Management of Endocrine Disease

Childhood-onset craniopharyngioma: state of the art of care in 2018

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Abstract

This review presents an update on current concepts of pathogenesis, diagnostics, multidisciplinary treatment and follow-up care, with special focus on neuropsychological sequelae of childhood-onset craniopharyngioma (CP) based on most recent publications on these topics. Recent insight in molecular pathogenesis of CP opens new perspectives on targeted therapy. Further research to elucidate pathogenic mechanisms and to prevent hypothalamic involvement of CP is warranted. Surgical treatment strategies should be based on a multidisciplinary approach involving experienced teams aiming at posterior hypothalamus-sparing treatment for prevention of quality of life impairments. Centralization of CP treatment in experienced ‘centers of excellence’ is recommended. However, such centralization includes high thresholds concerning infrastructure not achievable in all health systems. Alternatives such as multicenter-based networks used for reference assessments should be considered to assure high standards of treatment quality. Irradiation is efficient in preventing further growth or recurrence in CP patients with residual tumor. Proton beam therapy – available on a wider range in the near future – will help to avoid radiooncological side effects. Novel insights into neuropsychological sequelae after CP should be the basis for the development of future therapeutic neuropsychological interventions. Due to the rareness of the disease, common international efforts in research and treatment are recommended and should lead to an international registry for childhood-onset CP, as a first step toward efficient coordination of scientific and clinical initiatives.

Introduction

Almost 80 years ago, the father of modern neurosurgery, Dr Harvey Cushing, declared craniopharyngioma (CP) ‘the most formidable of intracranial tumors’. Back in 1939, Cushing learned that surgery for these tumors was extremely challenging and risky. The introduction of microscopy, corticosteroids and antibiotics
improved surgical outcomes and prognosis after CP. Adjuvant therapy, such as stereotactic radiosurgery and intracavitary chemotherapy, and progress in imaging and surgical techniques improved tumor control and reduced complications.

However, based on deeper insight into sequelae after CP gained during the last decades, the pendulum of treatment strategies swung back from gross-total resection (GTR) to more limited surgical approaches focused on preservation of hypothalamic integrity and quality of survival after CP (1, 2). Due to limitations of GTR with regard to patient outcome, multidisciplinary treatment approaches including radiooncological options are currently favored. As outcome after CP is related to the experience of treating multidisciplinary teams, health care issues such as definition and implementation of criteria for treatment centers of excellence are currently discussed. Furthermore, insights in pathogenic mechanisms of neuropsychological late effects as a basis for risk-adapted therapy and rehabilitation are warranted.

This review presents an update on current concepts of pathogenesis, diagnostics, multidisciplinary treatment and follow-up care, with special focus on neuropsychological sequelae of CP based on most recent publications on these topics.

**Diagnostics**

Visual impairments, headaches and polydipsia/polyuria are major clinical symptoms of childhood-onset CP at diagnosis frequently observed already for long periods in history before CP diagnosis (Fig. 1). Significant growth retardation is a frequent and early clinical manifestation of CP occurring already during early infancy (3). A positive correlation between duration of patient history and tumor size of CP at diagnosis was not detectable.

Magnetic resonance tomography (MRI) and computed tomography (CT) – limited to the sellar area and excluding orbital areas – are the standard imaging in neuroradiological diagnostics of CP. CT is recommended for the detection of calcifications. MRI T2-weighted diffusion sequences are recommended as most appropriate for diagnostics in CP (4).

Recent reports on potential associations between deep gray matter hyperintensities observed in unenhanced T1-weighted scans and previous exposure to Gadolinium-based contrast agents (GBCA) in MRI have caused concerns over the safety of GBCAs. Accordingly, the International Society for Magnetic Resonance in Medicine (ISMRM) published guidelines recommending to use caution when performing MRI with GBCA (5). As long-term MRI monitoring of CP is part of regular follow-up diagnostics, this potential risk should be taken into consideration.

Over the years, several algorithms have been published grading location and hypothalamic involvement/lesions with regard to prognosis after CP (6, 7, 8, 9). Comparable with other oncological diseases including malignant CNS tumors, standardized primary staging based on imaging diagnostics is essential for decision on risk-appropriate treatment strategies. Mortini et al. (9) analyzed previously published grading algorithms for primary staging of presurgical hypothalamic involvement and treatment-associated hypothalamic damage with special regard to predictive value of these grading systems and algorithms for outcome after CP. The sensitivity of these grading systems for risk estimation of hypothalamic obesity was analyzed by the authors in a single-center cohort. The grade of hypothalamic involvement was observed as the major parameter characterized by high predictive value for hypothalamic syndrome (Fig. 2). These results support previous reports on a strong association between tumor and/or treatment-related hypothalamic damage and outcome in CP long-term survivors (6, 7, 8, 9).

**Figure 1**

Manifestations before diagnosis of craniopharyngioma in children and adolescents. Frequency of occurrence of each manifestation before diagnosis (open columns) and frequency of occurrence as the initial manifestation (black columns). The median time (months) from the appearance of each initial manifestation until diagnosis is indicated above each black column. In the overall group, the median time from the initial manifestation of disease until diagnosis was 12 months, with a range of 0.01–96 months. Modified from Müller HL et al. Monatsschr Kinderheilkd 2003, 151, 1056-63 with kind permission of Springer.

https://eje.bioscientifica.com
Recently, Apps et al. (12) reported that cell clusters in aCP are molecularly analogous to the enamel knot, a major signaling structure for physiological tooth morphogenesis and that inflammasome activation plays a major role in specific inflammatory microenvironment of glial tissue reactive to aCP.

**Papillary craniopharyngioma (pCP)**

BRAF (V600E)-activating mutations are detectable in pCPs with a prevalence rate ranging from 81 to 100% (11, 13). A novel BRAF V600E mutation-specific antibody (VE1) might provide new diagnostic perspectives in pCP. Targeted therapy against BRAF (V600E) mutations in pCP provides novel and promising perspectives. Brastianos et al. (13) recently reported on impressive tumor reduction in a pCP patient with BRAFV600E mutation treated with a combination therapy of a BRAF inhibitor (dabrafenib) and a MEK inhibitor (trametinib). A rare case of a pediatric pCP patient presenting with a BRAF V600E mutation was recently reported by Borrill et al. (14). Another rare case of pediatric pCP with potential transition of Rathke cleft cyst metaplasia to pCP was recently published by Schlaffer et al. (15).

**Therapeutic strategies**

**Neurosurgery**

With regard to the high risk of sequelae due to hypothalamic damage after GTR in CP with initial involvement of hypothalamic structures, limited hypothalamus-sparing surgical strategies are recommended in these patients at special risk for hypothalamic syndrome (6, 7). There is still considerable debate, whether this approach prevents sequelae in terms of hypothalamic syndrome or presurgical hypothalamic involvement has major impact on outcome regardless of chosen surgical treatment approaches (6).

For cystic CP, decompression via an intracystic catheter can be performed repeatedly when connected with an Ommaya reservoir. Mainly for recurrent single cystic CP, intracavitary instillation of sclerosing substances such as interferon alpha is a treatment of choice (16). Due to neurotoxicity in case of leakage, bleomycin instillation is obsolete (17). Systemic interferon alpha treatment has not been proven to be efficient in prevention of solid CP progression.
Radiooncological treatment

The ‘inverse dose profile’ across tissues is characteristic for proton beams. The released dose of particles increases with penetration depth until reaching a maximum dose at the end of the particle range called Bragg peak. Beyond this Bragg peak, no further dose is deposited (Fig. 3). In a study of 15 CP patients receiving combined photon–proton irradiation for recurrent or residual CP, Fitzek et al. (18) reported on local control rates of 93 and 85% after 5 and 10 years, respectively, without relevant treatment-related neurocognitive deficits. In their cohort, functional capacity, professional abilities and academic skills were not impaired. Luu et al. reported on a 87% local tumor control rate in 16 proton beam therapy-treated CP patients (19) and on late sequelae in terms of newly diagnosed panhypopituitarism, one posterior fossa meningioma located out-of-proton-field and one cerebrovascular accident. In a study on cystic CP progression related to proton beam treatment, Winkfield et al. (20) observed cyst shrinkage in 5% and cyst enlargement in 24% requiring modifications of treatment planning. Ajithkumar et al. could show that reduced radiation doses to hypothalamus, optic chiasm and temporal lobe were achieved by proton beam therapy and associated with more favorable toxicities and similar disease control when compared with CP patients treated by photon irradiation (21).

Reliable data on long-term outcome are rare as long as the technique of proton beam therapy is only available in a limited number of centers (21). Based on better dose conformation to target volume, proton beam therapy provides potential advantages of sparing critical cerebral structures and reducing dose application to neighboring anatomical structures and the risk of secondary malignancies. Long-term follow-up data in CP patients treated with proton beam therapy are expected, as this radiooncological technique will become more available in the future (Table 1).

Stereotactic radiotherapy is a modality combining the accurate focal dose delivery of stereotactic radiosurgery with the radiobiological advantages of fractionation. Compared with conventional irradiation, it adopts reduced safety margins and offers optimal sparing of the normal tissue surrounding the tumor. The data on the usefulness of stereotactic radiotherapy for the management of CP are limited, but the larger series published thus far provide promising results (22, 23). The 10-year actuarial local control and overall survival rates were 100 and 83%, respectively. Side effects included mild acute toxicity and two patients developed initial enlargement of the cystic component.

Survival and late morbidity

Overall mortality rates in CP are reported to be three to five times higher than those observed in the general population (24). The overall survival rates described in pediatric series range from 83 to 96% at 5 years (25) and 65 to 100% at 10 years (25) and 65 to 100% at 10 years (26, 27) and average 62% at 20 years. In cohorts with mixed-age range, the overall survival rates range from 54 to 96% at 5 years (24, 28), from 40 to 93% at 10 years (24, 28, 29) and from 66 to 85% at 20 years (24, 29). It is still a matter of debate, whether age at CP diagnosis is a prognostic factor for survival. Several studies found that the youngest patients have better survival rates; others report on better outcome in older CP patients or similar survival rates in pediatric and adult cohorts (28). Some authors found higher mortality rates among females (24), whereas others did not observe any gender differences in terms of survival (28).

Figure 3
The figure shows an image of a sagittal CT with color-wash proton dose distribution in a child with craniopharyngioma. Bone defect present in base of skull after trans-nasal surgery and calcifications present in third ventricle corresponding to unresected tumor. Color legend: orange-red = 50.4–54 CGE; dark blue ≤10.8 CGE. Reproduced from Müller et al. (1) with kind permission of Springer Nature.
Table 1  Advantages and disadvantages of modern treatment technologies in radiotherapy of craniopharyngioma.

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<td>Conventional 2-D radiotherapy</td>
<td>Reliable clinical data and long-term follow-up indicating high efficacy of radiotherapy</td>
<td>Poor geometrical precision. No reliable protection of normal surrounding tissues</td>
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<td>Fractionated conformal radiation therapy/IMRT</td>
<td>Widely available, highly conformal, ease in adapting treatment to changing target</td>
<td>Highly conformal photon therapy requires exposure of a larger volume of normal tissue to low doses of radiation</td>
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<tr>
<td>Fractionated proton therapy</td>
<td>Normal tissue sparing. The volume or normal tissues exposed to low doses is significantly less compared to fractionated photon methods</td>
<td>Limited experience and significant costs. Image-guidance systems have lagged. Early passive scattering systems provided robust treatment yet lacked conformity of advanced photon systems. Newer pencil beam scanning systems require evaluation in clinical trials</td>
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<tr>
<td>Radiosurgery</td>
<td>Single treatment session. Highly conformal. Almost no dose to non-target tissue</td>
<td>Limited indications and experience. Only suitable for small volume solid residual and when tumor is not in contact with vital structures such as optic chiasm</td>
</tr>
<tr>
<td>Hypofractionated image guided radiosurgery (CyberKnife)</td>
<td>Fewer treatment sessions. Highly conformal. May have biological advantages under certain conditions</td>
<td>Very limited indications and experience. Role still unclear. No reliable data for tumor control or side effect reduction</td>
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<tr>
<td>Intracavitary colloid isotope application</td>
<td>High tumor control rates for cystic components. Applicable to tumors recurrent after prior irradiation</td>
<td>Advantages limited to cystic tumors. Underdosage of solid components. Complications related to leakage or high-doses when administered in proximity to vital structures such as visual pathways and brainstem</td>
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Late mortality rates are associated with tumor and/or treatment-related risk factors such as cerebrovascular disease, progressive disease with multiple recurrences, chronic neuroendocrine deficiencies (26, 27, 30, 31, 32, 33) and non-alcoholic fatty liver disease (NAFLD) leading to liver cirrhosis (26, 27, 34, 35, 36). The standardized overall mortality rate varied from 2.88 to 9.28 in cohort studies performed by Erfurth et al. The authors report that CP patients have a 3 to 19-fold increased cardiovascular mortality rate when compared with the general population. In female CP patients an even higher cardiovascular risk was observed (37).

The prognostic relevance of histological tumor type is also a matter of debate. Better 5-years overall survival rates have been observed in pCP when compared with aCP and combined histological types. Increased perioperative mortality was described in adult aCP, but other reports could not confirm prognostic differences between both histological subtypes. In adult-onset CP patients, a more favorable prognosis has been described in CPs lacking calcification, whereas no specific pathological feature predicted survival after childhood-onset CP. The prognostic impact of an initial hydrocephalus is also still a matter of debate. Increased mortality due to primary hydrocephalus has been reported as well as a lack of association between hydrocephalus and mortality (28, 38).

Sterkenburg et al. (39) observed that 20-year overall survival was significantly reduced in CP with hypothalamic involvement. On the other hand, the authors found that 20-year progression-free survival rate was not related to the degree of surgical resection, supporting their conclusion that gross total resection had no advantage in terms of CP recurrence (Fig. 4).

Endocrine sequelae and pharmacological treatment of hypothalamic obesity

Recent publications on safety and effects of GH substitution in CPs with panhypopituitarism show that GH substitution was safe with regard to risks of tumor relapse and progression. Quality of life (QoL) seemed to be stabilized in GH-treated CP patients during short-term follow-up, whereas beneficial GH effects on the development of obesity were not observed during the first 3 years after CP diagnosis (40). During long-term follow-up (assessed >12 years after diagnosis), patients substituted with GH during childhood age showed better QoL, height and weight development, when compared with CP patients in whom GH substitution was initiated at adult age (41).

Due to impairments in energy expenditure, central sympathetic output and satiety regulation, CP patients suffering from hypothalamic syndrome typically develop morbid obesity, which is unresponsive to conventional treatment such as lifestyle modifications (Fig. 5). Based
on the observed impairment of sympathetic activation leading to reduced hormonal response to hypoglycemia, treating this disorder with amphetamine derivatives has been supposed \((42, 43)\). Dextroamphetamine medication was observed to reduce continuous weight gain, to stabilize BMI \((44)\) and to increase physical activity. Even short-term dextroamphetamine treatment resulted in subjective improvement of daytime sleepiness \((45)\). Elfers et al. reported on beneficial effects of a medication with central stimulating agents (particularly methylphenidate) on weight development in CP patients \((46)\).

CP patients suffering from hypothalamic obesity present with a so-called parasympathetic predominance due to vagal activation and manifesting with lowering of heart rate, reduced body temperature and increased daytime sleepiness. Parasympathetic stimulation results in insulin hypersecretion by direct activation of \(\beta\) cells. The somatostatin analogue octreotide is a somatostatin analogue reducing insulin secretion. In a double-blind randomized controlled study in children with hypothalamic obesity, Lustig et al. observed moderate reductions in weight gain under octreotide medication \((47)\). A larger trial performed using octreotide LAR in 60 patients with hypothalamic obesity showed no changes...
in BMI. Due to increased risk of gallstone formation, the open-label segment of the trial was terminated.

Hamilton et al. hypothesized that dual therapy with metformin and diazoxide decreases insulin secretion and the risk for hyperglycemia (48). Insulin secretion is reduced by diazoxide binding to the KATP channel of the β-cell. Metformin improves insulin sensitivity by decreasing hepatic gluconeogenesis. A combination therapy of metformin and diazoxide was studied in nine pediatric CP patients with hypothalamic obesity. The synergism of lower insulin levels and enhanced insulin action lead to an improved weight gain of +1.2 ± 5.9 kg when compared to +9.5 ± 2.7 kg weight gain during the 6 months prior to therapy. High pretreatment insulin levels were associated with the most robust weight loss (48). Limitations of the study were small cohort size and adverse events in one patient withdrawing due to development of peripheral edema and another due to emesis and elevated hepatic enzymes.

Zoicas et al. (49) treated eight adult patients with hypothalamic obesity – including six CP patients – with GLP-1 receptor agonists. The authors reported on improvements in metabolic and cardiovascular risk profiles associated with a sustained weight loss.

Energy expenditure is increased by triiodothyronine (T3) through induction of thermogenesis. In a case series, Fernandes et al. (50) reported on three patients (one adult, two children with suprasellar masses, no CP) experiencing weight reduction and improved daytime lethargy under T3 supplementation for up to 24 months. Van Santen et al. (51) analyzed metabolic brown adipose tissue activity in a T3-treated CP patient with hypothalamic obesity. Presumably due to damage of hypothalamic pathways, no changes in energy expenditure or brown adipose tissue activity were observed suggesting that adjunct therapy with T3 had no beneficial effects.

Methionine aminopeptidase 2 (MetAP2) inhibitors were initially developed as anti-angiogenesis agents for oncological therapy. MetAP2 inhibitors were subsequently found to induce weight loss, increase adiponectin and decrease leptin concentrations, which results in increased lipolysis and fat oxidation and decreased lipogenesis. Simmons et al. (52) treated 14 adult patients with hypothalamic obesity with the MetAP2 inhibitor beloranib for 8 weeks and reported on an average weight loss of 3.2 kg in the first 4 weeks and 6.2 kg at 8 weeks of treatment. Unfortunately, although consistent weight reduction was observed with beloranib treatment, further development of the pharmaceutical agent was stopped due to venous thromboembolic events occurring in clinical studies on Prader–Willi syndrome patients with hypothalamic obesity treated with the MetAP2 inhibitor beloranib (53).

Sibutramine, a noradrenaline and serotonin uptake inhibitor, prevents reduced energy expenditure after weight loss and reduces appetite. However, sibutramine-induced weight reduction in children with hypothalamic obesity was less efficient when compared with non-hypothalamic obesity (42). Future trials with sibutramine are not expected as sibutramine was withdrawn from major markets in 2010 due to concerns over increased cardiovascular risk (54).

Dexamphetamine improved daytime wakefulness and resulted in weight loss or weight stabilization in a study on 12 patients treated for an average of 13 months (45). Furthermore, dexamphetamine has been shown to improve concentration abilities and to decrease appetite in five patients with hypothalamic obesity treated for 24 months (44).

A combination therapy with metformin and fenofibrate was studied in 22 CP children (55). Fenofibrate is a peroxisome proliferator-activated receptor alpha (PPARα) agonist. PPARα has been hypothesized to reduce triglycerides concentrations and to improve insulin sensitivity. Treatment did not result in significant improvements of BMI development; however, improved insulin resistance and lipid profiles were reported (55).

CP patients with specific hypothalamic damage limited to anterior hypothalamic areas were recently reported by Daubenbüchel et al. (56) to present with decreased fasting oxytocin levels. CP patients with hypothalamic obesity showed impaired variation in oxytocin secretion due to nutrition. Changes in oxytocin saliva concentrations before and after standardized breakfast correlated with BMI. The authors hypothesized that oxytocin medication might have beneficial effects on neurobehavioral deficits and/or hypothalamic obesity in CP patients with specific anterior hypothalamus lesions. In a small pilot study on 11 aCP patients, Hoffmann et al. tested this hypothesis by single nasal application of 24 IU of oxytocin (57). Before nasal oxytocin administration, all CP patients presented with detectable oxytocin levels in saliva. Nasal oxytocin administration was well tolerated and lead to increased oxytocin concentrations as measured in saliva and urine. After oxytocin administration, CP patients with surgical hypothalamic lesions limited to anterior hypothalamic areas presented improvements with regard to emotional identification compared to CP patients with anterior plus posterior hypothalamic lesions.
Our current knowledge on long-term effects of oxytocin treatment in CP is mainly based on rare case reports. Parental-observed pro-social behavior improved after 22 months of oxytocin treatment in a pediatric case (58). In another case, 10-week oxytocin therapy induced improvement of hyperphagia and weight loss followed by a combined 38-week therapy with oxytocin and naltraxone (59). A controlled randomized trial (ClinicalTrials.gov Identifier: NCT 02849743) in patients with hypothalamic obesity is currently testing if nasal administration of oxytocin promotes weight loss.

Although promising therapeutic approaches are available as above-mentioned, it has to be pointed out that there is currently no bariatric or pharmacological treatment option for hypothalamic obesity in childhood-onset CP, which has been proven to be effective in controlled randomized trials.

Bariatric treatment of hypothalamic obesity

Short-term BMI reduction due to bariatric surgery was reported in studies on childhood-onset CP patients with hypothalamic obesity (60, 61). Clinically significant improvement of binge-eating behavior was observed immediately after laparoscopic adjustable gastric banding (LAGB) in CP patients. LAGB was well tolerated. However, long-term weight reduction after LAGB was not achieved (62).

Bretault et al. (63) reported on the 12-month outcome after bariatric surgery for hypothalamic obesity due to CP based on a meta-analysis of the literature. At 1 year, 6 of 18 cases presented with a 20% loss of initial body weight; all had undergone either Roux Y gastric bypass (n=3), biliopancreatic diversion (n=1) or sleeve gastrectomy (n=2). All CP patients presenting with a loss of less than 5% of their initial body weight were treated by LAGB, except one Roux Y gastric bypass case. The authors could show that sleeve gastrectomy, biliopancreatic diversion and Roux Y gastric bypass are the most efficient bariatric treatment options in childhood-onset CP with hypothalamic obesity. Individualized treatment approaches based on an algorithm reflecting clinical domains affected by hypothalamic syndrome were recently recommended by van Iersel et al. (64). Bariatric treatment with non-reversible surgical techniques is controversially discussed in the pediatric age cohort because of legal, medical and ethical concerns (62).

It should be emphasized that currently no bariatric or pharmacological therapy for hypothalamic obesity in CP has been proven to be effective in randomized controlled trials (65).

Neuropsychological and psychosocial functioning

Studies assessing psychosocial and physical functionality during long-term follow-up after CP report on variable results, ranging from impaired function in almost 50% to excellent function in the majority of CP patients (26, 66, 67, 68). Impairments of emotional and social functioning are the most frequently observed impairments, with CP patients rating their physical health to be better than their psychosocial status (26). Other complaints are somatic symptoms such as pain, reduced mobility and self-care (26). Behavioral studies observed frequent psychopathological symptoms, such as depression, withdrawal and anxiety. Difficulties in emotional control, learning, concerns with regard to body image and physical appearance and unsatisfactory peer relationships are frequent problems in children’s daily functionality (69, 70).

Presurgical functional impairments as well as younger age at diagnosis are known risk factors associated with reduced neurocognitive and psychosocial functionality. Large tumor volume and involvement of hypothalamic structures and the 3rd ventricle are known risk factors for survival and sequelae after CP. Ophthalmological, neurological and endocrine side effects adversely affect neuropsychological outcome (26, 66). The clinically most relevant negative impact on physical ability, social functioning and body image is contributed to hypothalamic dysfunction (25, 26, 66).

Cognitive problems, particularly those affecting attention, executive function, working memory and episodic memory, are major long-term neurocognitive complications after CP (26, 69, 70, 71, 72). Özyurt et al. (73) reported on reduced performance scores for memory and executive functioning in childhood-onset CP patients. The degree of hypothalamic involvement and hypothalamic lesions had a negative impact on executive functions and functional capabilities.

Psychological and educational deficits were also observed in long-term CP survivors after primary subtotal surgical resection followed by irradiation (70). Reported neurocognitive impairments include behavioral instability, slower cognitive speed, memory disturbances and attention problems (69, 70, 71). In up to 82% of patients, intact intellectual functioning has been observed (69, 70).
Studies analyzing intervention efforts with regard to neurocognitive deficits are rare. Case studies on efficacy of cognitive rehabilitation for behavioral lability and dysexecutive deficiencies have demonstrated that goal management therapy and functional behavioral analysis seem to be useful diagnostic and therapeutic options for cognitive rehabilitation, compensating for psychosocial and cognitive impairments (74).

Animal studies have shown that electrical stimulation of the amygdala, septal nuclei and posterior hypothalamus causes aggression attacks and intermittent, explosive behavior. In cat models, electrical stimulation of posterior lateral hypothalamic structures resulted in hyperphagia and the above-mentioned aggressive behavior attacks. In cases with involvement of the ventromedial nucleus, both hyperphagia and disinhibited aggressive behavior were observed.

In humans, hypothalamic lesions may result in emotional lability, abnormal sexual behavior, fury attacks and deficits in memory and intellectual capacities. Neurobehavioral syndrome is characterized by four main symptoms: (1) episodic tantrums, (2) emotional instability, (3) hyperphagia and (4) intellectual impairment. Furthermore, problems in the field of attention spans and deficits in impulse control and motivation are observed. Children with tumors of the third ventricle display symptoms of amnesia, confusion and consciousness impairment. The syndrome is especially associated with lesions of the ventromedial nucleus. Patients with lesions of the ventromedial prefrontal cortex present with symptoms of poor impulse control and attention deficits. Treatment approaches for this neurobehavioral syndrome such as high doses of an antipsychotic neuroleptic and/or psychotherapeutic behavior interventions are ineffective.

Posterior hypothalamic structures and their relationship to components of the limbic system are postulated to play a significant role in socialized inhibition of aggressive behavior. Aggressive behavior attacks are known to be due to tumor and/or treatment-related disruption of tissue connections between the posterior hypothalamus and the limbic system. Due to small cohort sizes and a broad variety of study methodologies, reports on neuropsychological conditions in CP patients appear to be controversial in the current literature. Data on preoperative neuropsychological conditions are rare and studies on postoperative, neuropsychological outcomes are frequently extremely difficult to interpret in the absence of preoperative baseline investigations. Comparative evaluations of pre and postoperative neuropsychological deficits should be the basis for planning risk-appropriate treatment strategies with regard to long-term effects.

The predominant indicator reported in the literature is postoperative normal intelligence quotients (IQ) for adult-onset CP patients, yet only anecdotal reports have been published on diminished postoperative intelligence results. However, several studies of children with CP showed disturbances of memory, attention, impulse control, motivation and socialization. The correlation between cognitive interferences and radical resection remains controversial. There is a consensus that neuropsychological consequences following irradiation in childhood-onset CP patients are dependent on age at diagnosis, irradiation volume, individual dosages, fractionated method and the total dosage, as well as illness-contingent and other therapy-associated variables. Neuropsychological deficits appear more serious in CP patients following relapses and/or relapse surgery. As yet, there are no published prospective investigations regarding neuropsychological prognoses of children and adolescents with CP.

In a first review on cognitive performance in childhood-onset CP patients, Özyurt et al. (72) recently summarized and systemized findings obtained with formalized neuropsychological testing. Notably, detailed neuro-radiological assessment of the tumor or lesion site with respect to the hypothalamus was only performed in few of the studies (8, 73). A systematic assignment of test results to subcomponents of cognition contributed to a comprehensive picture of spared and impaired cognitive functions associated with CPs or their removal. With few exceptions, IQ scores were shown to be in the normal range (69, 73, 75, 76), albeit Bawden et al. (76) found significantly lower IQ scores when compared to a healthy control group. Despite well-preserved overall cognitive abilities, several studies showed significant deficits in tests assessing memory, attention, processing speed and executive functioning.

In accordance with frequent complaints of children and their caregivers, memory is the most frequently investigated cognitive domain in childhood-onset CP. Typically, deficits were shown for episodic memory, which is a consciously accessible memory system that allows to re-experience past events or episodes in life including their spatial and temporal context. Tests used to assess episodic memory most frequently include list-learning tasks, story memory tasks or complex geometric designs. In several studies, encoding in long-term memory and/or episodic long-term retention was shown to be impaired, including verbal as well as visual/visuo-spatial information (8, 69,
73). Waber et al. (75) reported on severe impairments in a narrative memory task. In the study performed by Fjalldal et al. (8), additional analyses indicated that patients with hypothalamic involvement were mainly responsible for the deficits reported for the whole CP patient group. Noteworthy, in the two studies that tested delayed recognition memory, performance was found to be preserved, despite findings of deficient episodic memory recall (71, 73). When tested, verbal and visuo-spatial short-term memory were also found to be in the normal range (71, 75) or not different from controls (73).

Only few studies tested executive functions with formalized questionnaires or tests in CP patients. In a study that used a standardized questionnaire to assess everyday problems with executive functions, Laffond et al. (77) reported on a high proportion of children who suffer from deficits. In studies using neuropsychological testing, cognitive flexibility, which is of vital importance for the ability to adapt to changing situations and goals, was often shown to be impaired (73). However, Bawden et al. (76) did not find any deficits in tasks assessing executive performance (verbal and figural fluency, cognitive flexibility and concept formation). Results on sustained attention are inconsistent with findings of both impaired (8, 73) and unimpaired performance (75). Studies that tested cognitive processing speed found abnormal slow performance in the CP patient group (8, 75). The inconsistent results for attentional control in particular may be partly due to the small and heterogeneous patient cohorts in the currently published studies on cognitive performance after childhood-onset CP.

Considerable new insights on neuropsychological deficiencies in CP patients have been achieved during recent years. However, findings have to be confirmed in larger cohorts and should be the basis for novel therapeutic interventions.

**Socio-emotional performance**

Besides cognitive deficits, CP patients often suffer from social impairments and emotional dysregulation. These impairments represent significant challenges for families, friends and the patients’ ability to perform in school and working environments (26, 69, 78). Frequently reported abnormalities include anxiety, mood swings, depression, emotional outburst and irritability in the emotional domain and hostility and aggressiveness in the social domain. Emotional dysfunctions were reported for 40% of the childhood-onset CP patients. Social withdrawal was reported for 35% of CP patients. By using the Child Behavior Checklist (CBCL) and the Youth Self Report, Foretti et al. (26) observed that 33% of the pediatric patients reported social problems in their everyday interactions. Interestingly, parents’ ratings of children’s social problems were much higher (58%), a discrepancy which they also reported for other dimensions, such as externalizing behavior. However, it should be noted that studies on social-emotional functioning are all based on questionnaires. Hence, objective data based on experimental tasks or neuropsychological testing are not available yet.

Disease-related changes such as loss of functional abilities due to severe obesity may trigger significant social-emotional reactions, including anxiety, depression and social withdrawal. At the same time, neuropathological changes in the hypothalamus and the associated limbic networks clearly increase the likelihood of adverse outcomes in mood and behavior (79). However, most of the studies investigating social-emotional abnormalities in CP patients did not report tumor or lesion location with respect to the hypothalamus and some of them not even considered the relevance of these factors. This is remarkable, as some of the patients’ deficits are similar to abnormalities reported for hypothalamic lesions in single case studies of humans and in animals (80). In studies, which explicitly considered the role of the hypothalamus for neurobehavioral performance, deficits in emotion and interpersonal relationships were shown to be worse in patients with hypothalamic involvement, compared to those without hypothalamic involvement (26, 77, 78). A further shortcoming of the current literature is the virtual lack of a detailed assessment of specific social and emotional domains. Almost all studies in the field used QoL questionnaires and the Child Behavior Checklist, which both provide a first valuable assessment, but are not suitable for providing detailed information on specific subdomains of social-emotional functions. Moreover, several functional domains, which may be impaired due to the location of the tumor and potential damage in associated limbic networks, have not been considered yet (e.g., emotion regulation strategies and social cognition).

**Quality of life**

Childhood-onset CP and its treatment frequently result in long-term somatic and psychosocial consequences with negative effects on QoL. Additional factors involved are rehabilitation and social reintegration back into school and professional occupation, as they impact patients’
long-term life planning. Systematic detection of health-related QoL and long-term consequences has not yet been established. Existing reports are based on single-center, cross-sectional investigations of small collectives that provide rough estimates regarding somatic and neuropsychiatric long-term consequences based on QoL.

**Brain abnormalities in childhood-onset CP**

CPs bear a significant risk for the integrity of fronto-limbic networks, even beyond the damage directly resulting from tumor growth. Similar as in other brain tumors, a number of treatment-related factors, such as surgical approaches, radiation therapy and complications may worsen tumor-related damage and may also result in damage to other areas (81). Hypothalamic lesions may trigger proximal and distal changes in connected brain areas (through diachisis or transneuronal degeneration), which add to impairments in cognitive, social and emotional performance often observable in patients (82). Such secondary processes are likely to be spread along hypothalamic connections with

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<tr>
<td>Neuroradio-logical monitoring</td>
<td>MRI 3 months after OP, 3–6 months intervals during first 3 years after dgy, yearly intervals afterwards (w/o gadolinium)</td>
<td>T₁-weighted sagittal + coronary images (max. 3-4 mm thick slices), Proton- + T2-weighted axial images of the entire brain</td>
<td>In case of progression/relapse consider OP or XRT, intracystic interferon alpha in case of cystic progression</td>
<td>Cave: reports on cerebral Gadolinium deposits after frequent application</td>
</tr>
<tr>
<td>Endocrine pituitary deficiencies</td>
<td>Height, weight, growth rate, Tanner stage, fluid input/output, bone age</td>
<td>Melatonin profile in serum and/or saliva</td>
<td>Endocrine substitution/monitoring</td>
<td>Training of patients/families in prevention of Addisonian crises</td>
</tr>
<tr>
<td>Hypothalamic neuroendocrine deficiencies</td>
<td>Disturbed circadian rhythm, Daytime sleepiness</td>
<td>Melatonin profile in serum and/or saliva</td>
<td>Consider melatonin substitution</td>
<td>No reports on long-term effects</td>
</tr>
<tr>
<td>Neuro-psychological deficiencies</td>
<td>Neurocognitive deficiencies, Emotional disturbances</td>
<td>Neuropsychological testing</td>
<td>Experimental approach: memory training</td>
<td>Only case reports, no trials on efficacy</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Monitoring at 3 months intervals during 1st year after diagnosis, yearly intervals afterwards</td>
<td>Visual acuity, retina, and optic disk examination, field of vision assessment, ocular motility (cover test)</td>
<td>Visual deterioration might be indicative for progression or residual status after OP/XRT</td>
<td>Only case reports, no trials on efficacy</td>
</tr>
<tr>
<td>Hypothalamic obesity</td>
<td>Weight gain starts during first year after surgery</td>
<td>BMI, waist-height ratio, lipids, RR, HbA1c, body composition, oxytocin</td>
<td>Consider experimental approaches: GLP1-R-agonist, oxytocin, bariatric treatment</td>
<td>Monitoring of visual acuity and field of vision as early symptom of progression</td>
</tr>
<tr>
<td></td>
<td>Non-alcoholic fatty liver disease (NAFLD)</td>
<td>Hepatic parameters, steatosis hepatitis</td>
<td>Weight reduction</td>
<td>Due to legal and ethical considerations irreversible bariatric options only in adults</td>
</tr>
<tr>
<td>Psychosocial status</td>
<td>Related to coexisting neuropsychological sequelae</td>
<td>Education, driver’s license, partnership, social functionality</td>
<td>Psychosocial support, patient support groups</td>
<td>Cave: potential hepatotoxicity of central stimulating agents</td>
</tr>
<tr>
<td>Craniopharyngioma with aggressive growth</td>
<td>Rapid non-cystic, solid tumor progression</td>
<td>Neuroradiological assessment (MRI), genetic analysis of tumor tissue</td>
<td>First promising in vitro results for the inhibition of the MAPK pathway using trametinib (12)</td>
<td>Continuous support during follow-up</td>
</tr>
</tbody>
</table>

**Table 2** Recommendations and clinical challenges in long-term follow-up monitoring of childhood-onset craniopharyngioma.
Brain abnormalities associated with surgical procedures in CP have only been investigated recently. In a PET study involving childhood-onset CP patients, several tumor and treatment-related metabolic abnormalities were found postsurgically and before proton beam therapy. A hypometabolism was observed in parts of the frontal lobe, medial/inferior temporal lobe, limbic areas, caudate nucleus and cingulate gyrus, together with a hypermetabolism in parts of the contralateral temporal and parietal lobes (81). Main predictors for the hypometabolism were hydrocephalus, sex and the number of surgical interventions. Interestingly, the authors also reported on a patient with transsphenoidal surgery only, that is, without operative trauma to limbic or frontal areas. In this patient, hypometabolism was observed in fronto-limbic areas, indicating the potential consequences of hypothalamic lesions for the integrity of connected brain areas. This result is in line with findings of an fMRI study, which focused on childhood-onset CP patients with hypothalamic involvement and was the first to provide evidence for distal effects of hypothalamic injury in humans (73). As patients in this study were highly selected due to exclusion criteria, included CP patients had a very low rate of complications and additional surgeries compared to those in the PET-study. Nevertheless, when compared to age and intelligence-matched healthy controls, patients with hypothalamic involvement had a failure of task-related deactivation in orbital and adjacent medial frontal cortex during memory recognition. This failure of deactivation was assumed to be functionally related to the altered functional coupling, which was observed between CP patients’ thalamus and their rostral medial prefrontal cortex (85).

Fjalldal et al. (86) recently reported on associations between microstructural white matter alterations in cingulum and hypothalamus and cognitive deficits in CP. Furthermore, the authors presented a novel method for neuroradiological assessment of hypothalamic damage showing that decreases in hypothalamic volume were associated with increased metabolic risk for obesity (87).

Conclusions and perspectives

Recent insights in molecular pathogenesis of CP open new perspectives on targeted therapy. Further research to elucidate pathogenic mechanisms and hopefully prevent hypothalamic involvement of CP is warranted. Surgical treatment strategies should be based on a multidisciplinary approach involving experienced teams aiming at posterior hypothalamus-sparing treatment for prevention of QoL impairments. Centralizing treatment of CP in experienced ‘centers of excellence’ is recommended. However, such centralization includes high thresholds concerning infrastructure not achievable in all health systems. Alternatives such as multicenter-based networks for reference assessments should be considered to assure high standards of treatment quality. Irradiation is efficient in preventing further growth or recurrence in CP patients with residual tumor. Proton beam therapy – available on a wider range in the near future – will help to avoid radiooncological side effects. Novel insights into neuropsychological sequelae after CP should be the basis for the development of future therapeutic neuropsychological interventions. Due to the rareness of the disease, common international efforts in research and treatment are recommended and should lead to an international registry for childhood-onset CP, as a first step toward efficient coordination of scientific and clinical initiatives (Table 2).

Declaration of interest

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References


