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

Anika Hoffmann¹, Svenja Boekhoff¹, Ursel Gebhardt¹, Anthe S Sterkenburg¹,², Anna M M Daubenbüchel¹,², Maria Eveslage³ and Hermann L Müller¹

¹Department of Pediatrics, Klinikum Oldenburg, Medical Campus University Oldenburg, Rahel-Straus-Strasse 10, 26133 Oldenburg, Germany, ²University of Groningen, Groningen, The Netherlands and ³Institute of Biostatistics and Clinical Research, University of Münster, Münster, Germany

Correspondence should be addressed to H L Müller
Email mueller.hermann@klinikum-oldenburg.de

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 at presentation to 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.

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 ¹) 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×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 χ²-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 presurgical manifestations could be analyzed based on records in 325 of 411 patients (79%). A total 142 CP

<p>| Table 1 Characteristics of 411 patients with childhood-onset CP recruited in HIT Endo and KRAIOPHARYNGIOMA 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). |</p>
<table>
<thead>
<tr>
<th>Symptom in history</th>
<th>n (y/n)</th>
<th>Tumor size at diagnosis (cm²)</th>
<th>Hypothalamic involvement at diagnosis (%)</th>
<th>Tumor location at diagnosis (%)</th>
<th>BMI at diagnosis (SDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>206/96</td>
<td>2.8 (1.1–9.6)</td>
<td>0.82</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Nausea</td>
<td>42/80</td>
<td>2.0 (0.0–1.2)</td>
<td>0.89</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>167/130</td>
<td>2.6 (1.2–8.7)</td>
<td>0.79</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Neurological deficits</td>
<td>60/324</td>
<td>1.9 (0.4–1.8)</td>
<td>0.79</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Weight gain</td>
<td>49/251</td>
<td>2.6 (0.1–2.0)</td>
<td>0.80</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Growth failure</td>
<td>110/191</td>
<td>2.0 (0.0–0.4)</td>
<td>0.83</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Polydipsia/Polyuria</td>
<td>23/97</td>
<td>2.6 (0.4–0.8)</td>
<td>0.81</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>BMI SDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.00</td>
<td>9.8</td>
<td>9.0 (0.4–1.2)</td>
<td>0.80</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5.00–7.55</td>
<td>9.0</td>
<td>9.0 (0.4–1.2)</td>
<td>0.80</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>7.55–9.90</td>
<td>8.9</td>
<td>9.0 (0.4–1.2)</td>
<td>0.80</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>&lt;9.90</td>
<td>9.8</td>
<td>9.0 (0.4–1.2)</td>
<td>0.80</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

$y/n$, yes/no; 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

### 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).

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

Bold values and ranges indicate significant differences.
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; \( P<0.01 \)) (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
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 KRANIOPHARYNDEOM 2000. BMI SDS according to the references of Rolland-Cachera et al. (17).

<table>
<thead>
<tr>
<th>Symptom in history</th>
<th>Overall survival (10 years)</th>
<th>Progression-free survival (10 years)</th>
<th>BMI (SDS) at last visit</th>
<th>Functional capacity at last visit (RMH %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (y/n)</td>
<td>Yes 0.96 ±0.02</td>
<td>Yes 0.96 ±0.02</td>
<td>Yes 0.96 ±0.02</td>
</tr>
<tr>
<td>Headache</td>
<td>206/96</td>
<td>0.99 ±0.02</td>
<td>0.99 ±0.02</td>
<td>0.99 ±0.02</td>
</tr>
<tr>
<td>Nausea</td>
<td>42/80</td>
<td>0.95 ±0.05</td>
<td>0.95 ±0.05</td>
<td>0.95 ±0.05</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>16/130</td>
<td>0.94 ±0.02</td>
<td>0.94 ±0.02</td>
<td>0.94 ±0.02</td>
</tr>
<tr>
<td>Neurological deficits</td>
<td>68/254</td>
<td>0.92 ±0.03</td>
<td>0.92 ±0.03</td>
<td>0.92 ±0.03</td>
</tr>
<tr>
<td>Weight gain</td>
<td>49/251</td>
<td>0.92 ±0.05</td>
<td>0.92 ±0.05</td>
<td>0.92 ±0.05</td>
</tr>
<tr>
<td>Growth failure</td>
<td>110/191</td>
<td>0.93 ±0.03</td>
<td>0.93 ±0.03</td>
<td>0.93 ±0.03</td>
</tr>
<tr>
<td>Polydipsia/Polyuria</td>
<td>23/97</td>
<td>1.00</td>
<td>0.94 ±0.03</td>
<td>0.94 ±0.03</td>
</tr>
</tbody>
</table>

y/n, yes/no; bold values and ranges indicate significant differences.
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 KRANIOPHARYNDEOM 2000. BMI SDS according to the references of Rolland-Cachera et al. (17).

<table>
<thead>
<tr>
<th>First symptom in history</th>
<th>n (y/n)</th>
<th>Duration of history (months)</th>
<th>Hypothalamic involvement at diagnosis (%)</th>
<th>BMI (SDS) at diagnosis</th>
<th>Tumor size at diagnosis (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>P</td>
<td>Yes</td>
</tr>
<tr>
<td>Headache</td>
<td>158/138</td>
<td>6.0 (0.5–108.0)</td>
<td>9.5 (0.0–108.0)</td>
<td>0.22</td>
<td>80.0 70.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>4/292</td>
<td>1.0 (0.3–48.0)</td>
<td>6.0 (0.0–108.0)</td>
<td>0.01</td>
<td>100.0 71.2</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>45/251</td>
<td>2.8 (0.3–96.0)</td>
<td>8.0 (0.0–108.0)</td>
<td>0.03</td>
<td>75.0 70.8</td>
</tr>
<tr>
<td>Neurological deficits</td>
<td>23/273</td>
<td>2.0 (0.3–48.0)</td>
<td>8.0 (0.0–108.0)</td>
<td>&lt;0.01</td>
<td>80.0 70.7</td>
</tr>
<tr>
<td>Weight gain</td>
<td>12/284</td>
<td>24.0 (6.0–60.0)</td>
<td>6.0 (0.0–108.0)</td>
<td>&lt;0.01</td>
<td>72.7 71.4</td>
</tr>
<tr>
<td>Growth failure</td>
<td>4/255</td>
<td>24.0 (3.0–108.0)</td>
<td>6.0 (0.0–108.0)</td>
<td>&lt;0.01</td>
<td>58.9 73.6</td>
</tr>
<tr>
<td>Polydipsia/Polyuria</td>
<td>1/285</td>
<td>6.0 (1.0–60.0)</td>
<td>6.0 (0.0–108.0)</td>
<td>0.42</td>
<td>63.6 71.8</td>
</tr>
</tbody>
</table>

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 KRANIOPHARYNDEOM 2000. BMI SDS according to the references of Rolland-Cachera et al. (17).

<table>
<thead>
<tr>
<th>First symptom in history</th>
<th>n (y/n)</th>
<th>Overall survival (10 years)</th>
<th>Progression-free survival (10 years)</th>
<th>BMI (SDS) at last visit</th>
<th>Functional capacity at last visit (FMH %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>P</td>
<td>Yes</td>
</tr>
<tr>
<td>Headache</td>
<td>158/138</td>
<td>0.96 ± 0.02</td>
<td>0.96 ± 0.02</td>
<td>0.96</td>
<td>0.58 ± 0.05</td>
</tr>
<tr>
<td>Nausea</td>
<td>4/292</td>
<td>1.00</td>
<td>0.96 ± 0.01</td>
<td>0.70</td>
<td>0.00</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>45/251</td>
<td>1.00</td>
<td>0.95 ± 0.02</td>
<td>0.64</td>
<td>0.49 ± 0.09</td>
</tr>
<tr>
<td>Neurological deficits</td>
<td>23/273</td>
<td>0.90 ± 0.07</td>
<td>0.96 ± 0.01</td>
<td>0.57</td>
<td>0.56 ± 0.16</td>
</tr>
<tr>
<td>Weight gain</td>
<td>12/284</td>
<td>0.92 ± 0.08</td>
<td>0.96 ± 0.01</td>
<td>0.05</td>
<td>0.34 ± 0.18</td>
</tr>
<tr>
<td>Growth failure</td>
<td>4/255</td>
<td>0.93 ± 0.05</td>
<td>0.97 ± 0.01</td>
<td>0.99</td>
<td>0.48 ± 0.12</td>
</tr>
<tr>
<td>Polydipsia/Polyuria</td>
<td>1/285</td>
<td>1.00</td>
<td>0.96 ± 0.01</td>
<td>0.32</td>
<td>0.6 ± 0.18</td>
</tr>
</tbody>
</table>

y/n, yes/no; bold values and ranges indicate significant differences.
significantly the DOH, and CPs causing hydrocephalus are
to 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. 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 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.

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 does not seem to be adequate to discriminate a real infiltration/invasion of the tuber cinereum from the displacement of
the third ventricle floor. 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. In our study, the combination of headache and
growth failure (18%) was most frequent. This finding is
supported by a previous report on reduced growth rate as an early clinical manifestation in childhood CP. The
most specific combination of symptoms 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. 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,
ad and as indicated, some observations are speculative at this
point. A specific grading of HI, as performed in recent
prospective studies, 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
This manuscript was composed in the absence of any commercial or
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