The Diagnosis and Treatment of Craniopharyngioma

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Keywords

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Abstract

Craniopharyngioma (CP) is a rare embryonic malformation of the sellar/parasellar region with a low histological grade. Clinical manifestations are related to hypothalamic/pituitary deficiencies, visual impairment, and increased intracranial pressure. Recent insight into the molecular pathogenesis of CP opens new perspectives on targeted therapy in papillary CP harboring *BRAF-V600E* mutations. Further research to elucidate pathogenic mechanisms and hopefully prevent hypothalamic involvement of CP is warranted. If the tumor is favorably localized, the therapy of choice is complete resection, with care taken to preserve the optical and hypothalamic functions. In patients with unfavorable tumor localization (i.e., hypothalamic involvement), the recommended therapy is a limited hypothalamus-sparing surgical strategy followed by local irradiation. Surgical treatment strategies should be based on a multidisciplinary approach involving experienced teams. Centralizing the treatment of CP in experienced "centers of excellence" and multicenter-based networks for reference assessments should be considered to assure a high

standard of treatment quality. CP recurrence and progression are frequent. Irradiation has proven effective in reducing recurrences and progression. Proton beam therapy, available in a wider range in the near future, will help to avoid radio-oncological side effects. Anatomical involvement and/or surgical lesions of posterior hypothalamic areas can result in serious sequelae that compromise quality of life (QoL), such as hypothalamic obesity and psychopathological symptoms. Novel insights into neuropsychological sequelae after CP occurrence should be the basis for the development of therapeutic neuropsychological interventions. CP should be managed as a frequently chronic disease, providing ongoing care of pediatric and adult patients' clinical and QoL consequences by experienced multidisciplinary teams.

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Introduction

Craniopharyngioma (CP) is a rare embryonic malformation with a low histological grade (WHO I^o) originating from the remnants of the craniopharyngeal duct in the sellar and parasellar area. Overall survival rates at 20 years after childhood-onset CP are high (87–95%). However, long-term quality of life (QoL) is frequently impaired due

Fig. 1. Manifestations before diagnosis of symptomatic craniopharyngioma (sym-CP) in children and adolescents recruited in the KRANIOPHARYNGEOM 2007 trial 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 (in months) from the appearance of each initial manifestation until diagnosis is indicated as an insert or above each column. The median time interval between the initial manifestation of disease and CP diagnosis was 5 months (range 0.01–108 months). Reproduced from [19] with permission from Springer.

to the sequelae caused by the anatomical proximity of the tumor to the hypothalamic-pituitary axis and optic nerve/chiasm [1–4]. Initial hypothalamic involvement of CP and/or treatment-related lesions to the hypothalamic-pituitary axis result in hypothalamic obesity (HO). Unfortunately, no generally accepted lifestyle interventions or pharmacological and bariatric therapy for hypothalamic obesity in CP have been proven effective in randomized controlled trials. Currently, the prevention of hypothalamic sequelae is recommended including hypothalamus-sparing therapeutic approaches that respect the integrity of nuclei located in posterior hypothalamic areas.

Pathology and Molecular Genetics

Adamantinomatous CP (ACP) and papillary CP (PCP) are the 2 CP subtypes. ACP is driven by somatic mutations in *CTNNB1* (encoding β -catenin), mostly point mutations within exon 3 affecting regulatory residues involved in β -catenin protein stability [5–7]. The consequence of these mutations is that β -catenin cannot be efficiently degraded, accumulates within the cell, and overactivates the WNT/ β -catenin pathway [8, 9].

PCP, like ACP, also has a low mutational rate (15 mutations/MB), but instead of *CTNNB1* mutations, it harbors somatic *BRAF-V600E* mutations. So far, no other recurrent mutations or genomic aberrations have been identified [7, 10]. The expression of oncogenic *BRAF-V600E* is observed in the vast majority of the tumor cells [7, 11]. However, the activation of the MAPK pathway is not observed in all tumor cells, as would be expected, but

is rather restricted to a few tumor cells (i.e., the basal cells surrounding the fibrovascular cores) [12]. Based on these novel findings in molecular genetics, targeted therapy has provided new promising perspectives for treating PCP harboring *BRAF-V600E* mutations, exclusively detected in adult-onset PCP [13–16].

Clinical Manifestations

The diagnosis of childhood-onset CP is often made late, frequently years after the initial manifestation of symptoms [17–19], with a clinical picture characterized by symptoms of increased intracranial pressure (e.g., nausea and headache) at the time of diagnosis (Fig. 1). Further primary manifestations are endocrine deficits (52–87%) and visual impairments (62–84%). Endocrine deficiencies are frequently caused by tumor- and/or treatment-related lesions to the hypothalamic-pituitary axis that affect the secretion of growth hormone (GH, 75%), gonadotropins (LH/FSH, 40%), thyroid-stimulating hormone (TSH, 25%), and adrenocorticotrophic hormone (ACTH, 25%). At the time of CP diagnosis, 40–87% of patients present with at least 1 endocrine deficit [20–22]. Other hormonal symptoms such as neurohormonal diabetes insipidus are observed preoperatively in 17–27% of all CP patients [21–23]. An analysis of anthropometric data obtained in routine checkups before CP diagnosis in 90 children [18] revealed reduced growth velocity in infants as young as 12 months. Weight gain, predictive of hypothalamic obesity, occurred as a later manifestation, shortly before CP was diagnosed. Hoffmann et al. [17]

Fig. 2. BMI and MRI imaging at diagnosis and 36 months after surgery in 3 cases of childhood craniopharyngioma (CP) with different grades of hypothalamic involvement/lesion. **a, b** Patient with CP confined to the intrasellar space: 0° no hypothalamic involvement (**a**)/surgical lesion (**b**). BMI at diagnosis: -1.96 SD; BMI 36 months after complete resection: -1.62 SD. **c, d** Patient with CP involving the anterior hypothalamus: I° hypothalamic involvement (**c**)/surgical lesion of the anterior hypothalamic area (**d**). BMI at diagnosis: $+1.01$ SD; BMI 36 months after complete resection: $+0.59$ S.D. **e, f** Patient with CP involving the anterior and posterior hypothalamus: II° hypothalamic involvement (**e**)/surgical lesion of the anterior and posterior hypothalamic area (**f**). BMI at diagnosis: $+6.08$ SD; BMI 36 months after complete resection: $+6.79$ SD. Mammillary bodies define the border between anterior and posterior involvement/lesion. Reproduced from [53] with permission from Bioscientifica.

observed that the median duration of history before CP diagnosis was 6 months, ranging from 0.1 to 108 months, and correlated positively with patient age at diagnosis. Tumor size, degree of surgical resection, hypothalamic involvement, and body mass index (BMI) at diagnosis were not associated with duration of history. Neurological deficits and visual impairment were associated with larger tumor size at diagnosis and reduced the 10-year overall survival rate. Endocrine deficiencies, growth retardation, and weight gain were the symptoms observed with the longest duration of history [17]. A combination of headache, visual impairment, growth retardation, and polyuria/polydypsia is highly indicative of CP and should lead to further neuroradiological diagnostics.

Neuroradiological Imaging

While PCP is usually a noncalcified and solid entity, the typical combination of imaging features of ACP can be summarized by the so-called 90% rule, i.e., that about 90% of tumors are predominantly cystic, 90% show more

or less prominent calcifications, and about 90% take up contrast in the cyst walls. On MRI before contrast, the solid parts and cyst walls may show a variety of T1 signals. On T2-weighted images, the tumors are usually hypo- and hyperintense [24–27]; this variability is due to the inhomogeneous distribution of calcified parts and the broad individual variation of MR signals in calcifications. Accordingly, the proof of calcifications in CP is usually not possible on MRI. The ideal sequences for the identification of calcifications are T2*-weighted or susceptibility-weighted image (SWI) sequences, both of which are hampered by the air content of the sinuses. Therefore, computed tomography (CT) remains the gold standard for the identification of calcifications in this area, despite the disadvantages of X-ray use in children. The proof of calcifications on imaging is important for the differential diagnosis of other sellar masses and the detection of post-operative small remnants after resection (undetectable on MRI) [24]. The main differential diagnoses of sellar/parasellar masses in children are low-grade glioma and germ cell tumor [24, 28].

For appropriate staging, it is important to assess CP location. A classification by de Vile et al. [29] defined the extent of the postoperative hypothalamic damage as 1 of 3 grades depending on the postoperative defects in the floor of the third ventricle. In German CP studies, a similar classification according to CP contact with or compression of the hypothalamic structures was used. The posterior hypothalamic nuclei are localized in the lateral walls of the third ventricle, beginning at the level of the mammillary bodies and posterior to them. Grade 0 defines a CP without contact to the floor of the third ventricle. Grade I is for a CP with contact or compression of the hypothalamus anterior to the mammillary bodies, and grade II is a tumor that results in dislocation, compression, or destruction of the hypothalamus beginning at the level of the mammillary bodies or dorsal to them (Fig. 2). Routine imaging during follow-up should be confined to MRI without gadolinium application in order to decrease the radiation burden and the potential risk of gadolinium deposition [30].

Neurosurgery

Surgical management, especially in children, remains controversial. The best treatment for CP is the one that involves the least long-term morbidity. Treatment may include surgery only, irradiation only, or, more commonly, a combination of the two. Surgery alone implies radical resection, and is, therefore, appropriate for tumors that may be completely resected without neurovascular injury and visual impairment. A major factor that affects patients with ACP is hypothalamus dysfunction. In the pediatric population, preoperative hypothalamic involvement (Fig. 1) increases the likelihood of pre- and postoperative obesity, and hypothalamus damage during surgery increases the risk of postoperative weight gain [31–34]. Although not well established, postoperative weight gain in adults is also a problem and correlates with hypothalamic involvement [35]. Accordingly, avoiding irreversible hypothalamic damage is a key goal in the treatment of CP [1, 36].

Limited surgery and radiation therapy are appropriate for most patients including those for whom radical surgery might be considered. The concept of limited surgery and radiation therapy involves the use of surgery to alleviate and prevent symptoms, improve a patient's ability to tolerate and complete irradiation, and potentially enhance or optimize dose delivery. Limited surgery comes in many forms including partial resection, cyst fenestra-

tion or aspiration, catheter and Ommaya reservoir placement, or cerebrospinal fluid (CSF) diversion. It may be performed to decompress or resect portions of the tumor to reduce its impact on vision, mass effect on the brain or brainstem, reduce its volume for irradiation and dose to critical normal tissue volumes, and restore CSF flow. Like radical surgery, a limited surgery approach depending on the size, location, and extent of the tumor, and the goals of the overall procedure and treatment plan. Additional surgical options may include stereotaxic aspiration, catheter placement, or endoscopic procedures. One should be cautioned that cyst aspiration or fenestration, while important to reduce tumor volume and symptoms, may be of temporary benefit, and the reaccumulation of cyst fluid during irradiation is almost certain. Catheter placement should be considered when justified and feasible.

Radiation Therapy

Radiation therapy implies external beam radiation therapy using photons or protons [37] (Table 1). In most cases, radiation therapy is administered at the time of progression after prior surgery. The first scenario is where radical resection has been performed and recurrence is unexpected. The second scenario is where attempted radical resection is performed, near-total resection is achieved, and the patient is observed until the time of progression. It is hoped that, in both scenarios, the impact of combined therapies will not be additive, and that additional surgery and its attendant morbidity will not be required prior to definitive irradiation.

CP is one of the pediatric brain tumors for which proton therapy holds great promise. Conventional radiation therapy uses X-rays directed from multiple directions to conform the prescription dose to the targeted volume at the expense of nontarget tissue, which receives a collateral dose associated with the entrance and exit of the traversing beams. Proton therapy deploys fewer beams that deposit the dose along a path that ends in the target, and the dose to nontarget tissue is significantly reduced. While the potential for tumor control is equal in the two modalities, patients, and their parents and caregivers, prefer the newer modality, hoping that the difference in normal tissue doses will provide an advantage. Regardless of modality, the hypothalamic-pituitary axis, optic nerves, and chiasm, the principle components of cerebral circulation as well as portions of the brainstem receive the prescription dose in most cases. This leaves cognitive effects as one of the few functional outcomes that might be used

Table 1. Advantages and disadvantages of modern treatment technologies in radiotherapy of craniopharyngioma.

Technology	Advantages	Disadvantages
Conventional 2-dimensional radiotherapy	reliable clinical data and long-term follow-up indicating high efficacy	poor geometrical precision; no reliable protection of normal surrounding tissues
Fractionated conformal radiation therapy/IMRT	widely available; highly conformal; ease in adapting treatment to changing target	highly conformal photon therapy requires exposure of a larger volume of normal tissue to low doses of radiation
Fractionated proton therapy	spares normal tissue; the volume of normal tissue exposed to low doses is significantly less than with fractionated photon methods	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
Radiosurgery	a single treatment session; highly conformal; almost no dose to non-target tissue	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
Hypofractionated image-guided radiosurgery (CyberKnife)	fewer treatment sessions; highly conformal; may have biological advantages under certain conditions	very limited indications and experience; role still unclear; no reliable data for tumor control or reuction of side effects
Intracavitary colloid isotope application	high tumor control rates for cystic components; applicable to tumors recurrent after prior irradiation	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

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to demonstrate the advantage of proton therapy over photon therapy. In 2011, a prospective study using passively scattered (first-generation) proton therapy was activated. A total of 94 children aged 0–21 years were enrolled up to early 2016. The targeted volume for proton therapy included the postoperative tumor bed with an added clinical target volume of 0.5 cm which was meant to account for microscopic tumor extension. Dated from the start of proton therapy, the patients were followed every 3 months for 1 year, and then every 6 months for 5 years. Preliminary reports suggested that the rate and pattern of failure, and the rate of necrosis, vasculopathy, and severe neurological complications associated with the target volume were equivalent to photon therapy [38]. Preliminary results also suggested that when corrected for the distribution of radiation dose in the normal brain, those treated with proton therapy had no change in academic achievement scores (reading and maths) compared to patients treated with photon therapy who demonstrated a significant decline [39]. Since 2016, a newer

generation of proton therapy (pencil-beam scanning) has become available. The advantage of this second-generation method over the first generation is the use of small, individually weighted beams to further conform the prescription dose to the target and reduce the volume that receives the highest doses, in addition to the volume that receives the lowest doses.

Instillation of Sclerosing Substances for Cystic CP

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- α is a treatment of choice [40, 41]. Due to neurotoxicity in the case of leakage, bleomycin instillation is obsolete [42]. Systemic interferon alpha treatment has not been proven to be efficient for the prevention of solid CP progression.

Fig. 3. Weight development in 109 childhood-onset craniopharyngioma (CP) patients, recruited with primary involvement of anterior and posterior hypothalamus in the KRANIOPHARYNGEOM 2007 trial, with regard to surgical hypothalamic lesions (HL) graded as previously described [28, 53]. No HL; HL of the anterior hypothalamus not involving mammillary bodies and hypothalamic areas dorsal to mammillary bodies; HL of anterior and posterior (Ant + post) hypothalamic areas, involving mammillary bodies and areas dorsal to mammillary bodies. Body mass index (BMI) SDS [107] is shown at the time of diagnosis and at 3 time points after diagnosis (1 and 3 years after diagnosis and the last visit). White boxes, BMI SDS at diagnosis; hatched boxes, BMI SDS at 1-year follow-up; gray boxes, BMI SDS at 3-year follow-up; black boxes, BMI SDS at the last visit. 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. Reproduced from [36] with permission from Bioscientifica.

Sequelae

Hypothalamic Syndrome

Hypothalamic involvement of CP and/or lesions to hypothalamic structures due to surgical and/or radio-oncological interventions are associated with severe sequelae, mainly HO, with a negative impact on the QoL of CP survivors [43–50]. 35% of CP patients present with clinical manifestations associated with hypothalamic dysfunction, such as HO, neuropsychological deficits, and disturbances of circadian rhythms at the time of diagnosis [50]. The incidence of hypothalamic dysfunction increases to 65–80% following radical surgical treatment [50].

Treatment of suprachiasmatic lesions with hypothalamic involvement is challenging and is associated with high morbidity [51]. HO is caused mainly by surgical lesions of posterior hypothalamic structures including the mammillary bodies [52, 53] (Fig. 3). Several reports have shown that the degree of HO is clearly associated with the grade of hypothalamic damage in CP patients [53, 54].

Treatment Options for Hypothalamic Syndrome

Lifestyle and Dietary Interventions

Due to disturbances in satiety regulation, central sympathetic output, and energy expenditure, CP patients often develop morbid HO that is mostly nonresponsive to conventional lifestyle modifications (diet and exercise) [55–59] (Table 1). Only 1 case report observed a clinical significant effect of a dietary intervention by a protein-sparing modified fasting program (PSMF) [60]; however, once it had been discontinued, weight gain occurred.

Endocrine Substitution of Hypopituitarism

Hypopituitarism should be treated by substitution of the deficient hormones according to existing guidelines [61]. Although safe with regard to the risk of CP recurrence, the beneficial effects of GH substitution on long-term body composition after CP are a topic for debate

Table 2. Pharmacological treatment approaches for hypothalamic obesity

Pharmacological agent	Mechanism of action	Patient cohorts	Outcomes	First author, [ref.], year
Dextro-amphetamine	central stimulant, stimulation of noradrenalin, dopamine secretion, and dopamine reuptake inhibition	5 ped CP	increase in physical activity, reduction in continuous weight gain, stabilization of BMI	Mason [68], 2002
		9 ped CP 2 ped astrocytoma 1 ped glioma	reduction in continuous weight gain and stabilization of BMI in 10/12 pts, improved daytime sleepiness in 11/12 pts	Ismail [69], 2006
		4 CP (3 ped) 1 ped astrocytoma 1 ped ganglioglioma 1 ped meningitis	reduction in continuous weight gain and stabilization of BMI	Denzer [70], 2019
Caffeine + ephedrine-HCl	metamphetamine analog with sympathicomimetic effect	2 ped CP	mean weight loss 13.9%, 6 months after 2.6–5.5 years of intervention	Greenway [72], 2008
Mazindol	sympaticomimetic amine similar to amphetamine	1 adult CP	weight reduction, i.e., from 70 to 60 kg after a 3-week intervention	Sadatomo [71], 2001
Methyl-phenidate	central stimulant, dopamine reuptake inhibition	1 ped CP	beneficial against weight gain	Elfers [73], 2011
Octreotide	somatostatin analog, reduced β cell activation	13 ped CP 4 ped astrocytoma 1 ped germinoma 2 ped ALL	reduced insulin secretion, moderate to no improvement in BMI, increased risk of gall stone formation	Lustig [108], 2003
Diazoxide	potassium channel activator, inhibition of insulin secretion	18 pts	no BMI change	Brauner [74], 2016
Diazoxide + metformin	reduced insulin secretion, reduced hyperglycemia, improved insulin sensitivity	9 ped CP	reduced weight gain, weight loss, peripheral edema, emesis, elevated hepatic enzymes	Hamilton [75], 2011
Fenofibrate + metformin	PPAR α agonist, improved insulin sensitivity	10 ped CP	improved insulin resistance and lipid profiles, no effect on BMI	Kalina [76], 2015
Exenatide	GLP-1 receptor agonists, improved insulin sensitivity, increased satiety, reduced speed of gastric emptying	5 adult CP 1 ped hamartoma 1 adult astrocytoma 1 adult germinoma	improved cardiovascular profile, improved metabolic profile, sustained weight reduction	Zoicas [78], 2013
		4 ped CP 2 adult CP	no significant weight loss in total cohort, stable or decreased weight in responders (60%)	Lomenick [77], 2016
Liraglutide		1 adult CP	BMI reduction, i.e., from 41.8 to 35.3 after an 8-month intervention	Zoicas [78], 2013
Oxytocin + naltraxone	naltroxane (opiate antagonist) decreases appetite and potentiates anorexigenic oxytocin effects	1 ped CP	improvement of hyperphagia and weight loss	Hsu [86], 2018
Supraphysiologic supplementation of T3	T3 increases energy expenditure by induction of thermogenesis	1 adult pt (no CP) 3 ped pts (no CP) 1 ped CP	weight reduction under $3 \times 10 \mu\text{g}$ T3/day for 11–27 months no weight reduction under $3 \times 12.5 \mu\text{g}$ T3/day for 2 months	Fernandes [109], 2002 Van Santen [110], 2015

Table 2 (continued)

Pharmacological agent	Mechanism of action	Patient cohorts	Outcomes	First author, [ref.], year
Substitution with recombinant GH	beneficial effects of GH on body composition and metabolism	199 ped CP	no BMI reduction during 3 years of GH substitution	Geffner [63], 2004
		260 ped CP	no BMI reduction during 5 years of GH substitution	Yuen [64], 2013
		47 ped CP	no BMI reduction under GH during the first 3 years after diagnosis	Heinks [65], 2018
		79 ped CP	beneficial long-term effect of GH on BMI when substituted during childhood and adulthood	Boekhoff [62], 2018

GH, growth hormone; ped, pediatric; CP, craniopharyngioma; BMI, body mass index; GLP-1, glucagon-like receptor-1; pts, patients; RCT, randomized controlled trial; METAP2, methionine aminopeptidase 2; PPAR α , peroxisome proliferator activated receptor α ; T3, tri-iodothyronine.

[62–65]. Glucocorticoid overreplacement should be avoided and levothyroxine should be substituted in a dose sufficient to achieve free T4 levels in the mid-to-upper half of the reference range [61].

Pharmacological Treatment of HO

Based on the observed reduction of epinephrine secretion and sympathoadrenal activation manifesting as an impaired endocrine response to hypoglycemia, pharmaceutical therapy with amphetamine derivatives has been analyzed [66–73]. Dextroamphetamine medication for 24 months, starting 10 months after surgery, stabilized BMI, diminished continuous weight gain, and increased spontaneous physical activity level [68]. An improvement in daytime sleepiness was observed even after shorter-term dextroamphetamine medication [69]. Elfers and Roth [73] observed beneficial effects of methylphenidate on weight development after CP.

Several trials have analyzed the effects of antidiabetic agents on weight development in patients with HO [74–82] (Table 2). Zoicas et al. [78] analyzed the effect of treatment with GLP-1 receptor agonist on weight development in 8 patients (6 CP) with HO. They reported a sustained weight loss and an improvement in cardiovascular and metabolic risk profiles.

Hamilton et al. [75] hypothesized that a combination therapy of diazoxide and metformin reduces insulin secretion and the risk of hyperglycemia. Insulin secretion is decreased by diazoxide binding to the KATP channel of

β cells. Metformin improves insulin sensitivity by decreasing hepatic gluconeogenesis. A combination therapy of diazoxide and metformin was evaluated in 9 CP patients with HO. The synergism of lower insulin levels and enhanced insulin action led to an improved weight gain of $+1.2 \pm 5.9$ kg versus the $+9.5 \pm 2.7$ kg weight gain during the 6 months prior to therapy. High pretreatment insulin levels were associated with the most robust weight reduction [75]. The limitations of this trial were the small cohort size and the adverse events (1 patient withdrew due to the development of peripheral edema and another withdrew due to emesis and elevated hepatic enzymes).

Kalina et al. [76] treated 22 pediatric CP patients with a combination of fenofibrate and metformin. Fenofibrate is a peroxisome proliferator-activated receptor (PPAR) α agonist hypothesized to improve insulin sensitivity and reduce serum triglyceride concentration. Improved insulin resistance and lipid profiles were reported under metformin and fenofibrate medication. However, treatment with these agents did not result in an improvement in BMI.

CP patients with surgical damage limited to specific anterior hypothalamic structures were recently reported to present with reduced fasting oxytocin levels [83]. Furthermore, changes in oxytocin saliva concentrations before and after a standardized breakfast showed a significant correlation with BMI. CP patients with HO presented with impaired variation of oxytocin secretion due to their nutrition. The authors hypothesized that oxytocin medication might exert beneficial effects on neuropsychological deficiencies in CP patients with specific surgi-

Table 3. Bariatric interventions for treatment of hypothalamic obesity

Intervention	CP cohort	BMI or weight before intervention (range)	BMI or weight at last visit after intervention (range)	Median follow-up interval (range)	Complications and side effects due to intervention	First author [ref.], year
LAGB	4 ped	BMI 46.4 BMI 44.9 BMI 51.9 BMI 40.0	BMI 49.6 BMI 53.6 BMI 53.6 BMI 42.7	7.1 (5.3–9.1) years	none reported	Müller [92], 2011
	6 ped	mean BMI 40.2 (44.7–61.6)	no change	5.5 (1–9) years	band readjustment, explantation of device	Weismann [87], 2013
SG	3 ped	mean BMI 49.2 (41.6–58.1)	mean BMI 35.3 (31.2–40.6)	2.0 years	minor bleeding, folic acid and vitamin D deficiency	Trotta [96], 2017
	2 pts	BMI 51.0 BMI 37.6	BMI 41.0 BMI 34.0	30 months	none reported	Gatta [93], 2013
	2 ped	BMI 55.6 BMI 43.3	no BMI change	2.0 (0.5–4) years	vomiting, impaired effectiveness of desmopressin	Weismann [87], 2013
	3 pts	mean BMI 31.1	mean weight loss 10%	24 months	none reported	Wijnen [88], 2017
RYGB	1 ped	BMI 51.5	BMI 39.0	9 months	none reported	Page-Wilson [90], 2012
	1 ped	BMI 65.0	BMI 43.0	4.0 years	diarrhea, dumping syndrome, psychological deterioration	Rottembourg [91], 2009
	3 pts	BMI 59.6 BMI 42.3	mean weight loss 20 kg	18 months	none	Bretault [94], 2016
	5 pts	mean BMI 43.4, +5.2 SD	mean weight loss 25%	24 months	none reported	Wijnen [88], 2017
RYGB with vagotomy	1 ped	weight 223 kg	weight loss 49 kg	2.5 years	mild iron deficiency	Inge [89], 2007
Biliopancreatic diversion + duodenal switch	1 ped	BMI 45.0	BMI 32.0	2.0 years	bradycardia, pacemaker, intestinal stenosis	Rottembourg [91], 2009
Gastric bypass	4 pts	BMI 49.2 BMI 59.5 BMI 41.0 BMI 46.1	BMI 29.4 BMI 53.6 BMI 32.5 BMI 28.7	33 months 65 months 17 months 13 months	none reported	Wolf [95], 2016
	2 pts	BMI 43.7 BMI 37.7	BMI 37.5 BMI 49.0	48 months 64 months	septicemia, esophagus ulceration	Gatta [93], 2013
	1 ped	BMI 48.6	weight loss	36 months	none reported	Weismann [87], 2013

LAGB, laparoscopic adjustable gastric banding; SG, sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass; ped, pediatric; CP, craniopharyngioma; BMI, body mass index; pts, patients.

cal lesions of the anterior hypothalamic structures. In a small pilot study on 11 CP patients, Hoffmann et al. [84] tested their hypothesis by means of a single nasal application of 24 IU of oxytocin. Before administration, all CP patients presented with detectable oxytocin saliva concentrations. The oxytocin was very well tolerated and resulted in an increase in oxytocin concentration in the sa-

liva and urine. After administration, the CP patients with surgical hypothalamic lesions limited to the anterior hypothalamic areas presented an improvement with regard to emotional identification compared to CP patients with anterior and posterior hypothalamic lesions. Daubenbüchel et al. [83, 85] analyzed the association between oxytocin saliva concentration and eating behavior in CP

Fig. 4. Results of the linear mixed models for self-assessed quality of life (QoL) in craniopharyngioma patients recruited in the KRA-NIOPHARYNGEOM 2007 trial ($n = 131$). The PEDQOL score was modeled separately in each domain as a function of time, the factor in question, and the interaction between time and the factor in question. The results are displayed as differences of least-square estimates, with the associated 95% confidence intervals and p values, to describe the mean difference in PEDQOL scores between the 2 categories of each factor. The size of the circles is proportion-

ate to the mean difference; circles representing positive and negative effects on QoL are colored green and red, respectively (opaque when $p \leq 0.05$). A box corresponds to the results of a model. The higher the PEDQOL score, the lower the subjective QoL; a minus sign thus indicates a beneficial influence on QoL. HL, hypothalamic lesion; HI, hypothalamic involvement, Ant/ant, anterior; post, posterior; PEDQOL, Pediatric Quality of Life Questionnaire; res., resection; XRT, radiotherapy. Reproduced from [104] with permission from the Deutscher Ärzteverlag.

patients and healthy controls. CP with anterior hypothalamic lesions and CP with anterior and posterior hypothalamic lesions presented with specific patterns of eating behavior. Reduced postprandial compared to fasting oxytocin saliva concentrations were associated with HO in CP patients and with adverse eating behavior and eating disorders in both CP patients and controls. Our current knowledge on the effects of long-term oxytocin medication for CP is based on a few case reports [86].

Bariatric Treatment of HO

Several reports on the effects of bariatric intervention for weight development in HO have been published with mixed results (Table 3) [87–96].

Neuropsychological and Psychosocial Functioning

The studies assessing physical and psychosocial functionality during long-term follow-up after CP report variable observations, ranging from reduced function in almost 50% to excellent function in the majority of patients [97–100]. A reduction in social and emotional functioning is the most frequently observed impairment, with CP patients rating their psychosocial status as worse than their physical health [97]. Other complaints are somatic symptoms such as reduced mobility and pain [97]. Behavioral studies observed frequent psychopathological symptoms, such as anxiety, depression, and withdrawal; recently, an increased risk of apathy in long-term survivors of childhood-onset CP was reported [101]. Difficulties in learning, emotional control, concerns about physical appearance and body image, and unsatisfactory peer relationships are frequent problems in children's daily functioning [102, 103].

Quality of Life

Systematic analysis of long-term health-related QoL has not yet been established. Eveslage et al. [104] recently reported on short-term QoL in patients recruited in the multinational KRANIOPHARYNGEOM 2007 trial [105]. CP patients treated with radical surgical strategies such as gross total resection resulting in surgical lesions of posterior hypothalamic areas presented with significantly lower self- and parent-assessed QoL during the short-term follow-up of 3 years after CP diagnosis (Fig. 4).

Conclusion

Although novel therapeutic approaches provide promising perspectives, it must be pointed out that currently no bariatric or pharmacological therapy for HO in CP patients has been proven to be effective based on randomized trials. Treatment approaches with combinations of pharmaceutical agents seem to be the most promising. Prevention of HO is recommended [1], with special regard to hypothalamus-sparing therapeutic approaches [32] that respect the integrity of essential nuclei located in posterior hypothalamic areas (Fig. 3) [36]. Any clinically significant improvement in the prognosis and outcome of CP patients will require the development of risk-adapted, multidisciplinary neurosurgical and radio-oncological treatment strategies that provide medical as well as psychosocial support for these patients who suffer from what is a mostly chronic disease [4, 106].

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