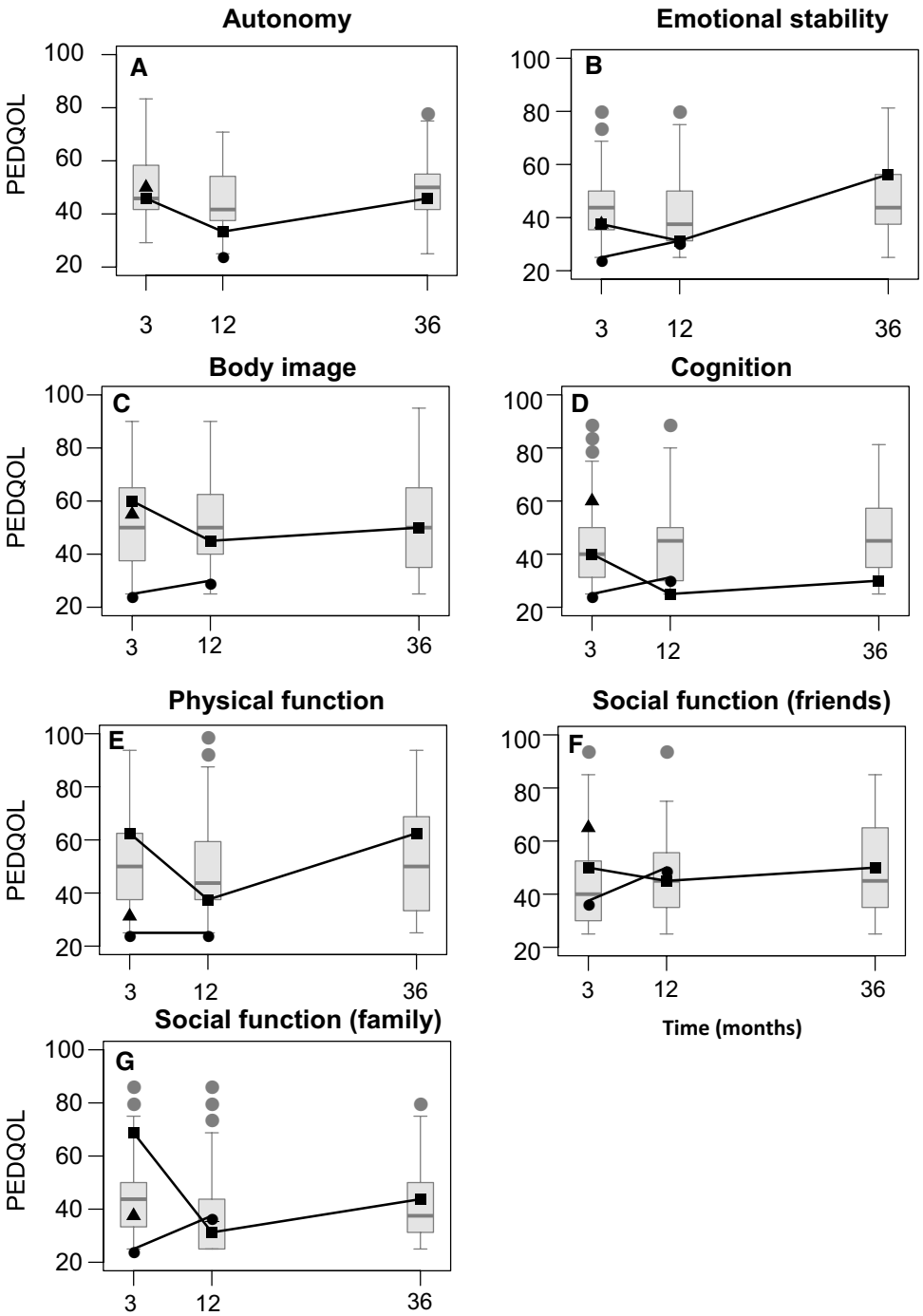

Fig. 4 Self-assessed health-related quality of life (QoL) as measured by the Pediatric Quality of Life (PEDQOL) [24] questionnaire in patients diagnosed and recruited with incidentaloma craniopharyngioma (incCP) and symptomatic craniopharyngioma (symCP) in the trial KRANIOPHARYNGEOM 2007 between 2007 and 2014. Self-assessments by PEDQOL at the time points 3, 12, and 36 months after CP diagnosis are depicted for the PEDQOL domains autonomy (**a**), emotional stability (**b**), body image (**c**), cognition (**d**), physical function (**e**), social function (friends) (**f**), and social function (family) (**g**). PEDQOL provides negative ratings, i.e. a high score is equivalent to more negative self or parental QoL assessment. Individual PEDQOL scores for incCP are depicted as circle for case 1, triangle for case 3, and square for case 4. PEDQOL scores for sympCP are shown as boxplots. 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

In spite of smaller tumor volume at diagnosis, incCP patients had similar outcome in terms of body composition (BMI, height), QoL and functional capacity when compared with symCP patients. We speculate that tumor location i.e. presurgical hypothalamic involvement and surgical hypothalamic lesions, which were detectable in similar frequency in the subgroups, resulted in similar findings in terms of long-term outcome.

The interpretation of our study results has certain limitations. Obviously the rate of incCP (1.8%) is low. Only 4 of 218 CP patients recruited in KRANIOPHARYNGEOM over 7 years presented as incCP. Our Craniopharyngioma Registry recruits CP patients with a high degree of completeness, so that the incidence rate of incCP seems valid. Due to missing data, we unfortunately cannot exclude that incCP patients could have been symptomatic based on

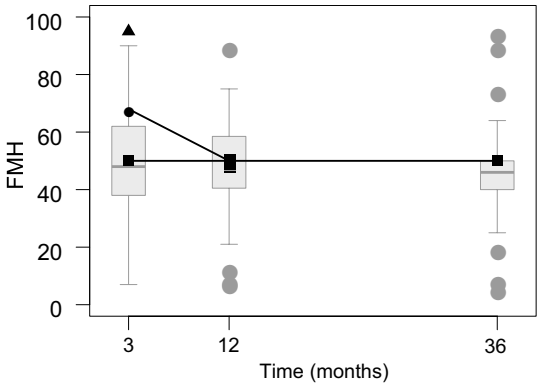

Fig. 5 Functional capacity as measured by Fertigkeitenskala Münster Heidelberg (FMH) [27] in patients diagnosed and recruited with incidentaloma craniopharyngioma (incCP) and symptomatic craniopharyngioma (symCP) in the trial KRANIOPHARYNGEOM 2007 between 2007 and 2014. Individual FMH scores for incCP at the time points 3, 12, and 36 months after CP diagnosis are depicted as circle for case 1, triangle for case 3, square for case 4. FMH scores for sympCP are shown as boxplots. 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

reduced growth rates before CP diagnosis. However, all incCP patients presented with normal height at the time of diagnosis, i.e. body height ranging from − 1.25 to + 1.07 height SDS.

Based on our findings, we conclude that headache, visual impairment, growth retardation, neurologic symptoms, weight gain, symptoms of central diabetes insipidus, and disturbances of pubertal development are frequent symptoms observed in CP at the time of diagnosis. A long duration of history is typical with regard to reduced growth rates and weight gain. IncCP cases occur with low frequency especially in CP patients with tumors of low tumor volume and without increased intracranial pressure at the time of CP diagnosis. In the observed cases of incCP, outcome in terms of survival rates, anthropometric parameters, endocrine deficiencies, QoL and functional capacity was similar to symCP patients.

The question, what should be considered to achieve earlier diagnosis in CP based on our findings in incCP has no clear answer. However, based on the observed duration of history regular monitoring of height and growth velocity is recommended. A combination of the symptoms reduced growth rate, visual impairment, headache and polyuria/polydipsia should lead to imaging diagnostics.

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Author contributions SB researched the data and wrote the manuscript. BB did neuroradiological assessment of all imaging. BB is the neuroradiologist, who performs reference-assessment of imaging in all patients recruited in KRANIOPHARYNGEOM 2007. She prepared the imaging data and their presentation and reviewed/edited the manuscript. ME supervised statistical analyses and reviewed/edited the manuscript. PS contributed to the analytical plan and discussion and reviewed/edited the manuscript. HLM 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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Compliance with ethical standards

Conflict of interest HLM has received reimbursement of participation fees for scientific meetings and continuing medical education events from the following companies: Ferring, Lilly, Pfizer, Sandoz/Hexal, Novo Nordisk, Ipsen, and Merck Serono. He has received reimbursement of travel expenses from Ipsen and lecture honoraria from Pfizer. The other authors declare that they have no conflict of interest.

Ethical approval 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. The study KRANIOPHARYNGEOM 2007 (Clinical trial registration number: NCT01272622) was approved by the local standing-committee on ethical practice of the Medizinische Fakultät, Julius-Maximilians-Universität Würzburg, Germany (approval: 94/06), and written parental and/or patient consent was obtained in all cases.

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