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CRANIOPHARYNGIOMA – A CHILDHOOD AND ADULT DISEASE WITH DIFFERENT CHARACTERISTICS

Hosted by
Hermann L. Mueller, Rolf-Dieter Kortmann and Jörg Flitsch

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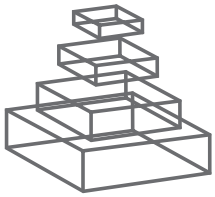

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CRANIOPHARYNGIOMA – A CHILDHOOD AND ADULT DISEASE WITH DIFFERENT CHARACTERISTICS

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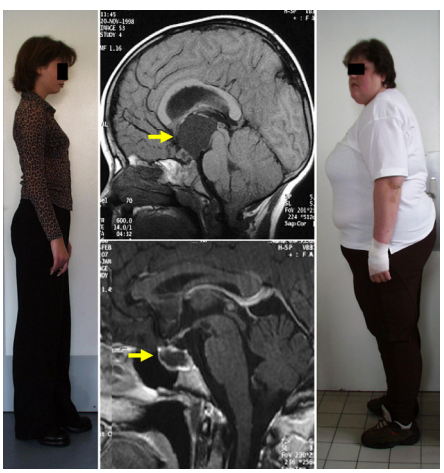

Craniopharyngiomas are benign, partly cystic embryogenic malformations of the sellar region, presumably derived from Rathke cleft epithelium. With an overall incidence of 0.5–2 new cases per million population per year, approximately 30-50% of all cases represent childhood craniopharyngioma. Typical manifestations at primary diagnosis are headache, visual impairment, polyuria/polydypsia, growth retardation, and weight gain.

One of the biggest challenges in treating craniopharyngioma is identifying the best candidates for the radical versus the conservative approach. It appears there is a trend towards radiotherapy in centers with past prevalent surgical approaches, and towards more radical surgical treatment strategies in centers historically conservative-oriented. There are current prospective studies underway on a national and multinational level to adopt strategies tailored to risk factors for morbidity and QOL. Therapy of choice in patients with favorable tumor localization is total resection with the intention to maintain optical nerve and hypothalamic-pituitary functions. In patients with unfavorable tumor localization (hypothalamic tumor involvement), a limited resection followed by local irradiation is recommended. The overall survival rates are high (92%). Recurrences after complete resection and progressions of residual tumor after incomplete resection are anticipated subsequent events after primary surgery.

In clinical practice, the timing of postoperative residual tumor irradiation is both unclear and inconsistently regarded. Some favor immediate postoperative irradiation in the event of life-impairing clinical conditions, proactively preventing tumor progression. On the other hand, some favor a wait-and-see procedure, delaying irradiation in order to reduce both its necessity and the negative consequences associated with radiation therapy. Inarguably, immediate postoperative irradiation significantly delays tumor progression. However, progression-contingent irradiation has proved effective, as overall survival is statistically unaffected by this wait-and-see strategy. Accordingly, the appropriate time point of irradiation after incomplete resection is currently under investigation in a randomized trial (KRANIOPHARYNGEOM 2007). Quality of life is substantially reduced in appr. 50% of long-term survivors due to sequelae, notably extreme obesity due to hypothalamic involvement. Due to the lack of satisfactory long-term treatment modalities for hypothalamic sequelae, further research on molecular characteristics of craniopharyngioma, pathophysiology of hypothalamic disorders, and pharmaceutical agents to treat hypothalamic obesity are warranted.

Risk-adapted surgical strategies at initial diagnosis should aim at a maximal degree of resection, respecting the integrity of optical and hypothalamic structures in order to prevent severe sequelae and therein minimizing consequences that could negative impact patient QOL. Because initial hypothalamic tumor involvement has an apriori effect on the clinical course, childhood craniopharyngioma should be recognized as a chronic disease requiring constant monitoring of the consequences and medical resources for treatment in order to provide not only optimal QOL for patients, but also to garner additional information with the intent of minimizing what at present are severe consequences of both the disease and its treatment.

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EDITORIAL
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Craniopharyngioma – a childhood and adult disease with challenging characteristics

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Craniopharyngiomas are rare embryogenic malformations of the sellar area with low-grade histological malignancy. Despite high survival rates (87–95% in recent series), quality of life is frequently impaired in long-term survivors due to sequelae caused by the anatomical proximity of the tumor to the optic nerve, pituitary gland, and hypothalamus – in many cases even entanglement with the hypothalamus (Cohen et al., 2011; Müller, 2011; Zoicas and Schöfl, 2012). One of the most serious quality of life complications of craniopharyngioma is hypothalamic obesity or so-called "hypothalamic syndrome," a problem that can manifest before and/or after treatment. Novel insights into mechanisms of neuroendocrine satiety regulation and the pathogenic relevance of the autonomous nervous system are expected to facilitate future therapeutic approaches for hypothalamic syndrome (Elfers and Roth, 2011; Lustig, 2011; Roth, 2011).

For the time being, current treatment options for craniopharyngioma patients suffering from hypothalamic syndrome are limited, the most effective to date being bariatric surgery. Bariatric surgery is tolerable and effective in weight-reduction for severely obese adult craniopharyngioma patients (Bingham et al., 2012), but considered intrusive and therefore controversial for younger patients. A substantial improvement in prognosis of craniopharyngioma will require the development of risk adapted neurosurgical (Flitsch et al., 2011; Bartels et al., 2012; Puget, 2012; Trippel and Nikkhah, 2012) and radiooncological (Kortmann, 2011) treatment strategies in a multidisciplinary approach. Recent multicenter cooperation in this area has already led to beneficial results.

The consequences of both the surgical treatment and post-surgical management of the disease are as complicated and hypothalamic-intertwined as the tumors themselves. Risk adapted surgical strategies at initial diagnosis should aim at a maximal degree of resection, respecting the integrity of optical and hypothalamic structures in order to prevent severe sequelae and therein minimize consequences that could negatively exacerbate patient quality of life. Because initial hypothalamic tumor involvement typically has an *a priori*, life-long effect on the clinical course (Müller, 2011) experienced by the patient, childhood, and adult onset craniopharyngioma should be recognized as chronic diseases requiring constant monitoring of the consequences and developing medical resources for treatment in order to provide not only optimal quality of life for patients, but also to garner additional information with the intent of minimizing what at present are severe consequences of both the disease and its treatment.

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Diagnostics, treatment, and follow-up in craniopharyngioma

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Craniopharyngiomas are partly cystic embryogenic malformations of the sellar and parasellar region, with up to half the 0.5–2.0 new cases per million population per year occur in children and adolescents. Diagnosis profile for pediatric and adult craniopharyngioma is characterized by a combination of headache, visual impairment, and polyuria/polydipsia, which can also include significant weight gain. In children, growth retardation, and/or premature puberty often occur later or postoperatively. Recommended therapy with favorable tumor localization is complete resection; with unfavorable tumor localization (optic nerve and/or hypothalamic involvement), consensus is still pending whether a limited resection followed by local irradiation is more prudent. Even though overall survival rates are high (92%), recurrences after complete resection and progressions after incomplete resection can be expected. Accordingly, a randomized multinational trial (KRANIOPHARYNGEOM 2007) has been established to identify optimal diagnosis, treatment (particularly the ideal time point of irradiation after incomplete resection), and quality of life strategies of this chronic disease – most notably the morbid hypothalamic obesity in ∼50% of long-term survivors. We report on craniopharyngioma origins, its pathological manifestations, and specific challenges these sequelae pose regarding diagnosis, treatment, and life-long multi-discipline quality of life management for both adult and childhood craniopharyngioma patients.

Keywords: craniopharyngioma, obesity, hypothalamus, pituitary, quality of life, neurosurgery, irradiation, brain tumors

INTRODUCTION

Craniopharyngioma is a rare, non-glial, non-malignant intracranial tumor derived from a malformation of embryonal tissue. The pathogenesis of craniopharyngioma is currently debated between two primary hypotheses: one describes tumor origin as ectodermal remnants of Rathke's pouch; the second argues craniopharyngioma represents a malformation of residual embryonal epithelium of the anterior pituitary gland and anterior infundibulum (Garré and Cama, 2007; Müller, 2010). Anywhere from 30 to 50% of the 0.5 to 2 cases per million persons per year manifest during childhood and adolescence (Bunin et al., 1998; Nielsen et al., 2011), representing 1.2–4% of all childhood intracranial tumors. In childhood and adolescence, histological type is usually adamantinomatous with cyst formation (Müller-Scholden et al., 2001; Rushing et al., 2007). Incidences of adult onset craniopharyngioma (usually between ages 50 and 75) most often present with a squamous-papillary histological type (Rushing et al., 2007). More than 70% of craniopharyngioma of the adamantinomatous type bear a mutation of the β-catenin gene, which is not detectable in the papillary type of craniopharyngioma (Hölsken et al., 2010).

The German Childhood Cancer Registry obtained data on 496 patients in whom a craniopharyngioma was diagnosed at age ≤18 years from 1980 to 2007. Of these, 451 patients (91%) were younger than 15 years-of-age at the time of diagnosis. The sex ratio was 1:1 and the median age at primary diagnosis was 8.6 years; survival rate (1980–2007) was 97% at 3 years, 96% at 5 years, and 93% at 10 years after diagnosis. Patients who were diagnosed and treated in the 1980s had a lower survival rate than those diagnosed in the 1990s. For example, the survival rate at 5 years was 91% for patients diagnosed in the 1980s versus 98% for those diagnosed in the 1990s (Müller et al., 2003c). This observation is supported by other reports (Sherlock et al., 2010), indicating that mortality is increased in childhood craniopharyngioma patients compared to general population.

DIAGNOSIS – CLINICAL MANIFESTATIONS AND IMAGING METHODS

A background study of craniopharyngioma patients reveals initial symptoms often occur long before diagnosis is made (Müller, 2010, 2011), the non-specific manifestations of increased intracranial pressure such as headache and nausea often going unrecognized as primary symptoms of craniopharyngioma. Other manifestations of the craniopharyngioma diagnostic profile can include visual impairment (62–84%) and endocrine deficits (52–87%; **Figure 1**). Craniopharyngioma tumors that involve the hypothalamic–pituitary axis can affect the secretion of growth hormone (75%), gonadotropins (40%), adrenocorticotropic hormone (ACTH; 25%), and thyroid-stimulating hormone (TSH; 25%). Growth impediment caused by these hormonal disturbances often appears as early as 12 months of age; however, premature puberty and/or unmanageable weight gain are more often the precipitating factors preceding clinical diagnosis in older children

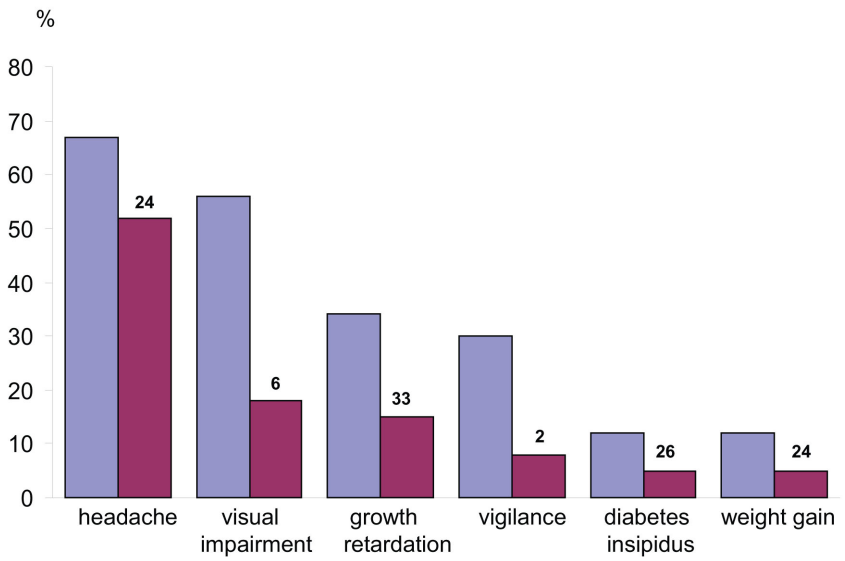

FIGURE 1 | Manifestations before diagnosis of craniopharyngioma in children and adolescents. Frequency of occurrence of each manifestation before diagnosis (blue) and frequency of occurrence as the initial manifestation (red). The median time (month) from the appearance of each initial manifestation until diagnosis is indicated above each red 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 et al., 2003c, with the kind permission of Springer).

(Müller, 2010). In summary, young children presenting symptoms of decreased growth rate, older children presenting symptoms of premature puberty and/or unmanageable weight gain, patients (adults or children) presenting headache, visual impairment, and/or unmanageable weight gain, and/or polydipsia/polyuria should arouse suspicion of craniopharyngioma (Müller, 2010).

The combination of solid, cystic, and calcified tumor components is an important radiological clue to craniopharyngioma diagnosis (Warmuth-Metz et al., 2004). The signal intensity of craniopharyngioma in magnetic resonance imaging (MRI) is highly variable, as it depends on the protein content of the cysts. Solid tumor portions and cyst membranes appear isointense in T1-weighted images, often with a mildly heterogeneous structure (**Figure 2**). MRI before and after gadolinium application is the standard imaging for detection of craniopharyngioma, but because CT is the only way to detect or exclude calcification, which is found in approximately 90% of tumors, (Warmuth-Metz et al., 2004), a sellar or parasellar mass detected on MRI should be further imaged by native CT for detection of calcifications.

TREATMENT – CHALLENGES AND STRATEGIES

Disturbance of cerebrospinal fluid (CSF) flow often causes hydrocephalus, which, depending on severity, must be stabilized by surgical treatment. Tumor resection is the first-choice treatment for restoring normal CSF flow, but a pre-surgery shunt operation may also be required. For a craniopharyngioma with large cystic components, stereotactic, or open implantation of an intracystic catheter is a proven treatment both for the relief of pressure and, in some cases, for the instillation of sclerosing substances (bleomycin). An intracystic catheter with a subcutaneous reservoir can be effective for reducing cyst volume and is particularly appropriate for infants and toddlers where extending the interval until radiotherapy or surgical resection is advantageous in some cases. For patients experiencing preoperative visual impairment due to large cysts exerting pressure on the optic nerve, a two-staged treatment approach is proposed, with cyst drainage to relieve pressure and improve vision, followed by resection (Choux et al., 1991).

After preoperative assessment of calcifications by CT, the recommended therapy for favorably tumor localized tumors is complete resection while preserving visual, hypothalamic, and pituitary functions (Choux et al., 1991; Müller, 2006). However, radical resection, especially in infants and small children, is problematic due the heightened risk of surgically induced deficits (mainly hypothalamic) and the susceptibility of children to recurrence (23%), even in apparently complete resections. For topographical–anatomical reasons, transsphenoidal surgery is the proven neurosurgical technique for minimizing disturbance to these structures (Fahlbusch et al., 1999). Following postoperative MRI confirmation of complete resection, a post-surgical native CT of the sellar/parasellar area is recommended for reconfirmation of complete resection. A right frontotemporal operative approach is standard, although localization of craniopharyngioma should dictate the approach. Intrasellar craniopharyngioma can be approached via transsphenoidal route. However, childhood craniopharyngioma usually extends to the suprasellar area and must be removed through a transcranial approach. For topographical–anatomical reasons, transsphenoidal surgery has proven advantageous for minimizing disturbance to hypothalamic functions (Fahlbusch et al., 1999).

For unfavorably localized tumors (optic nerve and/or hypothalamic involvement), a limited resection followed by local irradiation is statistically favorable: the risk of progression is 71–90% without postoperative radiotherapy (**Figure 3**), but drops to 21% if combined with postoperative radiotherapy (Becker et al., 1999;

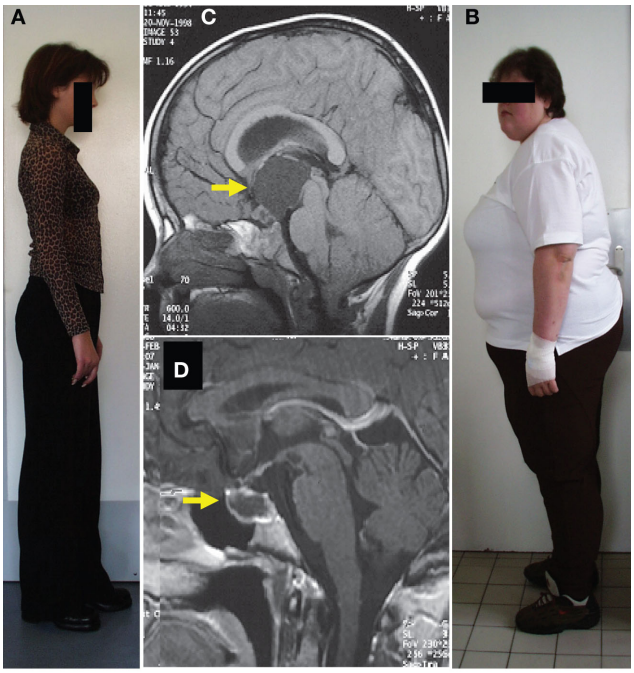

FIGURE 2 | Degree of obesity in relation to the localization of childhood craniopharyngioma. In both patients craniopharyngioma (as indicated by arrow on MRI before surgery) could be completely resected. Both patients had complete hypopituitarism after surgery requiring endocrine substitution of all hypothalamic–pituitary axes. The patient depicted in **(B)** developed severe obesity due to hypothalamic lesions of suprasellar parts of craniopharyngioma **(C)**. The patient depicted in **(A)** presented with a small tumor confined to the sellar region **(D)**. After complete resection she kept normal weight without any eating disorders. (Modified from Müller et al., 2003c, with the kind permission of Springer).

Einhaus and Sanford, 2007). Nevertheless, neurosurgical strategies to treat craniopharyngioma are a matter of debate in the literature (Fischer et al., 1990; Yasargil et al., 1990; Hetelekidis et al., 1993; Rajan et al., 1993; Merchant et al., 2002b; DiRocco et al., 2006; Puget et al., 2006).

The difficulty in striking the correct decision regarding treatment is reflected in two recent reports that reflect some telling trends: the first is Necker Hospital (Puget et al., 2007), which historically is more surgically oriented; and the second is in North America (Merchant et al., 2006), which historically has practiced a more conservative approach. The North American report states that current cases are now treated with moderate to aggressive surgery where 42% of patients undergo limited surgery before irradiation. Puget et al., authors of the Necker report state that 96% of recent cases are surgically treated (23% achieving complete resection, 73% subtotal resection), and that combined treatment (surgical plus radiotherapy) is performed in half the cases following subtotal resection. The trend seems to be toward combined treatment (surgery plus post-surgical radiotherapy) in centers with historically prevalent surgical approaches, and toward more radical surgical treatment strategies in centers historically conservative-oriented.

In addition to difficulties in deciding the degree of resection, the timing of postoperative residual tumor irradiation remains unclear and controversial (Regine and Kramer, 1992; Stripp et al., 2004; Moon et al., 2005; Tomita and Bowman, 2005; Merchant et al., 2006; Müller et al., 2006b). Some favor immediate irradiation following surgical procedure and some purport a wait-and-see approach to minimize both the necessity for irradiation and sequelae associated with radiation therapy. Proactive post-surgical irradiation to prevent tumor progression is favored by the above-mentioned North American Center (Merchant et al., 2006). But even though immediate postoperative irradiation significantly delays tumor progression, progression-contingent irradiation is effective, reflected in its unaffected overall survival rates. These contrasting approaches have been retrospectively compared by three series (Stripp et al., 2004; Moon et al., 2005; Tomita and Bowman, 2005). Moon et al., reported no overall survival rate differences between the two strategies. Tomita et al., reported that for those patients undergoing immediate postoperative irradiation after complete resection, 83% were relapse-free after 5 years and 70% were relapse-free after 10 years. For those undergoing incomplete resection followed by immediate irradiation, 71% were relapse-free after 5 years and 36% were relapse-free after 10 years. Only 9% were relapse-free after 5 years when incomplete resection was not immediately combined with radiation therapy. Progression-contingent irradiation achieved similar survival- and progression-free survival rates of 90 and 70%, respectively, meaning progression-contingent irradiation in this series also was highly effective. However, the interpretation of these studies is confounding by different indications for treatment. They also only reflect relapse-free survival rates and do not include consequences of craniopharyngioma QoL sequelae.

The target volume of irradiation is calculated based on CT and/or MRI images. Current imaging techniques with enhanced resolutions allow a safety margin ideally no greater than 5 mm, depending on the tumor location, size, composition (solid, cystic, calcified), and adjacent structure involvements (hypothalamic–pituitary axis and/or optic nerve or chiasm), requiring a larger safety margin if the hypothalamus is involved. Three-dimensional planning and multi-field techniques with individual field configurations (collimation) are recommended to protect radiosensitive structures and to provide a maximal dose fall-off between the tumor and the adjacent structures (Becker et al., 1999; Einhaus and Sanford, 2007).

Due to the low histological malignancy of craniopharyngiomas and especially because they are located near essential structures regulating eyesight, growth, and energy homeostasis, proton beam therapy appears to be a promising therapeutic option, offering a more protective radio-oncological technique than conventional external irradiation (Baumert et al., 2004; Fitzek et al., 2006; Luu et al., 2006). Also reported as a promising treatment technique is the intracystic instillation of interferon alpha (Ierardi et al., 2007). The stereotactic instillation of radioisotopes is mainly applicable to monocystic recurrences of craniopharyngioma, which is recommended for pre-surgical treatment of large cystic tumors and for tumors that recur after both surgery and percutaneous radiation therapy.

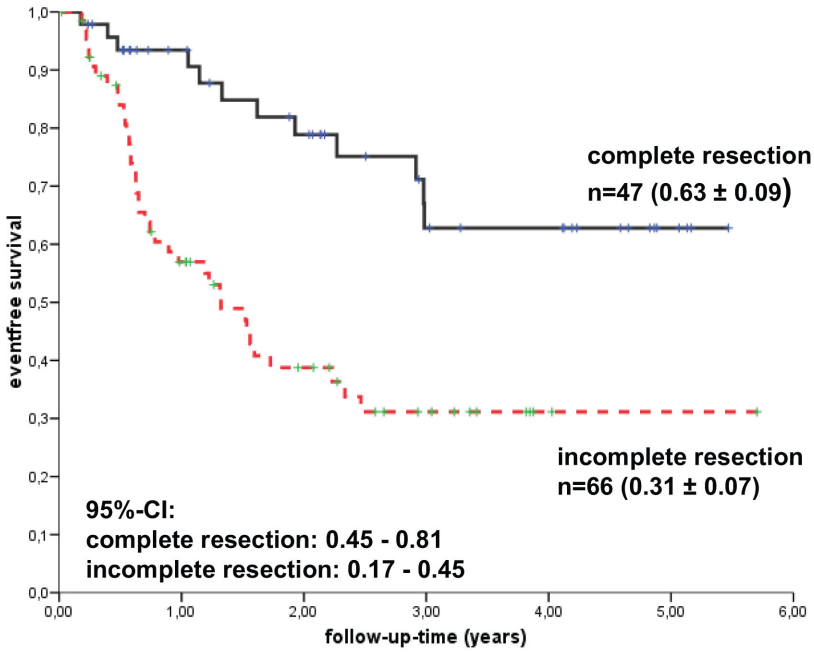

FIGURE 3 | Kaplan–Meier analyses of event-free survival rates (EFS) depending on the extent of resection among the 117 craniopharyngioma patients recruited in the trial KRANIOPHARYNGEOM 2000. (Modified from Müller et al., 2010, with the kind permission of Karger).

Other therapeutic options, including stereotactic gamma-radiotherapy (Gamma Knife), are less promising due to limited experience; and in the case of single-dose convergence irradiation, of little treatment value due to reasons related to radiation biology.

Beyond treatment success ratings of craniopharyngioma related to diagnostic and treatment strategies is the experience level of the neurosurgeon. A few studies have analyzed treatment outcome related to the neurosurgeons' experience (Sanford, 1994; Boop, 2007; Müller et al., 2011b). Both Sanford and Boop report a marked difference in outcome according to the neurosurgeons' experience with the condition. The most recent of the three reports (Müller et al., 2011b) analyzed craniopharyngioma outcome and prognosis relative to patient load of the treating neurosurgical centers, finding centers with lower craniopharyngioma patient load – and therefore relatively less experience treating craniopharyngioma – tended to use more radical surgical approaches, resulting in less favorable outcomes regarding obesity and other QoL considerations. Current literature advises a multidisciplinary team approach to craniopharyngioma treatment, enabling micro- and macro-examinations of pre-surgical, intraoperative surgical, and post-surgical radio-oncological options, as well as long-term QoL issues.

QoL MANAGEMENT – PRE- AND POST-TREATMENT CONSIDERATIONS

KRANIOPHARYNGEOM 2007, a prospective, European multinational trial (Müller et al., 2003c, 2006b; Müller and Sörensen, 2007; Müller, 2010, 2011), is currently evaluating craniopharyngioma patients' prognoses (QoL, event-free, and overall survival rates) following defined therapeutic strategies. A stratified randomization of two treatment arms is conducted with respect to timing of postoperative irradiation (immediate irradiation versus irradiation at the time of progression) for the subgroup of patients ≥5 years-of-age at the time of incomplete resection (**Figure 4**). The schedule of prospective data collection and the set and definition of parameters in KRANIOPHARYNGEOM 2007 are based on a European consensus (Müller et al., 2006a,c). The trial is open for international recruitment (www.kraniopharyngeom.net). There are also other current prospective studies underway on national and multinational levels to adopt strategies tailored to risk factors for morbidity and QoL (Garré and Cama, 2007; Puget et al., 2007).

A recent report (Müller et al., 2011b) shows that especially tumor involvement and surgical lesions of posterior parts of hypothalamic structures predisposes to adverse late effects such as obesity and consecutively impaired quality of life (**Figure 5**). The primary craniopharyngioma sequelae affecting patients' quality of life are visual impairment (Choux et al., 1991), hypothalamic lesions causing neuropsychological deficits (emotional instability, rage attacks, abnormal sexual behavior, and deficits of memory and intellectual capacities; Fischer et al., 1990; Fisher et al., 1998; Riva et al., 1998; Müller et al., 2005a,b; Pierre-Kahn et al., 2005), and endocrine deficits (including diabetes insipidus, hormonal deficiencies causing growth and puberty disturbances, hyperphagia and hypothalamic obesity, and eating disorders, which are observed in 40–50% of craniopharyngioma patients (DeVile et al., 1996b,c; Müller et al., 2001, 2003b,d, 2004a; Srinivasan et al., 2004).

Most patients (85–95%) suffer from multiple deficits of hypothalamic–pituitary function, ranging to complete pituitary insufficiency (DeVile et al., 1996a; Merchant et al., 2002a), and full restoration of preoperatively deficient hormonal function occurs

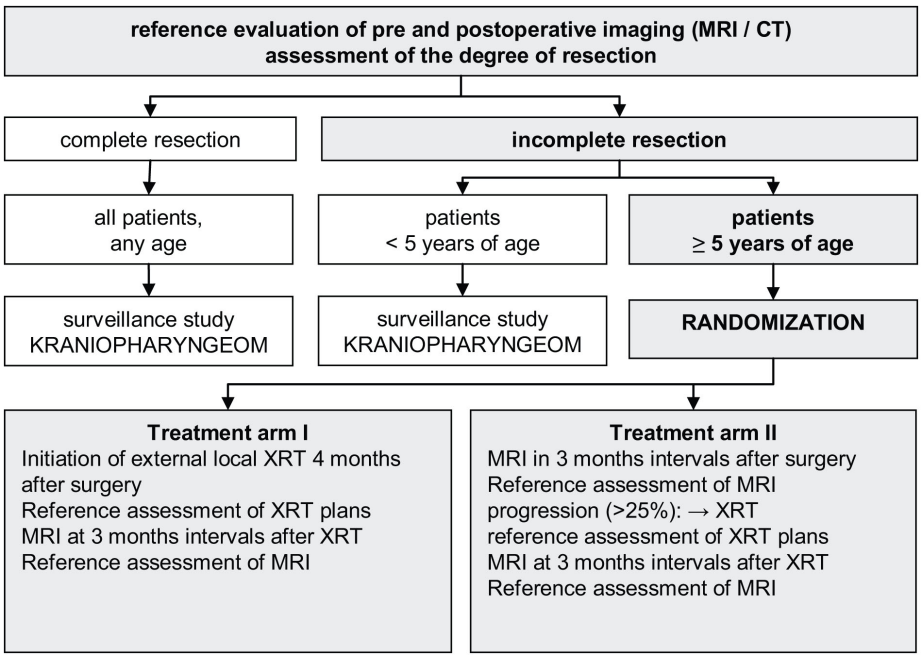

FIGURE 4 | Study design of KRANIOPHARYNGEOM 2007 (www.kraniopharyngeom.net; modified from Müller et al., 2006b, with the kind permission of Thieme).

only in rare cases (Honegger et al., 1999). Growth hormone substitution therapy is reported as a well-documented effective and safe treatment option in patients with growth hormone deficiency (Lustig et al., 2003b; Müller et al., 2010). Nevertheless, the disturbance of hypothalamic structures by the tumor and/or its treatment is considered to be the major pathogenic factor for hyperphagia and obesity, confirmed by an imaging study assessment of the extent of hypothalamic involvement and consequential sequelae (DeVile et al., 1996b). Another study performed by Roth et al. (1998) measured serum leptin levels in craniopharyngioma patients and found significantly elevated leptin concentrations in relation to BMI in patients with a suprasellar tumor components, finding that the body mass index (BMI) of affected patients positively correlated with the degree of hypothalamic damage. Normal inhibition of appetite after eating fails to occur because of disruption of the negative feedback loop involving leptin, formed in adipocytes, which binds to hypothalamic leptin receptors. Weight gain occurs in craniopharyngioma patients, even when caloric intake is similar in craniopharyngioma patients compared to BMI-matched controls (Harz et al., 2003).

Exacerbating the management of weight gain caused by craniopharyngioma and its treatment is that children with craniopharyngioma have a markedly lower than normal level of physical activity caused by daytime and disturbances of circadian rhythms (Müller et al., 2002). Initial trials with melatonin substitution in childhood craniopharyngioma patients have proved promising (Müller et al., 2006c). Polysomnographic studies in craniopharyngioma patients with severe daytime sleepiness reveal sleeping patterns typical for secondary narcolepsy (Müller et al., 2006d), confirming this sequela to be a major contributor to depreciated QoL. Mason et al. (2002) reported a significant weight loss in childhood craniopharyngioma patients treated with a central stimulating agent (dextroamphetamine).

Both the cause and treatment of weight gain in craniopharyngioma patients has been approached on several fronts. Lustig et al. (2003a,b) postulated hypothalamic disinhibition of vagal output as a cause of increased beta-cell stimulation, leading to hyperinsulinism and obesity. In a randomized, double-blinded study, treatment with a somatostatin analog (octreotide) to suppress beta-cell activity resulted in weight reduction. Due to reduced concentrations of catecholamine metabolites in the urine of patients with childhood craniopharyngioma correlating with the degree of obesity and the level of physical activity, Roth et al. (2007) hypothesized that craniopharyngioma patients' decreased physical activity and severe obesity might be related to decreased central sympathetic output. In another study, Roth et al. (2011) analyzed the gastrointestinal hormones ghrelin and peptide YY and their effect on satiety in patients with childhood craniopharyngioma and obesity, supporting that reduced ghrelin secretion coupled with reduced postprandial suppression of ghrelin leads to disturbed regulation of appetite in these patients. Peptide YY levels did not differ between normal weight, obese, and very obese patients with childhood craniopharyngioma. Recently reported (Roth et al., 2010) is a possible pathogenic role of peripheral alpha-melanocyte-stimulating hormone in childhood craniopharyngioma obesity. Even though initial experiences with bariatric surgery (laparoscopic adjustable gastric banding, LAGB) to treat severe craniopharyngioma obesity have been encouraging, long-term follow-up will be necessary to analyze its efficacy, safety, and long-term effect on weight development (Müller et al., 2007,

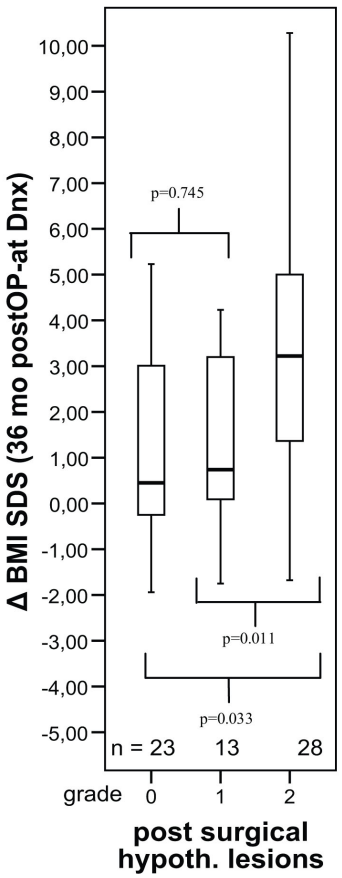

FIGURE 5 | Changes in body mass index (BMI SDS) during first 36 months after diagnosis of 117 childhood craniopharyngioma patients recruited in KRANIOPHARYNGEOM 2000 relative to the extent of surgical hypothalamic lesions (grade 0–2). The horizontal line in the middle of the box depicts the median. Edges of box mark the 25th and 75th percentile. Whiskers indicate the range of values that fall within 1.5 box-lengths. (Modified from Müller et al., 2011b, with the kind permission of BioScientifica).

2011a). As of this writing, there is no generally accepted pharmacological nor surgical therapy for craniopharyngioma obesity.

CONCLUSION

A retrospective study of functional capacity using the FMH instrument that quantifies patients' abilities to perform everyday psychomotor tasks (Wolff et al., 1996) found significantly lower rankings for craniopharyngioma patients compared to age-matched controls (Müller et al., 2003a, 2004b), with craniopharyngioma patients' morbid hypothalamic obesity cited as responsible for their low functional capacity self-rating. Age-dependent differences between childhood and adult onset craniopharyngioma are related to histological diagnosis, biological behavior, clinical manifestations, treatment options and follow-up (Koranyi et al., 2001; Attanasio et al., 2002; Kendall-Taylor et al., 2005). The Kendall-Taylor et al. (2005) study compared childhood craniopharyngioma with adult onset craniopharyngioma and reported a poor state of health and QoL in both cohorts. The majority of childhood and adult craniopharyngioma patients displayed pituitary insufficiency, with 60% suffering from diabetes insipidus. Nearly all patients were overweight or obese, reporting a poor QoL. What we can take away from this and other reports of both childhood and adult onset craniopharyngioma is that craniopharyngioma involves a series of chronic morbidities ranging from visual impairment to life-long, seemingly untreatable, unmanageable obesity that require on-going patient monitoring to optimize their QoL. Such monitoring provides a two-way communication platform that serves as both a data collection medium on how sequelae unfolds after treatment, as well as a patient-reporting medium of new treatment options that may be revealed as continuing research develops on this all-too confounding disease.

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Long term sequelae of pediatric craniopharyngioma – literature review and 20 years of experience

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Craniopharyngioma are rare histologically benign brain tumors that develop in the pituitary–hypothalamic area. They may invade nearby anatomical structures causing significant rates of neurological, neurocognitive, and endocrinological complications including remarkable hypothalamic damage. Information regarding long term implications of the tumors and treatment in the pediatric population is accumulating, and treatment goals appear to be changing accordingly. In this review we aim to present data regarding long term complications of craniopharyngioma in children and adolescents and our experience from a large tertiary center. Hypothalamic dysfunction was noted to be the most significant complication, adversely affecting quality of life in survivors. Obesity, fatigue, and sleep disorders are the most notable manifestations of this dysfunction, and treatment is extremely difficult. Changes in management in recent years show a potential for improved long term outcomes; we found a trend toward less aggressive surgical management and increasing use of adjuvant treatment, accompanied by a decrease in complication rates.

Keywords: child, craniopharyngioma, complications, hypothalamic obesity, sleep, pituitary, neurocognitive, recurrence

INTRODUCTION

Craniopharyngioma (Cp) tumors are rare epithelial brain tumors that develop from remnants of Rathke's pouch. They can be located along an axis extending from the sella turcica, through the pituitary stalk, to the hypothalamus. Tumors are partly cystic and have benign histological appearance (Bunin et al., 1998; Muller, 2010). As craniopharyngiomas enlarge they invade nearby anatomical structures and despite their histology can have an aggressive clinical course. Both the tumor and its treatment can lead to significant neurological and endocrinological complications; the most devastating being related to hypothalamic dysfunction (Sughrue et al., 2011). Long term survival is high (Poretti et al., 2004); however complications have serious implications on quality of life. These tumors present a great challenge to the neurosurgeon due to their location and proximity to vital structures, and controversy as to the preferable method for treatment exists. In the past decade treatment goals appear to be changing, with many centers adopting a less aggressive approach. Advancements in radiation technology as well as in chemotherapy methods and medications have been remarkable and these provide a variety of potential adjuvant treatments. In this report we aim to review the long term complications of Cp tumors and their treatment in the pediatric population; including data from the literature as well as our own experience.

CRANIOPHARYNGIOMA TREATMENT

The preferable approach for treatment of Cp tumors in children remains controversial despite many years of experience. In the past, gross total resection (GTR) of the tumor was the method of choice (Hoffman et al., 1992; De Vile et al., 1996; Van Effenterre and Boch, 2002; Poretti et al., 2004; Caldarelli et al., 2005) and it remains so in some centers (Caldarelli et al., 2005; Elliott and Wisoff, 2010). Based on the benign histology of the tumor this approach is aimed at achieving cure. However, these patients were found to have a considerable rate of recurrences, occurring in up to one-third of patients (Hoffman et al., 1992; Jung et al., 2010; Steno et al., 2011) as well as a high rate of complications and morbidity (Crom et al., 2010; Sughrue et al., 2011). Hypopituitarism, hypothalamic dysfunction, and neurocognitive impairments in areas of memory, learning, and school performance, are prevalent in series using primarily GTR (Hoffman et al., 1992; De Vile et al., 1996; Poretti et al., 2004). Taking into consideration the great significance of these morbidities, in recent years a surgical approach that is more patient and tumor specific is gaining acceptance; reserving extensive resections for favorably located tumors, not involving the hypothalamus (De Vile et al., 1996; Poretti et al., 2004; Steno et al., 2011). Endoscopic transsphenoidal surgery is used for smaller, primary intrasellar tumors (Elliott et al., 2011). Characteristically Cp tumors have single or multiple cysts within the tumor (Steinbok and Hukin, 2010) and limited resection or cyst decompression is an alternative surgical approach that addresses Cp more as a chronic disease. In cases of emergent decompression, this procedure may allow time for better planning of future treatment, and a catheter implanted in the cyst can be used later for administering intra-cystic treatment. In our experience, even with decompression as a sole treatment, patients can have a stable course not requiring additional treatment for prolonged periods.

Adjuvant treatment: In patients with predominantly cystic tumors, installation of medications, or radioisotopes to shrink the tumor may be of benefit (Hukin et al., 2007; Cavalheiro et al., 2010; Steinbok and Hukin, 2010). Intra-cystic bleomycin (ICB) for pediatric Cp has been in use in Canada since 1995 (Hukin et al., 2007), although side effects such as local leakage into adjacent brain tissue have raised some concerns and warrants close monitoring (Lafay-Cousin et al., 2007). Intra-cystic interferon-α for treatment of patients with Cp has shown good results, with a reduced complication rate and minimal side effects (Cavalheiro et al., 2010; Steinbok and Hukin, 2010). Radiation therapy for pediatric Cp has been in use for more than half a century (Kiehna and Merchant, 2010); it can be used both as an adjuvant in primary treatment and for disease recurrence. Limited surgery followed by radiation might induce favorable outcomes when compared to more aggressive solely surgical treatments (De Vile et al., 1996; Merchant et al., 2002; Kiehna and Merchant, 2010). Radiotherapy might have significant short and long term adverse effects and these pose a major limitation to the use of this treatment modality in children (Merchant et al., 2002; Caldarelli et al., 2005; Kiehna and Merchant, 2010).

Determining the exact prevalence of outcomes for the different treatment modalities is complicated by multiple factors and no randomized control trials exist in the pediatric population. Decisions regarding surgery and adjuvant therapy are done based on tumor and child characteristics as well as the treating team's approach and experience. Late outcomes are also influenced by treatments given for disease recurrence. In addition, outcomes are not uniformly assessed or presented. Despite these limitations, there are data from the literature suggesting improved outcomes for less aggressive surgical approaches combined with radiation in terms of disease recurrence, neurocognitive functioning, and prevalence of diabetes insipidus (DI) and severe obesity. These are presented in more detail in the following sections.

Over the past decade, the surgical approach to Cp in our institution has changed to become less aggressive (**Figure 1**). In the years 1975–1989 90% of children had a total resection (Hoffman et al., 1992), between 1990 and 2001 86% (Ahmet et al., 2006) had a total resection and from 2001 to 2011 only 10% had a total resection. In recent years radiation and intra-cystic chemotherapy are given to a larger percent of patients.

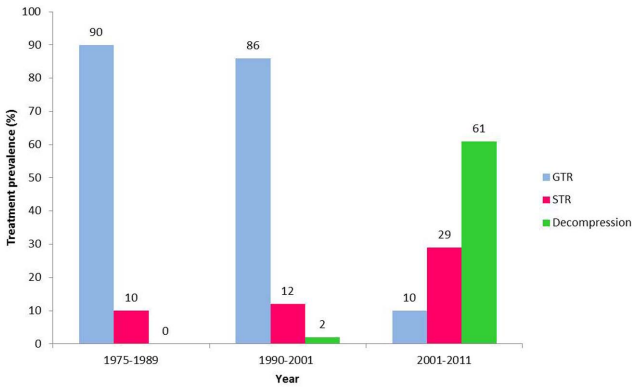

FIGURE 1 | Trends in the surgical approach to craniopharyngioma 1975–2011. Prevalence of gross total resection (GTR – blue), subtotal resection (STR – red), and cyst decompression (Decompression – green) surgery as the primary treatment for pediatric craniopharyngioma in our institution over more than three decades; 1975–1989 (Hoffman et al., 1992), 1990–2001 (Ahmet et al., 2006), 2001–2011.

TUMOR RECURRENCE AND REGROWTH

Recurrence and regrowth in Cp are not uncommon and can be expected even with extensive resection. Tumor recurrences are often asymptomatic and diagnosed on routine follow-up imaging (Hoffman et al., 1992; Elliott and Wisoff, 2010). Rates of recurrence following GTR range between 17 and 36% (Hoffman et al., 1992; Merchant et al., 2002; Poretti et al., 2004; Ahmet et al., 2006; Elliott and Wisoff, 2010; Jung et al., 2010; Elliott et al., 2011; Steno et al., 2011); however some report much lower rates of 7.7–10% following neuroradiologically confirmed total resection by transcranial approach (De Vile et al., 1996; Caldarelli et al., 2005), or with trans-sphenoidal GTR (Elliott et al., 2011). Regrowth rates after incomplete removal are higher, ranging between 43 and 67% (Jung et al., 2010; Steno et al., 2011). The 10-year recurrence rate after combined surgical and radiation treatment is reported to be lower, ranging between 0 and 30%, with some reports demonstrating improved disease control for a combination of biopsy or cyst resection and radiation compared with subtotal resection and radiation (Clayton et al., 1988; Stripp et al., 2004; Lin et al., 2008; Kiehna and Merchant, 2010). Recurrences occur at variable time intervals from the initial surgery, including many years after surgery (Hoffman et al., 1992; De Vile et al., 1996; Merchant et al., 2002; Caldarelli et al., 2005; Elliott and Wisoff, 2010) and occasionally appear in a location away from the original Cp site (Caldarelli et al., 2005). Mean interval from treatment to recurrence is most commonly reported to be approximately 3 years (Hoffman et al., 1992; Poretti et al., 2004; Caldarelli et al., 2005; Elliott and Wisoff, 2010). Risk factors for recurrence include a large tumor size, young age, and severe hydrocephalus at presentation; incomplete tumor resection and previous recurrence are additional risk factors (Hoffman et al., 1992; De Vile et al., 1996; Van Effenterre and Boch, 2002; Poretti et al., 2004; Caldarelli et al., 2005; Elliott and Wisoff, 2010; Jane et al., 2010; Jung et al., 2010; Steno et al., 2011).

PITUITARY DEFICIENCIES

Pituitary hormone deficiencies are common in children treated for Cp. At diagnosis 40–87% of patients (Hoffman et al., 1992; Caldarelli et al., 2005; Muller, 2008) have been identified to have at least one hormone deficiency and 17–27% (Hoffman et al., 1992; Muller, 2008; Elliott and Wisoff, 2010) have been reported to have DI. Post surgery, the rate of pituitary hormone deficiencies increases and has been reported to be 80–100% (Hoffman et al., 1992; De Vile et al., 1996; Merchant et al., 2002; Muller et al., 2004; Poretti et al., 2004; Caldarelli et al., 2005; Elliott and Wisoff, 2010; Jung et al., 2010; Steno et al., 2011). Prevalence is comparable even with pituitary stalk preservation (Jung et al., 2010). We have found rates similar to those reported in the literature for individual deficiencies and an encouraging decrease in rates of panhypopituitarism with less aggressive treatment (**Figure 2**). A majority of patients need both anterior and posterior pituitary hormonal replacement. The evaluation of anterior

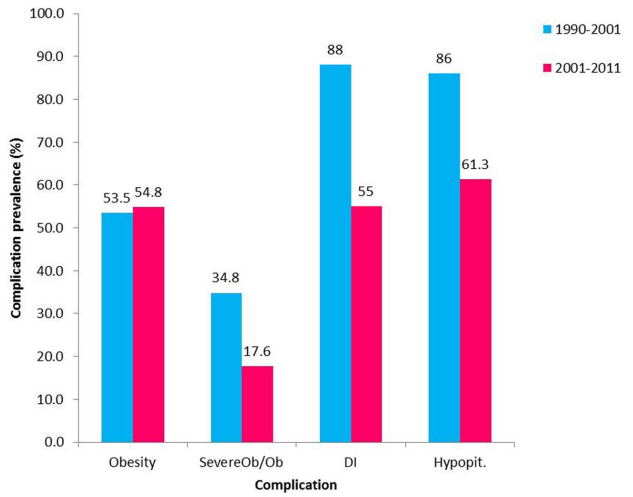

FIGURE 2 | Prevalence of complications following Cp treatment in the past two decades. Prevalence of hypopituitarism (Hypopit), diabetes insipidus (DI), and obesity between the years 1990–2001 (Ahmet et al., 2006; blue) and 2001–2011 (red). Obesity (Ob) defined as BMI > 95th percentile for age and gender. Severe obesity defined as BMI > 99th percentile for age and gender or BMI > 40 kg/m^2 if more than 18 years old); Severe Ob/Ob – the percent of obese patients with severe obesity.

pituitary hormone deficiencies is not uniform in reports from different studies. Those based on rates of hormone replacement might underestimate the prevalence of growth hormone (GH) and gonadotropin deficiencies or overestimate ACTH deficiency if reporting hormone replacement at any time point. Overall, ACTH deficiency is described to range between 70 and 95%, with no clear trend related to treatment modality. TSH deficiency ranges between 80 and 96% in different series with a slightly higher rate for the combination of surgery and radiation compared to more aggressive surgery. Gonadotropin deficiency is most commonly described to be around 30–40%. Clinical or biochemical GH deficiency has been described at diagnosis in 26–75% of children with Cp (Ahmet et al., 2006; Muller, 2008), and decreases in height SD score (SDS) may occur years before diagnosis (Muller et al., 2004). GH deficiency following treatment for Cp is common, found in about 70–92% of patients, the literature does not clearly delineate a significant difference between the treatment modalities (Muller et al., 2004, 2011; Halac and Zimmerman, 2005; Crom et al., 2010) and a good response to GH treatment is described (Geffner et al., 2004).

Transient post-surgical DI is a prevalent finding that has been described to occur in almost all patients in some series (Poretti et al., 2004; Caldarelli et al., 2005). In our experience, the rapid shifts in serum sodium that commonly complicated the course post GTR and significantly prolonged the post-surgical admission have decreased remarkably in magnitude when using less aggressive surgical procedures. We also noted a decrease in prevalence of permanent DI (**Figure 2**). Permanent DI after treatment was found in different series to range between 60–90% after aggressive surgery and 50–55% after less aggressive surgery combined with radiation therapy (Hoffman et al., 1992; De Vile et al., 1996; Merchant et al., 2002; Poretti et al., 2004; Caldarelli et al., 2005; Ahmet et al., 2006; Elliott and Wisoff, 2010; Elliott et al., 2011; Muller et al., 2011). Replacement treatment for pituitary hormones is in most instances readily accessible; however hypothalamic injury in this population might interfere with thirst regulation complicating the DI management and putting the children at risk for life threatening electrolyte imbalances. Pituitary hormone deficiencies might also occur late, particularly when adjuvant treatment is used, therefore monitoring pituitary function is a life-long requirement.

LINEAR GROWTH

Despite the common occurrence of GH deficiency after treatment for Cp not all require GH replacement for growth induction. In a study of Cp-related hypothalamic obesity (CRHO) conducted by our group, one-third of the patients were growing despite GH deficiency and no supplementation (O'gorman et al., 2010b; Simoneau-Roy et al., 2010); another study found an even higher rate of normal growth without GH (Srinivasan et al., 2004). Patients with hypothalamic involvement were found to achieve normal height at last follow-up more often than patients without hypothalamic involvement (Muller et al., 2004). This phenomenon of "growth without GH" has been described in Cp patients almost five decades ago (Matson, 1964). The physiology of growth in these cases is not fully understood. Insulin and leptin are thought to induce growth in the fetus and in obese children and are hypothesized to induce growth in Cp (Costin et al., 1976; Geffner, 1996; Phillip et al., 2002). Leptin was shown to have characteristics of a bone growth factor acting directly at the level of bone growth centers, independently of GH (Phillip et al., 2002). Mechanisms by which insulin stimulates growth include its known anabolic effects; at high levels it may bind to the insulin-like growth factor-1 (IGF-1) receptor and induce growth, and through its actions to decrease IGF-binding protein 1 levels it may increase levels of free IGF-1 (Phillip et al., 2002). In support of this theory, obese Cp patients were found to have a higher height SDS at diagnosis and at last follow-up with no difference in the usage of GH, thyroxine, or hydrocortisone (Muller et al., 2001); and increased insulin levels were found in children with Cp. In contrast, another study found that children who were growing despite GH deficiency were not different from those requiring GH treatment in terms of anthropometrical measures, body composition, and metabolic indexes; including insulin levels (Srinivasan et al., 2004). Sex hormones may also induce growth in these patients (Phillip et al., 2002). Finally, the effects of other local growth factors acting on bone have been hypothesized to contribute to this phenomenon (Geffner, 1996; Phillip et al., 2002).

HYPOTHALAMIC DYSFUNCTION

Hypothalamic dysfunction in children with Cp is common and has been found at diagnosis in 35% of patients (Elliott and Wisoff, 2010). It dramatically increases following treatment; in some series occurring in up to 65–80% of patients (Poretti et al., 2004; Elliott and Wisoff, 2010). This complication can significantly compromise health-related quality of life (HRQoL) and be extremely resilient to treatment. Some of the manifestations such as obesity can be quantified by relatively simple anthropometric measures;

however, others may be more elusive in nature. Fatigue, behavioral changes, circadian rhythm, and sleep irregularities and imbalances in regulation thirst, body temperature, heart rate, or blood pressure might be more difficult for both patients and physicians to appreciate. These dysfunctions are inter-related in a way that can worsen outcome. The pre-surgical evaluation of hypothalamic damage might be difficult both clinically and radiologically (Steno et al., 2011); tumor involvement of the third ventricle, or obstructive hydrocephalus are suggestive findings (Caldarelli et al., 2005).

SLEEP DYSREGULATION

Hypothalamic injury may result in disturbances in sleep–wake patterns. Our and others' clinical experience is that patients with CRHO commonly suffer from an altered pattern of circadian rhythm with early morning awakening, followed by an extra period of sleep during the afternoon. Thus, sleep fragmentation and increased daytime sleepiness are common. Increased daytime sleepiness has been reported by one-third of children with Cp that were surveyed with a prevalence of 40% in the severely obese children (Muller et al., 2002, 2006b; Snow et al., 2002; Poretti et al., 2004). Actigraph recording in three patients with Cp and daytime hypersomnolence demonstrated irregular bedtimes, frequent night-time activity, and inappropriate daytime episodes of rest, consistent with our clinical experience (Lipton et al., 2009). Melatonin secretion occurs during hours of darkness; it affects sleep patterns and potentially has a role in circadian rhythm regulation. An altered pattern of diurnal melatonin secretion with decreased night-time melatonin levels was detected in severely obese Cp patients (Muller et al., 2002; Lipton et al., 2009). Nocturnal levels had a negative relation to both the degree of obesity and the sleepiness scoring. Melatonin treatment in Cp patients with severe daytime sleepiness resulted in an increment in morning and night melatonin levels, improvement in daytime sleepiness and physical activity (Muller et al., 2006b).

Modafinil is a wake-promoting agent that has shown beneficial effects in adults with Cp-related hypersomnolence (Crowley et al., 2011). We have offered this medication to two patients with hypothalamic obesity (HO) and significant daytime fatigue related to treatment for tumors in the hypothalamic area. Both patients reported a remarkable improvement in alertness and activity tolerance, and the medication was well tolerated; no significant effect on weight has been noticed. Future research on the effects of this medication in children with Cp is warranted.

In addition to the effect of hypothalamic damage, the obesity and metabolic dysfunction in patients with Cp might be associated with sleep-disordered breathing (Redline et al., 2007). Our group found sleep-disordered breathing to be increased in adolescents with Cp-related obesity compared with BMI-matched controls (O'gorman et al., 2010b). Specifically, increased sleep fragmentation and reduced sleep efficiency were found in children with Cp; the obstructive apnea–hypopnea index was higher and correlated negatively with adiponectin levels, an adipokine with insulin sensitizing properties. We propose considering routine polysomnography in obese patients with craniopharyngioma.

ACTIVITY AND ENERGY EXPENDITURE

Weight gain in patients with Cp was traditionally thought to be induced by hyperphagia; however a number of studies suggest that although subjective hunger may be higher, energy intake is not increased when compared to control subjects (Harz et al., 2003; Holmer et al., 2010). A decreased metabolic rate (both resting and total energy expenditure) has been suggested to contribute to weight gain in this population. Adults with childhood onset Cp as well as children with Cp were found to have a lower resting energy expenditure (REE) compared to controls (Shaikh et al., 2008b; Holmer et al., 2010; Kim et al., 2010). This difference was not explained by differences in body composition. The energy intake/REE ratio was significantly lower in those with tumors involving the third ventricle (Holmer et al., 2010). Patients with childhood Cp were also found to have decreased physical activity compared to healthy obese and normal weight controls contributing to overall lowering of total energy expenditure (Harz et al., 2003; Shaikh et al., 2008b; Holmer et al., 2009, 2010). Factors that could potentially contribute to decreased activity are neurological and visual deficits, increased daytime sleepiness, low levels of testosterone and GH and psychosocial difficulties such as teasing and bullying leading to self-consciousness about engaging in physical activity.

WEIGHT GAIN AND OBESITY

Of the manifestations of hypothalamic damage in children treated for Cp, rapid weight gain is the most concerning complication for patients, their families, and practitioners. This occurs despite adequate replacement of pituitary hormone deficiencies. The hypothalamic disturbance in energy management contributes to obesity and is further augmented by factors limiting activity. There is evidence demonstrating increased weight gain in children with Cp occurring years before diagnosis (Muller et al., 2004). At diagnosis 12–19% of patients were reported to be obese (Hoffman et al., 1992; Poretti et al., 2004; Ahmet et al., 2006; Muller, 2008). Obesity develops early after treatment and weight gain was found to rapidly increase in the first 6–12 months after treatment (Muller et al., 2001; Ahmet et al., 2006); later on BMI stabilizes but obesity continues to remain a problem (Ahmet et al., 2006; Holmer et al., 2010). Following treatment, the prevalence of obesity is higher, reaching up to 55% (Hoffman et al., 1992; Muller et al., 2001, 2003b; Poretti et al., 2004; Srinivasan et al., 2004; Ahmet et al., 2006; Lek et al., 2010; O'gorman et al., 2010b; Elliott et al., 2011). Review of our patients indicates a lower prevalence of severe obesity associated with less aggressive surgery (**Figure 2**). This is supported by more recent reports of lower rates of severe obesity after combined surgical and radiation approaches (Lin et al., 2008; Crom et al., 2010). However the literature does not demonstrate a significant change in the prevalence of overall obesity with the change in treatment approach. This might be related to the small number of patients in studies as well as to the approach to assessment of obesity; more detailed stratification of the degree of obesity appears to provide additional information. When evaluating body composition and fat distribution in children with Cp, results are conflicting; some studies have demonstrated patients to have increased fat free mass and muscle mass when compared to controls (Holmer et al., 2010; Kim et al., 2010) while others

found comparable fat mass in Cp patients and controls (Srinivasan et al., 2004; Shaikh et al., 2008a). Excess weight has a significantly adverse effect on HRQoL and self-esteem (Hoffman et al., 1992; Muller et al., 2001) and is associated with difficulties at school as well as at home. Adults with childhood onset Cp and obesity also reported a higher tendency to restrict food intake for controlling body weight compared with controls (Holmer et al., 2010). Risk factors for HO include hypothalamic involvement of the tumor or treatment, tumor growth inside the cavity of the third ventricle, pre-operative hydrocephalus, large tumor size, a lower rate of successful GTR, higher radiation doses to the hypothalamus (>51 Gy), higher BMI in early childhood, higher BMI, and height SDS at diagnosis and familial predisposition for obesity (Muller et al., 2001, 2003b, 2004, 2011; Lustig, 2002; Lustig et al., 2003b; Caldarelli et al., 2005; Ahmet et al., 2006; Holmer et al., 2009, 2010; Lek et al., 2010; Roth et al., 2011; Steno et al., 2011). The dose and duration of post-operative dexamethasone treatment was found to have only a short term effect on weight gain and treatment correlated with weight gain during the first post-operative year but not with long term development of obesity (Muller et al., 2003b).

METABOLIC SYNDROME

In a study conducted by our group, children and adolescents with CRHO were found to have an increased rate of the metabolic syndrome (MS) occurring in 10 out of 15 subjects studied (66%) compared to 3 out of 15 BMI-matched controls (20%; Simoneau-Roy et al., 2010). Impaired glucose tolerance was more prevalent in the Cp subjects; they also demonstrated higher levels of free fatty acids and TNF-alpha, molecules associated with MS (**Figure 3**). In agreement with our results, children and adolescents following Cp removal were found to have features of the MS, including higher abdominal fat and less favorable lipid profiles when compared with matched controls (Srinivasan et al., 2004). In contrast, adults with childhood onset Cp, were demonstrated increased risk for cardiovascular disease compared to a control group; however, after adjustment for BMI, these differences disappeared (Holmer et al., 2009). Further work is needed to assess longer term outcomes related to risk for type 2 diabetes and cardiovascular disease in this population.

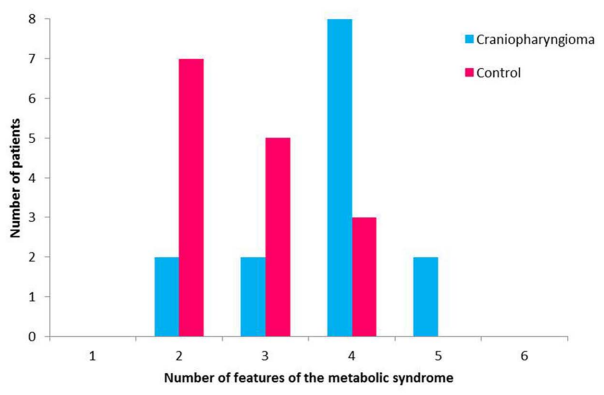

FIGURE 3 | Features of the metabolic syndrome in patients with craniopharyngioma and control subjects.

AUTONOMOUS NERVOUS SYSTEM BALANCE IN CRANIOPHARYNGIOMA

The hypothalamic regulation of appetite and energy homeostasis is a complex system involving hormonal and neuronal pathways connecting the hypothalamus with the alimentary system and periphery, including adipose tissue which also produces hormones and cytokines. The hypothalamus receives input regarding adipose accumulation, satiety, and metabolism from peripheral hormones including leptin, ghrelin, and insulin respectively (Lustig, 2002); it exerts its efferent signal via the autonomic nervous system (ANS). Damage that lowers the sympathetic nervous system (SNS) activity and/or increases the parasympathetic nervous system (PNS) activity could contribute to a positive energy balance and weight gain and both conditions have been theorized to contribute to the development of HO (Lustig, 2002; Hochberg and Hochberg, 2010). The common symptom of increased fatigue in these patients could also be related to a decreased sympathetic tone.

In support of decreased activity of the SNS, urine catecholamine levels were found to be lower in children with Cp compared to controls (Coutant et al., 2003) and levels negatively associate with the degree of obesity and physical activity (Roth et al., 2007). Further support comes from the improvement seen in terms of weight, activity, and attention when treating Cp patients with medications that increase sympathetic tone (Mason et al., 2002; Ismail et al., 2006; Danielsson et al., 2007; Schultes et al., 2009). SNS activity is thought to decrease insulin secretion through inhibition of pancreatic beta-cells and to inhibit insulin stimulated leptin release from adipocytes (Cammisotto and Bukowiecki, 2002; Lustig, 2003). Elevated levels of both hormones have been reported in Cp-related obesity, even after adjusting for fat mass, and may in part be due to an decreased sympathetic activity (Goldstone et al., 2005; Shaikh et al., 2008a; Guran et al., 2009; Holmer et al., 2009, 2010; O'gorman et al., 2010a; Simoneau-Roy et al., 2010; Roth et al., 2011).

Increased vagal activity as a result of hypothalamic damage may lead to increased pancreatic beta-cell stimulation and hypersecretion of insulin (Lustig, 2002). This is supported by the aforementioned increased insulin levels in patients with Cp-related obesity and by improvement in terms of weight gain with treatments targeted at suppressing beta-cell activity. Octreotide has been found to attenuate glucose induced insulin excursions; and to result in reduced weight gain, or in some cases, weight loss (Lustig et al., 1999, 2003a; Inge et al., 2007). Our group has investigated the combined effect of two medications on children with Cp and HO; diazoxide in order to decrease insulin secretion and metformin to enhance insulin action. A decrease in weight gain and BMI was also noted and the best response was seen in subjects with the highest glucose stimulated insulin secretion prior to receiving the medication (Hamilton et al., 2011).

NEUROLOGICAL AND VISUAL OUTCOMES

Due to the tumor's location, visual deficits in children with Cp are relatively common including impairments in both visual acuity and visual fields. Visual impairment was found to exist as an initial manifestation of pediatric Cp in more than half of the patients (Muller, 2008) with some improvement in vision in 41–48% of patients post-surgically (Caldarelli et al., 2005; Elliott et al., 2011).

Risk factors for post-surgical visual impairment include severe pre-surgical visual deficits and tumors located in the prechiasmatic area (Caldarelli et al., 2005; Steno et al., 2011). Despite potential visual improvement after treatment overall post treatment rates of visual impairment are reported in about 45–70% of patients; different treatment modalities result in comparable rates (De Vile et al., 1996; Stripp et al., 2004; Merchant et al., 2006; Lin et al., 2008; Crom et al., 2010). Improved results were found in patients that underwent a trans-sphenoidal procedure (Elliott et al., 2011).

Neurological abnormalities include hemiparesis, epilepsy, cranial nerve deficits, learning problems, hearing loss, cerebrovascular disease manifestations, and headaches (Merchant et al., 2002; Crom et al., 2010; Elliott and Wisoff, 2010). A significant part of these are transient and the total prevalence of long term neurological complications is reported to be 8% (Caldarelli et al., 2005), however rises to 36% for giant tumors (Elliott and Wisoff, 2010) and 30% when including visual and neurological complications together (Poretti et al., 2004).

HEALTH-RELATED QUALITY OF LIFE, PSYCHOSOCIAL FUNCTIONING AND NEUROCOGNITIVE OUTCOME

Health-related quality of life in children can be affected by both the Cp tumor itself and the treatment received. Reports assessing psychosocial and physical functioning, show variable results ranging from excellent in a majority of subjects to impaired function in almost half of the patients (Hoffman et al., 1992; Van Effenterre and Boch, 2002; Poretti et al., 2004). The most common areas of difficulty reported include social and emotional functioning, with patients rating their psychosocial health to be lower than their physical health (Poretti et al., 2004). Other challenges included somatic complaints such as pain, mobility, and self-care (Merchant et al., 2002; Poretti et al., 2004). Children with Cp were found to have lower HRQoL in all domains; and parental reports of children's social and total functioning were significantly lower compared to scores from parents of survivors of other cancers (Rakhshani et al., 2010). Behavioral questionnaires indicate more frequent presence of psychopathological symptoms, including depression, anxiety, and withdrawal. The most frequent problems in children's everyday functioning included inability to control emotions, difficulties in learning, unsatisfactory peer relationships, and concerns regarding physical appearance (Crom et al., 2010; Ondruch et al., 2011).

Factors associated with worse outcomes in terms of HRQoL as well as psychosocial and neurocognitive functioning include younger age at diagnosis and pre-operative functional impairment; tumor characteristics including larger size, hypothalamic, and third ventricle involvement at presentation. Treatment type has also been implicated, with worse outcomes for surgery alone compared to limited surgery and radiotherapy and for multiple operations for tumor recurrence (Merchant et al., 2002; Poretti et al., 2004). Neurological, ophthalmological, and endocrine sequelae adversely affect outcome (Hoffman et al., 1992; Merchant et al., 2002; Van Effenterre and Boch, 2002; Muller et al., 2003a; Poretti et al., 2004; Elliott and Wisoff, 2010; Steno et al., 2011) and hypothalamic dysfunction was found to have an important negative effect on physical ability, social functioning, and body image (Muller et al., 2001, 2003a; Poretti et al., 2004).

In addition to psychosocial function, long term neurocognitive complications following treatment for Cp may include cognitive problems, particularly affecting attention, executive function, working memory, and episodic memory (Cavazzuti et al., 1983; Riva et al., 1998; Carpentieri et al., 2001; Poretti et al., 2004; Sands et al., 2005; Kiehna et al., 2006; Crom et al., 2010; Ondruch et al., 2011). Various neurocognitive outcomes were assessed in different studies making comparison difficult. Series including children treated primarily with GTR report 57% of patients exhibit post treatment memory deficits (Hoffman et al., 1992; Poretti et al., 2004). A significant number of long term survivors of pediatric Cp treated primarily with radiation and subtotal surgical resection, were found to have psychological and educational deficits (Crom et al., 2010). Neurocognitive deficits have ranged to include memory disturbances, slower cognitive speed, attention problems, and behavioral lability (Cavazzuti et al., 1983; Colangelo et al., 1990; Carpentieri et al., 2001; Kiehna et al., 2006; Crom et al., 2010; Ondruch et al., 2011). While intact intellectual functioning has been reported in up to 82% of patients, visual memory is reduced, despite normal visual–spatial abilities (Crom et al., 2010; Ondruch et al., 2011). The acquired deficits in higher cognitive processing such as attention problems are considered precursors to poor academic achievement and vocational failure. Following radiation therapy IQ was found to remain stable overall, with improved results for older children (Kiehna and Merchant, 2010). The impact of conformal radiation therapy and clinical variables on measures of attention among children and young adults with brain tumors was prospectively examined (Kiehna et al., 2006). Over the first 5 years after treatment, patients with Cp demonstrated increased inattentiveness and profound inattentiveness was accompanied by markedly slower reaction time. Overall, newer focal beam radiation techniques demonstrated improved outcomes in terms of functional performance in up to 85% of patients (Merchant et al., 2002; Kiehna and Merchant, 2010).

Despite over a quarter of century of literature documenting the neurocognitive challenges encountered by individuals treated for Cp, intervention efforts have lagged. Recent case studies have examined the efficacy of cognitive rehabilitation for dysexecutive problems and behavioral lability (Metzler-Baddeley and Jones, 2010; Hammond and Hall, 2011). In a case report of a 2-month intervention using a combination of goal management therapy and naturally occurring distractions within the patients' work environment, significant improvements in cognitive tests requiring organized behavior were reported. Social, emotional, and/or behavior problems, most notably aggression, have been reported (Anderson et al., 1997; Riva et al., 1998; Poretti et al., 2004). Despite their occurrence, the assumption of the biological underpinning of the behavioral disturbance appears to have limited attempts to effectively manage it with intervention. Behavioral treatment was used for severe aggressive behaviors demonstrated by a 6-year-old post-Cp resection (Hammond and Hall, 2011); the intervention included functional behavioral analysis followed by differential reinforcement of alternative behaviors and extinction with the goal of decreasing the frequency of aggressive behavior. Aggressive

behavior subsequently decreased to below 88% of baseline levels and adaptive behaviors were found to increase significantly. These results suggest that the patient's aggression was maintained by inadvertent social reinforcement. Taken together, these case studies suggest that cognitive rehabilitation approaches such as goal management therapy and functional behavioral analysis may be useful in supporting survivors of Cp adept to and compensate for cognitive and psychosocial challenges.

In light of the cognitive, behavioral, and emotional sequelae associated with treatment for Cp, monitoring and support is warranted. Ongoing counseling, educational, and advocacy for this unique group of brain tumor survivors will be key to optimizing their potential.

GENERAL FOLLOW-UP MANAGEMENT OF CHILDREN WITH CRANIOPHARYNGIOMA

Follow-up surveillance of the residual tumor or assessment for recurrence is addressed by the neurosurgery and oncology teams (see other reviews in this issue). Endocrine follow-up and surveillance should be conducted at least annually in those with no pituitary abnormalities as these may evolve over time. During periods of active treatment, or for those with residual pituitary deficits follow-up should occur more frequently, usually every 3–6 months, to reassess hormone replacement status. When required, replacement with GH appears to be safe and has not been associated with an increased risk of tumor recurrence in children and adults with Cp (Clayton et al., 1988; Price et al., 1998; Karavitaki et al., 2006). However since there are potential concerns regarding GH mitogenic activity (Taguchi et al., 2010), ongoing surveillance is advised. For those patients with hypothalamic symptoms related to Cp management is more of a challenge. Obesity develops rapidly and early after treatment and appears to be resilient to traditional weight management methods. Visual deficits and increased fatigue add further obstacles for those attempting to increase physical activity. Cognitive and psychological challenges can further impact daily functioning at home and school. A multidisciplinary approach is essential to address these issues for the patient and their family.

In 2005, we established an interdisciplinary, comprehensive care clinic at the Hospital for Sick Children in Toronto (Rakhshani et al., 2010). The clinic provided family-centered treatment with medical, behavioral, dietary, and exercise support. Patients attended as frequently as once per month to routine visits every 6 months and at other times telephone or e-mail communication was available. Treatment was patient specific and included group sessions as well as individual therapy. In certain situations, pharmacologic agents or specific diets have been prescribed.

The rate of increase in percent BMI slowed in patients attending the clinic compared to their prior BMI change while in standard care. The majority of patients entering the clinic shortly after diagnosis exhibited stable weight as opposed to the early rapid weight gain seen in historical controls. There were also significant increases in the children's reported quality of life, physical functioning, and school functioning after 1 year in the program with a trend toward less time spent in sedentary activity. Parents reported improvement in coordination of health care and understanding of their child's disease. These results demonstrate the benefit of coordinated health care in improving the physical and psychological well-being of patients and their families.

As discussed earlier, additional therapies to target HO have been studied. Their mechanisms of action include increasing sympathetic tone (Mason et al., 2002; Ismail et al., 2006; Danielsson et al., 2007; Schultes et al., 2009), reducing insulin secretion, and improving sensitivity (Lustig et al., 1999, 2003a; Inge et al., 2007; Hamilton et al., 2011). Patients have experienced a decrease in weight gain or weight stabilization but without dramatic weight reduction. The effect of GH on weight gain has also been sought; however it was noted to have only a slight beneficial effect on BMI gain (Geffner et al., 2004). Similar to other populations with severe obesity, there is growing interest in bariatric surgery as a mode of therapy in HO. There is only sparse information about this treatment in Cp individuals with three case reports published on four patients (three adolescent, one adult) undergoing intestinal bypass surgery and one case series of four individuals (two adolescent, two young adult) receiving a laparoscopic adjustable gastric band (LAGB; Inge et al., 2007; Muller et al., 2007; Rottembourg et al., 2009; Schultes et al., 2009). Gastric bypass surgery induced significant and sustained weight loss, reduction in feelings of hunger and remarkable improvement in comorbidities (Inge et al., 2007; Rottembourg et al., 2009; Schultes et al., 2009). LAGB was reported to induce a continuous decrease in BMI in four patients with major improvements in eating behavior noted and improved ability to focus on non-food matters (Muller et al., 2007). In recent years three additional adolescents followed in our comprehensive care clinic underwent LAGB procedures with good results in terms of weight stabilization in one and weight reduction in two (unpublished data). One patient lost 51% of her excess body weight and was able to sustain a reduced weight with 2 years follow-up. A major caution, however, is that bariatric surgery of any kind is a relatively new treatment for adolescents and extensive pre-surgical assessment and close medical and psychological short and long term follow-up is needed to ensure that no untoward negative consequences arise. As such, these procedures should only be performed in experienced centers and with full support of an interdisciplinary team and careful assessment and follow-up of biomedical and psychosocial outcomes.

SURVIVAL AND LATE MORTALITY

Despite a relatively high rate of tumor regrowth, survival in children treated for Cp is generally good. However, disease related mortality can still occur many years after treatment. Data regarding survival includes primarily surgically treated patients. The reported post-surgical 5-year overall survival is 88–94% (De Vile et al., 1996; Muller et al., 2001, 2006a; Van Effenterre and Boch, 2002), and the reported 10-year overall survival is 70–92% (Hoffman et al., 1992; Van Effenterre and Boch, 2002; Poretti et al., 2004; Elliott and Wisoff, 2010; Visser et al., 2010) with a 20-year survival of 76%. Survival rates of patients treated with combined surgery and radiation are comparable (Stripp et al., 2004; Merchant et al., 2006; Lin et al., 2008; Crom et al., 2010). Causes of late mortality include causes directly related to the tumor or treatment such as progressive disease with multiple recurrences, hormonal deficiencies, chronic hypothalamic insufficiency, cerebrovascular disease,

and seizure related (De Vile et al., 1996; Poretti et al., 2004; Elliott and Wisoff, 2010; Visser et al., 2010; Steno et al., 2011). Other causes have been described including head trauma, drug abuse, or liver failure (Poretti et al., 2004; Caldarelli et al., 2005; Visser et al., 2010).

In a study that compared the primary treatment modality used in a group of survivors to that used in patients who died, no particular pattern emerged. This might be related the small numbers of patients in each survival–treatment group (Visser et al., 2010), however, this finding is further supported by similar 5 year survival rates in patients who did or did not receive radiotherapy (Muller et al., 2006a). Based on other reports, risk factors for decreased survival were recurrent resections of tumor regrowth (Elliott and Wisoff, 2010), and tumor location, with improved survival for tumors that grow beneath the sellar diaphragm (Steno et al., 2011).

CONCLUSION

Although treatment for pediatric Cp tumors remains challenging, changes in management show potential for improved long term outcomes. Common long term complications include endocrine, neurologic, psychosocial, and neurocognitive and metabolic morbidities. However, the most significant adverse effect on quality of life are those related to hypothalamic dysfunction and in particular, post-surgical weight gain and increased fatigue with daytime somnolence. In recent years there is a trend toward individualizing treatment based on patient and tumor characteristics as well as managing Cp more as a chronic disease with less aggressive surgical treatment and/or adjuvant radiation or chemotherapy. A coordinated interdisciplinary approach to management, beginning at the time of diagnosis, is very important to identify risk factors for adverse outcomes, and provide support and education for these patients and their families.

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Craniopharyngioma in adults

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Craniopharyngiomas are slow growing benign tumors of the sellar and parasellar region with an overall incidence rate of approximately 1.3 per million. During adulthood there is a peak incidence between 40 and 44 years. There are two histopathological types, the adamantinomatous and the papillary type. The later type occurs almost exclusively in adult patients. The presenting symptoms develop over years and display a wide spectrum comprising visual, endocrine, hypothalamic, neurological, and neuropsychological manifestations. Currently, the main treatment option consists in surgical excision followed by radiation therapy in case of residual tumor. Whether gross total or partial resection should be preferred has to be balanced on an individual basis considering the extent of the tumor (e.g., hypothalamic invasion). Although the overall long-term survival is good it is often associated with substantial morbidity. Preexisting disorders are often permanent or even exacerbated by treatment. Endocrine disturbances need careful replacement and metabolic sequelae should be effectively treated. Regular follow-up by a multidisciplinary team is a prerequisite for optimal outcome of these patients.

Keywords: craniopharyngioma, adults, treatment, diagnosis, complications

INTRODUCTION

Craniopharyngiomas are rare benign tumors derived from cell remnants of Rathke's pouch along a line from the nasopharynx to the diencephalon. The majority of these epithelial tumors occur in the sellar, para-, and suprasellar region (Jane and Laws, 2006; Karavitaki et al., 2006; Garnett et al., 2007). In the United States, craniopharyngiomas constitute approximately 2.5–3% of brain tumors with an incidence rate (IR) of 1.1–1.3 per million (Bunin et al., 1998; Jane and Laws, 2006; Karavitaki et al., 2006). In other parts of the world, like Japan or certain parts of Africa, IR seem to be higher (Stiller and Nectoux, 1994). A recent analysis calculated a worldwide overall IR of 1.34 in all ages (Nielsen et al., 2011). About half of the cases occur in adults with a peak IR between 40 and 44 years according to data from a Danish study (Nielsen et al., 2011). The male to female ratio is 1.1–1.4:1 (Nielsen et al., 2011). Although craniopharyngiomas are regarded as benign tumors they often infiltrate adjacent structures like the pituitary, hypothalamus, optic nerves, blood vessels, or the third ventricle thereby causing significant morbidity and mortality. As a consequence patients present with a wide range of symptoms which are often permanent or might even be exacerbated by therapy. Because of their infiltrative growth behavior and their high tendency for recurrence, the treatment is often challenging. In the present article we present an overview on craniopharyngiomas with special emphasis on patients with adult-onset of the disease.

PATHOLOGY AND PATHOGENESIS

Craniopharyngiomas are divided in two main histological subtypes, the adamantinomatous and the papillary type, but transitional and mixed variants have also been reported (Weiner et al., 1994; Crotty et al., 1995; Louis et al., 2007). The adamantinomatous type may develop at all ages, whereas the papillary type almost exclusively occurs in adults comprising about 14–50% of the tumors in this age group (Adamson et al., 1990; Weiner et al., 1994; Karavitaki et al., 2006). The papillary type rarely presents with calcifications, is generally well-circumscribed and compared to the adamantinomatous type tumor infiltration of surrounding tissue is less frequent (Weiner et al., 1994; Crotty et al., 1995). Macroscopically craniopharyngiomas are predominantly cystic or mixed lesions although solid lesion might also occur. The tumor size varies from small, solid, and well-circumscribed tumors to large multilocular cysts invading the sella turcica and displacing adjacent cerebral structures (Crotty et al., 1995; Karavitaki et al., 2005). Most tumors are located in the sellar/parasellar region with suprasellar tumor mass extension. A smaller number of tumors are confined to the sella, or arise in the third ventricle or within the optic system (Van Effenterre and Boch, 2002).

The molecular pathogenesis of craniopharyngiomas remains widely unknown. In patients harboring the adamantinomatous variant mutations in the beta-catenin gene CTNNB1 resulting in degradation-resistant mutant forms of beta-catenin have been identified (Sekine et al., 2002; Kato et al., 2004; Buslei et al., 2005; Campanini et al., 2010). Studies in rodents showed that permanent activation of the Wnt signaling pathway, which leads to high expression levels of beta-catenin, causes formation of pituitary tumors that resemble the human adamantinomatous craniopharyngioma. Thus, reactivation of the Wnt signaling pathway may be one factor in the pathogenesis of craniopharyngiomas of the adamantinomatous type (Gaston-Massuet et al., 2011). The formation of cysts and their size appears to be associated with the expression of carbonic anhydrase IX, an enzyme causing fluid production. The specific tumor-associated regulating mechanisms, however, of this enzyme have not been clarified yet (Proescholdt et al., 2011).

CLINICAL MANIFESTATION

The clinical manifestations are multiple and depend on the location of the tumor, its size, growth pattern, and relationship to adjacent cerebral structures (**Table 1**). As craniopharyngiomas are in general slowly growing, symptoms may develop gradually – a circumstance which may contribute to the reported delay of 1–2 years between symptom onset and diagnosis (Garnett et al., 2007). In adults the most common presenting clinical symptoms are visual field deficits and signs of hypopituitarism (Hoff and Patterson, 1972). In about 40–80% of the patients suprasellar tumor extension pressurizes the optic chiasm causing loss of visual acuity and visual field abnormalities (mostly asymmetric bitemporal hemianopsia; Crotty et al., 1995; Karavitaki et al., 2005, 2006). In a series of 78 adult patients 57% of the female patients reported about menstrual irregularities or amenorrhea and 28% complained about impaired sexual function (Karavitaki et al., 2005). Other symptoms like nausea and vomiting (26%), poor energy (32%), and lethargy (26%) are also frequent in the adult patient (Karavitaki et al., 2005). These symptoms are indicative for anterior pituitary dysfunction. Overall, growth hormone (GH) deficiency is most common, followed by gonadotropin, adrenocorticotropic hormone (ACTH), and thyroid stimulating hormone (TSH) deficiency, which are present in 86, 74, 58, and 42% of adult cases, respectively (Karavitaki et al., 2005). Compression of the pituitary stalk causes diabetes insipidus (DI) with polyuria and polydipsia in 17–38.5% of cases (Karavitaki et al., 2005; Mortini et al., 2011). Hypothalamic involvement may cause significant weight gain, which is a presenting symptom in 13–15.4% of adult patients (Karavitaki et al., 2005; Mortini et al., 2011). Severe headaches are also frequent (56%) and may be caused by raised intracranial pressure due to the tumor mass itself, to obstructive hydrocephalus resulting from compression of the third ventricle or due to leaked out cyst content which could lead to meningeal irritation (Karavitaki et al., 2006). Parasellar tumor extension with infiltration of the cavernous sinus could result in cranial nerve palsies with diplopia and paresis of ocular muscles. Involvement of the temporal lobe might trigger seizures and especially in the elderly, large tumors may cause deteriorating cognitive abilities and personality changes (Karavitaki et al., 2006).

Table 1 | Presenting symptoms and clinical manifestations of adults with craniopharyngioma.

Cause	Symptom	Percentage
Compression of the pituitary stalk or the pituitary gland	GH deficiency	86% (Karavitaki et al., 2005)
	FSH/LH deficiency	74% (Karavitaki et al., 2005) to 75.6% (Mortini et al., 2011)
	ACTH deficiency	51.3% (Mortini et al., 2011) to 58% (Karavitaki et al., 2005)
	TSH deficiency	42% (Karavitaki et al., 2005) to 48.7% (Mortini et al., 2011)
	Hyperprolactinemia	30.8% (Mortini et al., 2011) to 55% (Karavitaki et al., 2005)
	Galactorrhoea	8% (Karavitaki et al., 2005)
	Menstrual disorders	57% (Karavitaki et al., 2005)
	Reduction or loss of sexual drive	28% (Karavitaki et al., 2005) to 42% (Crotty et al., 1995)
	Cold intolerance	8% (Karavitaki et al., 2005)
Pressure on the optic nerves	Visual field defects	60% (Karavitaki et al., 2005), 80.8% (Mortini et al., 2011), 84% (Crotty et al., 1995)
	Decreased visual acuity	40% (Karavitaki et al., 2005)
	Optic atrophy	14% (Karavitaki et al., 2005)
	Blindness	3% (Karavitaki et al., 2005)
Hypothalamic involvement	Weight gain/hyperphagia	13% (Karavitaki et al., 2005) to 15.4% (Mortini et al., 2011)
	Diabetes insipidus	17% (Karavitaki et al., 2005) to 38.5% (Mortini et al., 2011)
	Polyuria/polydipsia	15% (Karavitaki et al., 2005) to 27% (Crotty et al., 1995)
Other causes	Personality changes	8% (Karavitaki et al., 2005)
	Headache	56% (Karavitaki et al., 2005) to 68% (Crotty et al., 1995)
	Somnolence	10% (Karavitaki et al., 2005)
	Nausea and vomiting	26% (Karavitaki et al., 2005)
	Loss of energy	32% (Karavitaki et al., 2005) to 48% (Crotty et al., 1995)
	Lethargy	26% (Karavitaki et al., 2005)
	Other cranial nerves palsies	9% (Karavitaki et al., 2005)
	Papilledema	6% (Karavitaki et al., 2005)
	Cognitive impairment	17% (Karavitaki et al., 2005) to 22% (Crotty et al., 1995)
	Anorexia/weight loss	8% (Karavitaki et al., 2005)
	Decreased consciousness/coma	4% (Karavitaki et al., 2005)
	Unsteadiness/ataxia	3% (Karavitaki et al., 2005)
	Hemiparesis	1% (Karavitaki et al., 2005)
	Meningitis	3% (Karavitaki et al., 2005)

DIAGNOSIS

The suspicion of a craniopharyngioma is based on clinical and radiological findings. The diagnosis is finally proven by histology. A proposal for the initial diagnostic work-up in patients suspicious for craniopharyngioma is given in **Table 2**.

Most adult patients present with visual field deficits and signs of hypopituitarism (Hoff and Patterson, 1972). Visual field and visual acuity assessment is therefore important to determine any deficit and to establish baseline values. In addition, an examination of the optic disks is required to rule out papilledema and visual evoked potentials are recommended. An endocrine evaluation should include the assessment of anterior and posterior pituitary functions. Signs and symptoms indicative for hypopituitarism including DI should be asked for. Basal ACTH and cortisol, TSH and free T4, LH and testosterone in men and FSH and estradiol in women, IGF-1 and prolactin as well as serum electrolytes, serum, and urine osmolality are determined. Further endocrine testings should be performed according to the results and the individual clinical situation.

Cranial computer tomography (CT) and/or magnetic resonance imaging (MRI) with and without contrast enhancement are part of the neuroradiological evaluation of craniopharyngiomas. Calcifications and bony structures are best evaluated on CT, while the delineation of tumor size and the involvement of neighboring structures can be assessed most accurately by MRI. The MRI scan is therefore the method of choice in order to prepare a surgical approach (Garnett et al., 2007). According to a recent study, there are no significant differences in neuroradiological characteristics of craniopharyngiomas between children and adults with the exception of lower rates of tumor calcification in adult patients (Mortini et al., 2011). In some studies hydrocephalus occurred less frequently in adults than in children, however other authors reported no differences in this regard (Van Effenterre and Boch, 2002; Karavitaki et al., 2005). Although several attempts have been made, no reliable discrimination between the two histological subtypes is possible based on neuroradiological criteria (Crotty et al., 1995; Eldevik et al., 1996; Sartoretti-Schefer et al., 1997). In some cases the presence of a craniopharyngioma is suggested by an incidental finding of a mass lesion on neuroimaging scans. The differential diagnosis comprises other sellar and parasellar tumors like Rathke's cleft cysts and other non-malignant cysts, pituitary adenomas, optic and hypothalamic gliomas, meningiomas, teratomas, germinomas, lymphomas, metastases, and infiltrative diseases, like sarcoidosis or systemic histiocytosis (Garnett et al., 2007).

Table 2 | Diagnostic work-up of patients with craniopharyngioma.

Anamnesis	Visual field deficits, loss of visual acuity?
	Loss of libido, amenorrhea?
	Polyuria, polydipsia?
	Headaches?
	Nausea, vomiting?
	Weight gain?
	Fatigue, tiredness
	Sleep disorders?
	Concentration deficits?
	Cold intolerance?
Neuroimaging	MRI
	CT
Laboratory tests	IGF-1, prolactin, ACTH, cortisol, TSH, fT4, LH, FSH, testosterone (♂)/estradiol (♀) serum electrolytes, serum-osmolality, urine osmolality
Ophthalmological evaluation	Visual acuity testing
	Visual field perimetry
	Optic disks evaluation (visual evoked potentials)

TREATMENT

Prospective and controlled studies comparing different treatment strategies in adult patients are missing. Most data come from retrospective analyses of mixed populations of patients with childhood- and adult-onset disease. There are no evidence-based guidelines or a clear consensus for best treatment of primary or recurrent craniopharyngiomas in adults. Like in children a radical approach with complete tumor resection and potential cure has to be balanced with a more conservative approach to avoid substantial treatment-associated long-term morbidity. Therefore, optimal treatment should always be individualized taking into account, e.g., the patient's symptoms, age, tumor localization, and extension. Endocrine and metabolic complications should be treated prior to any tumor-directed therapy such as surgery. This is especially important in case of adrenal or thyroidal insufficiency, as well as DI. It is generally agreed that a multidisciplinary team comprising endocrinologists, neurosurgeons, radiotherapists, and ophthalmologists is essential for optimized treatment of patients of any age (Garnett et al., 2007; Garre and Cama, 2007; Honegger and Tatagiba, 2008).

SURGERY

Surgery is the first-line approach to the treatment of craniopharyngiomas. Complete surgical resection is the goal of initial therapy and because of major advances in neurosurgical techniques, it is increasingly feasible. However, due to their size, their often irregular margins and intense peritumoral gliosis with adherence to vital neighboring neurovascular structures this is often difficult and potentially dangerous. According to the literature complete tumor removal by radical surgery can be achieved in 18–84% of selected childhood and adult cases (Weiner et al., 1994; Fahlbusch et al., 1999; Van Effenterre and Boch, 2002; Karavitaki et al., 2005, 2006). Aggressive surgery with gross total resection (GTR) of the tumor, however, may result in significant and devastating peri- and postoperative morbidity especially after resection of tumors invading the hypothalamus (Rutka, 2002). If complete tumor removal is unlikely to be achieved or too hazardous, subtotal, or partial resection (PR) of the tumor, e.g., to reduce pressure effects on adjacent structures like the optic pathways and/or to re-establish circulation of the cerebrospinal fluid with or without subsequent radiotherapy is an alternative approach (Habrand et al., 1999; Cama et al., 2006). In any case the benefits of surgery must be balanced against the risks of treatment-related morbidity. For pediatric patients a preoperative grading system has been proposed

according to the degree of hypothalamic involvement (Puget et al., 2007). Using this classification a significant relationship between the preoperative tumor grade and post-surgical morbidity could be demonstrated. GTR should only be attempted in patients without hypothalamic involvement (grade 0) or with a distorted or elevated but still visible hypothalamus (grade 1). In grade 2 craniopharyngiomas (hypothalamic structures not discernible) a subtotal resection leaving the hypothalamic part is recommended (Puget et al., 2007). Similar studies in adults are lacking. Nevertheless it appears reasonable to follow these recommendations established in pediatric patients. For craniopharyngiomas with major cystic portions stereotactic cyst decompression is another treatment option. This can be used for acute symptomatic therapy, prior to definite craniopharyngioma resection, or may be recommended as intermittent therapy whenever a total cyst excision is not possible (Fahlbusch et al., 1999; Honegger and Tatagiba, 2008).

RADIOTHERAPY

Radiotherapy (RT) is a therapeutic option in patients for whom surgery is contraindicated, with residual tumor tissue after subtotal or partial surgical resection, as well as in patients with recurrent disease. Advances in RT techniques allow higher treatment precision with less long-term toxicity by focusing the ionizing radiation on the tumor and limiting the exposure of adjacent tissues to a minimum. Techniques used for the treatment of craniopharyngiomas include stereotactic fractionated radiotherapy, radiosurgery, intensity modulated radiation therapy, and proton beam therapy (Fitzek et al., 2006; Minniti et al., 2009; Niranjan et al., 2010). For fractionated conformal RT schedules the probability of local tumor control is best with radiation doses above 54–55 Gy (Regine et al., 1993) but less than 61 Gy to lower the risk of radiation-associated side-effects such as visual impairment, pituitary deficiency, impaired cognitive function or development of secondary malignancies (Cavazzuti et al., 1983; Merchant et al., 2006). Application of radiosurgery with delivery of a single high-dose radiation to the tumor is an attractive technique but restricted to smaller tumor volumes and requires sufficient safety margins of adjacent critical structures. Although reports published so far are promising (Minniti et al., 2009; Iwata et al., 2012), further studies are needed to define its role in the prevention of tumor recurrence and its potential long-term adverse effects. Intracavitary irradiation with stereotactically guided instillation of radioisotopes is another approach to treat mono- or multicystic tumors (Voges et al., 1997; Barriger et al., 2011).

OTHER TREATMENTS

Other treatment options for predominantly cystic craniopharyngiomas comprise intracystic chemotherapy or immunological therapy with bleomycin or interferon alpha, respectively (Steinbok and Hukin, 2010). The experience regarding these treatments is mainly restricted to pediatric patients. In general, these options were used for temporary tumor control with the expectation for further therapies like surgery or radiotherapy. Systemic chemotherapy is generally regarded as ineffective (Karavitaki et al., 2006).

RECURRENT DISEASE

Recurrence of craniopharyngiomas remains a problem which highly impacts on the long-term prognosis of the patients. In a recent study with 106 patients including 78 adults, 24.5% experienced a relapse within a median follow-up of 83 months (Mortini et al., 2011). The risk of recurrence appears highest in the first 3 years after surgery and then tends to reach a plateau (Fahlbusch et al., 1999; Karavitaki et al., 2005). After GTR the risk of tumor recurrence has been reported to range between 0 and 26% (Maira et al., 1995; Fahlbusch et al., 1999; Duff et al., 2000). This is significantly lower than in patients with subtotal or partial tumor resection in whom tumor recurrence occurs in 25–100% of the patients (Fahlbusch et al., 1999; Duff et al., 2000; Karavitaki et al., 2005). In these patients adjuvant RT significantly improves the tumor control rates with recurrence rates ranging from 10 to 63% at 10-years follow-up (Karavitaki et al., 2006). Thus, patients with subtotal resection without subsequent RT have the highest risk of relapse (Duff et al., 2000; Karavitaki et al., 2005). In patients treated with RT alone tumor growth or recurrence was observed in 0–23% of the patients at 10 years follow-up (Hetelekidis et al., 1993; Rajan et al., 1993). The data about the prognostic significance of age at diagnosis, gender, tumor size, location, or consistency, as well as the histological subtype are inconsistent (Karavitaki et al., 2005, 2006; Mortini et al., 2011), but in general these factors do not seem to affect the risk of recurrence (Karavitaki et al., 2006).

TREATMENT OF RECURRENT DISEASE

Recurrent disease is difficult to treat. Because of scars and adhesions due to previous surgery or radiation, the surgical success rates for recurrent disease are significantly lower than for primary surgery and peri- and postoperative morbidity and mortality is significantly increased (Yasargil et al., 1990; Wisoff, 1994; Fahlbusch et al., 1999; Karavitaki et al., 2005). Therefore, the severity of clinical symptoms has to be taken into account and it has been suggested that repeated surgery should only be performed when acute pressure effects occur (Karavitaki et al., 2006). In patients not previously treated with RT irradiation is another option either instead of or following a second surgery, and it appears that RT is equally effective in the control of recurrent tumors as for primary treatment (Jose et al., 1992). Further options comprise cyst controlling procedures like aspiration, intracystic irradiation or application of bleomycin, salvage surgery in case of life-threatening solid lesions, or radiosurgery. In any case treatment decisions for recurrent disease should be made on an individualized basis.

DISEASE AND TREATMENT COMPLICATIONS

ENDOCRINE

Anterior pituitary dysfunction and DI are common in adult patients with craniopharyngiomas and the majority of adult craniopharyngioma patients present with signs and symptoms of hypopituitarism (Paja et al., 1995; Honegger et al., 1999; Karavitaki et al., 2005). Neuroendocrine dysfunction may worsen upon treatment. In a recent study by Mortini et al. (2011) 82.3, 75.9, 72.7, and 66.7% of patients with normal baseline values for GH, ACTH, TSH, and gonadotropins developed a new deficiency of the respective pituitary axis after surgery. Post-surgical onset of DI was observed in 69.6% of their patients. The risk for new

hormone deficiencies appears to be lower after transsphenoidal operation (Honegger et al., 1999; Mortini et al., 2011). In contrast to pituitary adenomas, recovery of preexisting pituitary dysfunction after surgery is rare (Webb et al., 1999; Mortini et al., 2011). Although symptomatic DI appears to occur more frequent in surgically treated patients (Hetelekidis et al., 1993; Karavitaki et al., 2006), long-term endocrine morbidity in general seems not to be affected by the type of therapy (Weiner et al., 1994; Habrand et al., 1999; Karavitaki et al., 2005). Most of the patients chronically suffer from partial or complete hypopituitarism as well as DI, with approximately 80% requiring the substitution of more than two hormones (Kendall-Taylor et al., 2005; Verhelst et al., 2005). Concerning GH substitution, observational studies suggest that GH replacement does not increase the risk of tumor recurrence (Abs et al., 1999). Because of the often complex endocrine morbidity lifelong surveillance by an endocrinologist is required.

VISUAL

In adults impaired visual function is common at first presentation (Crotty et al., 1995; Karavitaki et al., 2005, 2006). After surgical decompression visual deficits often improve, but may also remain unchanged or even become worse (Fahlbusch et al., 1999; Van Effenterre and Boch, 2002; Mortini et al., 2011). In a series of 173 patients treated with RT only or after limited surgery, improvement in visual field defects or in visual acuity was observed in 36 and 30%, respectively after a median follow-up of 12 years (Rajan et al., 1993). In about one-third of the patients pretreatment visual deficits deteriorated (Rajan et al., 1993). No radiation optic neuropathy developed by applying accurate RT techniques and doses below the tolerance limit of the optic system (Harris and Levene, 1976; Rajan et al., 1993). Karavitaki et al. (2005) reported in their series of patients with long-term follow-up about major visual field defects in 49 and 72% of the patients after 10 and 20 years, respectively. This reflects treatment-associated deterioration of visual function on the one hand and on the other hand the natural course of the disease with a high risk for recurrence. Risk factors for adverse visual outcome are the presence of visual symptoms at diagnosis, irradiation dose above 2 Gy per day, and a PR of the tumor, probably because of the increased risk of recurrence (Harris and Levene, 1976; Karavitaki et al., 2005, 2006). Long-term follow-up by an ophthalmologist is recommended.

HYPOTHALAMIC AND METABOLIC

Tumor- or treatment-related damage of the ventromedial hypothalamus may lead to the impairment of mechanisms controlling satiety, hunger, and energy expenditure resulting in severe obesity (Daousi et al., 2005). Hypothalamic obesity is the most common manifestation of hypothalamic complications. At presentation about 15% of adult patients complain about excessive weight gain or are obese (Karavitaki et al., 2005; Mortini et al., 2011). During long-time follow-up excessive weight gain has been reported in up to 67% of patients after surgery with and without adjuvant RT (Hoffman et al., 1992; Karavitaki et al., 2005). Hypothalamic obesity is often associated with disastrous metabolic and psychological consequences leading to severe morbidity, impaired quality of life, and reduced life expectancy (Karavitaki et al., 2006). Features of the metabolic syndrome like abdominal obesity, dyslipidemia, hyperinsulinemia caused by insulin resistance, and elevated blood pressure are commonly seen in patients with craniopharyngiomas (Kendall-Taylor et al., 2005; Pereira et al., 2005; Holmer et al., 2009). In a retrospective analysis from the KIMS database patients with adult-onset disease were more obese, had a greater waist circumference, and had higher cholesterol and triglycerides levels with similar HDL- and LDL-cholesterol when compared to patients with childhood disease onset (Kendall-Taylor et al., 2005). Together, these metabolic alterations increase the risk of hypertension, diabetes, and atherosclerosis, which all lead to cardiovascular disease and mortality from vascular events (Van Gaal et al., 2006). Thus, the necessity for treatment is vital but treatment of hypothalamic obesity is difficult and patients need to comply with dietary and behavioral modifications comprising regular physical activities, require anti obesity drugs, or even bariatric surgery (Karavitaki et al., 2006). DI with an absent sense of thirst is another hypothalamic complication resulting in serious water and electrolyte imbalances, which was observed in 19% of adult patients after surgery with and without adjuvant RT (Smith et al., 2004). Sleep disorders and increased daytime somnolence caused by disruption of the circadian rhythm occur in up to one-third of adult craniopharyngioma patients (van der Klaauw et al., 2008). Impaired thermoregulation with hyper- or hypothermia has also been observed in adults (Lipton et al., 1981; Griffiths et al., 1988). Risk factors for hypothalamic complications are preexisting disorders at diagnosis, young age at presentation of symptoms, hypothalamic invasion, tumor size, multiple operations due to recurrence, and hypothalamic radiation with doses above 51 Gy (de Vile et al., 1996; Lustig et al., 2003; Poretti et al., 2004).

NEUROPSYCHOLOGICAL AND COGNITIVE DYSFUNCTION

Behavioral problems and deteriorated cognitive functions are relatively common, which contribute to decreased academic and occupational performance, difficulties in maintaining family, and social relationships, resulting in a loss in quality of life (Cavazzuti et al., 1983; Karavitaki et al., 2006).

OTHERS

In patients who received RT vascular damage like aneurysms and secondary brain tumors may occur (Enchev et al., 2009; Liu et al., 2009).

LONG-TERM PROGNOSIS AND MORTALITY

Control of tumor growth and the disease- or treatment-related complications determine the long-term prognosis. Overall survival rates reported range from 89 to 94% at 5-years and from 85 to 90% at 10-years follow-up (Van Effenterre and Boch, 2002; Karavitaki et al., 2005). Nevertheless, overall mortality appears three to five times higher than those of the general population (Sherlock et al., 2010). Currently, it is unclear which therapeutic strategy (e.g., GTR or subtotal or PR followed by radiotherapy) is associated with a better survival (Karavitaki et al., 2005; Sherlock et al., 2010) and whether the histological subtype is of relevance (Weiner et al., 1994). Recurrent disease, however, is significantly associated with increased morbidity and mortality, resulting in lower 10-year survival rates (29–70%; Karavitaki et al., 2005; Honegger and

Tatagiba, 2008). Apart from mortality caused by the tumor itself or by surgical treatment, mortality from cardio- and cerebrovascular as well as respiratory causes is increased (Bulow et al., 1998; Tomlinson et al., 2001). It is therefore essential to optimize the treatment of any endocrine and metabolic sequelae of the disease in order to reduce mortality in this high risk patient population.

CONCLUSION

Although craniopharyngiomas are generally benign their location, size, and tendency to infiltrate adjacent cerebral structures makes their management rather demanding and may lead to sometimes devastating complications. According to the data available adult- and childhood-onset craniopharyngiomas behave similar in many aspects. Treatment decisions for primary or recurrent disease need to consider long-term tumor control as well as disease and treatment-related morbidity and they are often reached on an individualized basis. Surgery is the initial treatment approach, which should remove as much tumor as safely possible, while avoiding severe treatment-induced complications. There is some controversy as to whether a more radical surgical approach with gross total tumor resection should be aimed at or a more limited approach with reducing the tumor mass followed by radiotherapy in order to minimize long-term morbidity. As some patients with subtotal or partial tumor resection may have stable disease and since RT may cause long-term complications it is currently unclear, whether all patients with residual tumor should receive immediate postoperative RT. Likewise it is unknown which therapeutic strategy is best in patients with tumor recurrence despite RT. Posttreatment follow-up should include neuroimaging with MRI, visual assessment, and monitoring of endocrine functions and metabolic status. Endocrine and metabolic alterations need to be treated adequately. There is no doubt that for optimal results a lifelong surveillance of an experienced multidisciplinary team is essential.

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Hypothalamic obesity after craniopharyngioma: mechanisms, diagnosis, and treatment

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Obesity is a common complication after craniopharyngioma therapy, occurring in up to 75% of survivors. Its weight gain is unlike that of normal obesity, in that it occurs even with caloric restriction, and attempts at lifestyle modification are useless to prevent or treat the obesity. The pathogenesis of this condition involves the inability to transduce afferent hormonal signals of adiposity, in effect mimicking a state of CNS starvation. Efferent sympathetic activity drops, resulting in malaise and reduced energy expenditure, and vagal activity increases, resulting in increased insulin secretion and adipogenesis. Lifestyle intervention is essentially useless in this syndrome, termed "hypothalamic obesity." Pharmacologic treatment is also difficult, consisting of adrenergics to mimic sympathetic activity, or suppression of insulin secretion with octreotide, or both. Recently, bariatric surgery (Roux-en-Y gastric bypass, laparoscopic gastric banding, truncal vagotomy) have also been attempted with variable results. Early and intensive management is required to mitigate the obesity and its negative consequences.

Keywords: craniopharyngioma, hypothalamic obesity, leptin resistance, insulin, octreotide, vagus nerve, symapthetic nervous system, ghrelin

INTRODUCTION

When it comes to brain tumors, the three laws of New York real estate prevail: "Location, location, location." Craniopharyngiomas are problematic less for *what* they are than for *where* they are. The hypothalamus, as is true for most hormonal systems, is the anatomic seat of peripheral energy regulation. When the hypothalamus is damaged, a syndrome of intractable weight gain ensues. This syndrome, termed "hypothalamic obesity," originally described by Babinski (1900) and Frohlich (1901) at the turn of the twentieth century, documents the "organicity" of obesity. Hypothalamic obesity can occur due to the tumor itself, the surgery to extirpate it, or due to subsequent radiation therapy (Bray, 1984; Lustig, 2002). Although this co-morbidity usually manifests in children due to their increased incidence of tumors localized to the posterior fossa (Stahnke et al., 1984; Sorva, 1988; Pinto et al., 2000), adults can also exhibit similar weight gain after completion of therapy (Daousi et al., 2005). Craniopharyngioma accounts for half of the reported cases, with other posterior fossa tumors each contributing smaller numbers. However, the syndrome has also been reported in cases of pseudotumor cerebri, trauma, and infiltrative or inflammatory diseases of the hypothalamus (Bray, 1984).

INCIDENCE AND RISK FACTORS

Hypothalamic obesity can occur in response to any hypothalamic damage. Most studies have been performed in the acute lymphoblastic leukemia (ALL) survivor population (Lustig, 2002; Rogers et al., 2005), in which obesity may be due to several factors, including glucocorticoids and alterations in activity. Nonetheless, the majority of these studies document an abnormal increase in weight for height long after tumor therapy has been discontinued, and many of these studies demonstrate that cranial radiation is an important risk factor (Lustig, 2002).

An extremely high frequency of hypothalamic obesity of 30–77% has been documented after craniopharyngioma treatment (Stahnke et al., 1984; Sorva, 1988; Pinto et al., 2000; Muller, 2008; Vinchon et al., 2009). We analyzed the BMI curves of 148 children with brain tumors who survived longer than 5 years post-therapy, in order to determine risk factors for the development of obesity (Lustig et al., 2003a). We identified four parameters as being predictive. First, those with tumors localized to the hypothalamus or thalamus, along with those originating in the temporal lobe (due to stereoscopic position of the hypothalamus during radiation for this area) gained weight much more rapidly as did those with tumors in the posterior fossa or other hemispheric areas. Secondly, those with tumor histologies prominent in the diencephalon (craniopharyngioma, germinoma, optic glioma, prolactinoma, hypothalamic astrocytoma) also gained weight more rapidly. Third, those with quantitative direct radiation exposure of the hypothalamus of greater than 51 Gy gained excessive weight twice as rapidly after the completion of tumor therapy, even when those with hypothalamic or thalamic locations were removed from the analysis. Lastly, those with some other form of hypothalamic endocrinopathy (i.e., GH deficiency, hypothyroidism, precocious or delayed puberty, ACTH deficiency, diabetes insipidus) exhibited a BMI curve with a steeper upward slope. Thus, each significant risk factor was either linked to hypothalamic location, damage, or dysfunction. Factors not associated with obesity after tumor therapy included hydrocephalus, initial high-dose glucocorticoids, and peripheral or intrathecal chemotherapy.

More recently, Müller et al. (2011) respectively evaluated the long-term outcome data on the Kraniopharyngeom database in

Germany. In this analysis, pre-operative hypothalamic involvement was specifically implicated in the development of post-operative hypothalamic obesity, suggesting again that tumor location is the most important risk factor for obesity.

THE ENERGY BALANCE NEGATIVE FEEDBACK PATHWAY

Animal studies elaborating the negative feedback energy balance pathway have predicted the pathogenesis and symptomatology of hypothalamic obesity. This can best be described as "organic leptin resistance"; that is, a failure in leptin signaling in the afferent arm, due to hypothalamic damage; leading to autonomic dysfunction in the efferent arm, promoting inadequate energy expenditure, and excessive energy storage.

THE AFFERENT ARM

Circulating leptin (derived from peripheral adipocytes) crosses the blood–brain barrier, and synapses on receptors located on neurons within the ventromedial hypothalamus [VMH; which consists of the ventromedial nucleus (VMN) and arcuate nucleus (AN)]. In the energy replete state, both insulin and leptin levels are increased, which acts on a set of "anorexigenic" neurons to increase the synthesis and processing of proopiomelanocortin (POMC) in the VMH to its component peptides, including α-melanocyte stimulating hormone (α-MSH) and its co-localized neuromodulator cocaine–amphetamine regulated transcript (CART), both of which act at the lateral hypothalamic area (LHA) and paraventricular nucleus (PVN) to alter melanocortin receptor-4 (MC_4R) occupancy, which decreases appetite and food intake (Elmquist et al., 1999; Kalra et al., 1999; Schwartz et al., 2000; Balthasar et al., 2005). The stomach hormone ghrelin stimulates, while insulin and leptin inhibit a set of "orexigenic" neurons to inhibit the release of neuropeptide Y (NPY) and agouti-related protein (AgRP), further limiting feeding and providing for unantagonized MC_4R occupancy (Elmquist et al., 1998). Immediately after a meal, ghrelin levels are low, which prevents orexigenic neuronal activation and NPY neurotransmission (Kamegai et al., 2000), keeping hunger at a minimum; furthermore, PYY levels increase after a meal; this hormone binds to the Y_2 receptor on orexigenic neurons, activating gamma-amino butyric acid (GABA), which inhibits signal transduction of NPY to inhibit further food intake (Small and Bloom, 2004).

Conversely, in the fasting state, gastric secretion of ghrelin is increased (Kamegai et al., 2000; Tschöp et al., 2000), while leptin, insulin, and PYY levels are low, which leads to stimulation of the orexigenic pathway (NPY/AgRP), and antagonism of the anorexigenic pathway (α-MSH/CART). The resultant lack of anorexigenic pressure on the MC_4R results in increased feeding behavior and energy efficiency (with reduced fat oxidation), in order to store energy substrate as fat. This is accomplished through signal transduction within the efferent pathway, consisting of the sympathetic nervous system (SNS) and the vagus (see below).

THE EFFERENT ARM

From the PVN and LHA, efferent projections synapse in the locus coeruleus (LC), which controls the SNS; and in the dorsal motor nucleus of the vagus (DMV), which controls the vagus nerve, the chief output of the parasympathetic nervous system.

In the energy replete state, elevated leptin and insulin levels cause the anorexigenic arm to activate the SNS (Muntzel et al., 1994; Vollenweider et al., 1995; Rahmouni et al., 2003). Stimulation of β_2-adrenergic receptors by the SNS (Blaak et al., 1993) increase the expression of numerous genes in skeletal muscle (Viguerie et al., 2004), which promote mitochondrial biogenesis, glycogenolysis, thermogenesis, and increased movement (Boss et al., 1999; Lowell and Spiegelman, 2000), all associated with increased energy expenditure (Collins et al., 1996). The SNS also activates α_{2a}- and α_{2c}-adrenoreceptors on the β-cell, which stimulate G_i and inhibit adenyl cyclase, lower cAMP, and maintain potassium channels in an open configuration with a negative resting membrane potential (Sharp, 1996), in order to reduce pancreatic insulin secretion, and thus reduce energy deposition into adipose tissue. Lastly, SNS activation stimulates the β_3-adrenergic receptor on the adipocyte to promote lipolysis (Susulic et al., 1995). These coordinate sympathetic events serve to reduce adipose tissue leptin expression and secretion; thus this forms a negative feedback loop with the afferent system (**Figure 1**).

Conversely, in the fasting state, leptin and insulin are low, leading to reduced SNS tone, and reduced skeletal muscle thermogenesis, and reduced adipose tissue lipolysis. In addition, the LHA and PVN send efferent projections residing in the medial longitudinal fasciculus to the DMV nerve (Powley and Laughton, 1981). By slowing the heart rate, the vagus reduces myocardial oxygen consumption. Through its effects on the alimentary tract, the vagus promotes peristalsis, and energy substrate absorption. Through its effects on the adipocyte, the vagus promotes increased lipoprotein lipase activity to increase the clearance of energy substrate into adipose tissue (Boden and Hoeldtke, 2003). Lastly, through effects on the β-cell (D'Alessio et al., 2001), the vagus accentuates postprandial insulin hypersecretion in response to a meal, which promotes energy deposition into the adipocyte (Rohner-Jeanrenaud and Jeanrenaud, 1985; Marin et al., 1988; Peles et al., 1995; Lustig, 2003). Overactive vagal neurotransmission increases insulin secretion through three distinct but overlapping mechanisms (Gilon and Henquin, 2001; **Figure 2**):

1. Vagal firing increases acetylcholine availability and binding to the M_3 muscarinic receptor on the β-cell, which is coupled to a sodium channel within the pancreatic β-cell membrane (Miura et al., 1996). As glucose enters the β-cell after ingestion of a meal, the enzyme glucokinase phosphorylates glucose to form glucose-6-phosphate. This increases the generation of intracellular ATP, which induces closure of the β-cell's ATP-dependent potassium channel. Upon channel closure, the β-cell experiences an ATP concentration-dependent β-cell depolarization (Nishi et al., 1987; Zawalich et al., 1989), and the opening of a separate voltage-gated calcium channel within the membrane. Intracellular calcium influx increases acutely, which results in rapid insulin vesicular exocytosis. Concomitant opening of the sodium channel by vagally derived acetylcholine augments the β-cell depolarization, which augments the intracellular calcium influx, and results in insulin hypersecretion (Berthoud and Jeanrenaud, 1979; Komeda et al., 1980; Rohner-Jeanrenaud and Jeanrenaud, 1980).

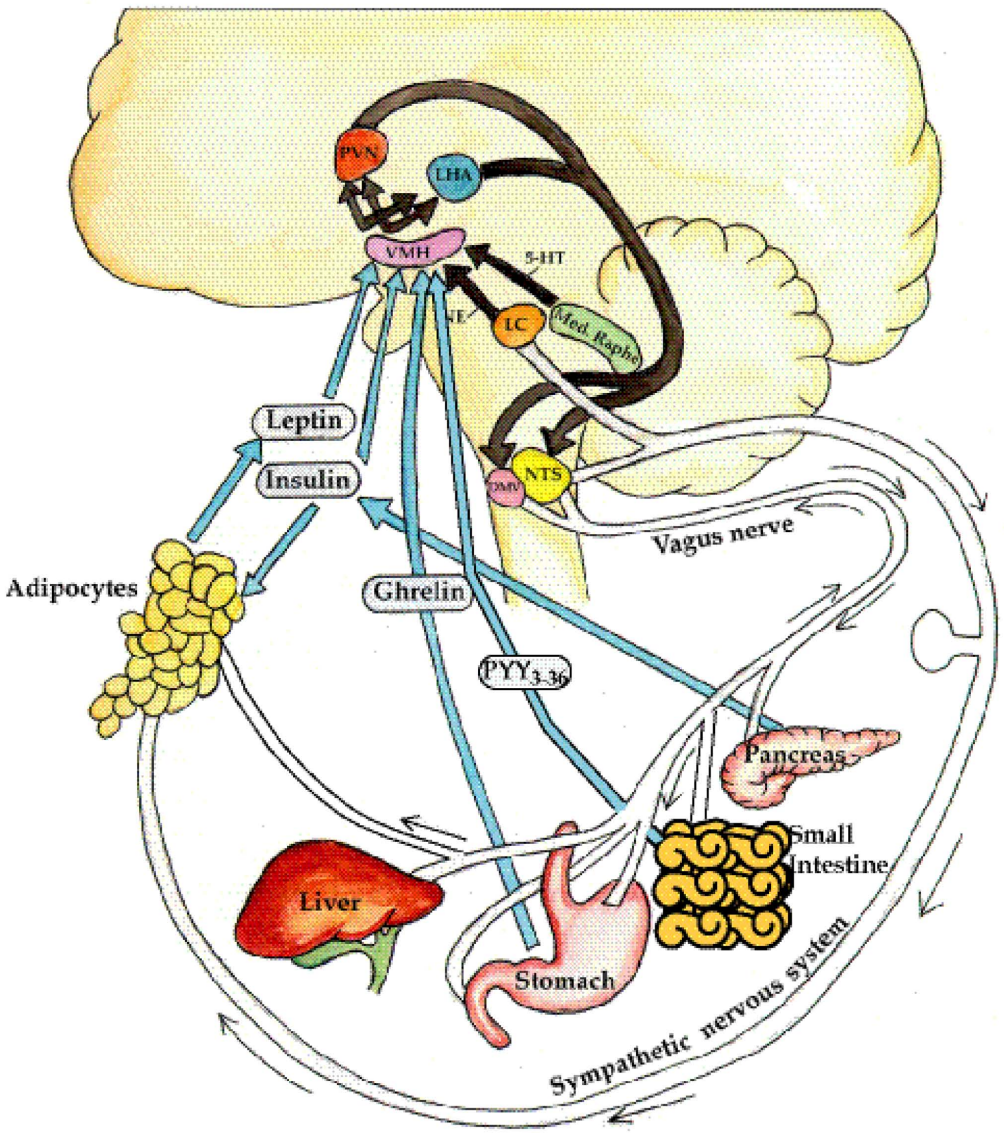

FIGURE 1 | Neuroendocrine regulation of energy balance. *The afferent system*: neural (e.g., vagal) and hormonal (ghrelin, insulin, leptin) signals are generated from the liver, gut, pancreas, and adipose. In addition, norepinephrine from the locus cœruleus and serotonin (5-HT) from the median raphe are elaborated. These signals of satiety vs. hunger, and thinness vs. fatness are interpreted in the ventromedial hypothalamus (VMH). These signals are then integrated in the paraventricular nucleus (PVN) and lateral hypothalamus (LHA). *The efferent system*: efferent signals from these areas in turn stimulate the sympathetic nervous system (SNS) to expend energy by activating β_3-adrenergic receptors and uncoupling proteins in the adipocyte, to release energy the form of lipolysis, heat, or physical activity. Conversely, the parasympathetic nervous system (efferent vagal) increases insulin secretion, with resultant adipogenesis and energy storage, and also increases insulin sensitivity through direct effects on the adipose tissue (Lustig, 2006). From Nature Publishing Group, with permission.

2. Vagally mediated acetylcholine increases phospholipases A_2, C, and D, within the β-cell, which hydrolyze intracellular phosphatidylinositol to diacylglycerol (DAG) and inositol triphosphate (IP_3; Gilon and Henquin, 2001). DAG is a potent stimulator of protein kinase C (PKC; Tian et al., 1996) which phosphorylates myristoylated alanine-rich Protein Kinase C substrate (MARCKS), which then binds actin and calcium–calmodulin, and induces insulin vesicular exocytosis (Arbuzova et al., 1998). IP_3 potentiates release of calcium within β-cells from intracellular stores, which also promotes insulin secretion (Blondel et al., 1994).
3. The vagus also stimulates the release of glucagon-like peptide-1 (GLP-1) from intestinal L-cells, which circulates and binds to the β-cell GLP-1 receptor. Activation of this receptor induces a calcium–calmodulin-sensitive adenyl cyclase, with generation of cAMP, which activates protein kinase A (PKA), stimulating phosphorylation of vesicular proteins, with resultant insulin exocytosis (Kiefer and Habener, 1999).

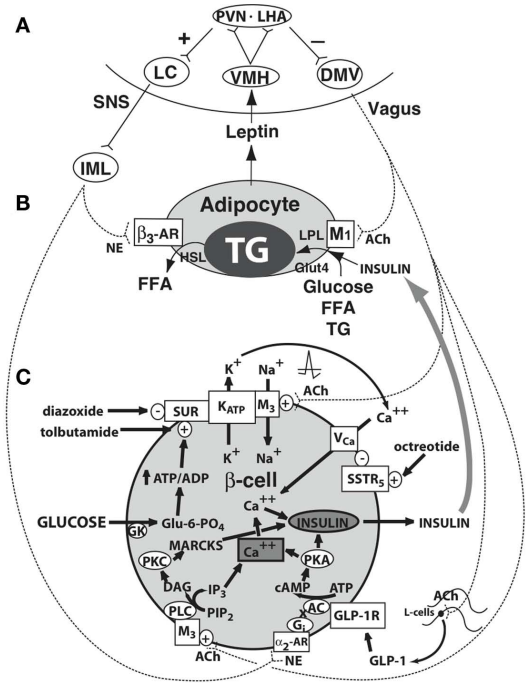

FIGURE 2 | Central regulation of leptin signaling, autonomic innervation of the adipocyte and β-cell, and the starvation response. **(A)** The arcuate nucleus transduces the peripheral leptin signal as one of sufficiency or deficiency. In leptin sufficiency, efferents from the hypothalamus synapse in the locus coeruleus, which stimulates the sympathetic nervous system. In leptin deficiency, efferents from the hypothalamus stimulate the dorsal motor nucleus of the vagus. **(B)** Autonomic innervation and hormonal stimulation of white adipose tissue. In leptin sufficiency, norepinephrine binds to the β_3-adrenergic receptor, which stimulates hormone-sensitive lipase, promoting lipolysis of stored triglyceride into free fatty acids. In leptin deficiency, vagal acetylcholine increases adipose tissue insulin sensitivity (documented only in rats to date), promotes uptake of glucose and free fatty acids for lipogenesis, and promotes triglyceride uptake through activation of lipoprotein lipase. **(C)** Autonomic innervation and hormonal stimulation of the β-cell. Glucose entering the cell is converted to glucose-6-phosphate by the enzyme glucokinase, generating ATP, which closes an ATP-dependent potassium channel, resulting in cell depolarization. A voltage-gated calcium channel opens, allowing for intracellular calcium influx, which activates neurosecretory mechanisms leading to insulin vesicular exocytosis. In leptin sufficiency, norepinephrine binds to α_2-adrenoceptors on the β-cell membrane to stimulate inhibitory G proteins, decrease adenyl cyclase and its product cAMP, and thereby reduce protein kinase A levels and insulin release. In leptin deficiency, the vagus stimulates insulin secretion through three mechanisms. First, acetylcholine binds to a M_3 muscarinic receptor, opening a sodium channel, which augments the ATP-dependent cell depolarization, increasing the calcium influx, and insulin exocytosis. Secondly, acetylcholine activates a pathway that increases protein kinase C, which also promotes insulin secretion. Thirdly, the vagus innervates L-cells of the small intestine, which secrete glucagon-like peptide-1, which activates protein kinase A, contributing to insulin exocytosis. Octreotide binds to a somatostatin receptor on the β-cell, which is coupled to the voltage-gated calcium channel, limiting calcium influx and the amount of insulin released in response to glucose. (Lustig, 2007; reprinted with kind permission of Humana, Totowa, NJ, USA). α_2-AR, α_2-adrenergic receptor; β_3-AR, β_3-adrenergic receptor; AC, adenyl cyclase; ACh, acetylcholine; DAG, diacylglycerol; DMV, dorsal motor nucleus of the vagus; FFA, free fatty acids; G_i, inhibitory G protein; GK, glucokinase; GLP-1, glucagon-like

(Continued)

FIGURE 2 | Continued
peptide-1; GLP-1R, GLP-1 receptor; Glu-6-PO_4, glucose-6-phosphate; Glut4, glucose transporter-4; HSL, hormone-sensitive lipase; IML, intermediolateral cell column; IP_3, inositol triphosphate; LC, locus coeruleus; LHA, lateral hypothalamic area; LPL, lipoprotein lipase; MARCKS, myristoylated alanine-rich protein kinase C substrate; NE, norepinephrine; PIP_2, phosphatidylinositol; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PVN, paraventricular nucleus; $SSTR_5$, somatostatin-5 receptor; TG, triglyceride; V_{Ca}, voltage-gated calcium channel; VMH, ventromedial hypothalamus; SUR, sufonylurea receptor (Lustig, 2006). From Nature Publishing Group, with permission.

In this way, the afferent system is entrained with the efferent system by an intricate servo-mechanism to coordinate central and peripheral signals either for appetite and energy storage, or satiety and energy expenditure.

PATHOGENESIS OF HYPOTHALAMIC OBESITY

Rat models of hypothalamic damage, either due to bilateral electrolytic lesions or deafferentation of the VMH, lead to intractable weight gain (Berthoud and Jeanrenaud, 1979; Rohner-Jeanrenaud and Jeanrenaud, 1980; Bray et al., 1981; Jeanrenaud, 1985; Satoh et al., 1997), even upon food restriction (Bray and Nishizawa, 1978). Similarly, children with hypothalamic obesity exhibit weight gain, even in response to forced caloric restriction (Bray and Gallagher, 1975). This seems paradoxical, as one would expect that if hyperphagia were the reason for the obesity, then caloric restriction would be effective in preventing further weight gain. In fact, analysis of energy intake in children with hypothalamic obesity demonstrates no difference vs. control patients with simple obesity (Harz et al., 2003). Instead, both resting energy expenditure (Shaikh et al., 2008) and voluntary energy expenditure (Harz et al., 2003) is severely compromised in these patients. Indeed, the most prominent and concerning complaint in patients with hypothalamic obesity is the persistent fatigue, lack of energy, and lack of physical activity. This generalized malaise is not due to hypopituitarism, as it persists even after full hormonal replacement.

The decrease in energy expenditure is mediated through suppression of SNS activity by the hypothalamic damage. Recent reports demonstrate an impaired ability of such patients to mount an epinephrine response to insulin-induced hypoglycemia (Schofl et al., 2002; Coutant et al., 2003), and document decreased 24-h epinephrine excretion (Coutant et al., 2003), along with decreased urinary homovanillic acid and vanillylmandelic acid (Roth et al., 2007); all pointing to decreased sympathetic tone. It is thought that this malaise and decrease in sympathetic tone may account for decreased rates of lipolysis through the adipocyte β_3-adrenergic receptor (al-Adsani et al., 1997), which results in decreased resting and voluntary energy expenditure.

In addition to "organic leptin resistance," it is possible that such patients also manifest "organic ghrelin resistance," in that ghrelin's suppression of hunger may be attenuated in children with hypothalamic obesity (O'Gorman et al., 2911). This may increase total food intake; although alterations in total food intake in these patients is not different from otherwise healthy obese controls (Harz et al., 2003).

DIAGNOSIS

A retrospective analysis of growth records of children with craniopharyngioma (Muller et al., 2004) indicates that increased weight and BMI gain is evident even before the diagnosis of the tumor. However, after surgery or radiotherapy, the weight gain is immediate, rapid, and highly exaggerated. Evidence of aberrant energy deposition is obvious within the first month. Physicians sometimes confuse this weight gain with glucocorticoid effect, and reduce the dose of maintenance hydrocortisone, which does not impact the obesity, and renders the patient with even more fatigue and malaise.

Children with hypothalamic obesity frequently have normal fasting insulin levels, especially during the rapid weight gain phase. It is important that such metabolic testing be dynamic, as the phenomenon that distinguishes hypothalamic obesity is insulin hypersecretion, not insulin resistance, and so may not be obvious with a fasting insulin level. In addition, stimulation of the alimentary tract so as to activate the vagal efferent component of insulin secretion is required to document the effect. Two sets of studies on insulin dynamics demonstrate insulin hypersecretion (as measured by an increased Corrected Insulin Response, or CIR; Sluiter et al., 1976) on oral glucose tolerance testing (OGTT); and surprisingly these patients also have insulin sensitivity (as measured by an increased Composite Insulin Sensitivity Index (Matsuda and DeFronzo, 1999) within the normal range, and certainly better than BMI-matched healthy obese children (Preeyasombat et al., 2005; Simoneau-Roy et al., 2010; **Figure 3**). However, other studies suggest that some hypothalamic obesity patients may also manifest signs of metabolic syndrome (Tiosano et al., 2003; Srinivasan et al., 2004). These patients may also have an increased incidence of obstructive sleep apnea, which may predispose them to the comorbidities of the metabolic syndrome (O'Gorman et al., 2010). It is not clear whether those patients with both hypothalamic obesity and metabolic syndrome represent a subgroup, or a different pathogenetic phenomenon entirely, or just the late evolution of their morbid obesity. A retrospective evaluation suggests that the degree of hypothalamic involvement of the tumor at its presentation predicts the degree of metabolic disturbance (Müller et al., 2011), though mechanisms for the metabolic alteration are still unclear.

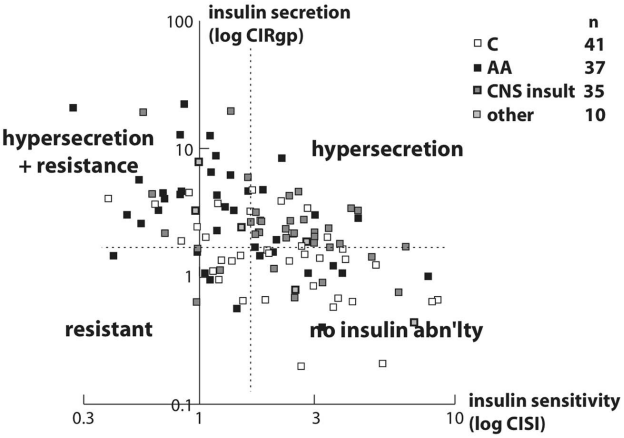

FIGURE 3 | Scatterplot of insulin secretion (Corrected Insulin Response, or CIRgp) vs. sensitivity (Composite Insulin Sensitivity Index, or CISI) plotted logarithmically in 113 obese non-diabetic children. A negative linear correlation was noted ($r = -0.54$, $p < 0.001$). Different racial and etiopathogenic groups tended to plot in different areas. Arbitrary cutoffs (dashed lines) for CIRgp (1.5) and CISI (1.7) divide the plot into four quadrants. The majority of Caucasian children (open squares) plotted in the lower right quadrant, with a CIRgp less than 1.5 and a CISI greater than 1.7, indicating lower insulin secretion and better insulin sensitivity. The preponderance of children with hypothalamic obesity (gray squares) plotted in the upper right quadrant, with a CIRgp of greater than 1.5, and with a CISI of greater than 1.7, indicating insulin hypersecretion with better insulin sensitivity. Finally the majority of African American children (filled squares) plotted in the upper left quadrant, with a CIRgp of greater than 1.5 and a CISI of less than 1.7, indicating both insulin hypersecretion and resistance (Preeyasombat et al., 2005). From Elsevier, with permission.

TREATMENT

The best treatment is prevention. The hypothalamus is extremely sensitive to both surgical intervention and/or external beam radiation (Lustig et al., 2003a). Rather than employing gross total or subtotal resection as a primary therapy for some posterior fossa tumors, newer strategies have been developed which treat them more conservatively, using stereotactic biopsy and conformal irradiation (Karavitaki et al., 2006; Spoudeas et al., 2006). A retrospective single-institutional followup of craniopharyngioma subjected either to gross total resection or stereotactic surgery and conformal radiation demonstrates equal survival and residual rates of hypopituitarism; however those treated with gross total resection exhibit higher incidences of obesity and neurological complications (Merchant et al., 2002).

Bray demonstrated the futility of lifestyle intervention by noting weight gain even with severe caloric restriction (Bray and Gallagher, 1975). Thus, treatment needs to be early and intensive to have any chance at success. A recent report suggests that intensive lifestyle can reduce the rate of BMI gain by half (from 8.4 kg/m^2/year to 4.5 kg/m^2/day), but the rate of increase is still quite unacceptable to rely on (Rakhshani et al., 2010).

PHARMACOTHERAPY

Since the hypothalamus is not amenable to therapy, and aberrant afferent hormonal signal transduction cannot be corrected, pharmacotherapy must instead address the alterations in the efferent pathways. Several attempts to use serotonin or norepinephrine reuptake inhibitors (e.g., phen–fen, fluoxetine, sibutramine) have been met with only salutary efficacy (Molloy et al., 1998). One study assessed the effects of sibutramine 10–15 mg PO qd, with a small but reproducible effect in BMI (Danielsson et al., 2007); however, sibutramine has been withdrawn from the market. These medications work centrally to reduce food intake, but do not work peripherally to stimulate skeletal muscle to increase energy expenditure, and thus have limited value. Mason et al. (2002) used dextroamphetamine 5 mg PO bid, which acts both centrally and peripherally, and achieved weight stability for an interval of 6 months. We have also seen improvement in affect and alertness, which is a major benefit of dextroamphetamine.

In an attempt to reduce hyperinsulinemia, Hamilton have attempted to treat patients with a combination of diazoxide and metformin (Hamilton et al., 2011). Weight gain over 6 months was

reduced as compared to pre-treatment; however, side-effects were significant, including edema, and there were some discontinuations.

In an attempt to reduce hyperinsulinemia and simultaneously enhancing insulin action, we examined the effects of the somatostatin analog octreotide (an agonist of the somatostatin-5 receptor on the β-cell, which inhibits the voltage-gated calcium channel; **Figure 2**). A pilot, open-label trial of octreotide 15 μg/kg/day subcutaneously for 6 months in eight subjects (Lustig et al., 1999) demonstrated BMI loss commensurate with the degree of insulin suppression, along with decrease in caloric intake, and subjective improvements in spontaneous physical activity and quality of life. A double-blind, placebo-controlled trial of 20 subjects (Lustig et al., 2003b) resulted in insulin suppression and stabilization of BMI, decreased leptin, decreased caloric intake, increased spontaneous physical activity, and improvement in quality of life commensurate with the degree of insulin suppression. A retrospective analysis demonstrated that octreotide was most effective in those patients who exhibited both insulin hypersecretion with continued insulin sensitivity (Preeyasombat et al., 2005).

SURGERY

The severity and morbidity of obesity in these patients, and the relative lack of alternatives, have led to attempts at bariatric surgery. Inge et al. (2007) reported a 25-kg weight loss after Roux-en-Y gastric bypass in one subject, but whose weight stabilized at an unacceptable level. Recently, Müller et al. (2007) reported in abstract form his experience with four subjects who underwent laparoscopic adjustable gastric banding, with reductions in food intake and slow reductions in BMI. Lastly, vagotomy may be effective in this syndrome (Smith et al., 1983), by reducing the efferent output to both beta-cells and adipocytes. We have recently performed laparoscopic truncal vagotomy in four subjects with hypothalamic obesity, with early results being supportive of this procedure, and with relatively few complications or side-effects (Lustig et al., 2009).

SUMMARY

The hypothalamus interprets afferent signals for energy balance, and transduces them into autonomic efferent signals to either expend or store energy. When this negative feedback system breaks down, as after craniopharyngioma therapy, the phenomenon of hypothalamic obesity ensues. While this disorder is a defect in the afferent pathway, treatment focuses on the efferent pathway, as it is modulable with drugs and surgical techniques that are currently available. Physicians need to explain the risks of this disorder to patients prior to tumor therapy, and must be willing to act quickly and decisively once the intractable weight gain begins, in order to provide intensive management so that the obesity will not get worse.

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Hypothalamic obesity in patients with craniopharyngioma: profound changes of several weight regulatory circuits

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One of the most striking examples of dysfunctional hypothalamic signaling of energy homeostasis is observed in patients with hypothalamic lesions leading to hypothalamic obesity (HO). This drastic condition is frequently seen in patients with craniopharyngioma (CP), an embryological tumor located in the hypothalamic and/or pituitary region, frequently causing not only hypopituitarism, but also leading to damage of medial hypothalamic nuclei due to the tumor and its treatment. HO syndrome in CP patients is characterized by fatigue, decreased physical activity, uncontrolled appetite, and morbid obesity, and is associated with insulin and leptin resistance. Mechanisms leading to the profoundly disturbed energy homeostasis are complex. This review summarizes different aspects of important clinical studies as well as data obtained in rodent studies. In addition a model is provided describing how medial hypothalamic lesion can interact simultaneously with several weight-regulating circuitries.

Keywords: hypothalamic lesion, hyperphagia, morbid obesity, neuropeptides, gut hormones, autonomous nervous system

HYPOTHALAMIC OBESITY IN PATIENTS WITH CRANIOPHARYNGIOMA: SUMMARY OF KEY CLINICAL FINDINGS

Excessive weight gain is one of the most distressing manifestations of hypothalamic injury associated with CP. In 30% of all patients with hypothalamic tumors, BMI is increased at the time of diagnosis (Muller et al., 2004). After surgery, hyperphagia and obesity occur on average in about 50% of all CP patients (Curtis et al., 1994; Muller et al., 2001; Muller, 2006), although study results vary from 6% (Galatzer et al., 1981) to 91% (Imura et al., 1987; Muller et al., 2004), with higher rates in patients with hypothalamic damage. In children and adolescents, the incidence of severe obesity following CP resection surgery is between 22 and 62% (Brauner et al., 1987; Sorva, 1988; Muller, 2008). Structural defects in parts of the medial hypothalamus due to surgery, irradiation, or the tumor itself often cause treatment resistant uncontrolled appetite and rapid weight gain. Tumor resection with and without radiotherapy represents the therapeutic standard of care. But following treatment, patients often suffer from partial hypopituitarism or panhypopituitarism. Despite optimal endocrine management, uncontrolled appetite and rapid weight gain are common, typically most pronounced during the first months after surgery (Sorva, 1988; Muller et al., 2004), making severe obesity a major risk factor for CP related morbidity. Risk factors for developing obesity in CP patients include large hypothalamic lesions affecting several medial hypothalamic nuclei such as the arcuate nucleus (ARC), ventromedial nucleus (VMN), and the dorsomedial nucleus (DMN), and tumors that reach the floor of the third ventricle; hydrocephalus; transcranial surgery, which often causes greater damage to the hypothalamus compared to transnasal surgical tumor removal; aggressiveness of resection; reoperation for tumor recurrence; and hypothalamic irradiation (Muller et al., 2007; Gardner et al., 2008; Vinchon et al., 2009; Roth et al., 2011c; **Figure 1**).

KEY BRAIN AREAS AND NEURONAL PATHWAYS INVOLVED IN ENERGY HOMEOSTASIS

HYPOTHALAMIC NUCLEI AND WEIGHT REGULATORY PATHWAYS

The hypothalamus is central to regulation of energy homeostasis. Hypothalamic nuclei are the target of circulating peptides, including leptin, insulin, peptide $YY_{3–36}$ (PYY), and ghrelin, as well as nutrients such as free fatty acids, glucose, and amino acids (Schwartz et al., 2000; Cota et al., 2006; Morton et al., 2006; Parton et al., 2007). Changes in the circulating level of these afferent inputs can trigger potent efferent responses affecting both food intake (FI) and energy expenditure (EE) in the regulation of energy homeostasis. It is well established that insulin and leptin are two peripherally secreted hormones that play critical roles in FI and EE (Schwartz et al., 2000) and that levels of both are proportionate to body fat and interact with their respective receptors expressed in the ARC, a key brain area transmitting peripheral weight-regulating signals to the brain. Many neurons are regulated by leptin and insulin, and central administration of either hormone reduces FI and body weight. The main mediators in the hypothalamic regulation of energy intake and EE appear to be proopiomelanocortin (POMC) and neuropeptide-Y/agouti-related peptide (NPY/AgRP) producing neurons, which are concentrated in the ARC and project mainly to the paraventricular nucleus (PVN) in the hypothalamus but also to the VMN, lateral hypothalamus (LHA), as well as the DMN and the median preoptic area (Bai et al., 1985; Kerkerian and Pelletier, 1986; Schwartz et al., 2000; Schwartz and Gelling, 2002). Alpha-melanocyte stimulating hormone (α-MSH), a posttranslational product of the prohormone POMC, is one of the key weight-regulating neuropeptides (Bai et al., 1985;

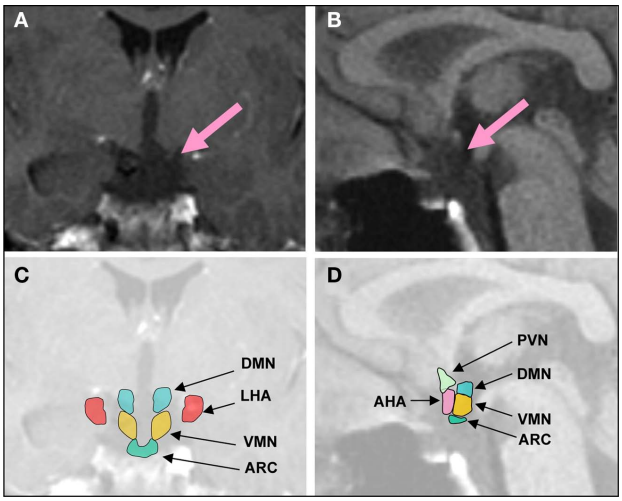

FIGURE 1 | Representative coronal (A), midsagittal brain MRI (B), and schematic overview (C,D) of a patient with hypothalamic obesity and hyperphagia following surgery for CP. Lesion affects the ARC, VMN, DMN, and the posterior part of the AHA, but not the LHA. DMN, dorsomedial nucleus; LHA, lateral hypothalamus; VMN, ventromedial nucleus; PVN, paraventricular nucleus; ARC, arcuate nucleus; AHA, anterior hypothalamic area.

Kerkerian and Pelletier, 1986; Schwartz et al., 2000; Schwartz and Gelling, 2002). The VMN contains gamma-amino butyric acid-(GABA)ergic and anorexigenic brain-derived neurotrophic factor (BDNF) neurons and is an important nucleus for insulin dependent neurotransmission and is an important site for the regulation of the autonomous nervous system outflow from the brain (Morton et al., 2006; Berthoud and Morrison, 2008). The DMN contains GABAergic neurons but also expresses NPY in particular in its compact region and expresses leptin receptors such as the ARC, VMN, and PVN (Choi et al., 1999; Glavas et al., 2007). NPY in the DMN may play a role in maintaining energy homeostasis (Bi, 2007). The PVN receives projections from NPY-synthesizing neurons located in the ARC, which are also present in the brainstem (Sawchenko et al., 1985; Sahu et al., 1988). Neurons that synthesize the hunger hormones, MCH or orexin A, are located in the LHA and are downstream mediators of feeding responses initiated by ARC neurons (Schwartz, 2006). The PVN contains a variety of appetite suppressing peptides, such as corticotropin-releasing factor (CRF), thyrotropin-releasing hormone (TRH), and oxytocin, that promote negative energy balance by conveying input from the ARC to other key brain areas such as the NTS (Schwartz, 2006; Blevins et al., 2009). Recent evidence also suggests that the adiposity hormones act in brain areas linked with food reward, which mediate motivation and the decision to eat. (Petrovich et al., 2002; Figlewicz and Benoit, 2009). Limbic and reward circuitry are densely innervated by neurocircuits originating in the hypothalamus and are directly responsive to ghrelin, leptin, and insulin (Figlewicz, 2003; Figlewicz et al., 2007). These structures receive significant cortical input as well, sending projections to the nucleus accumbens and pallidum, and from there, via the LHA, to motor regions charged with executing feeding behavior.

HINDBRAIN SIGNALING AND PERIPHERAL REGULATORS

Peptide YY3–36, glucagon-like peptide (GLP)-1, pancreatic polypeptide (PP), and cholecystokinin (CCK) are gastrointestinal-derived hormones that are released postprandially in proportion to the amount of calories ingested (Wynne et al., 2005). These anorexigenic hormones inhibit FI through neurons in the ARC, which is frequently damaged in CP patients, and/or neurons located in the hindbrain solitary tract nucleus, which is usually intact in CP patients (Batterham et al., 2002; Small et al., 2005). Additionally, plasma concentrations of orexigenic ghrelin decrease after FI. An intact vagal-brainstem-hypothalamic pathway is required in order for some of these hormones to exert their effects on FI which is controversial for PYY (Batterham et al., 2002; Small et al., 2005). Although there is published evidence that increased insulin secretion is caused by an increased vagal tone secondary to VMN lesions in humans (Lustig et al., 2003; Ahmet et al., 2006) as in rats (Bray and Nishizawa, 1978), it is unclear how the increased vagal tone and decreased sympathetic tone affect secretion of different gut peptides. It has been shown that the anorexigenic effects of peripheral administration of both PYY on FI and activation of ARC neurons are abolished following either bilateral subdiaphragmatic total truncal vagotomy or brainstem-hypothalamic pathway transectioning in rodents (Abbott et al., 2005). In addition, it has been reported that disturbed adrenergic sympathetic dysregulation in obesity influences anorexigenic gut hormone secretion, in particular PYY release (Lin et al., 2003). Even though vagotomy is currently a therapeutic approach for treating hypothalamic obesity (HO) in CP patients (Lustig et al., 2009), from a mechanistic standpoint it remains unclear if potential benefits, e.g., reduction of hyperinsulinemia, outweigh potential problems, e.g., disturbed post-meal gut hormone release. Long acting GLP-1 agonists, and orally active inhibitors of the incretin-degrading enzyme dipeptidyl peptidase-IV are approved for treating type-2 diabetes (Bailey, 2005; DeFronzo et al., 2005), and it is compelling to test in future studies the responsiveness to peripherally injected gut peptides in HO, as these might offer human obesity treatment opportunities.

HYPOTHALAMIC OBESITY: WHAT CAN BE LEARNED FROM ELECTROLYTIC AND CHEMICAL LESION MODELS IN RODENTS?

Patients with CP often complain about uncontrolled hunger. As early as, Brobeck et al. (1943) described rats with lesions in the VMN as "voracious," whereas lesions of the LHA led to anorexia and cachexia. Electrolytic or surgical lesions in the PVN produced extreme overeating and obesity, suggesting an important role for this nucleus in energy regulation. However, conflicting results have been published. PVN lesions lead to marked stimulation of FI, but variable frequencies of obesity (Tokunaga et al., 1991, 1993). VMN-lesioned rats showed lower activity levels and disturbed circadian rhythms, whereas rats with PVN lesions did not (Tokunaga et al., 1991). Rats treated at neonatal age with monosodium L-glutamate (MSG) develop neuroendocrine and metabolic abnormalities, resulting in a phenotype of adiposity characterized by GH deficiency (Kubota et al., 1994), hyperinsulinemia (de Souza et al., 2003), and hyperleptinemia, due to leptin resistance (Perello et al., 2004). Vagotomy decreased high insulin secretion induced in MSG-obese rats (Balbo et al., 2002). Neonatal

administration of MSG to rodents and monkeys destroyed 80–90% of the ARC, showing cell rarification and cell death most significantly in the rostromedial ARC, but also in the adjacent VMN where cell density was not distinctly reduced (Schoelch et al., 2002), resulting in several neuroendocrine and metabolic abnormalities and decreased thermogenesis. In hamster studies, MSG decreased numbers of hypothalamic neuropeptide-Y (NPY)- and agouti-related peptide (AgRP) fibers in the PVN, because the ARC has projections to the PVN, including α-MSH projections (Leitner and Bartness, 2008). MSG-treated animals develop an obesity syndrome in the absence of hyperphagia (Dawson et al., 1989; Elfers et al., 2011; Roth et al., 2011b), characterized by excess fat deposition and reduced lean body mass, accompanied by reduced metabolic rates, due to decreased sympathetic activation of brown adipose tissue (Poon and Cameron, 1978). Recently we developed a rat model of combined medial hypothalamic lesion (CMHL) affecting the VMN, DMN, and the ARC. Only the CMHL model exhibited all key features observed in patients with HO induced by CP (Elfers et al., 2011; Roth et al., 2011b). These features included excessive weight gain due to increased adiposity, increased FI, and pronounced hyperinsulinemia and hyperleptinemia. Similar to findings in CP patients (Roth et al., 2010), CMHL animals exhibited reduced plasma levels of alpha-melanocyte stimulating hormone and reduced ambulatory activity compared to weight-matched controls. Ablation of the ARC/VMN can destroy the leptin sensitive melanocortin ARC–PVN circuit affecting satiety signaling not only in the hypothalamus but also in the hindbrain (see model **Figure 2**). The CMHL model best mimics the complex metabolic abnormalities observed in obese CP patients compared to lesions to other hypothalamic areas and provides a foundation for future pharmacological approaches to treat obesity in children with hypothalamic damage.

HYPOTHALAMIC OBESITY: RESULTS FROM STUDIES IN HUMANS

IMAGING STUDIES AND FOOD REWARD

Risk factors for developing obesity in CP patients include: large hypothalamic lesions and tumors that reach the floor of the third ventricle; hydrocephalus; aggressive resection; and hypothalamic irradiation (Muller et al., 2007; Gardner et al., 2008; Vinchon et al., 2009). Extensive hypothalamic infiltration and a completely deficient third ventricle have been associated with the highest risk of obesity (DeVile et al., 1996; Pascual et al., 2008). however, results are not entirely consistent (Daousi et al., 2005). Disturbance of the hypothalamus by the tumor itself (Vinchon et al., 2009) and/or its radiation/surgical treatment has been discussed as a major cause of hyperphagia and obesity. In our own clinical series we found in patients with morbid obesity lesions affecting several medial hypothalamic nuclei such as ARC, VMN, and DMN (representative picture is shown in **Figure 1**). Functional magnetic resonance imaging (fMRI) is a powerful tool for observing the human brain's *in vivo* responses to stimuli. The question is whether damage to homeostatic centers, such as medial hypothalamic nuclei by CP, also alters eating behavior by alteration of neuronal activity in food reward brain areas (see for schematic overview **Figure 2**) and whether central processing of satiety is affected. In a pilot

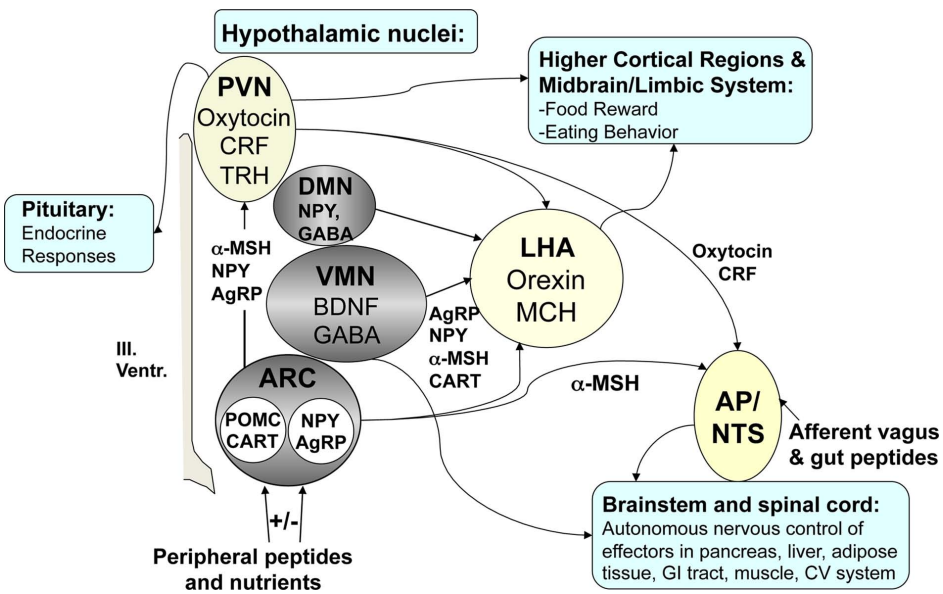

FIGURE 2 | Key regulators of energy homeostasis in the brain. Model of weight regulatory circuits and hypothalamic nuclei potentially affected by craniopharyngioma and surgery (gray area). The lesion of medial hypothalamic nuclei (ARC, VMN, DMN) typically does not involve the lateral hypothalamus (LHA) potentially leading to unbalanced expression and secretion of orexigens (MCH, orexigens A and B) by the LHA. Additionally the communication to (1) higher cortical brain areas and limbic system involved in food reward and eating behavior, (2) pituitary, and (3) hindbrain nuclei (AP, area postrema, NTS: solitary tract nucleus) affecting the autonomous nervous control of effectors in pancreas, liver, adipose tissue, GI tract, muscle, CV system might be affected as well. CRF, corticotrophin relasing factor; TRH, thyrotropin-releasing hormone; NPY, neuropeptide-Y; GABA, gamma aminobutyric acid; BDNF, brain-derived neurotrophic factor; POMC, proopiomelanocortin; AgRP, agouti-related peptide; CART, cocaine amphetamine regulated transcript; α-MSH, alpha-melanocyte stimulating hormone.

study, we utilized fMRI to examine food-related activity in brain centers that control appetite. We hypothesized that hypothalamic damage due to CP and its treatment results in enhanced perception of food reward. Participants viewed blocked photographs of food and mean *z*-scores for regions of interest (ROI; bilateral N. accumbens, insula, striatum, and medial orbitofrontal cortex) were calculated for the contrast of fattening > non-fattening food. Subjects underwent the first fMRI scan, received a high-calorie test meal to suppress appetite, and had a second fMRI scan 30 min after the test meal. Before and after the scans, hunger ratings were performed. Following the test meal, controls showed suppression of activation in ROIs while CP patients showed trends toward higher activation in ROIs (Roth et al., 2011a). These preliminary data support our hypothesis that perception of food cues may be altered in HO, especially after eating. The fMRI approach may be applicable for performing future mechanistic studies of the brains' response to food in patients with HO.

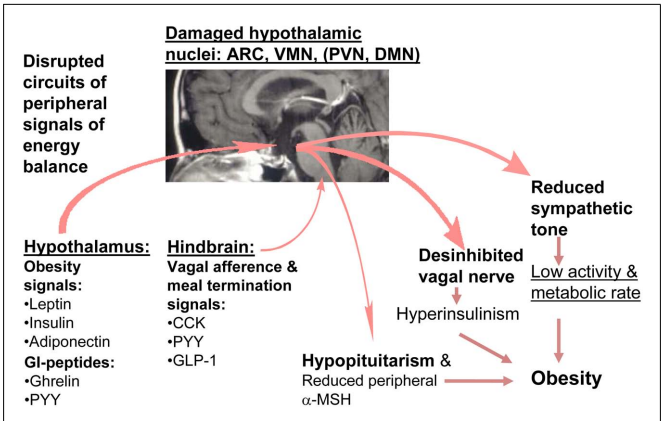

FIGURE 3 | Hypothetical model of disturbed energy homeostasis in hypothalamic obesity.

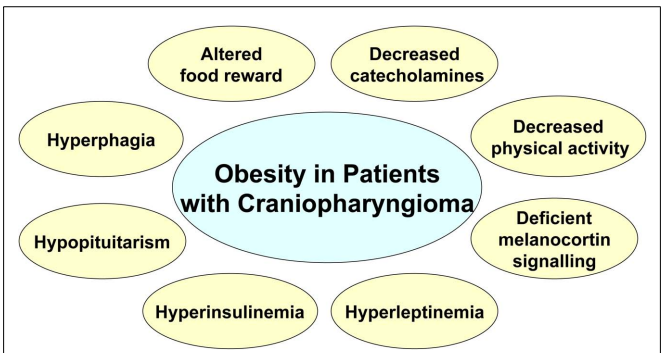

FIGURE 4 | Summary of metabolic and clinical findings involved in dysregulated energy balance in hypothalamic obesity.

CENTRAL AND PERIPHERAL PEPTIDES INVOLVED IN ENERGY HOMEOSTASIS

There is good evidence for alterations in peripheral hormone signaling in CP. Previous clinical studies showed that hypothalamic tumor involvement leads to greater leptin resistance in patients with CP than in obese controls (Roth et al., 1998). CP patients are reported to be less physically active than controls with comparable BMIs (Harz et al., 2003) and catecholamine levels are lower in CP patients, indicating low sympathetic tone (Roth et al., 2007). Plasma α-MSH levels were significantly reduced in CP, similar to findings in our CMHL rat model, which might explain lower EE in peripheral tissues via reduced fat and muscle fatty acid oxidation (Roth et al., 2010). In an ancillary study to the German multicenter study Kraniopharyngeom 2000, plasma insulin, and gut hormone responses, such as ghrelin and PYY, in response to meal tests were assessed in lean and obese CP patients and BMI matched controls. Obese CP subjects had significantly higher baseline and post-meal insulin and weaker post-meal changes for PYY compared to obese controls. Patients with hypothalamic CP had significantly weaker post-meal reduction of ghrelin levels than CP without hypothalamic localization (Roth et al., 2011c). In sum, prior studies of HO have shown impaired function of peripherally released hormones that act centrally to modulate responses to food (see **Figure 3**).

SUMMARY AND ETIOLOGICAL THEORIES

Damage of medial hypothalamic nuclei due to the tumor and its treatment is frequently seen in patients with CP leading to HO characterized by fatigue, decreased physical activity, uncontrolled appetite, and morbid obesity, and is associated with insulin and leptin resistance. Disruption of feeding circuits by damage of medial hypothalamic nuclei has the potential to increase hunger, by (i) enhancing the response to orexigenic signals such as ghrelin and by stimulating the orexigenic signaling through NPY/AgRP or (ii) blocking the response to adiposity signals such as leptin and inhibiting the anorexigenic POMC signaling in the hypothalamus (**Figure 2**). In either case, the result can involve unopposed activation of the LHA which increases FI while decreasing sympathetic nervous system (SNS)-mediated stimulation of EE. VMN damage can lead to disinhibition of the vagal tone, resulting in excess stimulation of pancreatic β-cells, hyperinsulinemia, and obesity (Lustig et al., 2003). Alternatively, the sympathetic nervous output might be reduced, leading to decreased physical activity (Harz et al., 2003; Roth et al., 2007). As the hypothalamic damage in CP frequently includes the ARC, which is the main hypothalamic binding site for hormones from the periphery (**Figures 2** and **3**), the hypothalamus might be unable to respond normally to adiposity and satiety signals such as insulin, leptin, and gut hormones, including PYY and ghrelin (Stellar, 1954; Blundell, 1982, 1990; Inge et al., 2007). In addition, excessive weight gain could be the result of deficient hypothalamic neural circuits communicating with corticolimbic and other brain regions to regulate appetite and thus leading to unbalanced eating (see summary **Figure 4**).

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Surgical strategies in childhood craniopharyngioma

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Craniopharyngiomas are biologically benign lesions (WHO Grade 1) of the sellar and suprasellar region, associated with a serious morbidity. About 50% of these tumors become clinically apparent during childhood. Clinical symptoms include headaches, chiasm syndrome, hydrocephalus, pituitary insufficiencies, and obesity. Growth arrest is a typical symptom in children. The treatment of craniopharyngiomas includes surgery as well as radiotherapy. The goal of surgery varies according to the tumor location and extension and may range from complete resection to biopsy. Surgical complications are well known and cause constant evaluation of surgical strategies. Diencephalic obesity is related to surgical manipulation of hypothalamic tissue. Therefore, a classification system for craniopharyngiomas based on preoperative MRI is suggested by the authors. Recurrences are frequent in craniopharyngiomas, even after complete or gross-total resection. Radiotherapy is therefore recommended to patients with incomplete resections. However, the ideal time for radiotherapy after surgery is under discussion. The treatment of craniopharyngiomas requires an interdisciplinary and multimodal approach. Each patient should receive an individually tailored treatment. Surgically, different approaches as well as different degrees of resection can be considered, depending on tumor location and tumor extension.

Keywords: craniopharyngioma, surgery, childhood, pituitary insufficiency, hypothalamic obesity

INTRODUCTION

Although considered benign lesions by biological means, the (surgical) treatment of craniopharyngiomas remains a true challenge for physicians (Komotar et al., 2009; Crowley et al., 2010). The problems accompanied by craniopharyngiomas are caused by the delicate location of these tumors, supposedly arising from remnants of the Rathke's pouch and connected to neuroendocrine tissue of the pituitary, the pituitary stalk, or/and hypothalamic structures. Especially during childhood, when body development and growth are immediately influenced by the hypothalamic–pituitary axis, any disruption of the neuroendocrine function has severe consequences for the patient. Impaired cognitive and social abilities are reported independent of endocrine insufficiencies (Ondruch et al., 2011). Any surgical treatment should consider the rule "*primum non nocere*" however, surgically induced complications/loss of functions are well known and lead to a continuous evaluation of surgical strategies.

Clinical symptoms of childhood craniopharyngiomas include growth arrest, headaches, chiasmatic syndrome, hydrocephalus, panhypopituitarism, and obesity, depending on the exact location of the tumor and its size. After CT- and MR-tomographic confirmation of a tumor in the sellar/suprasellar region and an endocrinological work-up, most patients are transferred to the neurosurgeon for surgical treatment. Preoperative imaging cannot replace the histological analysis and diagnosis "craniopharyngioma" – however certain typical characteristics make the diagnosis likely (Rennert and Doerfler, 2007). Goals of surgery can be: histological confirmation of diagnosis, relief of mass effects, treatment of hydrocephalus, preservation of hormonal function, avoidance of complications, and if possible, complete resection (CR) of the pathology. Especially in older publications, the surgical strategy generally opted for complete/gross-total tumor resection. It is indisputable, that aggressive surgical procedures more frequently lead to hypopituitarism or – even worse – hypothalamic damage and obesity (Lustig et al., 2003). Therefore, a different approach is to preserve endocrine function and avoid pituitary stalk and hypothalamic manipulation as much as possible, accepting an incomplete resection (Schubert et al., 2009). These patients are usually candidates for radiotherapy (Becker et al., 1999; Smee et al., 2011).

ANATOMICAL CONSIDERATIONS AND SUGGESTION OF A MRI CLASSIFICATION

As already mentioned, craniopharyngiomas are midline lesions of the middle cranial fossa, considered to arise from remnants of the Rathke's pouch. About 30% of the tumors have an intrasellar/infradiaphragmatic origin, whereas the rest either has its major extension above the sella turcica underneath the optic chiasm, or a mostly supra-/retrochiasmatic extension usually into the third ventricle, affecting hypothalamic structures and possibly leading to occlusive hydrocephalus. Depending on its location, the tumor causes different symptoms, e.g., hydrocephalus in intraventricular tumors, whereas growth arrest, pituitary insufficiency and Diabetes insipidus are more likely the leading symptoms in infradiaphragmatic and infrachiasmatic tumors. Tumors originating from the pituitary stalk are frequently leading to chiasmatic syndrome. All types are connected with headaches. In cases of intrasellar tumors or intra- and suprasellar tumors, the floor of

the sella turcica is usually enlarged. Most surgeons will advice transsphenoidal surgery for patients suffering from these lesions (Abe and Ludecke, 1997).

In supradiaphragmatic–infrachiasmatic lesions, the region may be reached by a transcranial as well as a transsphenoidal approach. Whereas the access morbidity is considered less in transsphenoidal approaches, the control of neurovascular structures may be limited. Recently, several reports have been published showing good results by extended transsphenoidal surgery (see below). In all lesions arising from the pituitary stalk, the attempt of a complete/gross-total surgical resection frequently leads to partial or complete hypopituitarism.

Suprachiasmatic lesions are generally considered difficult to treat, connected with high morbidity, and frequently incompletely resected. As published by Müller (2011) and Müller et al. (2011), the attempt of surgical removal of tumor tissue beyond the mammillary bodies endangers hypothalamic structures and may cause hypothalamic obesity. Taking these considerations into account, a classification according to preoperative MRI is suggested, since this may influence the surgical strategy (**Figure 1**). Type 1 craniopharyngiomas are located below the diaphragma sellae, whereas Type 2 tumors are supradiaphragmatic and infrachiasmatic. Type 3 craniopharyngiomas are located above the chiasm (and usually retrochiasmatic, extending into the third ventricle). The latter Type should be subdivided into Type A and B with respect to the mammillary bodies, since Type B can be connected to severe hypothalamic damage, when approached by aggressive surgery (Müller et al., 2011). Different transcranial approaches to reach the area can be considered, as discussed later. Only few Type 3 craniopharyngiomas (mostly cystic) are good candidates for transsphenoidal surgery.

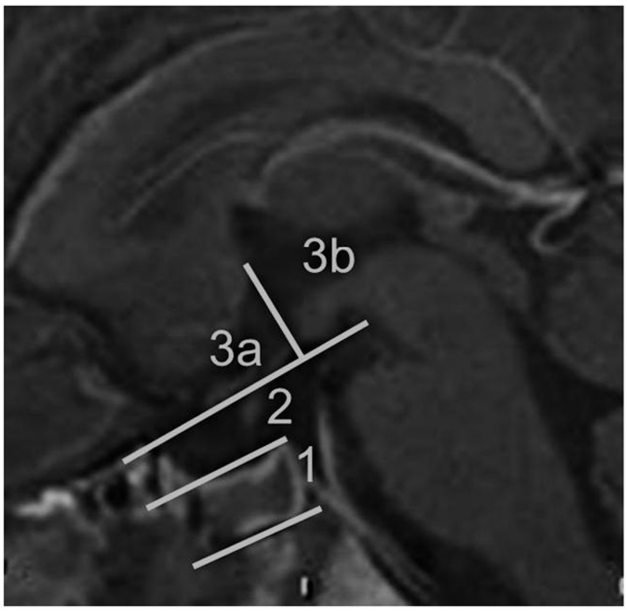

FIGURE 1 | Sagittal MRI of the midline. Suggestion of a classification system of craniopharyngiomas by preoperative MRI criteria. The intra- and suprasellar region can be divided into three sections. Section 1 is limited by the diaphragm sella, section 2 is below the optic chiasm and the mammillary bodies, section 3 is above the chiasm and mammillary bodies, subdivided into an area anterior and posterior of the mammillary bodies. In this particular patient, a transsphenoidal surgery of a Type 1 craniopharyngioma was performed previously, as can be seen by fluid within the sphenoid sinus. Section 1 is usually reached by the transsphenoidal route, whereas section 3a and 3b is mostly reserved for transcranial procedures. Depending on the tumor extension, section 2 can be reached by transcranial as well as transsphenoidal procedures.

SPECIAL CONSIDERATIONS IN CHILDHOOD

General precautions have to be taken in children aged 10 or younger, since the "normal" intraoperative blood loss may cause life-threatening hypovolemic hypotension. Therefore, an experienced anesthesiology team is mandatory, as well as a meticulous surgical hemostasis. The use of the Mayfield pin fixation has to be carefully performed especially in children, since impression fractures with consecutive epidural hematomas are known and published complications (Yan, 2007).

As for the development of the skull base, transsphenoidal surgery is possible in infants from aged 3 years and older, since the pneumatization of the sphenoid sinus should have started (**Figure 2**; Flitsch et al., 2000). For maximum safety in these patients, the use of a microdoppler, fluoroscopy, or/and neuronavigation is recommended to avoid vascular complications.

TRANSCRANIAL PROCEDURES

The treatment of Type 2 and Type 3 craniopharyngiomas can be performed via transcranial approaches. Craniopharyngiomas arising from the pituitary stalk and those lesions extending into the infundibulum can be reached by a classical *pterional* or *subfrontal* route (Liu et al., 2010). Limitations are that the optic nerves/optic chiasm usually lay in front of the tumor and therefore the surgical window is limited (**Figure 3**). Also, the identification of the pituitary stalk can be difficult and therefore is at high risk. Tumors extending into the third ventricle can be reached by opening of the lamina terminalis behind the optic chiasm (Maira et al., 2000). Tumor cysts can be opened, however, for removal of the cyst wall or solid parts, the adjacent hypothalamic tissue is more or less manipulated. Another approach for large tumors within the ventricle is the *transventricular* route through a lateral ventricle and the foramen of Monroi (Konovalov, 1993). This approach may be considered in obstructive hydrocephalus. *Retrosigmoid* approaches for uncommon posterior fossa tumor extensions are rarely necessary. In all cases of incomplete tumor removal during transcranial procedures, catheters connected with, e.g., a Rickham reservoir can be inserted into remaining cysts for later aspiration or instillation of sclerosing substances.

TRANSSPHENOIDAL PROCEDURES

Microscopic transsphenoidal surgery remains the standard approach to the pituitary region (Fahlbusch and Hofmann, 2008). Endoscopically assisted techniques have been developed over the last two decades and enrich the surgical options (Fernandez-Miranda et al., 2011). Except for very small children with lack of at least partial sphenoid sinus pneumatization (up to age 3), this approach is suitable for patients with infradiaphragmatic lesions as

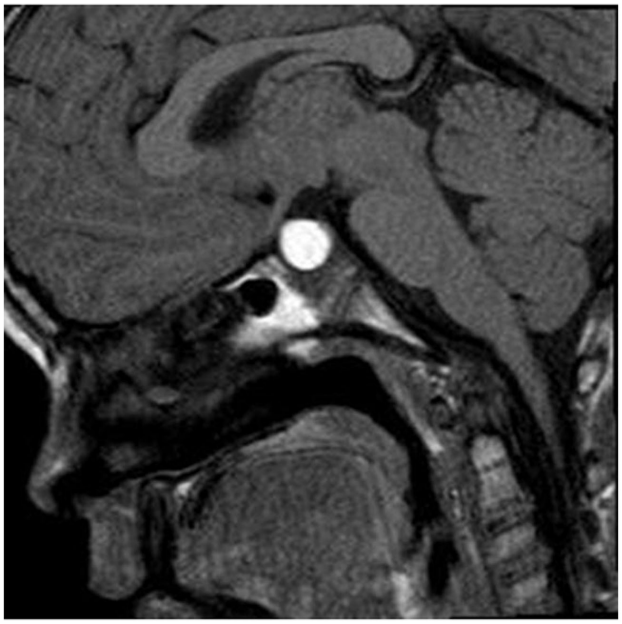

FIGURE 2 | Sagittal MRI of a child with an intra- and suprasellar craniopharyngioma reaching the optic nerves (Type 1). Special attention has to be given to the partial pneumatization of the sphenoid sinus, since the thick bone has to be drilled during the access to the sella. This can cause problems in orientation for the surgeon and endanger the carotid arteries, which may be solved by the use of a microdoppler and/or neuronavigation.

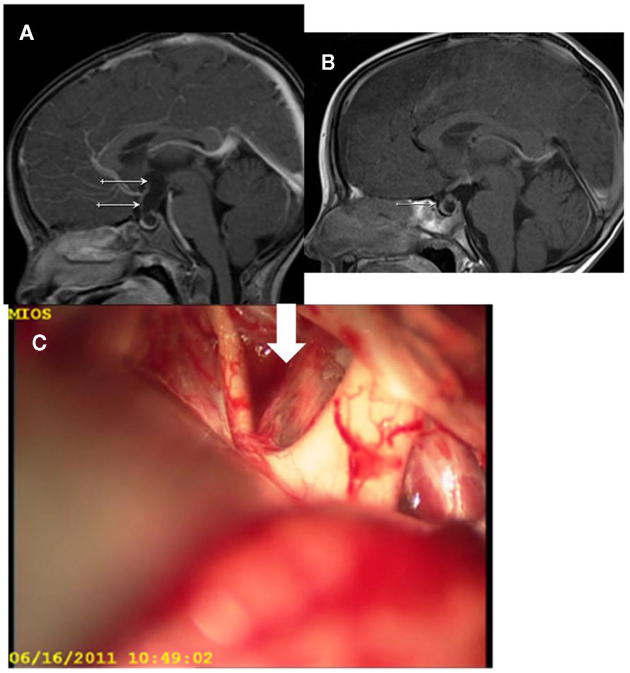

FIGURE 3 | (A,B) Pre- and postoperative MRI of a subtotal resection of a craniopharyngioma extending into the third ventricle up to the mammillary bodies in a 4-year-old child. The postoperative MRI shows remaining intrasellar cystic tumor. Because of missing pneumatization of the sphenoid sinus a transcranial, pterional approach was chosen. The pituitary stalk could be preserved in this case. The patient is under close follow-up, in case of tumor growth prior to pneumatization of the sphenoid sinus, radiotherapy will be considered. **(C)** The intraoperative photo shows the optic nerves up to the chiasm as well as the spread pituitary stalk (arrow) within the cystic tumor (see parallel running small vessels of the pituitary stalk).

well as supradiaphragmatic (cystic) Type 2 craniopharyngiomas. Reports of transsphenoidal resections of tumors within the third ventricle exist (Gardner et al., 2008; Kitano and Taneda, 2009; Coppens and Couldwell, 2010). Especially in childhood, the incomplete pneumatization of the sphenoid sinus may require extensive drilling to access the target (**Figure 2**). As mentioned, technical help of fluoroscopy, microdoppler, and neuronavigation are mandatory (**Figure 4**). It is of importance to mention, that in Type 1 lesions the pituitary is anterior of the tumor and has to be incised and moved laterally to access the tumor. For Type 2 lesions without extension into the sella, a supradiaphragmatic access is chosen, leading to an intraoperative CSF leak in all cases, which may be difficult to close. With the use of extended transsphenoidal approaches, transcranial approaches of Type 2 and also Type 3 lesions may be more and more replaced.

ENDOSCOPIC PROCEDURES

Endoscopic procedures are usually considered in occlusive hydrocephalus caused by tumor cysts of the foramen of Monroi. The small size of instruments insertable through the working canals of the endoscope allows only biopsies of the tumor and prevents larger resections. The standard access is a paramedian frontal burr hole in front of the coronal suture. After transcortical puncture of the lateral ventricle, the endoscope can be moved inside the inner CSF space through the foramen of Monroi within some limits. Besides cyst punctures and biopsies (Oppido et al., 2011), catheters can be placed under optic control (**Figure 5**).

INTRACYSTIC THERAPIES

Stereotactic placement of catheters into craniopharyngioma cysts with consecutive injection of either radioactive or chemotherapeutic agents has been performed (Steinbok and Hukin, 2010; Barriger et al., 2011). More recently, the use of interferon-alpha as a therapeutic agent was reported (Cavalheiro et al., 2010). These procedures are limited to mostly cystic lesions, which are difficult to reach by others procedures. Prior to injection of the chosen agent it has to be confirmed, that no leakage into the subarachnoid space is possible. Severe complications have been reported (Linnert and Gehl, 2009).

STRATEGIES

Complete resection of the tumor may be considered the most appealing strategy, if feasible. This strategy includes resection of the outer tumor capsule adjacent to healthy tissue and may sacrifice functional tissue, leading to endocrine dysfunction as well as hypothalamic damage. In cases of preoperative panhypopituitarism, less precautions have to be taken by the surgeon and an aggressive approach seems justified, as long as the hypothalamus is not involved. However, from our own experience as well as from the literature, a true CR is only achieved in a limited number of patients. Also, the criteria of "CR" vary, since some authors

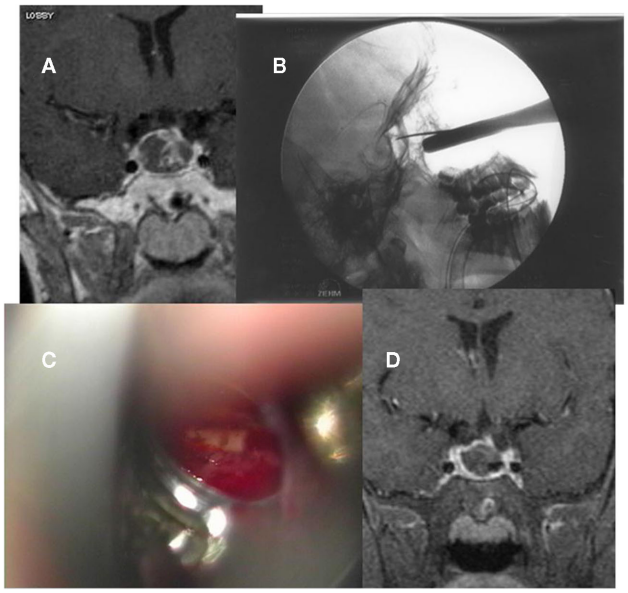

FIGURE 4 | (A) Preoperative contrast enhanced MRI showing an infradiaphragmatic tumor rest after a previous transcranial surgery of a large craniopharyngioma. **(B)** Intraoperative fluoroscopy showing the surgical approach prior to opening of the sellar floor. Notice the catheter connected to a Rickham reservoir reaching the suprasellar region, which was implanted during the previous procedure. **(C)** Intraoperative microscopic view showing the catheter tip from the sella using a special mirror technique (Lüdecke technique). **(D)** Early postoperative MRI showing the extent of tumor resection. Up to today, no recurrence is reported.

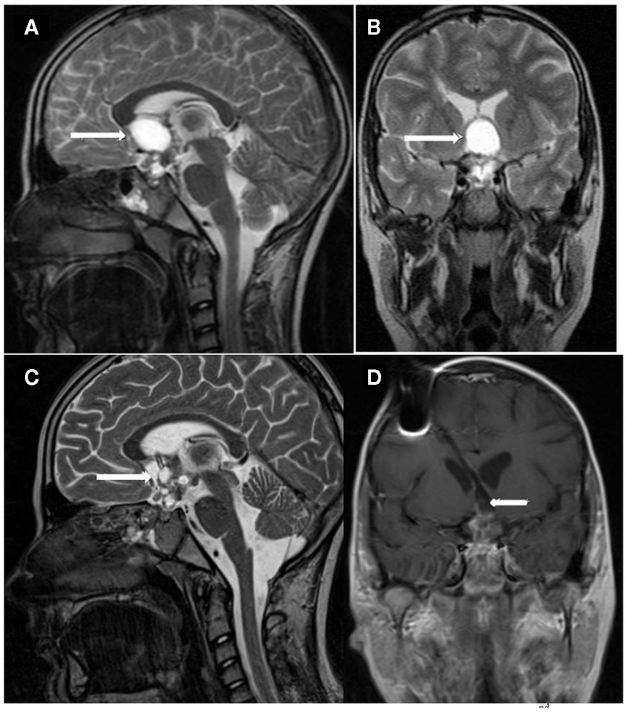

FIGURE 5 | (A,B) Preoperative solid and cystic lesion with large cyst within the third ventricle, causing headaches. T2 weighed images. **(C,D)** Postoperative MRI after endoscopic drainage of the cyst and insertion of a catheter into the cyst, connected with a frontal Rickham reservoir. Unfortunately, the infrachiasmatic cysts enlarged in size during follow-up prior to radiotherapy, requiring additional surgery (not shown).

consider the intraoperative surgical assessment, other papers a postoperative imaging study, or a combination of both. In general, Type 1 and Type 2 lesions may allow a CR without severe endocrine dysfunction, whereas in Type 3 lesions this strategy is usually combined with a high morbidity.

Gross-total resection (GTR) comprises near CR (>95%) of the lesion, leaving, e.g., calcified remnants to the pituitary stalk or minimal tumor rests within the hypothalamic tissue. This result is more frequently reported than CR, depending on the location of the craniopharyngioma. Tumor control rates seem acceptable, although combined with a high rate of endocrine morbidity. In general, radiotherapy will only be considered, after a recurrence of disease is visible in imaging studies. However, this topic is currently under investigation. The evaluation of resection extend and therefore the difference between GTR and CR should rely on imaging quality and the surgeon's intraoperative assessment but remains biased to some degree.

Subtotal resection (STR), leaving considerable tumor rests *in situ*, is a common result of craniopharyngioma surgery. For these patients, radiotherapy is considered after surgery. It is an ongoing discussion, whether radiotherapy should be administered immediately after surgery or only after proven regrowth of the residual disease. Tumor control rates of STR and radiotherapy are reported similar to GTR, however, morbidity rates seem lower.

A *Biopsy (BY)* is usually performed in cases of endoscopic cyst punctures for hydrocephalus to confirm the diagnosis or by stereotactic procedures, e.g., during catheter implantation prior to intracystic therapies.

DISCUSSION

Craniopharyngiomas are classified as WHO Grade 1 tumors. The 10 year survival rate is found to be over 90% (Mortini et al., 2011; Müller, 2011), however, morbidity is high and recurrences are common. The surgical expertise as well as the size of the tumor/site of origin seems to be the most reliable factors predicting outcome in patients with craniopharyngiomas (Reschke et al., 2006; Spoudeas et al., 2006; Zada and Cappabianca, 2010; Müller et al., 2011; Qi et al., 2011). Whereas the tumor size is an unchangeable preoperative factor, the surgical strategy can be varied in patients. Early publications already concluded, that no forceful attempt should be made to achieve CR to avoid resulting morbidity (Mori et al., 1980). Perioperative fatal complications are reported in up to 3% of craniopharyngioma surgery in recent publications (Yamada et al., 2010; Mortini et al., 2011). The "traditional" surgical strategy of choice is to aim for a complete/GTR of the lesion. Some surgeons report complete surgical removal in up to 70%, however, recurrence rates of 25% are reported by the same group (Mortini et al., 2011), leaving some doubt of the extent of resection. Therefore, the definition of complete surgical removal has to be strict to avoid misleading expectations

for follow-up. Nowadays, the intraoperative evaluation of resection extend should be confirmed by postoperative MR and CT imaging.

In cases of existing preoperative panhypopituitarism, an aggressive surgical strategy seems justified, since accompanied surgical damage is minimal. Exceptions are hypothalamic involvement; hypothalamic obesity is a feared complication especially in children. Karavitaki et al. (2005) found after a 10-year follow-up phase up to 40% of patients suffering from obesity. As known from histological specimen resected during surgery, the tumors show finger-like invasion into brain tissue (Burghaus et al., 2010). The surgical attempt to resect these parts will damage the adjacent brain tissue. Müller et al. (2011) found, that the risk of hypothalamic damage increased, when tumors extend beyond the mammillary bodies. Van Gompel et al. (2010) reported that hypothalamic signal changes in T2 weighed MR images as well as irregular contrast enhancement was found to correlate with and predict hypothalamic involvement. In another recent publication, Steno et al. (2011) found a higher morbidity after surgery for intraventricular tumors, when comparing suprasellar extraventricular tumor extension with intraventricular tumor extension.

There has been debate, whether a GTR is more favorable regarding outcome compared with STR. In terms of recurrence, Karavitaki et al. (2005) concluded, that gross-total removal provides favorable results. On the contrary, Schubert et al. (2009) found a more favorable outcome in patients with less invasive procedures compared to more radical approaches. Other authors found comparable rates of recurrence between GTR and STR combined with radiotherapy (Becker et al., 1999; Sughrue et al., 2011). Sughrue et al. performed a statistical analysis including 274 studies regarding craniopharyngioma-treatment in 2011 concluding that GTR results in higher rates of postoperative endocrinopathy and panhypopituitarism which might reach up to threefold compared to STR and radiotherapy (Sughrue et al., 2011). Recurrence rates of up to 36% after surgical treatment alone were reported by Winkfield et al. (2011) compared to recurrence rates of 5% when limited surgery was combined with postoperative radiotherapy (seven times higher risk for recurrence). As expected, the morbidity risk increases in these patients with more aggressive approaches. Sughrue et al. (2011) found that patients receiving GTR had over 2.5 times the rate of developing at least one endocrinopathy compared to patients receiving STR or STR plus radiotherapy. Abe and Ludecke (1997) concluded that the concept of subtotal removal with preservation of pituitary functions seemed justified, especially in childhood.

Regarding the surgical access strategy, it is generally accepted that the transsphenoidal approach is the first choice in infradiaphragmatic craniopharyngiomas with sellar enlargement (Abe and Ludecke, 1997; Yamada et al., 2010). Over the last years, several reports of extended approaches to suprasellar craniopharyngiomas have been published (Gardner et al., 2008; Jane et al., 2010; Yamada et al., 2010). These extended transsphenoidal approaches for supradiaphragmatic tumors are connected with a different incidence of endocrinopathies and neurological complications when compared to infradiaphragmatic lesions, especially when complete or GTR is attempted (Jane et al., 2010). CSF fistulas are another complication, which needs meticulous techniques for prevention. It seems necessary to mention, that success as well as complications are connected with the experience of the surgeon. In comparison to transcranial procedures, potential advantages include the avoidance of craniotomy and brain retraction and reduced neurovascular manipulation (Dehdashti et al., 2009). Whether the transsphenoidal approach will more and more replace transcranial techniques, has to be awaited.

CONCLUSION

The treatment of childhood craniopharyngioma requires an interdisciplinary approach. In many cases, surgical options alone provide immediate relief of compression symptoms. Restitution of preoperative pituitary insufficiencies is not common. CR cannot be achieved in many cases and without widespread consequences for the patients' quality of life. The choice of the "right" surgical approach, especially for Type 2 and Type 3 tumors, can be difficult and controversial and should – from the author's point of view – be in the hands of highly experienced neurosurgical/neuropediatric centers, offering all surgical techniques. Every patient should receive an individually tailored treatment. Recurrences are frequent and require a close and continuous follow-up of the children. Adjuvant radiotherapy should be considered after incomplete surgical resection. The best timing for postoperative radiotherapy remains to be examined.

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Treatment strategies in childhood craniopharyngioma

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The surgical management of craniopharyngiomas in children remains one of the more controversial topics in pediatric neurosurgery. Theoretically, the benign histology implies that total surgical excision would be sufficient to provide a cure. It has been widely established however, that in certain cases total excision may lead to unacceptable hypothalamic injury. The therapeutic goals for pediatric craniopharyngiomas therefore, require not just cure of the disease but also preservation of function. Over the last 15 years, there has been a growing worldwide advocacy for less extensive resection and for the utilization of multimodality therapy to limit morbidity. With this in mind, risk-adapted strategies designed to preserve hypothalamic structures have been developed. The preliminary results of these strategies appear to be encouraging. However, the long-term clinical outcome in terms of post irradiation complications and management of relapses is currently unknown.

Keywords: craniopharyngioma, children, surgery, radiotherapy, hypothalamus, quality of life

TRADITIONAL SURGICAL APPROACH

Surgery for craniopharyngiomas has long been undertaken with a degree of trepidation related in part to their intimate association to the hypothalamus and their tendency to be calcified. Resection of these lesions therefore became a testament to surgical prowess (Yasargil et al., 1990).

Historically, the fact that craniopharyngiomas are histologically benign made them an ideal target for curative radical surgical resection with one of the key goals being preservation of vision. This was particularly so at the beginning of the microsurgical era (Hoffman et al., 1977; Choux and Lena, 1979; Yasargil et al., 1990; Villani et al., 1997; Van Effenterre and Boch, 2002). Subsequent recognition of appropriate surgical approaches and the additional use of modern technologies including ultrasonic aspiration tools, image-guided techniques, and neuroendoscopy further enhanced the surgeon's ability to attain radical resection such that craniopharyngioma surgery reached a peak of enthusiasm during the 1990s. Leading figures such as Hoffman et al. (1992), Choux and Lena (1979), Pierre-Kahn et al. (1988), Caldarelli et al. (1998), and Zuccaro (2005) published large pediatric surgical series showing their surgical success in resecting craniopharyngiomas.

CRITICISM OF THE TRADITIONAL SURGICAL APPROACH

Following this enthusiasm for gross total resection, the associated mortality (up to 50% at 10 years) and the high rate of recurrence despite surgical clearance (up to 50% in some series) became apparent (Shapiro et al., 1979; Carmel et al., 1982; McLone et al., 1982; Sung, 1982; Till, 1982; Pierre-Kahn et al., 1988; Fischer et al., 1990; Yasargil et al., 1990; Hoffman et al., 1992; Hetelekidis et al., 1993; Tomita and McLone, 1993; De Vile et al., 1996b; Zuccaro et al., 1996; Villani et al., 1997; Caldarelli et al., 1998; Zuccaro, 2005).

Endocrine disorders associated with radical resection of these tumors were considered both inevitable and "acceptable." Progress in endocrinological medicine had enabled hormonal replacement that was thought to be compatible with a "normal life" (Brauner et al., 1987; Honegger et al., 1999). Endocrine dysfunction was reported in up to 75% of affected children at presentation with the most frequent being growth hormone deficiency (Thomsett et al., 1980; Brauner et al., 1987; Tomita and McLone, 1993; Villani et al., 1997; Van Effenterre and Boch, 2002). Diabetes insipidus was less frequent at diagnosis (6–35%) but its prevalence dramatically increased post-operatively (50–100%) as did panhypopituitarism (75%; Choux and Lena, 1979; Thomsett et al., 1980; Brauner et al., 1987; Yasargil et al., 1990; Hoffman et al., 1992; Tomita and McLone, 1993; Weiner et al., 1994; Crotty et al., 1995; Blethen et al., 1996; De Vile et al., 1996b; Zuccaro et al., 1996; Villani et al., 1997; Van Effenterre and Boch, 2002; Puget et al., 2007).

Peri-operative injury to the hypothalamus, incompatible with normal life due to hyperphagia, obesity, behavioral and memory disorders, loss of neurovegetative homeostasis, and an altered neuropsychological profile were also recognized (Fisher et al., 1998; Riva et al., 1998; Muller et al., 2005a; Pierre-Kahn et al., 2005; Puget et al., 2007; Bawden et al., 2009). Obesity was reported in 4–58% of children with craniopharyngiomas at diagnosis (Choux and Lena, 1979; Cabezudo et al., 1981; Carmel et al., 1982; Brauner et al., 1987; Hoffman et al., 1992; Tomita and McLone, 1993; Weiner et al., 1994; De Vile et al., 1996b; Zuccaro et al., 1996; Villani et al., 1997; Riva et al., 1998; Puget et al., 2007) but its prevalence increased dramatically, up to 81%, following surgery particularly when radical surgery had been attempted (Brauner et al., 1987; Yasargil et al., 1990; Hoffman et al., 1992; De Vile et al., 1996b; Villani et al., 1997; Riva et al., 1998; Hayward, 1999; Puget et al., 2007). De Vile et al. (1996a) showed that this obesity was related to peri-operative hypothalamic injury.

Up to 50% of children had evidence of memory and behavioral disorders following craniopharyngioma surgery. Post-operative performance scores of 1 (excellent) and 2 (good) were reported in 53–73 and 66–92% respectively, after gross total resection and partial resection with radiotherapy. These complications, associated

with aggressive surgical removal and the degree of hypothalamic dysfunction, had an impact on quality of life (Clopper et al., 1977; Hoffman et al., 1977; Cavazzuti et al., 1983; De Vile et al., 1996a; Anderson et al., 1997; Villani et al., 1997; Donnet et al., 1999; Habrand et al., 1999; Carpentieri et al., 2001; Merchant et al., 2002; Poretti et al., 2004; Pierre-Kahn et al., 2005; Sands et al., 2005; Dekkers et al., 2006; Karavitaki et al., 2006; Puget et al., 2007; Muller, 2011).

The recognition of hypothalamic involvement as the main factor associated with morbidity led many groups to develop treatment strategies to avoid hypothalamic injury (Cavazzuti et al., 1983; De Vile et al., 1996a; Fisher et al., 1998; Riva et al., 1998; Carpentieri et al., 2001; Muller et al., 2001; Poretti et al., 2004; Pierre-Kahn et al., 2005; Puget et al., 2007; Ondruch et al., 2011). Peri-operative factors that could predict hypothalamic injury were identified (De Vile et al., 1996a; Merchant et al., 2002; Albright et al., 2005; Marchal et al., 2005; Muller et al., 2005b, 2006; Thompson et al., 2005; Spoudeas et al., 2006; Garre and Cama, 2007; Puget et al., 2007). Several teams then utilized progress within radiotherapy, such as conformal planning and proton beam therapy, and built these into treatment strategies of multimodality therapy (Hayward, 1999; Merchant et al., 2002; Rutka, 2002; Spoudeas et al., 2006; Puget et al., 2007).

A NEW ERA OF SURGICAL MANAGEMENT WITH PRESERVATION OF HYPOTHALAMIC STRUCTURES

Initial craniopharyngioma management is tailored to presentation. Raised intracranial pressure or rapid visual loss is managed by treating the associated hydrocephalus and/or tumor cyst decompression. Purely cystic tumors may be managed with the placement of a catheter to allow repeated aspiration. The use of intracystic radiotherapy (Yttrium-90 and Phosphorus-32) or chemotherapy with Bleomycin has not proven to be consistently efficacious (Voges et al., 1997; Albright et al., 2005; Marchal et al., 2005; Takahashi et al., 2005; Steinbok and Hukin, 2010). With resolution of the intracranial hypertension, two-thirds of patients will experience visual improvement (Garre and Cama, 2007).

Surgical resection of craniopharyngiomas is traditionally performed via a transcranial route. The advent of the endoscope enabled utilization of a trans-nasal route with the latter having been claimed to avoid hypothalamic dysfunction (Fahlbusch et al., 1999; Zona and Spaziante, 2006). It should be noted however, that the majority of tumors approached via this route were infra diaphragmatic in location (Jane et al., 2010). The morbidity associated with transcranial resection of craniopharyngiomas is largely dependent on tumor location and may be modified by the surgical approach and treatment strategy. Thompson et al. (2005) reported their results in terms of morbidity, mortality, and tumor recurrence when comparing two series of patients, one where the goal was total resection versus one where the aim was to improve quality of life and reduce morbidity. Using a scoring grade for vision, cognition, motor function, hypothalamic dysfunction, and endocrine disturbances, they concluded that they were able to improve quality of outcome without compromising tumor recurrence in their latter series of patients.

In an attempt to analyze the role of aggressive surgical resection relative to the risk of significant morbidity associated with this approach, the authors critically reviewed a retrospective series where there had been an intention of gross total resection in all cases (Puget et al., 2007). Classification of tumors at presentation was performed in order to rationalize multimodality therapy. Specifically, the pre- and post-operative MRI were graded with respect to the degree of hypothalamic involvement/injury (**Figures 1** and **2**). As previously shown (De Vile et al., 1996a), it was confirmed that quality of life outcomes (using the Health Utility Index 2, HUI2) were correlated with the degree of hypothalamic injury as evident on the post-operative MRI ($p = 0.003$). The post-operative BMI and quality of life were linked to hypothalamic involvement as assessed on the pre-operative MRI ($p = 0.007$ and $p = 0.001$ for BMI Z score and HUI2 score respectively). This finding has subsequently been confirmed in a large, multicentre prospective study where the only independent risk factor for severe obesity, on multivariate analysis, was the degree of pre-operative hypothalamic involvement ($p = 0.002$; Muller et al., 2011) Using the MRI grading scheme described above (Puget et al., 2007). Van Gompel et al. (2010) in a large cohort of 296 adult patients, showed a good correlation between the degree of pre-operative hypothalamic involvement and post-operative weight gain ($p = 0.022$).

The likelihood of hypothalamic damage may be predicted by the degree of pre-operative hypothalamic involvement and

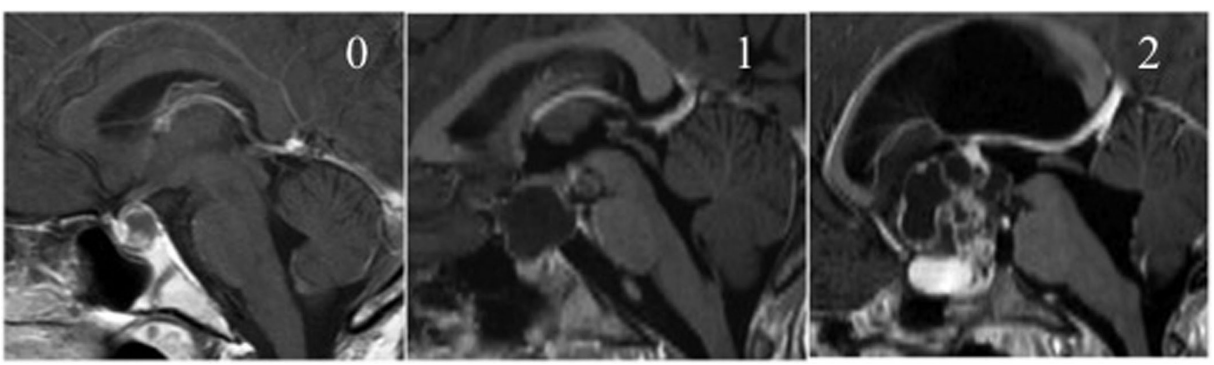

FIGURE 1 | Pre-operative MRI classification according to hypothalamic involvement. Type 0 pre-op: no involvement of the hypothalamus, Type 1 pre-op: distortion/elevation of the hypothalamus, Type 2 pre-op: the hypothalamus is not visible due to tumor invasion.

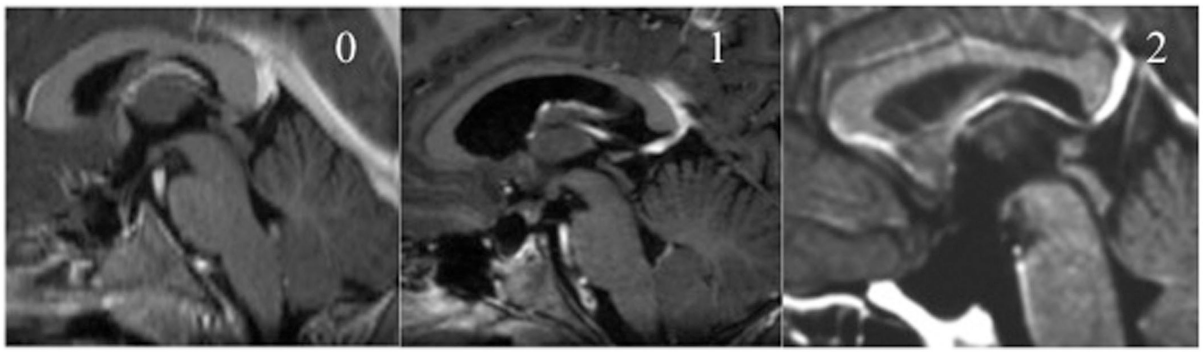

FIGURE 2 | Post-operative MRI classification according to hypothalamic injury. Type 0 post-op: intact hypothalamus, Type 1 post-op: breech/residue on the hypothalamus, Type 2 post-op: severe hypothalamic injury.

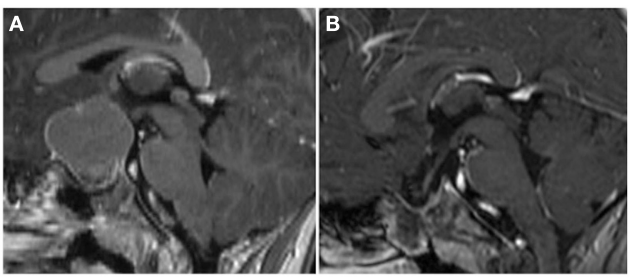

FIGURE 3 | Surgical strategy grade 0/1 pre-op. (A) On the pre-operative MRI, the hypothalamus appeared to be more displaced than invaded by tumor (Type 1 pre-op). **(B)** This was confirmed during surgery and a complete removal preserving the hypothalamus could be achieved (Type 0 post-op).

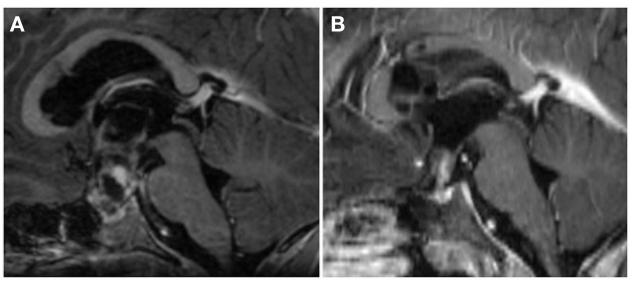

FIGURE 4 | Surgical strategy grade 2 pre-op. (A) At referral, the patient had severe intracranial hypertension secondary to obstructive hydrocephalus from a large intraventricular cyst of the third ventricle. An Ommaya reservoir was placed within the cyst as a matter of urgency. The tumor clearly invaded the hypothalamus (Type 2 pre-op) therefore the goal of surgery was to perform a subtotal removal leaving that component. **(B)** The residual lesion, attached to the infundibulum, which could not safely be removed.

surgical skill (Sanford, 1994; Boop, 2007; Puget et al., 2007). Treatment strategies should therefore be adapted to the degree of pre-operative hypothalamic involvement, MRI type 0, 1, and 2, in order to minimize morbidity. For those where the craniopharyngioma does not involve the hypothalamus (type 0 pre-op), total resection is suitable (**Figure 3**); when the tumor compresses the hypothalamus (type 1 pre-op), total resection may still be the best solution. However, the outcome will depend on the surgeon's skill in this domain. Finally, when the tumor involves the hypothalamus (type 2 pre-op), subtotal resection with respect to the involved hypothalamus combined with local irradiation currently appears to be the better option (**Figure 4**).

This surgical strategy was analyzed in a prospective series of 70 childhood craniopharyngiomas treated in our institution since 2002. Based on the above algorithm, half of the patients had a total removal; the others received radiotherapy after incomplete removal. We observed a significant statistical decrease in morbid obesity and in BMI *Z* scores in our prospective series when compared to the historical cohort (publication in press).

Children treated with an intention to avoid hypothalamic injury had less endocrine dysfunction than those previously reported in pure surgical series. Questions are starting to be raised about the "normality" achieved despite hormone replacement as more subtle issues such as fertility, adult growth hormone deficiency, and its association with low bone mineral density are being critically reviewed (Islas Cruz et al., 2004; Poretti et al., 2004; Holmer et al., 2011).

THE ROLE OF RADIOTHERAPY

In a recent extensive review of the literature, Kiehna showed that radiotherapy may provide long-term tumor control for pediatric craniopharyngiomas, with the more recent studies reporting at least 80% disease control at 10-years (Habrand et al., 2006; Kiehna and Merchant, 2010) and a favorable functional outcome in 42–86% of cases (Kiehna and Merchant, 2010). The main criticism of incorporating radiotherapy into a treatment strategy has been the well documented associated risks of late-onset vascular damage (particularly Moya–Moya syndrome; Sanford, 1994), secondary tumor genesis (Kranzinger et al., 2001; Caldarelli et al., 2005; Aquilina et al., 2010), and late cognitive effects (Merchant, 2006). Merchant et al. (2002) found a significant difference in full-scale IQ following gross total resection compared to limited resection followed by irradiation (9.8 points versus 1.25 respectively). They

also showed that IQ remained stable over 5 years of follow-up (Merchant, 2006).

Conformal radiation therapy is currently considered the most appropriate radiation technique for this disease inducing less neurocognitive dysfunction when compared to conventional external beam radiotherapy (Kiehna et al., 2006; Scarzello et al., 2006; Minniti et al., 2007; Kiehna and Merchant, 2010) with favorable outcomes occurring in at least 85% of children (Merchant et al., 2002). There is a growing interest in proton beam irradiation in this disease with its potential to reduce the incidence of neurocognitive disorders and the late effects of irradiation to the optic pathway and hypothalamus. Preliminary results are promising (Baumert et al., 2004; Fitzek et al., 2006; Luu et al., 2006). For Merchant and his team, proton therapy has the potential to significantly reduce whole-brain and -body irradiation (Beltran et al., 2012) and, using dose-cognitive effects models, have shown that a reduction in the lower-dose volumes or mean dose would have long-term, clinical advantage for children with craniopharyngiomas (Merchant et al., 2008). They also compared photon- and proton-based irradiation methods to determine the effect of tumor volume change on target coverage and normal tissue irradiation in craniopharyngiomas. They have shown that proton therapy efficacy and safety is highly sensitive to target volume changes. In light of this and the findings of Merchant we believe that it is important that irradiation is targeted to a mostly solid lesion with cystic components aspirated or resected prior to irradiation.

The risk of progression following incomplete resection alone is 71–90% whereas it is estimated to be in the order of 15–20% when followed by radiotherapy (Fischer et al., 1990; Habrand et al., 1999; Kiehna and Merchant, 2010). Muller et al. (2011) has shown in a prospective multicentre analysis that the risk of progression was 88% lower in irradiated patients than in patients without radiotherapy. However long-term follow-up, beyond the 5- to 10-years necessary to assess tumor recurrence relative to functional outcome, is lacking.

The most appropriate timing for radiotherapy following incomplete resection is still unknown. Moon et al. (2005) advocate early radiotherapy to improve quality of life rather than at tumor progression with further surgery and a potentially worse outcome. The optimal timing to prevent tumor recurrence following incomplete resection is currently being investigated in an international trial (Muller et al., 2011). This issue is of critical interest as the natural history of craniopharyngioma residua remains unpredictable with currently no clinical, radiological, or histological features able to differentiate those which will behave aggressively from those which will stay quiescent for many years.

THE ROLE OF BIOLOGY

The identification of specific biological markers of aggressiveness may therefore help to stratify patients and guide the development of risk-adapted strategies and novel treatments. To date, only a few studies have given insight into craniopharyngioma biology. Kato et al. (2004) showed nuclear/cytoplasmic accumulation of β-catenin in typical adamantinomatous type craniopharyngiomas. Moreover, β-catenin mutations have been found in a subset of adamantinomatous type craniopharyngiomas but not in other pituitary tumors (Sekine et al., 2002; Kato et al., 2004; Oikonomou et al., 2005). These findings suggest that the pathogenesis of pediatric craniopharyngiomas is associated with abnormalities of Wnt signaling, but thus far is unable to predict craniopharyngioma progression. Interestingly, in a mixed series of adults and pediatric craniopharyngiomas, Lefranc et al. (2003) found low levels of retinoic acid receptor β (RARβ), galectin-3, and Macrophage migration Inhibitory Factor (MIF) and high levels of retinoic acid receptor γ (RARγ) to be associated with a higher risk of relapse. The role of these proteins in craniopharyngioma pathogenesis is still unclear. The role of estrogen and progesterone receptors (ER and PR respectively) has been described in another mixed series (Izumoto et al., 2005) showing that positive immunostaining for these markers was inversely linked with the risk of relapse. The main criticism of these papers is the lack of multivariate analyses and the lack of analysis of the quality of resection.

CONCLUSION

The morbidity and mortality after total resection of pediatric craniopharyngioma is well documented. There is an increasing advocacy among experts for limited resection followed by radiotherapy in specific cases. With a more conservative approach becoming universally adopted it is important not to ignore those who present as an absolute surgical emergency with hydrocephalus or chiasmatic compression. Total resection must remain the goal for those craniopharyngiomas that do not involve hypothalamic structures. For the rest, we now have a wealth of knowledge and modern techniques in imaging, surgery, and radiotherapy at our disposal to customize treatment thereby avoiding hypothalamic injury with its consequent devastating effects. In the swinging pendulum from aggressive to conservative treatment (Sainte-Rose et al., 2005), we need to be cognizant not only of our surgical limitations but also the limitations of other treatment modalities.

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Stereotactic neurosurgical treatment options for craniopharyngioma

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Craniopharyngioma are the most common non-glial tumors in childhood. The results of different studies indicate that radical excision surgery is not an appropriate treatment strategy for childhood craniopharyngioma with hypothalamic involvement. Stereotactic neurosurgery provides save, minimal invasive and cost-efficient options in the treatment of childhood craniopharyngioma. In this review a summary of the contribution of the stereotactic neurosurgery in the interdisciplinary treatment regime of childhood craniopharyngioma will be given and discussed in detail.

Keywords: stereotactic neurosurgery, craniopharyngioma, stereotactic biopsy, internal drainage, cyst puncture, childhood craniopharyngioma, minimal invasive, ventriculocystostomy

INTRODUCTION

Craniopharyngiomas are the most common non-glial tumors with an incidence of 0.5–1.0 per million new patients per year, of which 30–50% occur in childhood. In children, they are often of the adamantinomatous type with cyst formations and are frequently associated with a mutation of the beta-catenin gene (Müller, 2010). These benign tumors are located in the sellar and parasellar regions and are typically semisolid, cystic, and calcifying. Compression or infiltration of the surrounding structures, such as the optic chiasm, hypothalamus, and the floor of the third ventricle, is common.

Over the last 40 years there exists an open-ended controversy concerning the best treatment for craniopharyngioma. One group favors open surgery which is in many cases associated with increased morbidity. The other group proposes minimal-invasive procedures combined with subsequent radiotherapy to minimize risk and morbidity.

Due to the high variability in the appearance of these tumors the treatment strategy must be individually tailored to the patient. Important parameters for treatment planning are the volume of the solid part of the tumor, the presence and volume of cysts, its proximity and adhesion to the hypothalamus, the compression of optical structures, the overall neuro-ophthalmological, and endocrinological state.

Microsurgical resection should be preferred when the solid part of the tumor is large and space occupying and if there is a good chance for a total resection with low risk, especially of a hypothalamic syndrome. A similar approach is also valid for many intrasellar and transsphenoidally accessible tumors. In contrast, if the solid part of the tumor is small or if there is a substantial risk for a visual or endocrinological degradation or a hypothalamic syndrome an alternative interdisciplinary approach, including stereotactic procedures, should be considered (Ostertag et al., 2003).

The stereotactic approach can facilitate the histopathological diagnosis from a stereotactic serial biopsy obtained from the solid part of the tumor or from the wall of a cyst (Tilgner et al., 2005). Furthermore, in the case of cysts, this approach can be used to evacuate the cystic parts of the lesion by aspiration or perform an internal drainage (ventriculocystostomy) by the implantation of a catheter. Cyst evacuation results in decreased compression of the surrounding structures (optical pathway, hypothalamus) and reduction in the total volume of the lesion, which prepares it for a possible subsequent, small volume, fractionated, external radiotherapy (Schubert et al., 2009; Veeravagu et al., 2010).

Stereotactic procedures are applied under general anesthesia for children, whereas juveniles and adults are mostly treated using local anesthesia (**Figure 1**). Optimized planning of the stereotactic approach is accomplished on a stereotactic workstation (STP, Stryker-Leibinger, Freiburg, Germany or Precisis Plus, Inomed, Emmendingen, Germany; **Figure 2**) based on preoperatively acquired high resolution MRI (MP-Rage post contrast and T2 – Space, 1 mm, transversal or longitudinal orientation, Avanto, Siemens, Germany,) and intraoperative computed tomography (1 or 2 mm, transversal, Somatom Plus, Siemens, Germany) following stereotactic head fixation. Image fusion is performed, which allows stereotactic planning in any imaging modality with good visualization of the tumor, cysts, calcifications, optic pathway, hypothalamus, pituitary stalk, vessels, and nerves.

A small skin incision is performed (∼12 mm), followed by a stereotactically guided burr hole. A probe with 1.4 mm diameter is advanced to the cyst, and a biopsy is taken from the cyst's wall. Then, the content of the cyst is aspirated and the detritus is washed out by rinsing with body-temperature saline solution. The cyst is left either emptied or refilled with saline solution if a Rickham catheter is to be placed (either for inner drainage or with a subcutaneous reservoir for later transcutaneous punctures

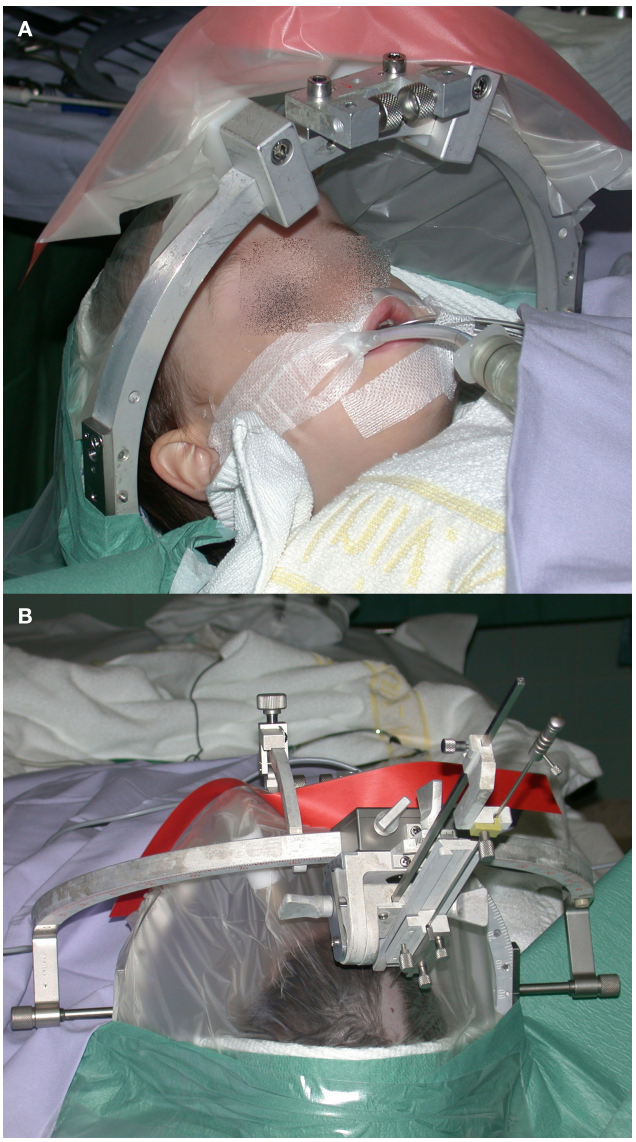

FIGURE 1 | (A) Child fixed in a stereotactic ring under general anesthesia in preparation for a stereotactic procedure. **(B)** Stereotactic aiming bow with a probe pointing to the shaved frontal entry point.

or treatment; **Figure 3**). The total time for the procedure is 60–90 min, followed by three to five in-patient days. Perioperative stress prophylaxis with hydrocortisone and optional single-shot antibiosis are applied. Following the procedure the liquid balance is documented in order to detect a temporary central diabetes insipidus, which would require Desmopressin substitution.

Before making a possible catheter implantation, a preliminary intraoperative histopathological diagnosis is obtained from a stereotactic biopsy taken from the cyst wall and is confirmed by the presence of cholesterol crystals in the cyst fluid.

The stereotactic procedure can be followed by a high precision, small volume, fractionated, external radiotherapy (30–40 Gy) depending on tumor growth, patient's age, and taking into account aspects like the possibility of genesis of secondary tumors in the low dose areas. For slow-growing craniopharyngioma there are arguments for protecting the developing brain of small children by delaying the time of irradiation to an age older than 6 years.

In the case of a tumor cyst recurrence following open resection and percutaneous irradiation some centers use local intracavitary irradiation by instillation of ^{32}P (Zhao et al., 2010), ^{90}Y (Blackburn et al., 1999; Kolumbán et al., 2011), colloidal ^{186}Re (Derrey et al., 2008; Guo et al., 2010), or ^{198}Au (Tian et al., 1992) radioisotopes to induce fibrosis in order to suppress cyst fluid production. This is done by using stereotactically implanted catheters with subcutaneous reservoirs. Other groups describe the intracystic bleomycin therapy (Hukin et al., 2007) to induce cyst sclerosis with the intent to delay the need for surgery or radiation therapy for a few years. Serious or even fatal adverse events and long-term neurotoxicity have been reported for bleomycin use (Savas et al., 2000). For these intracavitary therapies the catheter-system must first be radiologically controlled after contrast injection before initiating therapy to avoid leakage or a connection to the ventricular system, which could induce serious, adverse side effects. Brachytherapy by the stereotactic implantation of temporary ^{125}I-seeds in the solid part of a craniopharyngioma is also a possible treatment option (Barlas et al., 2000; Schubert et al., 2009).

Stereotactic neurosurgery can deliver several options for permanent internal drainage in a multidisciplinary approach following limited resection when recurrent cysts become space occupying, compress the optical pathway, or block the foramina Monroi: The stereotactic implantation of catheters connecting the ventricular system with the cyst (Schubert et al., 2009), the stereotactically guided endoscopic fenestration of cyst walls, or a combined stereotactic/endoscopic stent-assisted ventriculocystostomy (Berlis et al., 2006). In a series of eight patients, Pettorini et al. (2009) reports the use of neuroendoscopic positioning of intracystic catheters for treatment of craniopharyngioma as being safer than stereotactic approaches. This observation could not be confirmed in our series.

CLINICAL SERIES

From 1990 to 2010, 208 (total group) stereotactic procedures in patients with craniopharyngioma were performed in the Department of Stereotactic Neurosurgery in Freiburg. Seventy of these patients were under the age of 18 ("children," 33 male, 37 female), 138 were older ("adults," 67 male, 71 female). Eighty-three percent (children) and 10% (adults) had treatment under general anesthesia. Sixty-one percent (children) and 60% (adults) had a cyst puncture. Twenty-one percent (children) and 43% (adults) underwent a stereotactic biopsy. Twenty-nine percent (children) and 15% (adults) underwent ventriculocystostomy by the implantation of a catheter. No procedure related lethality or permanent morbidity was observed with these patients. The patients were followed for 10.5 ± 5.3 years (median) and the 5/10-years progression-free survival was 82/80%, respectively. In the group of children, following stereotactic treatment, the patients' vision improved in 61%, remained unchanged in 39%, and the visual field ameliorated in 75% or remained stationary (25%). While 6% experienced temporary minor visual degradation, which recovered within days, there was no permanent visual deficit due to stereotactic surgery. Following cyst drainage the endocrinological

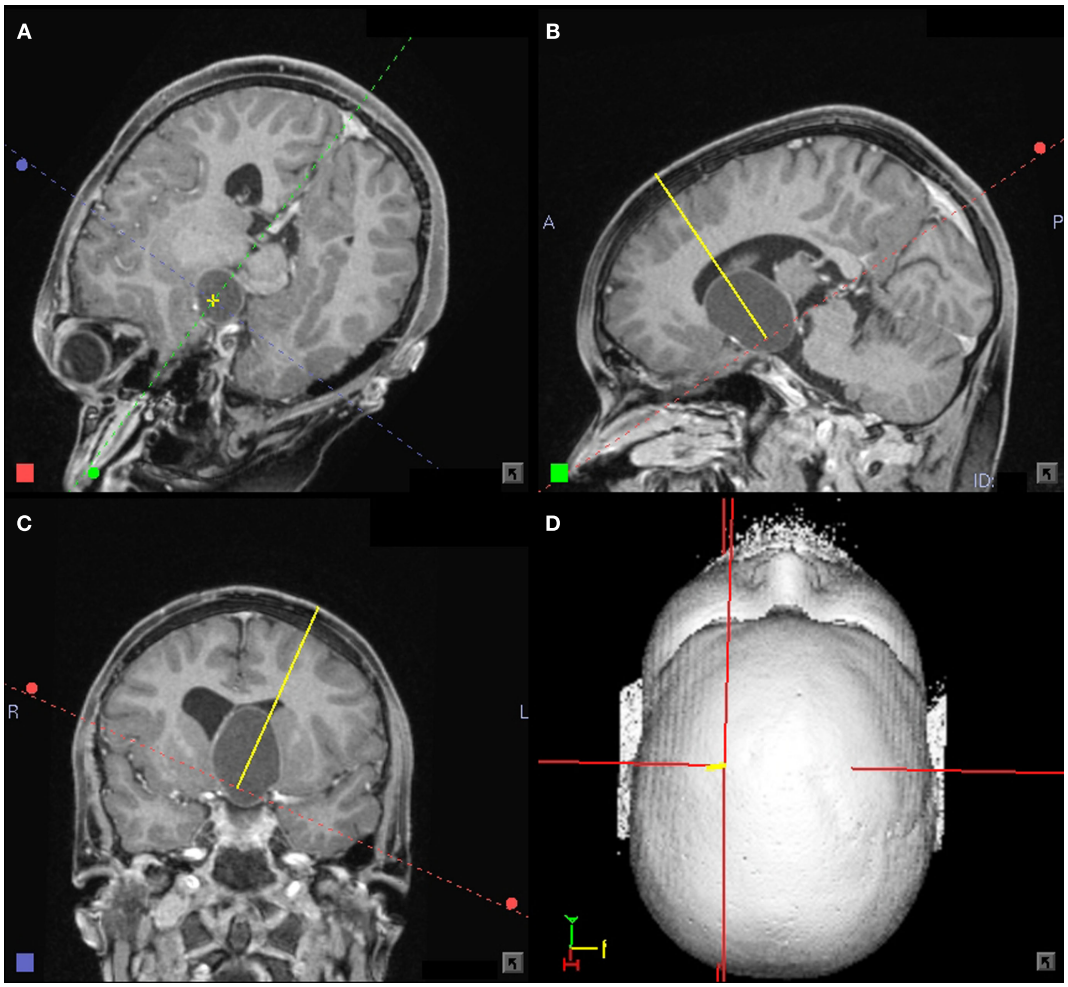

FIGURE 2 | (A–D) Eleven-year-old boy with a large craniopharyngioma cyst. Planning for a stereotactic biopsy and a cyst puncture with subsequent internal drainage showing the trajectory in an approach oriented view. Stereotactic planning system: STP4 – workstation (Stryker-Leibinger, Freiburg, Germany).

state remained unchanged in 93%. Temporary treatment with Desmopressin was necessary in 6% of the patients due to diabetes insipidus. There was no permanent, additional endocrinological deficit observed due to the stereotactic procedure (Guthoff, 2000; Ostertag et al., 2003).

In a retrospective study Schubert et al. (2009) compared three groups of children (<18 years of age) with craniopharyngioma ($n = 32$). The first group included patients treated with microsurgical resection. The second group underwent stereotactic cyst drainage, implantation of a Rickham catheter, and fractionated three-dimensional conformal multi-field radiotherapy with 54 Gy volume dose. The third group received various combined approaches. In this study, the 8.5-years of freedom from tumor recurrence was 24% in the resection group as compared to 71% for children with combined stereotactic and radio-therapeutic treatment ($p = 0.05$). There was no permanent postoperative morbidity related to stereotactic cyst puncture and drainage. Two children with preoperative visual impairment improved, the endocrinological state was constant. At last follow up, obesity was reported in four patients (24%) in the resection group as compared to one patient (14%) in the stereotactic cyst drainage group. All groups identified tumor recurrence as a criterion for a less favorable outcome. Combined stereotactic and radio-therapeutic treatment leads to good, long-term tumor control, and quality of life due to a low morbidity rate.

DISCUSSION

Stereotactic neurosurgery offers useful minimal-invasive treatment options in the interdisciplinary treatment regime of craniopharyngioma. These options must especially be considered if the solid part of the tumor is small, if there is a hypothalamic involvement, or if the probability for a complete resection is not favorable (Yaşargil et al., 1990). The results of the Kraniopharyngeom 2000 study indicate that radical excision surgery is not an appropriate treatment strategy for childhood craniopharyngioma with hypothalamic involvement (Müller, 2010, 2011; Steňo et al., 2011).

Childhood craniopharyngiomas are a rare tumor entity. Therefore, many clinical series reported in the literature comprise only a limited number of patients (Backlund et al., 1989, $n = 42$;

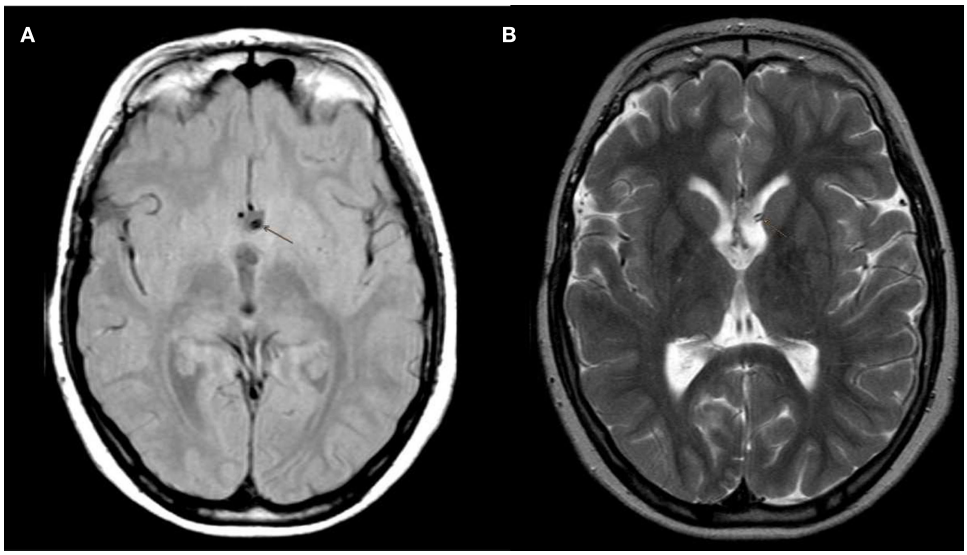

FIGURE 3 | (A,B) Postoperative MRI (T1 and T2 weighted) control showing the Rickham catheter for internal drainage ending in the shrunken hypothalamic cyst.

Hoffman et al., 1992, $n = 50$; Schubert et al., 2009, $n = 32$). In contrast, standardized prospective international multicenter studies, like Kraniopharyngeom 2007, which are based on a consensus of international brain tumor committees, applying identical datasets, can easily increase the cohort size, facilitate data evaluation, and can thereby advance scientific evidence (Müller, 2010).

Stereotactic biopsy can easily facilitate the histopathological diagnosis. The target volume can be significantly reduced by the evacuation and drainage of large cysts preceding fractionated external radiation therapy. Stereotactic neurosurgical methods provide safe, minimally invasive, and cost-efficient treatment options in the interdisciplinary treatment of craniopharyngioma. The final approach should be tailored and discussed in an interdisciplinary and specialized tumor board in a dedicated and experienced center before starting the treatment.

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Intracystic therapies for cystic craniopharyngioma in childhood

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Introduction: Craniopharyngioma of childhood are commonly cystic in nature. An intracystic catheter insertion and subsequent instillation of substances inducing cyst shrinkage seems a beneficial strategy avoiding additional morbidity in a highly vulnerable brain location. **Methods:** A systematic review of the medical literature was performed to identify potentially relevant, all languages articles using Ovid MEDLINE and EMBASE from inception to July 2011 and Cochrane Central Register of Controlled Trials to third quarter 2011. All references were examined for relevancy. **Results:** Of 142 unique references, 71 referred to substances used for intracystic craniopharyngioma treatment. General aspects of intracystic catheter insertion as well as response rates, risks, and outcomes of children treated with intracystic radioisotopes, bleomycin, and interferon (IFN) are critically reviewed and an outline for potential future endeavors provided. **Conclusion:** IFN seems currently the intracystic substance with the best benefit risk ratio. The authors advocate for consensus on prospective data collection and standardized intracystic treatment strategies to allow reliable comparisons and herewith optimize treatment and outcome.

Keywords: intracystic therapy, craniopharyngioma, radioisotopes, bleomycin, interferon, children

INTRODUCTION

Craniopharyngioma of childhood are commonly cystic in nature. These tumors are histologically benign, corresponding to WHO grade I and are usually not life threatening. Benign lesions in the brain are considered cured when amenable to surgical resection, however even gross total resection of craniopharyngioma is not always curative and may be associated with significant additional morbidities (Müller, 2010). Craniopharyngioma diagnosed in childhood will affect the developing child, the maturing brain and body via effects on the visual, endocrinological, metabolic, and neurocognitive functions in a more significant way as compared to adults. Therefore the Hippocrates' basic principle "to help or at least to do no harm" is the ultimate challenge when determining the best means for treating childhood craniopharyngioma and minimizing morbidity is a major goal.

Hence the prospect of a minimally invasive intervention – such as an endoscopic insertion of a catheter with a subcutanous Ommaya reservoir – and subsequent instillation of substances inducing shrinkage of the craniopharyngioma cyst(s), seems a promising strategy. The following article reviews the experiences and outcomes of children treated with intracystic therapies providing a critical summary and an outline for potential future endeavors.

METHODS

A systematic review of the medical literature was performed to identify potentially relevant, all languages articles using Ovid MEDLINE and EMBASE from inception to July 2011 and Cochrane Central Register of Controlled Trials to third quarter 2011. The search strategy comprised a text search with medical subject headings (MeSH) and free text terms used in combination including craniopharyngioma, intracystic treatment, cyst*, antineoplastic, and antibiotic. The total retrieval was 211 references from the 3 databases. All references were saved in an EndNote library used to identify the 69 duplicates for a total of 142 unique references. All references were examined for relevancy.

RESULTS

NEUROSURGICAL ASPECTS OF INTRACYSTIC CATHETER INSERTION

Fenestration as a "minimal" surgical intervention in the treatment of cystic craniopharyngioma was employed by Cushing in 1930. He and others recognized early on that the benefit from this intervention was of short duration with recurrence of symptoms within a short period of time (Kramer et al., 1961). This still holds true in a recent study which confirmed high recurrence rates when surgery was limited to cyst fenestration even with combined adjuvant Gamma knife surgery (Park et al., 2011).

An insertion of a catheter into a cystic craniopharyngioma may prevail over the transient success of a cyst fenestration by allowing repetitive drainage of the tumor cyst and the opportunity of instillation of intracystic substances. Different neurosurgical techniques are employed for the placement of catheters.

Surgical strategies for intracystic catheter placement are reported in a retrospective review of 50 cystic craniopharyngioma patients treated at two French (Paris, Marseille) and three Brazilian (Belo Horizonte, Goiânia, São Paulo) institutions between 1990 and 2000. The authors distinguish three different patient groups according to the different surgical approaches. Although

with limited certainty from the data provided, the study included mainly pediatric patients. There is an age range (9 months to 21 years) given for the 25 female patients; a median age of 10 years is indicated for the male patients. Group one ($n = 26$) had their catheters placed either via frontal or pterional craniotomy under direct vision. Group two ($n = 14$) underwent stereotactic placement and group three ($n = 11$) had free hand placement through a burr hole. All catheters were connected to either a Rickham ($n = 23$) or an Ommaya reservoir subcutaneously. One to two weeks after the surgical intervention a permeability study (injection of contrast medium into the cyst via reservoir) using either X-ray or CT was undertaken revealing contrast leakage or misplacement of the intracystic catheter in eight children (16.3%). This study did not find a difference in complications between the three different surgical methods and reported that no other catheter placement related complication occurred in this series (Zanon et al., 2008).

Pettorini et al. (2009) advocate that neuroendoscopic positioning of the catheter is a safer option than open or stereotactic approaches. In their case series of eight patients (five children with a mean age 3.8 years) with symptomatic cystic craniopharyngioma the placement of the catheter via endoscopy with a Storz rigid ventriculoscope was without complications except one technical failure (12.5%). The technical failure occurred in a child with an extensively calcified cyst wall that made positioning of the catheter impossible. For planning reasons a pre-op CT seems important as calcifications could be missed on MRI scans which are commonly the preferred imaging modality in children in order to minimize radiation exposure. Other advantages in using the endoscopic approach are the possibility to perform a septostomy at the same time, an intervention that establishes connection between lateral ventricles and subsequently facilitates successful shunting.

Stereotactic endoscopic technique as a safe and effective procedure for catheter insertion in cystic craniopharyngioma is supported by Joki et al. (2002). Hellwig et al. (1995) describe effective management in more than 70 cystic intracerebral space occupying lesions without major tissue traumatization. They reported an operative morbidity of less than 3% and no operative mortality.

There are anatomic constraints that may limit the stereotactic accessibility of a craniopharyngioma cyst which relate to infra- or suprasellar location and the vulnerability of the adjacent critical structures such as optic apparatus, pituitary gland, and hypothalamus (Floyd et al., 2009).

The experience of the operating neurosurgeon in a certain technique will ultimately affect the outcome. Interestingly in a study by Sanford (1994) the experience of the operating neurosurgeon was proven statistically significant with respect to the quality of life of craniopharyngioma patients.

INSTILLATION OF SUBSTANCES

The majority of cystic craniopharyngioma arise from squamous epithelium (Ingraham and Scott, 1946; Kramer et al., 1961; Louis et al., 2007). Intracystic instilled substances should have the ability to destroy the secretive properties of the epithelial cell lining to induce cyst shrinkage and ideally subsequent adhesion of the cyst wall. Substances should remain within the cyst and should not cause any harm to the surrounding brain in case of leakage. Substances used for cystic craniopharyngiomas have been radioisotopes, Bleomycin, and Interferon (IFN) (**Table 1**).

Intracystic instillation of β *emitting radioisotopes* including aurum^{198}, rhenium^{186}, yttrium^{90}, and phosphorus^{32} has been reported successful in inducing craniopharyngioma cyst shrinkage in multiple studies over more than four decades (Backlund, 1973, 1989; Musolino et al., 1985; Voges et al., 1997; Hasegawa et al., 2004).

While phosphorus^{32} is the only β emitting radionucleotide available for use in the USA, rhenium^{186}, yttrium^{90}, and phosphorus^{32} are available and used in Europe (France/Hungary/Germany) (Voges et al., 1997; Julow et al., 2007; Derrey et al., 2008). Physical characteristics of β emitting radioisotopes may determine preferences. Some authors favor phosphorus^{32} with a lower energy (mean β energy of 0.69 MeV), longer half life (14.3 days), and less tissue penetration (2–8 mm; Pollock et al., 1995) while others argue that yttrium^{90} (mean β energy of 0.93 MeV, 2.7 days half life, tissue penetration 11 mm) is superior due to its higher emitting dose during a shorter time period (Blackburn et al., 1999). Clinical studies, mostly institutional retrospective series, are equivocal regarding the clinical superiority of a radioisotope. Voges et al. (1997) observed no cyst response to intracystic rhenium^{186}, while intracavitary irradiation using yttrium^{90} or phosphorous^{32} was highly effective resulting in 79.5% response rates. In a more recent study including 11 children within 42 eligible patients, the instillation of colloidal rhenium^{186} resulted in 74% response rate including 17 patients with complete cyst retraction and 12 patients with >50% reduction in cyst volume (Derrey et al., 2008). Barriger et al. (2011) report an overall cyst control rate of 67% with intracystic phosphorus^{32} in 19 patients between 3 and 54 years of age.

Radioisotope doses require adjustment to cyst volume. The optimal prescribed dose to the cyst wall is 200–300 Gy (Hechtman et al., 2005; Sadeghi et al., 2007) up to 400 Gy with significant increased risks especially to the optic apparatus once doses surpass 400 Gy (Derrey et al., 2008; Floyd et al., 2009). There is evidence that cyst volumes exceeding 100 ml will not respond well (Albright et al., 2005).

Instillation of phosphorus^{32} into a recurrent infrachiasmatic cystic craniopharyngioma of a 36-old-female via an neuroendoscopic transnasal route was described recently (Floyd et al., 2009) and is certainly an elegant minimal invasive intervention. A therapeutic effect was achieved with one instillation only and therefore the insertion of a permanent catheter with reservoir was not required. However a catheter implantation is usually employed for radioisotopes injection and removal (Derrey et al., 2008).

Access to radioisotopes is only available in a limited number of institutions requiring sophisticated equipment and a multidisciplinary team of experts and there is advocacy using this treatment approach only for tumors that recur after both surgery and external beam radiation therapy (Becker et al., 1999; Merchant et al., 2006).

In 1974 the effect of *bleomycin* for cultured craniopharyngioma cells and intracystic concentration of bleomycin was published by Kubo et al. (1974). Based on their morphological observations of destruction of cell arrangement, cytolysis, and karyopyknosis they concluded its local cytotoxic potency to craniopharyngiomas.

Table 1 | Intracystic treatment modalities in craniopharyngiomas – retrospective reviews including children.

Reference	Patients (kids)	*Median*/mean age (range) in years	CR	PR	*Median*/mean f/up (range) in years	*Median*/mean PFS (range) in years	Reported complications or toxicities
ISOTOPES							
Pollock et al. (1995)	30 (10)	35 (3–70)	0.10	0.83	3.1 (0.6–9.7)	NR	Three new behavioral problems, visual decline, three new onset DI
Voges et al. (1997)	62 (32)	*17* (4–71)	0.45	0.35	*11.9* (1.5–16.4)	NR	Three amaurosis, one visual field cut, three endocrine deficits, one death 9 months after treatment
Hasegawa et al. (2004)	49 (15)	29 (3–74)	0.17	0.59	4.1	NR	Visual or endocrine deterioration
Julow et al. (2007)	60 (13)	27.7 (2.9–67.5)	0.45	0.30	NR	NR	Three visual deterioration, six transient CN III palsy, one death/meningoventriculitis 6 weeks after intervention, two hypothalamic/thalamic vascular injury
Derrey et al. (2008)	42 (11)	38.7 (5–85)	0.44	0.44	3.6 (0.7–12.3)	NR	Two septic meningitis, two chemical meningitis, one intracranial hypertension, two central hyperthermia; three visual acuity or field decline, one memory loss
Barriger et al. (2011)	19 (NR)	20 (3–54)	0.05	0.26	*5.2* (0.7–11.3)	*0.8* (0.1–4.5)	Six increased pituitary deficiencies, one new field deficit
BLEOMYCIN							
Takahashi et al. (1985)*	(7)	8.4 (2–13)	NR	NR	NR (21–26)	12 (0.1–26)#	Transient mild fever
Hader et al. (2000)	(9)	8.4 (2.5–14)	0.14	0.71	3 (0.5–5)	NR	Two transient headaches and fever, one panhypopituitarism
Mottolese et al. (2001)	24 (20)	14.3 (0.25–64)	0.38	0.63	5	5 (2–10)	One blindness (after toxic dose) +
Park et al. (2002)	10 (5)	30.2 (3–65)	NR	NR	2.8 (1–6.6)	NR	One visual disturbance, one cerebellar infarction/death, one hypersomnia/memory impairment, one transient mental changes, one bedridden
Mottolese et al. (2005)	(24)	NR (6–16)	0.50	0.25	6.7 (1–14)	NR	One blindness (after toxic dose)+; three new onset of DI, 11 endocrine insufficiency, visual deterioration
Takahashi et al. (2005)	(11)	NR (2–14)	0.27	0.64	NR (3–16)	NR	One hypothalamic–pituitary insufficiency/death during f/up
Hukin et al. (2007)	(17)	*6* (1–14)	0.29	0.35	*5* (0.5–10.2)	*0.7* (0.3–6.1)$	Decreased level of consciousness/ panhypopituitarism, one multiple CN deficits/hemiparesis
Hsu et al. (2009)	(9)	*7.8* (3.3–11.8)	NR	NR	*3.7* (0.8–6.6)	*2.4* (0.2–6.6)	NR
INTERFERON							
Cavalheiro et al. (2005)	(9)	10 (1.8–18)	0.78	0.22	1.8 (1–3.5)	NR	One arthralgia/chronic fatigue/depression
Ierardi et al. (2007)	(21)	10 (1–19)	0.50	0.50	2.25 (0.5–4)	NR	NR
Cavalheiro et al. (2010)	(60)	11 (1.6–18)	NR	0.78	3.7 (0.3–7)	NR	Transient headache/fever/fatigue/arthritis; eight new endocrinological dysfunction

**Including f/up data provided in Takahashi et al. (2005).*

#Estimate from authors based on provided data.

+Likely same patient.

$Refers to 12 patients treated at the time of the initial diagnosis.

NR, not reported; PFS, progression free survival; CR, complete response; PR, partial response (≥50% shrinkage); f/up, follow-up; CN, cranial nerve.

They were the first to report on intracystic bleomycin treatment in an 8-year-old boy with craniopharyngioma who had failed radiation. A mixture of bleomycin, dextran sulfate, and dexamethasone was injected into his cyst via ommaya reservoir. Treatment was given twice during the first week. No significant side effects were observed and subsequently intracystic injections were given 5 days during the second week, followed by instillations every second day on an outpatient basis. A total dose of 30 mg bleomycin

was administered resulting in partial cyst reduction as evaluated with pneumocystography. The boy was reported well at 1 month follow-up.

Takahashi et al. (1985) published a case series on seven children with craniopharyngioma treated with intracystic instillation of Bleomycin.By labeling Bleomycin with cobalt-57 and subsequent measurements with a gamma-ray camera a 3 h half life of intracystic Bleomycin with a drop to 10% of the initial activity 24 h later was calculated. This surveillance determined the subsequent treatment regimen administering intracystic instillation of 1–5 mg bleomycin every other day. The authors further observed that with ongoing intracystic instillation of bleomycin the initial motor-oil like fluid content changed to nearly colorless fluid and initial high lactate dehydrogenase (LDH) levels dropped. Hence treatment was given until cystic fluid became almost colorless and LDH levels decreased below 1000 units. The seven children received a mean dose of 46 mg of intracystic bleomycin ranging from 13 to 95 mg. Four children had sustained response without evidence of progression at 2, 4, and 7 years follow-up. Three children died, two of them due to recurrent disease 1.5 and 2 years later respectively. One child died 1.5 months later without evidence of progression; further details are lacking. Autopsies in two of the children did not reveal any bleomycin associated changes in the adjacent brain structures.

Since Takahashi's publication in 1985 several pediatric case reports (Cavalheiro et al., 1996; Savas et al., 1999; Alen et al., 2002) and retrospective institutional case series confirmed intracystic bleomycin's effectiveness in inducing craniopharyngioma cyst shrinkage with sustained response rates in children (Takahashi et al., 1985, 2005; Hader et al., 2000; Franzini et al., 2001; Mottolese et al., 2001, 2005; Hernandez et al., 2002; Park et al., 2002; Hukin et al., 2005, 2007; Kim et al., 2007; Hsu et al., 2009; Yang et al., 2009). All studies refer to small sample sizes including a maximum of 22 pediatric patients (Franzini et al., 2001) with five studies reporting response to treatment in all patients (Mottolese et al., 2001; Park et al., 2002; Hukin et al., 2005; Takahashi et al., 2005; Kim et al., 2007). Complete response rates in children vary from 29% as provided by the Canadian experience (Hukin et al., 2007) to 67% (Mottolese et al., 2005) in the Lyon experience, where 12 of 18 children showed disappearance of the cyst with maintained responses at a mean follow-up of 6 years 8 months.

The schedules of bleomycin administration and doses vary and range from daily to weekly administrations with single doses ranging from 1 to 15 mg and total doses ranging from 14.5 to 180 mg per course (Takahashi et al., 1985; Jiang et al., 2002; Park et al., 2002). No standardized regimen has been established. Of note is that the former bleomycin mg dose was labeled a misnomer and should be substituted by Unit (1 mg equals 1 U). Stefanou underscored the considerable problems and dangers due to different bleomycin nomenclature in the US, Europe, and Australia and advocated for standardization as a mean to minimize dosing errors (Stefanou and Siderov, 2001).

Several studies investigated intracystic fluid LDH to prognosticate tumor response. While some studies observed decreased LDH levels consistent with response and increased LDH levels with recurrence (Takahashi et al., 1985; Park et al., 2002) others did not confirm LDH levels reflective of tumor response (Cavalheiro et al., 1996; Mottolese et al., 2001; Jiang et al., 2002; Caceres, 2005).

Intracystic bleomycin is usually well tolerated and most common acute side effects include mild headaches (with or without nausea/vomiting) and transient fever. However serious concerns relate to the risk of leakage of the neurotoxic bleomycin into the cyst surrounding parenchyma with associated morbidities and even mortality. Despite verification of appropriate positioning of the catheter intracystic bleomycin is associated with a risk of significant toxicities including transient and persistent hypothalamic injury (Haisa et al., 1994; Park et al., 2002; Lafay-Cousin et al., 2007), seizures and hemiparesis (Jiang et al., 2002; Park et al., 2002; Belen et al., 2007; Hukin et al., 2007), panhypopituitarimus (Hader et al., 2000; Hukin et al., 2007), blindness (Mottolese et al., 2001; Belen et al., 2007), and death (Savas et al., 2000). A prospective randomized study evaluating intracystic bleomycin ($n = 5$), intracystic radiotherapy with phosphorus^{32} ($n = 5$), and a combination of both substances ($n = 9$) revealed severe complications for the combined therapy resulting in thalamic infarction and death in two patients (Jiang et al., 2002).

Jakacki et al. (2000) used *subcutanous IFN* for the treatment of cystic craniopharyngioma based on the fact that craniopharyngioma and squamous cell skin carcinoma originate from the same cells and evidence of clinical activity of IFN in squamous cell skin carcinoma in early trials. In their study 15 craniopharyngioma patients (4.2–19.8 years old) underwent daily subcutanous IFN-α 2a (8,000,000 U/m^2) injections. Three patients could not be evaluated for response. Of the remaining 12 patients, 3 patients had a radiologically confirmed response to IFN. All patients experienced fever during the first few days of treatment, usually accompanied by chills and myalgias. Seven patients required temporary discontinuation of the drug and/or dose reductions.

Intracystic instillation of interferon was first used by Cavalheiro and colleagues who published the first and largest experiences on children with cystic craniopharyngiomas (Cavalheiro et al., 2005, 2010; Ierardi et al., 2007). Their most recent publication (Cavalheiro et al., 2010) included 60 children with a mean age of 11 years (20 months–18 years) who were treated at three different institutions (Sao Paulo/Brazil, Santiago/Chile, Rome/Italy) from 2000 to 2009. Twenty-nine of the 60 patients received intracystic IFN after initial surgery ($n = 18$) or bleomycin treatment ($n = 3$) had failed and 31 were treated with IFN as a first line treatment. In 37 patients cyst volume was measured before and after therapy. The mean cyst volume of 27.7 ml (3.3–134.5) before treatment decreased to a mean volume of 9.6 ml (0.14–70.7) after therapy. While in 47 children (78%) more than 50% cyst shrinkage was achieved at completion of therapy, 13 children progressed and required surgical intervention. Only one-third of the patients experienced some side effects consisting of either headaches ($n = 6$), palpebral edema (5), fever (5), chronic fatigue (1), or arthritis (1) not necessitating discontinuation of treatment. One patient required optic decompression due to lack of visual improvement despite cyst shrinkage and eight patients developed new endocrinological dysfunctions. There was no mortality.

ADMINISTRATION SCHEDULE:

Drug	Route	Dose	Weeks	Days
Interferon-alfa-2b (Intron A – ready to use solution)	Intracystic injection	3,000,000 IU	Weeks 1 – 4	Monday, Wednesday & Friday
1 cycle = 4 weeks treatment (total dose per cycle = 36,000,000 IU) Cycle may be repeated depending on response				
Suggested dosage modifications: None				

Treatment Plan:

Before initiation of treatment a permeability study should have ruled out leakage of contrast and confirmed appropriate position of the tip of the Ommaya catheter within the cyst. Permeability study recommended 2 weeks after catheter placement or later.

One Treatment Course encompasses 3 weekly (Mo, Wed, Fri) cystic aspirations followed by injection of 3,000,000 IU INTRON A ("ready-to-use") via Ommaya reservoir over 4 weeks time period (=12 injections resulting in a total dose of 36,000,000 IU INTRON A).

At start of treatment course (day 1) the maximum possible amount of cystic fluid should be removed before injection of INTRON A, taking the result of the permeability study (cyst volume) into account. For all following aspirations/injections the following procedure description applies:

Procedure description:

Cystic fluid aspiration **prior** to INTRON A injection (at least 1.5 - 2 ml if possible)

Injection of a total volume of 1 mL consisting of 3,000,000 IU Intron A "ready to use solution" diluted in preservative free normal saline (NS) provided in a vial from pharmacy followed by 0.7-1 mL NS flush.

FIGURE 1 | SickKids standard of care protocol for intracystic interferon administration.

Based on Cavalheiros experience and initial publication a standard of care protocol was developed for intracystic IFN administration (**Figure 1**) in Toronto. The former intracystic treatment with bleomycin injection was discontinued due to our experience of bleomycin associated neurotoxicity (Lafay-Cousin et al., 2007). Roferon-A® (IFN-α 2a), the product used by Cavalheiro et al. (2005, 2010) is not available in Canada. Intron-A® (IFN-α 2b) is available in Canada and although not specifically studied in the treatment of craniopharyngiomas, the ready to use formulation has been given intraventriculary via Ommaya reservoir for subacute sclerosing panencephalitis (SSPE; Gascon, 2003). In this randomized clinical trial including 121 SSPE patients with a median age 8.5 (3–22) years, IFN-α 2b was initiated with a 5-day escalating regime from 100,000 U/m^2 on day 1 to 1,000,000 U/m^2 on day 5 followed by treatment of 1,000,000 U/m^2 twice a week for 6 months. Fifty-nine patients were randomized to the IFN group. The main adverse effect reported was hyperpyrexia ($n = 7$) an expected side effect and well

managed with regular antipyretics. From a clinical perspective, IFN-α 2a and IFN-α 2b are considered interchangeable for their licensed indications, at equivalent doses. An "ideal" formulation of IFN has not been developed for administration via an Ommaya reservoir.

Since adoption of intracystic IFN at our institution six children between 4 and 18 years of age (mean 10.8 years) were treated. Response was measurable in five children with one complete response (>90% cyst shrinkage; **Figure 2**), three partial response (>50% shrinkage), and one stable disease. Sustained response was achieved after two to four treatment cycles with a median follow-up of 17 (1–30) months. All patients suffered manageable episodes of headaches, one associated with nausea and vomiting in the initial treatment period. None of the children suffered new endocrinological dysfunction, evidence of hypothalamic damage and none of them is obese.

Interferon belongs to a family of proteins with antiproliferative and immunomodulatory functions and its efficacy has been explained via FasL mediated activation of the apoptotic pathway (Ierardi et al., 2007). As such Pettorini et al. (2010) investigated protein content of the cystic fluid in six pediatric craniopharyngioma patients (mean age 4.5 years) and reported change in fluid content. Those three children who were treated with intracystic IFN resulting in near complete response after a one 4-week lasting course had significant decrease in their total alpha-defensins (1–3) determined as relevant components of cyst fluids while the untreated control ($n = 3$) showed increased nanomoles of alpha-defensins.

CONCLUSION

Intracystic treatment options for cystic craniopharyngioma provide data suggestive of durable cyst shrinkage and benefit beyond a pure volume reduction due to repeated fluid aspirations. The effect however is limited to the cystic craniopharyngioma portion without an effect on the solid component. There are multiple challenges relating to technical practicalities: Multicystic occurrence may limit treatment to one cyst only and therefore this approach does not provide the clinical benefit as wished. The thickness of the cyst wall may not allow successful penetration of the scope/catheter into the cyst and different catheter designs make the correct intracystic positioning of the catheter and its holes difficult. Intraoperative ultrasound and computer tomography (CT) have aided to confirm correct catheter position; however volume changes during subsequent treatment may influence the intracystic catheter tip location.

Most institutions will perform a permeability study prior to the start of intracystic treatment. The timing of the permeability study/dye test depends on the specific institution and ranges from 5 days postoperatively to several weeks later (Caceres, 2005; Cavalheiro et al., 2010). A permeability study refers to a CT done after contrast is injected into the craniopharyngioma cyst to confirm that contrast will remain within the cyst and not leak outside (**Figure 3**). Leakage documented on an early performed permeability study has often resolved without further intervention on a follow-up test after some weeks (Hader et al., 2000). Outflow of substances may occur during treatment either as a result of cyst shrinkage exposing catheter holes outside of the cyst or as a result

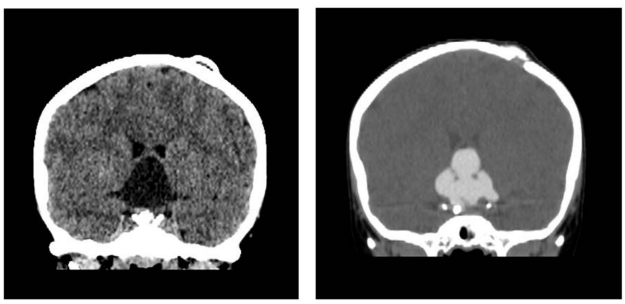

FIGURE 3 | Permeability study.

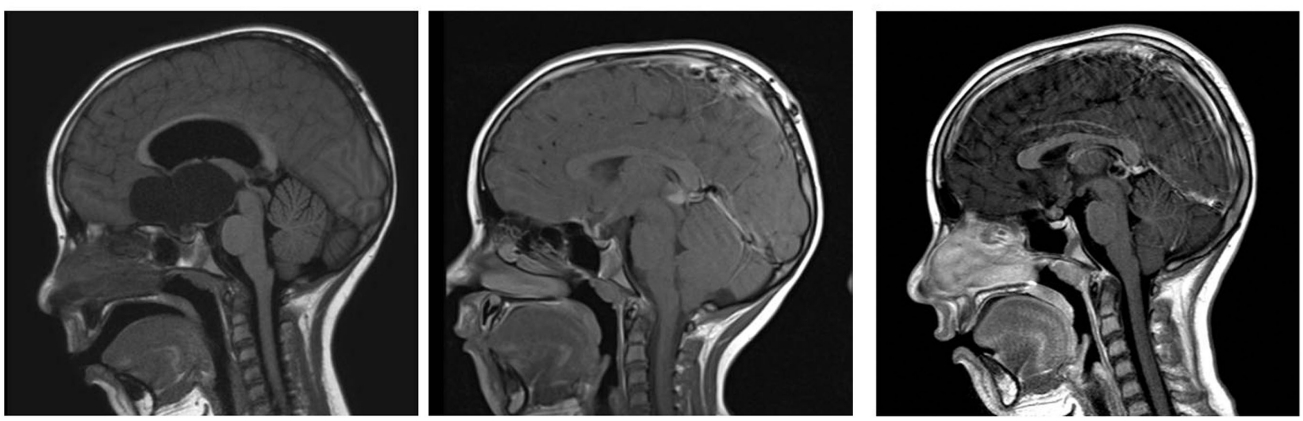

FIGURE 2 | Child with complete maintained response after 2 courses with intracystic interferon.

of increased permeability of the cyst wall (Lafay-Cousin et al., 2007).

Hence, despite all diligence, leakage of an intracystic substance remains a potential risk. Therefore a non-neurotoxic intracystic medication such as IFN presents a safer treatment option than radioisotopes or bleomycin and achieved impressive 78% complete and partial response rates after a one to nine treatment cycles (average 5; Cavalheiro et al., 2010).

Is cyst shrinkage the appropriate response measurement? A reduced cyst size will reduce increased pressure to the neighborhood structures and should translate into clinical benefit regarding visual, neurocognitive, endocrine, and metabolic function. However Cavalheiro et al. (2010) describe visual or endocrinological worsening in one and eight children respectively despite response to intracystic treatment.

Literature reviews concerning intracystic craniopharyngioma treatment strategies published over the recent years (Caceres, 2005; Hargrave, 2006; Linnert and Gehl, 2009; Steinbok and Hukin, 2010) capture the challenge of combining retrospective data from different institutions that refer to different doses, schedules, response definitions, and meaning of success. Cystic response and final outcome may not necessarily correlate. Prognostic marker need yet to be identified (Ierardi et al., 2007, 2009; Pettorini et al., 2010). Furthermore the role and value of intracystic treatment in postponing more aggressive surgery or radiation therapy will need to be defined.

Comparisons and reliable conclusions will remain difficult unless we as a medical community are agreeable on systematic evaluations and definitions. While randomized clinical trials are the gold standard for evaluation of best treatment strategies, they are certainly difficult in the context of rare tumors. Even so thoughts should be given to potential national and international cooperation for standardized intracystic treatment strategies. It's been 7 years that a European consensus was achieved regarding prospective data collection and definition of parameter for craniopharyngioma at a meeting of the International Society for Pediatric Oncology (SIOP; Müller et al., 2006). It is time to expand consensus on prospective data collection on craniopharyngioma patients to an international level. In doing so we will increase the size of comparable study cohorts, be able to evaluate meaningful differences and contribute to improved tailored patient care and wellbeing.

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Different approaches in radiation therapy of craniopharyngioma

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Radiation therapy is a cornerstone in the therapeutic management of craniopharyngioma. The close proximity to neighboring eloquent structures pose a particular challenge to radiation therapy. Modern treatment technologies including fractionated 3-D conformal radiotherapy, intensity modulated radiation therapy, and recently proton therapy are able to precisely cover the target while preserving surrounding tissue, Tumor controls between 80 and in access of 90% can be achieved. Alternative treatments consisting of radiosurgery, intracavitary application of isotopes, and brachytherapy also offer an acceptable tumor control and might be given in selected cases. More research is needed to establish the role of each treatment modality.

Keywords: craniopharyngioma, radiotherapy, post-operative

INTRODUCTION

Surgery and radiotherapy are the cornerstones in therapeutic management of craniopharyngioma. Radical excision is associated with a risk of mortality or morbidity particularly as hypothalamic damage, visual deterioration, and endocrine complication between 45 and 90% of cases. By contrast, recurrent disease after partial excision alone is observed between in 50 and 91% (Becker et al., 1999). Today less radical surgery in combination with radiation therapy are favored achieving a progression-free survival between 70 and 90% (Fahlbusch et al., 1999; Chiou et al., 2001; Tomita and Bowman, 2005).

New technologies are currently under investigation to achieve a better balance between tumor control and the risk for hazardous effects for surrounding eloquent structures such as the pituitary gland, hypothalamus, optic apparatus, and arteries at the base of the skull.

ROLE OF RADIOTHERAPY/CONVENTIONAL TECHNOLOGIES

External fractionated radiotherapy is presently standard of care to achieve an optimal progression-free survival after non-radical excision (Wen et al., 1989; Hetelekidis et al., 1993; Merchant et al., 2002; Stripp et al., 2004; Karavitaki et al., 2005; Lin et al., 2008). An excellent long-term outcome of conventional radiotherapy was found in many retrospective series reporting 10 and 20 years progression-free survival up to 95 and 54% (**Table 1**).

MODERN TECHNOLOGIES IN RADIATION THERAPY

Advances in radiation therapy technologies have opened up new approaches in the radio-oncological management of craniopharyngioma. The selection of the adequate treatment technology is of ongoing debate.

FRACTIONATED CONFORMAL RADIOTHERAPY/INTENSITY MODULATED RADIATION THERAPY

With the use of modern imaging technologies and treatment planning systems a precise coverage of the tumor area can be achieved by using stereotactic irradiation technologies. Stereotactic irradiation can be given in a single dose as stereotactic radiosurgery or in multiple doses as fractionated stereotactic radiotherapy. The modern systems permit an exact calculation of dose distribution within the tumor and provide a steeper dose gradient to surrounding normal tissue. If a cystic component is present, careful monitoring during radiotherapy is necessary (Winkfield et al., 2009). The results are shown in **Table 2**.

PROTON THERAPY

The major advantage of proton therapy is the high degree of dose conformity to the target. Beltran et al. (2011) retrospectively evaluated proton treatment plans with IMRT plan. He concluded that compared with photon IMRT proton therapy has the potential to significantly reduce whole brain and body irradiation. Fitzek et al. treated 15 patients with craniopharyngioma with a mix of photon and protons. The tumor control rates at 5 and 10 years were 93 and 85%, respectively (Fitzek et al., 2006). Luu et al. (2006) treated 16 patients. Local control could be achieved in 14 of 15 patients (Luu et al., 2006).

TIMING OF RADIATION THERAPY

Often immediate post-operative radiation therapy is favored in order to obviate early tumor progression leading to a functional deterioration caused by tumor growth or the necessity for repeat surgery. Others favor a watch-and-wait strategy fearing the long-term adverse effects of radiation therapy. The recent series of Stripp et al. (2004), Tomita and Bowman (2005), and Moon et al.

Table 1 | Post-operative radiotherapy in craniopharyngioma/conventional techniques (tumor control and survival).

Author	Patients	PFS (%)		OS (%)	
		5 years	10 years	5 years	10 years
Carmel et al. (1982)	14	78	78	90	80
Habrand et al. (1999)	32	78	56	91	65
Flickinger et al. (1990)	21	95	95	89	89
Rajan et al. (1993)	173	–	83	–	77
Hetelekidis et al. (1993)	46	–	86	–	91
Mark et al. (1995)	25	96	–	96	96
Varlotto et al. (2002)	24	89.1 (10 years)	54 (20 years)	100 (10 years)	92.3 (20 years)
Pemberton et al. (2005)	87	77 (10 years)	66 (20 years)	86 (10 years)	76 (20 years)

PFS, progression-free survival; OS, overall survival.

Table 2 | Results after modern external fractionated radiotherapy techniques.

Author	Patients	Technique	Dose	PFS	OS
Combs et al. (2007)	40	3-D conformal fractionated stereotactic radiotherapy	Median 52.2 Gy, range 50.4–56 Gy, 1.8–2 Gy single dose	100% local control at 5 and 10 years	5/10 years 79/89%
Minniti et al. (2007)	36	3-D conformal fractionated stereotactic radiotherapy	50 Gy in 30–33 fractions	3–5 years 97/92%	3/5 years 100%
Kanesaka et al., 2011 (adults)	16	3-D conformal fractionated stereotactic radiotherapy	30 Gy in 6 fractions	3 year local control 82.4%	3 year 94.1%
Hashizume et al. (2010)	10	FSRT Novalis IMRT	30–39 Gy in 10–15 fractions (median 33 Gy)	Control rate 100%	Not reported
Selch et al. (2002)	16	3-D conformal fractionated stereotactic radiotherapy	55 Gy fractionated	75% at 3 years	93% at 3 years

(2005) showed no differences between progression-free and overall survival between the different approaches (**Table 3**). However, in the recent series of Lin et al. (2008) early radiation therapy yielded a 100% local control rate at 10 years as compared with 32% when radiation therapy was performed at relapse.

Table 3 | Early versus delayed radiation therapy/impact on progression-free and overall survival.

Author (year)	Patients	Early RT	RT at relapse
Sung et al. (1981)	10	–	70.9%, 10 years OS
Regine et al. (1993)	58	78%, 20 years OS	25%, 20 years OS
Stripp et al. (2004)	40	83%, 10 years OS	86%, 10 years OS
Tomita and Bowman (2005)	30	71%, 5 years PFS	90%, 5 years PFS
Moon et al. (2005)	50	91.3%, 10 years PFS	91.2%, 10 years PFS
Lin et al. (2008)	31	100%, 10 years LC	32%, 10 years LC

RT, radiotherapy; OS, overall survival; PFS, progression-free survival; LC, local tumor control.

OTHER TECHNOLOGIES

RADIOSURGERY

Stereotactic radiosurgery is an alternative to fractionated treatments in patients with craniopharyngioma harboring smaller lesions. The reported results of radiosurgery, however, suggest that tumor control is inferior to fractionated treatments and might carry the risk for optic neuropathies unless only smaller lesions are treated away from the optic apparatus (Tishler et al., 1993). Minniti et al. (2009) reviewed eight published series and found an average tumor control rate of 90% for solid tumors, 88% for cystic tumors, and 60% for mixed tumors (**Table 4**).

CYBERKNIFE

CyberKnife includes a compact linear accelerator mounted on a robotic arm combined with the pair of diagnostic X-ray sources permitting an online reproducibility of the incident beams and a subsequent adjustment of the beam with a precision below 1 mm. Lee et al. reported results obtained in 16 patients treated for residual recurrent craniopharyngioma Tumor shrinkage was achieved in 7 of these 11 patients and tumor control in another 3 patients. The overall tumor control was achieved in 91% of patients without complications (Lee et al., 2008).

INTERSTITIAL BRACHYTHERAPY

There is one report from Barlas et al. (2000) in two patients in whom iodine^{125}-seeds were implanted delivering a dose of 67 and 60 Gy to tumor periphery. Response was partially observed in one and tumor completely resolved in the other patient 24 months after treatment. Radiation induced

Table 4 | Outcome after stereotactic single dose radiosurgery in craniopharyngioma (Gamma Knife).

Author	Patients	Dose	PFS	OS
Kobayashi et al. (2005)	98	Marginal dose 11 Gy	61 and 54% at 5 and 10 years	94.1 and 91% at 5 and 10 years
Ulfarsson et al. (2002)	21	3–25 Gy	34%	n.a.
Amendola et al. (2003)	14	14 Gy (11–20 Gy)	86%	All alive 6–86 months
Chiou et al. (2001)	10	Median 16.4 Gy	58%	n.a.
Yu et al. (2000)	46	Marginal dose 8–18 Gy	89.5%	n.a.
Chung et al. (2000)	31	9.5–16 Gy	87%	n.a.
Mokry (1999)	23	Marginal dose 8–9.7 Gy	74%	n.a.
Prasad et al. (1995)	9	13 Gy	62.5%	n.a.

n.a., not analyzed.

Table 5 | Intracavitary instillation of radionuclides/impact on tumor control and visual function (modified according to Derrey et al., 2008).

Author	Patients	Isotope	Complete remission	Reduction	No change	expansion	Tumor control	Visual impairment
Voges et al. (1997)	62 78 C	Y 90 Rhe 186 P 32	35/78	27/78	12/78	4/78	10 years OS Solid: 31% Cystic: 64%	4/62
Blackburn et al. (1999)	6 9 C	Y 90	0	6	1	2	n.a.	1/5
Hasegawa et al. (2004)	41 41 C	P 32	7	24	5	5	10 years: 70% Solid comp.: 32% increase	3/40 (RT induced)
Derrey et al. (2008)	39 44 C	Rhe 186	17	17	5	5	n.a.	3/39

C, cysts; Y 90, Yttrium 90; Rhe 186, Rhenium 186; P 32, Phosphorus 32; OS, overall survival.

Table 6 | Advantages and disadvantages of modern treatment technologies in radiotherapy of craniopharyngioma.

Technology	Advantages	Disadvantages
Conventional 2-D radiotherapy	Reliable clinical data and long follow-up indicating high efficacy of radiotherapy	Poor geometrical precision. No reliable protection of normal surrounding tissue
Fractionated conformal radiation therapy/IMRT	Excellent adjustment of treatment portals to tumor site. In 3-D. Sparing of normal tissue	Rigid head fixation (relocatable). Few patient numbers and not yet long follow-up
Fractionated proton therapy	Optimal coverage of tumor site. With maximal sparing of surrounding tissue	Few patient numbers. Limited access, high costs
Radiosurgery	Only one session. Excellent coverage of tumor. Almost no dose to non-target tissue	Limited clinical settings. Tumor control inferior to fractionated treatments? Low patient numbers. No long follow-up
Hypofractionated image guided radiosurgery (CyberKnife)	Only few session. The biological advantages of fractionation can be utilized. Excellent coverage of tumor. Almost no dose to non-target tissue	Very few experiences. Role still unclear. No reliable data for tumor control. No long-term follow-up. Only selected clinical settings
Intracavitary colloid isotope application	High tumor control rates for cystic components	Only cystic tumors. Underdosage in solid components. Leakage possible. Detrimental effects on visual function reported
Interstitial irradiation (Iodine seeds)	Excellent dose conformity. Optimal protection of normal tissue	Very few clinical data

toxicity or recurrence has not been reported 6 years after treatment.

INTRACAVITARY APPLICATION OF ISOTOPES

Approximately 90% of craniopharyngioma display a cystic component often leading to a space occupying clinically relevant effect. There are different series reporting on the intracavitary application of different isotopes such as Rhenium^{186}, Yttrium^{90}, or Phosporus^{32}. The nuclides emit β-rays with a therapeutic range within only a few millimeters. Response rates and cyst controls can be achieved in more than 80% of case. Tumors with a solid component, however, are insufficiently controlled (Voges et al., 1997; Hasegawa et al., 2004). Deterioration of visual function due to ionizing irradiation of the nuclides can occur (**Table 5**).

CONCLUSION

Standard treatments today consist of fractionated external irradiation therapy. The recent developments in modern treatment technologies permit an exact delineation of target and non-target surrounding normal tissue (Merchant et al., 2006). Tumor control and overall survival might be improved as compared with the excellent results obtained with conventional treatments at shorter follow-up periods. Longer follow-up periods, however, are warranted. Today the 5-year progression-free survival after modern fractionated irradiation is in the range between 80 and 100%. Good results are achieved with a combined approach (surgery + radiation therapy) using standard fractionation. The recently introduced proton therapy opens up the possibility for a better sparing of normal surrounding tissue. Presently data are, however, limited and the expected improvement of functional outcome remains yet to be proven.

Post-operative radiation therapy is superior to surveillance after non-radical resection in terms of progression-free survival. The impact of different timing on functional outcome is still unknown. The current prospective German study Craniopharyngioma 2007 is addressing this issue in a randomized prospective study.

Radiosurgery as an option for circumscribed small lesions away from the optic apparatus is an attractive option because normal surrounding tissue is excellently spared. Single dose radiotherapy is, however, associated with an inferior tumor control according to retrospective data. CyberKnife as a new technological development utilizing image guided high precision stereotactic radiotherapy is able to use the radiobiologically advantageous fractionation concept. Interstitial treatments like the intracystic application of radioactive colloids might be used in selected cases in which only cystic tumors are present. It is, however, more a historical experience and should not be favored in the area of modern treatment technologies. Brachytherapy is of limited importance and the experiences so far obtained are very scarce. Minimizing the dose to non-target tissue will be the future step to reduce the risk for late effects. Reproducible data in prospective settings including neurocognitive function, quality of life, visual, and endocrinological function are still missing and require further research and evaluation. **Table 6** gives an overview of the current technologies.

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Effects of methylphenidate on weight gain and food intake in hypothalamic obesity

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For patients with a craniopharyngioma (CP), treatment of hypothalamic obesity (HO) and hyperphagia following resection and/or radiotherapy is extremely difficult and few reports have been published on potential drug therapies. Psychomotor stimulant methylphenidate (MPH) has been reported to inhibit food intake (FI). In this paper, we report reduction of body mass index (BMI) and appetite in an adolescent CP patient suffering from HO. We then tested the ability of MPH to attenuate the FI and body weight (BW) gain in a rat model consistent with the neuroanatomical and metabolic disturbances commonly observed in obese CP patients. Specifically, we used a novel electrolytically generated combined medial hypothalamic lesion (CMHL) affecting the arcuate nucleus, ventromedial hypothalamic nucleus, and dorsomedial hypothalamic nucleus to induce hyperphagia, rapid weight gain, and adiposity. Both CMHL and control animals ($n = 7$ per group) were administered either methylphenidate HCl (MPH; 20 mg kg^{-1} day^{-1}) or saline for 4 days in a crossover design experiment 28 weeks post-surgery. A significant decrease in percent baseline FI (CMHL −23%, $p = 0.008$; control −20%, $p = 0.002$) and percent change in BW (CMHL −1.97%/4 days, $p = 0.011$; control −1.75%/4 days, $p = 0.003$) was observed during MPH treatment as compared to saline. **Conclusion:** This study shows MPH treatment of severely obese CMHL rats resulted in significantly reduced FI and BW loss.

Keywords: hypothalamic lesion, hyperphagia, methylphenidate, weight gain, food intake

INTRODUCTION

Severe hypothalamic obesity (HO) and hyperphagia are common sequelae following tumor resection in child and adolescent craniopharyngioma (CP) patients, ranging in rate from 22 to 62% (Brauner et al., 1987; Sorva, 1988; Muller, 2008). Radical tumor resection and subtotal tumor resection with or without radiotherapy are the current therapeutic standard. Post-resection and/or treatment, a distinct trend in weight gain has been observed in children who developed HO. Specifically, a rapid gain in body mass index (BMI) SDS for the first 6 months followed by long-term stabilization with little appreciable decline (Ahmet et al., 2006). Even more distressing, attempts at weight loss through caloric restriction and exercise are largely unsuccessful (Lustig et al., 2003; Eyal et al., 2006). Pharmacological treatment of HO and hyperphagia has shown success in a few clinical studies and case reports (Mason et al., 2002; Lustig et al., 2003; Danielsson et al., 2007; Hamilton et al., 2011) though weaker weight reductions were observed compared to uncomplicated obesity (Danielsson et al., 2007). A recent study of both normal weight and obese CP patients showed that insulin resistance and altered gut hormone secretion are not exclusively a result of obesity but hypothalamic disruption caused by the tumor and/or its treatment (Roth et al., 2011b).

Animal models utilizing electrolytically and chemically generated lesions produce similar effects to those observed clinically and are thereby an excellent model in which to study therapeutic interventions for HO (Dawson et al., 1989; Tokunaga et al., 1991, 1993; Schoelch et al., 2002; Leitner and Bartness, 2008). Recently we developed a novel combined medial hypothalamic lesion (CMHL) model that utilizes electrolytic lesions in the arcuate nucleus (ARC), ventromedial hypothalamic nucleus (VMN), and dorsomedial hypothalamic nucleus (DMN) to model the sequelae commonly observed in HO resulting from resection and/or treatment of CP (Roth et al., 2011a). Similar effects were observed when combining chemically induced ARC lesion with electrolytically induced VMN lesions (Elfers et al., 2011). Specifically, the CMHL model exhibits rapid weight gain, hyperphagia, hyperinsulinemia, and hyperleptinemia.

One potential therapeutic target for the treatment of hyperphagia in HO is the dopaminergic system. Methylphenidate HCl (MPH), a psychomotor stimulant used in the treatment of attention deficit hyperactivity disorder in children, produces an increase in brain synaptic dopamine (DA) signaling with the side effect of anorexia (Leddy et al., 2009). However, there is variance in the reported long-term ability of MPH to sustain weight loss ranging from 3 months to the duration of administration of a clinically effective dose (Leddy et al., 2009).

The aim of our study was to test the inhibitory effect of MPH treatment on food intake (FI) in our novel CMHL rat model of HO. We hypothesized that administration of MPH to severely obese CMHL rats will result in reduction of FI and body weight (BW) gain.

CASE REPORT

A 5.9-year-old male presented with short stature, headaches, nausea, and vomiting. Neuroimaging (CT, MRI) indicated a large sellar and suprasellar mass causing obstructive hydrocephalus.

Following gross total resection of a large CP, the patient was diagnosed with panhypopituitarism. Two years later the patient underwent cranial radiation therapy due to tumor relapse. At the time of tumor diagnosis, height was 110 cm (25th percentile), weight 23.4 kg (75th percentile), and BMI 19.3 kg/m^2 (+1.9 *z*-score). Following resection, the patient noted a very low level of energy, increased hunger, and difficulty becoming satiated. One year post-tumor resection, height was 117 cm (25th percentile), weight 34.1 kg (3 kg >97th percentile), and BMI 24.5 kg/m^2 (+2.5 *z*-score). Despite optimal endocrine management, the patient continued to experience significant weight gain that was unable to be mediated by lifestyle changes. As part of hormone replacement therapy desmopressin acetate (DDAPV), hydrocortisone, growth hormone, and levothyroxine were prescribed. At age 15 years, height was 184 cm (>90th percentile), weight 154 kg (70 kg >97th percentile), and BMI 45.5 kg/m^2 (+2.9 *z*-score).

MPH was identified as a potential therapeutic to attenuate hunger due to its frequently observed anorexic side effect. MPH treatment began at age 15 years with a 20 mg day^{-1} dose (morning: 10 mg; evening: 10 mg; 30–45 min prior to meals) and was gradually increased to 50 mg day^{-1} dose (morning: 30 mg; noon: 10 mg; evening: 10 mg; 30–45 min prior to meals) over the course of 10 weeks. Following start of MPH treatment, overall weight gain ceased (**Figure 1**) and patient noted a dose dependent decrease in hunger. After 31 weeks treatment, the MPH dose was adjusted to 60 mg day^{-1} dose (morning: 30 mg; noon: 10 mg; evening: 20 mg; 30–45 min prior to meals) due to a slight increase in BMI. After this last dose adjustment, the patient has had continued decrease in BMI for over 56 weeks. After 87 weeks of MPH treatment, height was 186 cm (>90th percentile), weight 142 kg (47 kg >97th percentile), and BMI 41.4 kg m^{-2} (+2.8 *z*-score). It is important to note that this patient was not under any exercise regimen during this time and therefore any change in BMI is independent of exercise.

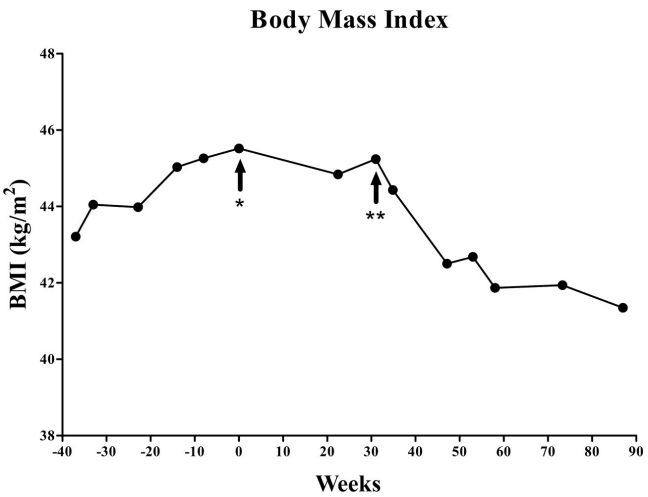

FIGURE 1 | Changes of BMI in the patient course of methylphenidate treatment. At the start of the methylphenidate treatment the patient was 76 kg over ideal weight given height and age. After 87 weeks of treatment the patient lost 12 kg of excess weight. *Start of methylphenidate treatment (20 mg day^{-1} dose; morning: 10 mg; evening: 10 mg). **Start of final dose (60 mg day^{-1} dose; morning: 30 mg; noon: 10 mg; evening: 20 mg).

MATERIALS AND METHODS FOR RAT STUDY

ANIMALS

Young adult male Sprague Dawley rats, weighing 250–260 g, were purchased from Charles River Laboratory (Wilmington, MA, USA). Animals were individually housed on a 12/12-h light/dark cycle (lights on at 07:00 h) in a temperature (23˚C) and humidity (50 ± 10%) controlled room. *Ad libitum* access to regular chow (5053 Pico Lab Rodent Diet, Purina LabDiet, Richmond, CA, USA) and water was provided. Following surgery, the animals' BW and FI were recorded. All procedures performed were approved by the Institutional Animal Care and Use Committee at the Seattle Children's Research Institute and were in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

ELECTROLYTIC LESION

To electrolytically induce the CMHL, animals were placed under a surgical-plane of anesthesia (isoflurane/oxygen mix, 5% induction, 2–4% throughout the procedure) and were mounted in a Kopf stereotaxic frame (Tujunga, CA, USA). The upper incisor bar was 3.5 mm above the interaural line. Lesions were targeted to the ARC, VMN, and DMN through the placement of an insulated stainless steel electrode at stereotaxic coordinates based on our previous study (Roth et al., 2011a). Specifically, an anodal electric current (110 V, 1.7 mA for 15 s) was passed through the tip of the electrode while placed 2.6 mm posterior to the bregma, 0.5 mm lateral to the midsagittal line, and both 10 mm (ARC) and 8.6 mm (VMN/DMN) ventral from the skull according to the method described in our recent paper (Roth et al., 2011a).

INJECTION OF METHYLPHENIDATE AND DATA COLLECTION

A crossover experimental design was utilized to determine the effects of daily MPH injections (20 mg kg^{-1} BW) on FI and BW. For 6 days prior to the start of the injections, FI was recorded and averaged to determine baseline values ($n = 7$ per group). Four animals from each group received daily i.p. injections of 20 mg kg^{-1} MPH (Letco Medical, Decatur, AL, USA) while three animals from each group received i.p. saline injections (0.9% sodium chloride inj., USP, Hospira) for a period of 4 days, after which, the treatments were switched for an additional 4 days of testing. Administration of all injections as well as measurement of FI and BW occurred in the evening (18:30 h, 30 min prior to lights out). MPH has been show to have a half-life of approximately 1 h in rats (Kuczenski and Segal, 2002), therefore we did not provide a washout period between treatments. Lee index [LI; BW$^{-1/3}$/snout to anus length (mm)] measures were taken pre- and post-treatment as a indicator of total adiposity.

STATISTICAL ANALYSIS

Statistical analyses were performed using GraphPad Prism Software (La Jolla, CA, USA). Outcome variables between study groups were compared using Student's *t*-tests for continuous variables. Two-way ANOVA modeling with a Bonferroni *post hoc* was used for contrasts of two factors between study groups. In all instances, a two-sided $p < 0.05$ was considered significant unless otherwise stated.

RESULTS FOR RAT STUDY

GENERAL RESULTS

Pre-surgery BW, body length (BL), and LI were comparable in lesion and control groups ($p = 0.539$, $p = 0.533$, $p = 0.122$, respectively). An immediate increase in FI and BW (1 day post-surgery) was observed in the lesion group and significant changes in BW were observed 3 weeks post-surgery ($p = 0.034$). At the time of MPH treatment (28 weeks post-surgery), there was a significant difference in pre-treatment LI ($p = 0.025$) indicating a greater degree of obesity in the lesion group (**Table 1**).

BODY WEIGHT

Both control and lesion groups exhibited a slight trend of weight gain during the 4 days of saline injection (control: $0.155 \pm 0.213\%$ BW, lesion: $0.340 \pm 0.388\%$ BW). Significant weight loss was experienced by both groups when administered MPH with respect to the saline (control: $-1.752 \pm 0.410\%$ BW, $p = 0.003$; lesion: $-1.968 \pm 0.628\%$ BW, $p = 0.011$; **Figures 2A,B**). No significant difference was observed in either the absolute or percentage change in BW between the lesion and control groups within one treatment.

FOOD INTAKE

Lesion vs. control animals displayed no significant difference in baseline FI ($p = 0.183$). A reduction in FI compared to baseline was observed as a trend in both control ($92.0 \pm 2.4\%$ of baseline, $p = 0.131$) and lesion ($87.4 \pm 3.9\%$ of baseline, $p = 0.288$) groups when receiving injections of saline. When treated with MPH, a significant reduction in FI relative to saline injection was seen in the control ($80.1 \pm 4.1\%$ of saline, $p = 0.002$) and lesion ($76.9 \pm 3.6\%$ of saline, $p = 0.008$) groups (**Figures 2C,D**).

Table 1 | Characteristics of experimental groups.

	Control	Lesion	*p*-Value
Pre-surgery BW (g)	295.3 ± 5.8	300.4 ± 5.7	0.539
Pre-surgery body length (mm)	217.4 ± 1.4	216.1 ± 1.4	0.533
Pre-surgery Lee index	0.306 ± 0.001	0.310 ± 0.002	0.122
1 day post-surgery BW (g)	302.4 ± 4.7	325.3 ± 7.2	**0.023**
3 week post-surgery BW (g)	383.9 ± 8.2	428.6 ± 15.9	**0.034**
3 week post-surgery FI (g)	27.3 ± 0.6	31.5 ± 1.1	**0.002**
Pre-treatment BW (g)	674.0 ± 25.5	800.7 ± 55.6	**0.035**[(a)]
Pre-treatment body length (mm)	273.6 ± 3.5	265.6 ± 6.3	0.291
Pre-treatment Lee index	0.320 ± 0.002	0.349 ± 0.010	**0.025**
Post-treatment BW (g)	661.7 ± 23.0	783.3 ± 50.5	**0.029**[(a)]
Δ BW during treatment (g)	-12.3 ± 3.3	-17.4 ± 6.1	0.237
Post-treatment Lee index	0.318 ± 0.002	0.347 ± 0.009	**0.021**

Data are mean ± SEM, p-values from 2-sided t-test, except [(a)] 1-sided t-test.

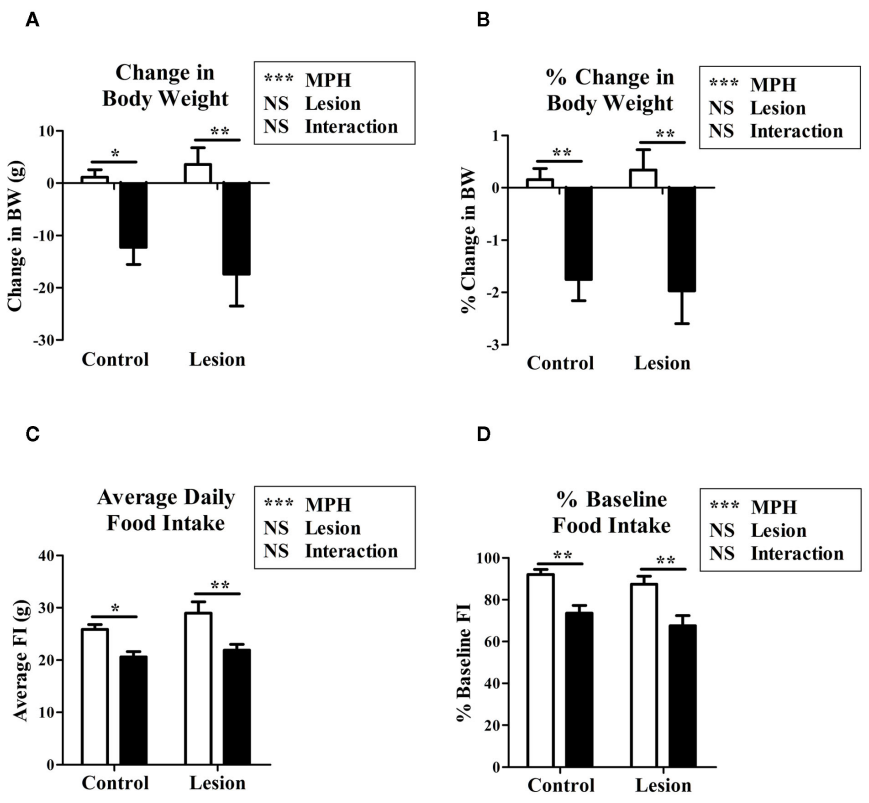

FIGURE 2 | The effects of methylphenidate on either lesion or control animals on change in body weight during treatment (A), percentage change in body weight (B), average daily food intake (C), percentage baseline (6 day average prior to treatment) food intake (D), in methylphenidate injected (black bars) vs. saline injected (white bars) rats. Two-way ANOVA modeling with a Bonferroni *post hoc* was used for contrasts of two factors between study groups. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

DISCUSSION

Our current study examined the inhibitory effect of MPH on FI through daily evening i.p. injections (MPH, 20 mg kg^{-1} in saline) on our CMHL rat model of HO. MPH treatment significantly reduced FI in both the control and lesion group when compared with saline treatments. Significant weight loss was observed in both groups during MPH treatment whereas no change occurred during saline treatment. Given that drugs might be less effective in reducing BW in HO (Danielsson et al., 2007), these results are remarkable in that lesion group experienced similar weight loss to the control group while being administered MPH. This experiment also illustrates the dualism of hedonic and homeostatic regulation of FI. The CMHL model of HO by nature results in severe dysregulation of homeostatic regulatory pathways through partial destruction of the hypothalamus. The ability of MPH to attenuate homeostatic dysfunction reflects the ability of hedonic regulation to override homeostatic pathways.

The observed weight loss is likely a result of more than just a reduction in FI. It has been shown that i.p. injections of MPH lead to a significant increase in locomotor activity when compared to both i.p. vehicle and intragastrical MPH administration (Gerasimov et al., 2000). Additionally, as a psychomotor stimulant, MPH has been used clinically to treat narcolepsy (Roth, 2007). While locomotor activity and duration of sleep cycles were not quantified in this experiment, they are likely confounding factors responsible for the weight loss and should not be omitted from this discussion.

It should be noted that the MPH dose administered to rats is significantly higher than dosages ordinarily administered to humans; this is to account for metabolic differences between rats and humans. An i.p. dose of 2.5–10 mg kg^{-1} MPH in a rat is comparable to the clinical dosage administered to children and adults for the treatment of ADHD (Yang et al., 2006) although a 20 mg kg^{-1} dose is commonly used in rat studies (Crawford et al., 1998; McDougall et al., 1999; Meririnne et al., 2001; Teo et al., 2003). In a study by Teo et al. (2002) examining long-term (90 day) oral gavage toxicity levels for MPH, the no-observed- effect-level was determined to be 40 mg kg^{-1} MPH. Given that this was a short exploratory study, the higher 20 mg kg^{-1} dose was used to determine if any change in FI or BW could be observed.

We are aware of three clinical studies that have examined the anorexic effect of MPH with differing results. One study showed a 34% reduction in FI in obese males after administration of the lowest effective dose of MPH (0.5 mg kg^{-1} in seven of nine subjects; Leddy et al., 2004); where a similar study reported an 11% reduction in energy intake following MPH administration in both obese and non-obese adults (0.5 mg kg^{-1}; Goldfield et al., 2007). In contrast, a third study in obese and non-obese adults found a reduction in FI along with lower appetite and food craving ratings following MPH (0.5 mg kg^{-1}) administration in everyone except obese males. The obese males experienced increases in all three categories after MPH administration (Davis et al., 2011). The results in our model are comparable to the Leddy et al. (2004) and Goldfield et al. (2007) studies with a 19.9 and 23.1% decrease in FI in control and lesion animals respectively following MPH administration when compared to saline treatment.

In our presented case report, the patient experienced significant weight gain and hyperphagia following resection of a CP that was unable to be mediated by lifestyle modification. MPH dosage was gradually increased to a dose that resulted in sustained decrease in BMI. These findings are significant in that MPH treatment has resulted in 87 weeks of nearly consistent reduction of BMI in a patient with HO independent of an exercise regimen. Moreover, the last 56 weeks after final dosage adjustment have resulted in even more dramatic reduction in BMI. These results indicate that MPH may be a potential therapeutic for weight loss in HO.

The mechanism by which MPH induces anorexia is not completely known, although it is attributed to being an effect of MPH action on the dopaminergic system to elicit a reward response. It has been shown that MPH increases DA signaling through actions at the synapse, specifically, through blockade of DA reuptake into the presynaptic terminal, increasing availability of pre-synaptic DA D2 autoreceptors and activation of D1 receptors on the post-synaptic neuron (Wilens, 2008). It is possible that MPH elicits a reward response normally induced by FI, therefore suppressing the normal drive to eat. Interestingly, imaging studies have shown that striatal DA D2 receptors are reduced in obese subjects compared to non-obese controls and in proportion to their BMI (Wang et al., 2001). Furthermore, in morbidly obese subjects, DA D2 receptor availability was associated with metabolic activity in prefrontal cortical regions implicated in the regulation of FI and hyperphagia (Volkow et al., 2009). This suggests that obese individuals have a dysfunction in their DA systems and therefore do not have the same capacity to elicit reward and thus compensate with increased FI.

Several limitations exist in this exploratory experimental design; most notable is the relatively short duration of treatment. Clinically, the anorexic side effect of MPH has been observed to decrease over time, therefore a longer exposure is needed in follow up experiments. In addition, the current study did not focus on the hormone changes associated with this model and treatment. Additionally, in humans the therapeutic effect of MPH requires sustained brain levels, a condition that is not easily met in rats due to their high rate of clearance of MPH as indicated by the relatively short half-life. In the current study this was addressed by administering a single large dose once per day that would effectively saturate DA transporters for a longer time. In future experiments this will be addressed through the use of several smaller doses administered over the course of the day or implantation of a micro infusion pump. Other factors this experiment did not directly address are any potential effects due to changes in psychomotor stimulation or alterations in the animal's sleep cycle. Finally, given the potential variability of the lesions, the study size ($n = 7$ per group) is rather small and will be expanded in future studies.

In conclusion, the results of this exploratory study indicate that MPH significantly attenuates FI and elicits BW loss in our novel CMHL rat model. These results correlate well with our clinical observations in patients with HO as well as previous clinical studies reported by others on the anorexic effect of MPH in normal weight and obese subjects. The presented results are significant in that they present a model, which may be used to elucidate the mechanisms by which MPH improves some of the most distressing sequelae of HO. A better understanding of these mechanisms could illuminate new targets for future drug therapies for the treatment of HO. This reinforces the need for future hypothesis driven studies focused on the underlying mechanisms that address changes in hormones (leptin, gut hormones), insulin resistance and body composition.

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Bariatric surgery in hypothalamic obesity

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Craniopharyngiomas (CP) are epithelial neoplasms generally found in the area of the pituitary and hypothalamus. Despite benign histology, these tumors and/or their treatment often result in significant, debilitating disorders of endocrine, neurological, behavioral, and metabolic systems. Severe obesity is observed in a high percentage of patients with CP resulting in significant comorbidities and negatively impacting quality of life. Obesity occurs as a result of hypothalamic damage and disruption of normal homeostatic mechanisms regulating energy balance. Such pathological weight gain, termed hypothalamic obesity (HyOb), is often severe and refractory to therapy. Unfortunately, neither lifestyle intervention nor pharmacotherapy has proven effective in the treatment of HyOb. Given the limited choices and poor results of these treatments, several groups have examined bariatric surgery as a treatment alternative for patients with CP–HyOb. While a large body of evidence exists supporting the use of bariatric surgery in the treatment of exogenous obesity and its comorbidities, its role in the treatment of HyOb has yet to be defined. To date, the existing literature on bariatric surgery in CP–HyOb is largely limited to case reports and series with short term follow-up. Here we review the current reports on the use of bariatric surgery in the treatment of CP–HyOb. We also compare these results to those reported for other populations of HyOb, including Prader–Willi Syndrome, Bardet–Biedl syndrome, and hypothalamic melanocortin signaling defects. While initial reports of bariatric surgery in CP–HyOb are promising, their limited scope makes it difficult to draw any substantial conclusions as to the long term safety and efficacy of bariatric surgery in CP–HyOb. There continues to be a need for more robust, controlled, prospective studies with long term follow-up in order to better define the role of bariatric surgery in the treatment of HyOb.

Keywords: craniopharyngioma, bariatric surgery, gastric bypass, hypothalamic obesity

INTRODUCTION

Craniopharyngiomas (CP) are generally benign, slow-growing tumors that are thought to arise from rests of embryonic cells residing within the remnants of the craniopharyngeal duct or Rathke's pouch (Abeloff, 2008). Thus, tumors may originate from anywhere along the path of the craniopharyngeal duct, from nasopharynx to tuber cinereum, although most are located in the sellar/parasellar region (Harwood-Nash, 1994; Karavitaki et al., 2005). Although histologically benign, these tumors are often locally aggressive with invasion of adjacent tissues and structures. While mortality is generally low, morbidity as a result of tumor mass effect and/or therapy (resection ± radiotherapy) is substantial and nearly universal (Mortini et al., 2011; Winkfield et al., 2011).

Because of the close proximity to the visual nerve tracts, hypothalamus, pituitary, and ventricular system, CPs predispose patients to a number of adverse endocrine, metabolic, psychologic, and neurologic sequelae. As a primary result of the tumor, the majority of patients present with one or more hypothalamic-pituitary deficits including growth hormone (GH; ∼75%), gonadotropins (∼60%), adrenocorticotropic hormone (ACTH; ∼30%), thyroid-stimulating hormone (TSH; ∼25%), and/or antidiuretic hormone (ADH; ∼20%; Karavitaki et al., 2006; Muller, 2008). In addition, approximately one-third can develop new or additional endocrinopathies following surgical resection.

HYPOTHALAMIC OBESITY

In addition to pituitary hormone deficiencies, hypothalamic involvement has been shown to result in severe metabolic disturbances and weight gain (Muller et al., 2001; Srinivasan et al., 2004). While a minority (15–20%) of CP patients complain of weight gain as a presenting symptom, more than 50% develop significant obesity following surgical resection (Muller et al., 2004; Ahmet et al., 2006). This number may be as high as 90% in those with demonstrable hypothalamic damage, whether from direct tumor infiltration or as a result of surgical and/or radiation therapy (de Vile et al., 1996; Muller et al., 2004). Such pathological weight gain, termed hypothalamic obesity (HyOb), is often severe, refractory to therapy, and has a significant negative impact on the quality of life for patients with CP (Muller et al., 2005; Eyal et al., 2006; Inge et al., 2007).

Over the last 75 years, experience with animal and human models has shown the basal medial hypothalamus to be a key center of metabolic regulation by the central nervous system (CNS; Hetherington and Ranson, 1940; Sorva, 1988). The hypothalamus receives and integrates a variety of afferent signals communicating the metabolic state of the organism and adjusts autonomic outputs with the ideal physiologic outcome of maintaining adequate energy stores. The afferent arm of the homeostatic loop consists of hormones, such as leptin, insulin, and peptide YY,

that target receptor fields within hypothalamic nuclei to convey information on meal size, nutrient composition, and adipose tissue stores. In addition, neurons within the hypothalamus directly sense and respond to nutrients, such as free fatty acids, glucose, and amino acids. Within the hypothalamus, neuropeptides such as neuropeptide Y (NPY), agouti-related protein (AgRP), and alpha-melanocyte stimulating hormone (α-MSH), integrate and convey this information to other brain centers responsible for controlling appetite/satiety, thermogenic, and motor effectors (Schwartz et al., 2000).

A number of monogenetic obesity syndromes have now been shown to involve mutations in such regulatory hypothalamic pathways (Clement et al., 1998; Lubrano-Berthelier et al., 2006; Savastano et al., 2009; Hochberg and Hochberg, 2010). In addition, several complex genetic syndromes, including Prader–Willi (PWS) and Bardet–Biedl syndromes (BBS), are associated with obesity, presumably from hypothalamic dysfunction. PWS results from the loss of paternally imprinted genes on chromosome 15q11-15 and is characterized by an array of multisystemic defects including neonatal hypotonia, short stature, hypogonadism, behavioral and psychiatric phenotypes, aggressive food-seeking behavior, hyperphagia, and obesity (Goldstone et al., 2008). PWS patients have significantly elevated levels of the orexigenic hormone ghrelin, a finding not observed in other causes of HyOb (Cummings et al., 2002a; DelParigi et al., 2002). Interestingly, even young, underweight patients with PWS exhibit higher BMI-adjusted body fat and serum leptin levels, suggesting some intrinsic leptin resistance in PWS (Eiholzer et al., 1999). BBS is a multisystemic disorder characterized by retinal degeneration, hypogonadism, polydactyly, renal dysfunction, mental retardation, and obesity resulting from defects in ciliary function. Hypothalamic dysfunction in these patients is suggested by the study of mice harboring mutations in BBS genes. BBS mutants have been shown to be hyperleptinemic and have defective hypothalamic leptin signaling (Seo et al., 2009; Guo and Rahmouni, 2011).

Thus, damage to, or dysfunction of the hypothalamus results in an inability of the CNS to receive proper feedback. Patients, thus, inappropriately sense a perpetual state of starvation. To correct the perceived negative energy balance, efferent outputs are adjusted to promote caloric intake and decreased caloric expenditure. Decreased sympathetic activation of β_2-, β_3-, and α_2-adrenergic receptors reduce skeletal muscle thermogenesis, reduce adipose tissue lipolysis, and promote pancreatic insulin secretion, respectively. Conversely, increased parasympathetic output through the vagus nerve slows the heart rate reducing myocardial oxygen consumption, promotes gastrointestinal peristalsis and substrate absorption, and accentuates post-prandial insulin secretion (Lustig, 2008). The net result of this reduced sympathetic/parasympathetic ratio is significantly decreased energy expenditure with partitioning of calories away from energy consuming tissue such as muscle and toward energy storage depots such as adipose tissue.

Accumulating evidence supports the hypothesis that CP and its therapies often result in dysfunction of the normal homeostatic mechanisms regulating appetite and metabolism. Leptin, a potent anorexigenic peptide secreted by adipocytes, has been found to be elevated in CP patients compared to obese controls suggesting a defect in the normal feedback inhibition of appetite. In addition, some CP patients have a blunted post-meal increase in the anorexigenic hormone peptide YY. Hypersecretion of the orexigenic gastric hormone ghrelin is thought to contribute to hyperphagia and obesity in PWS, although this does not seem to be the case in CP where pre-meal ghrelin levels are lower than weight-matched controls. Recently, however, Roth et al. found that there may be a reduction in the expected magnitude of post-meal suppression of ghrelin levels in CP patients (Roth et al., 1998, 2011; Holmer et al., 2010).

While there are reports of hyperphagia and obsessive food-seeking behavior after CP (Skorzewska et al., 1989), a number of studies have now shown that caloric expenditure, and not caloric intake, may be the largest contributor to post-CP–HyOb (CP–HyOb). Adults and children with CP–HyOb have been found to have impaired sympathoadrenal activation in response to hypoglycemia, although this defect does not appear to always correlate with development of obesity or hypothalamic involvement (Schofl et al., 2002; Coutant et al., 2003). In a larger study, CP–HyOb patients were found to have lower levels of urine catecholamines than BMI-matched controls (Roth et al., 2007), suggesting decreased sympathetic tone.

As sympathetic tone correlates with spontaneous motor activity, one might also expect lower levels of physical activity in CP patients. Indeed, CP patients consistently report reduced physical activity, even when compared to controls with similar BMI (Roth et al., 2007). Using accelerometric data, Harz et al. demonstrated that obese CP patients had decreased spontaneous motor activity compared with age and BMI-matched controls. Using food diaries, this same group showed that caloric intake was lower in CP patients with hypothalamic damage, despite a significantly increased BMI (Harz et al., 2003). These findings were substantiated by a recent study by Holmer et al. in 42 adult patients with childhood CP, where CP patients were found to have a significantly reduced basal metabolic rate when adjusted for body weight, than age and sex matched controls. Analysis of energy intake showed lower caloric consumption in CP patients which was attributed to cognitive restraint in eating (Holmer et al., 2010). Aside from reduced sympathetic drive, the roadblocks to physical activity are substantial and likely contribute to reduced energy expenditure and risk for obesity. Neurological and visual deficits may contribute to limited movement in some CP patients. In addition, there is evidence that CP patients have disordered sleep patterns secondary to decreased melatonin and/or secondary narcolepsy causing daytime sleepiness (Muller et al., 2002, 2006). Obstructive sleep apnea (OSA) in these patients also likely contributes to poor sleep hygiene.

Under- or overtreatment of hormonal deficiencies may also contribute to poor metabolic parameters and weight gain in CP patients. Glucocorticoid excess is a known cause of significant weight gain, impaired glucose metabolism, sleep disturbance, and defects in bone metabolism and growth (Debono et al., 2009). Most significantly, excess glucocorticoid dosing has been associated with increased mortality from cardiovascular disease. In a large cohort of Scandinavian patients with hypopituitarism, Filipsson et al. (2006) showed that those receiving higher doses of glucocorticoid replacement had significantly higher waist circumference, total cholesterol, serum triglycerides, and HbA1c. Daily

cortisol production rates range from 6 to 8 mg/m^2/day, much less than previous estimates (Linder et al., 1990; Esteban et al., 1991; Kerrigan et al., 1993; Brandon et al., 1999). Thus, the classic adult dosing of 20 mg of hydrocortisone in the A.M. and 10 mg in the P.M., is likely an excessive dose. Unfortunately, no objective test of adequate glucocorticoid replacement has been shown to be sufficiently consistent to aid in dosing management and patients must be followed closely for clinical signs of glucocorticoid deficiency or excess.

Hypothyroidism also results in poor metabolic health and is associated with fatigue, low basal metabolic rate, increased BMI, and increased cholesterol and triglyceride levels (Kronenberg and Williams, 2008) and adequate replacement has beneficial effects on these parameters (Slawik et al., 2007). Management of thyroid hormone replacement is made more challenging in CP patients by the absence of the patient's own endogenous "thyrostat" as TSH levels cannot be used to judge adequacy of treatment. The significance of this handicap is highlighted in a recent study comparing free T4 (fT4) levels in TSH deficient patients to those in primary hypothyroid patients where TSH levels are used to guide therapy. Nearly 40% of TSH deficient patients were found to have fT4 levels below the 20th centile range compared to 13.4% of primary hypothyroid patients (Koulouri et al., 2011).

Growth hormone deficiency is present in a majority of CP patients and likely contributes to the metabolic derangements seen in this patient population. These metabolic effects are particularly important in adults, where GH replacement results in increased lean body mass and decreased body fat (Kronenberg and Williams, 2008). GH-deficiency has been shown to contribute to increased cardiovascular risk in hypopituitarism (Abs et al., 2006; Verhelst and Abs, 2009). The decision to replace GH in patients with a previous history of CP remains controversial although GH replacement does not appear to have any adverse effect on reoccurrence rates of CP in short term follow-up (Muller et al., 2010; Rohrer et al., 2010).

Hypogonadism and inadequately treated diabetes insipidus (DI) can also potentiate the effects of hypothalamic damage on excessive weight gain. Testosterone replacement, in hypogonadal men has been shown to have beneficial effects on body composition, blood pressure, and glucose homeostasis (Katznelson et al., 1996; Boyanov et al., 2003; Wittert et al., 2003). The effects of estrogen replacement on weight gain and body composition are more mixed and unclear, but premenopausal women who are hypogonadal should be physiologically replaced barring other contraindications (Norman et al., 2000). Inadequate control of DI can lead to excessive drinking of calories, poor sleep quality, and increased appetite (Beccuti and Pannain, 2011).

Altered carbohydrate and insulin dynamics have been shown to occur with CP and its treatment. While fasting glucose levels are generally no different from controls, CP patients have an exaggerated first and second phase insulin response to carbohydrate challenge (Lustig et al., 1999). Hyperinsulinism in hypothalamic damage is a result of both decreased inhibitory tone by sympathetic pathways and augmented vagal parasympathetic signaling to the pancreatic β-cell, and is not primarily a response to insulin resistance. Vagally mediated acetylcholine, acting through M_3 muscarinic receptors, promotes depolarization of the β-cell through increased sodium influx, and mobilization of intracellular calcium stores through activation of the phospholipase C pathway (Miura et al., 1996). In addition, increased vagal activity stimulates release of the intestinal peptide glucagon-like peptide-1, itself a potentiator of insulin secretion (Rocca and Brubaker, 1999; Lustig, 2008). Increased insulin secretion in turn directs calories toward storage within the adipocyte.

Thus, the disruption of hypothalamic centers that occurs as a direct result of CP or its treatment creates a situation in which efferent drives to consume and store energy are disengaged from afferent signals that would otherwise dampen such drives. The obesity that results, driven by neural and biochemical stimuli, is often severe and intractable to therapy. While lifestyle changes such as caloric restriction and increased exercise should be encouraged, these interventions alone are often not successful, leaving patients frustrated with cravings, constant hunger, and lack of progress. Further, in addition to panhypopituitarism, HyOb patients are susceptible to the same metabolic derangements seen in other types of obesity such as diabetes, dyslipidemia, and heart disease (Srinivasan et al., 2004). For patients already facing significant challenges as a result of their primary disease, the negative impact of such comorbidities on quality of life adds insult to injury.

Unfortunately, in the last several years pharmacologic agents available for weight loss treatment have significantly declined, as the most effective agents (i.e., phen–fen, sibutramine) have been withdrawn from the market for unacceptable side-effect profiles. Small studies in CP of stimulants such as modafinil, methylphenidate, and dextroamphetamine have been shown to improve daytime sleepiness, affect, and alertness in HyOb (Mason et al., 2002; Muller et al., 2006), but none have proven truly effective at reversing the severe weight gain seen in this condition. Targeting the hyperinsulinism seen in HyOb, Lustig et al. (2006) demonstrated that octreotide could induce a modest decrease in BMI (0.79 kg/m^2). A recent preliminary trial of diazoxide and metformin combined therapy demonstrated a slowing of weight gain with a stabilization of BMI over the 6-months of therapy (Hamilton et al., 2011). Taken as a whole, the efficacy of pharmacotherapy in treating CP–HyOb is tepid at best. Because CP–HyOb results from damage to the afferent target centers of the hypothalamus, agents targeting the efferent pathways to increase metabolic rate and/or thermogenesis may prove to be more effective (Bays, 2004). Newer agents targeting these efferent pathways are desperately needed.

SURGICAL TREATMENT OF HyOb

Given the limited choices and poor results of pharmacotherapy, combined with emerging data suggesting that gastrointestinal surgical procedures effect weight loss by altering the body's weight regulatory signaling pathways, several groups have looked to bariatric surgery as a viable option for producing sustained weight loss for patients with CP–HyOb. A range of procedures are available and are generally divided into three categories: restrictive, malabsorptive, and hybrid procedures. Restrictive procedures, such as gastric banding (GB) or vertical banded gastroplasty (VBG), aim to reduce stomach volume resulting in early satiety and smaller meal consumption. The natural course that nutrients follow is not altered, however. Pure malabsorptive procedures including

jejunoileal and duodenal–jejunal bypass, as well as biliopancreatic diversion (BPD) involve the diversion of ingested food, bypassing one or more sections of intestine. The former two of these procedures have largely fallen out of favor secondary to associated nutritional deficits (Organ et al., 1984). A hybrid procedure, the Roux-en-Y gastric bypass (RYGB) has become the "gold standard" and the most commonly performed bariatric surgery for weight loss. It entails dividing the stomach to create a small gastric pouch which is anastomosed to a roux limb of jejunum. An enteroenterostomy is then made between the excluded biliopancreatic limb and the roux alimentary limb (Karra et al., 2010).

Bariatric surgery remains the most effective treatment for morbid obesity and is indicated for adult patients with a BMI $> 40\,kg/m^2$ or a BMI of $>35\,kg/m^2$ and significant obesity-related comorbidities (Pories et al., 1995). More conservative indications have generally been advocated for weight loss surgery in adolescent patients (see Discussion and Future Directions). An extensive body of research has shown that patients often show measurable improvement in metabolic parameters including glucose homeostasis in the early post-operative period, independent of weight loss. While the exact mechanisms of this phenomenon are still unclear, it appears that gastric bypass alters the secretion of gut hormones that favor improved metabolism and may also counteract certain elements of the orexigenic and energy conserving hypothalamic response to voluntary weight loss. Indeed, a number of studies over the last 30 years have shown that GLP-1, an incretin hormone secreted by enteroendocrine cells of the distal ileum, is increased following bariatric surgery. The evidence is especially consistent for bypass procedures, whereas restrictive procedures have been associated with no change or a decrease in GLP-1 levels (Sarson et al., 1981; Koopmans et al., 1984; Laferrere et al., 2008).

GLP-1 has been shown to have a number of positive effects on glucose metabolism including potentiating glucose-dependent insulin secretion, improving insulin sensitivity, and suppressing glucagon secretion. In addition, it has been shown to slow gastric emptying and promote early satiety. GLP-1 exerts these pleiotropic effect by acting on specific receptors located on pancreatic β-cells, peripheral vagal afferent fibers, as well as centrally located neurons (Baggio and Drucker, 2007). In addition, bariatric surgery has been shown to increase other anorexigenic hormones such as PYY and decrease orexigenic hormones such as ghrelin (Cummings et al., 2002b; le Roux et al., 2006). Human and animal studies appear to indicate that exposure of the distal gut to nutrient-rich, partially digested food results in increased secretion of hormones such as GLP-1 and PYY. This altered hormonal milieu accounts for the greater than 80% remission in diabetes following RYGB, often within days to weeks of surgery, and a combination of malabsorption, gastric restriction, and hormonal changes that accounts for the consistent and durable weight loss seen following such procedures (Buchwald et al., 2004; Karra et al., 2010).

Despite the large body of evidence demonstrating the benefits of bariatric surgery in treating exogenous obesity and its comorbidities, its role in the treatment of HyOb has yet to be defined. To date, the existing literature on bariatric surgery in CP–HyOb is largely limited to case reports and series with short term follow-up. A PubMed search for "craniopharyngioma" and "bariatric surgery" results in four citations with a total of eight patients. Procedures performed include two RYGB, four laparoscopic adjustable band (LAGB), one distal gastric bypass, and one biliopancreatic derivation with duodenal switch.

In the first report of RYGB for CP–HyOb, we reported on an 18-year-old male who underwent a successful RYGB with anterior truncal vagotomy (due to the presumed importance of vagal efferents in CP-related hyperinsulinemia) for massive weight gain following the resection of a CP 3 years previous. At the time of CP diagnosis, his BMI was $25\,kg/m^2$. During the 2-years following CP resection, he developed hyperphagia and significant weight gain (70 kg/year) despite outpatient and inpatient dietary and physical activity interventions. Significant hyperinsulinism was noted and the patient was started on octreotide therapy with significant deceleration in weight gain but no weight loss. At the time of his bariatric surgery consultation, he had developed severe OSA, left ventricular hypertrophy, and hypertriglyceridemia. The post-operative course was significant for a 49-kg weight loss over 2.5 years, although weight appeared to stabilize thereafter (BMI $\sim 50\,kg/m^2$). Further, serum triglycerides and left ventricular hypertrophy normalized. Hyperphagia decreased and food cravings (as measured by a Food Craving Inventory) diminished for all food types. Ten days following RYGB surgery, there was a fivefold decrease in fasting insulin, with normalization of fasting levels by 7 months. His post-prandial insulin excursion completely normalized by 14 months. As well, measurements of the orexigenic hormone ghrelin revealed a moderate decrease over the same time period.

In a different approach, Schultes et al. describe their approach to bypass surgery in a 29-year-old male with childhood CP. Following CP resection 21 years previous, the patient had experienced continuous weight gain, developed type 2 diabetes, and OSA requiring continuous positive airway pressure therapy at night. At the time of HyOb surgical consultation, this patient was on hormone replacement for panhypopituitarism as well as metformin and nateglinide for diabetes treatment. To promote preoperative weight loss, he was started on 15 mg sibutramine and enrolled in a rigorous supervised diet and exercise regimen which resulted in 9 kg weight loss over 9 months. Because bypass-induced hormonal alterations may exert their influence via hypothalamic mechanisms, it was felt that this patient, with complete hypothalamic atrophy, may not benefit. Therefore, a distal gastric bypass, producing a significantly shorter common channel of 80 cm, was performed with the goal of inducing a strong malabsorption component. Following surgery, the patient experienced a precipitous weight loss, losing over 50 kg (∼30% of preoperative weight) over 18 months. In addition, the patient exhibited complete resolution of his diabetes and OSA and distinct reduction feelings of hunger and disinhibition on the three factor eating questionnaire (Schultes et al., 2009). The post-operative course was largely uneventful, although the patient did develop mild nutritional deficiencies despite standardized supplementation. These included anemia, deficiencies in vitamin D, B12, and zinc as well as hypoproteinemia.

In a series of four adolescent patients with childhood CP and obesity, Muller et al. found significant weight loss in all patients after LAGB. Patients participated in the German multicenter surveillance study on childhood CP termed "HIT-Endo-Kraniopharyngeom." The age of the patients ranged from 13 to

24 years of age and BMI–SDS scores ranged from +7.3 to +13.9. Following surgery, BMI–SDS scores improved on average by −0.7 per year of follow-up, with follow-up ranging from 1.5 to 4.5 years. Patients also reported significant changes in eating behavior, with reduced food cravings especially for sweets. Quality of life and functional capacity, measured by a standardized and validated scale, remained stable following surgery. Of the four patients, two experienced dislocation of the LAGB resulting in temporary weight gain and requiring laparoscopic revision. No other side-effects were reported (Muller et al., 2007).

Rottembourg et al. (2009) reported on two adolescents with post-CP–HyOb who underwent bariatric surgery as treatment for morbid obesity associated with significant comorbidities. The first was a 12-year-old female diagnosed with CP at age of 6 years. After gross total resection she developed panhypopituitarism and exhibited a rapid weight gain of 20 kg in the first 6 months. At the time of RYGB her BMI was 65 kg/m^2 and she had developed dyslipidemia, hepatosteatosis, frequent respiratory tract infections, and evidence of hypoventilation. Postoperatively, she demonstrated sustained weight loss over 4 years (BMI 43 kg/m^2 at last follow-up). In addition, dyslipidemia normalized, sleep patterns improved, and she had no further respiratory infections. She was subsequently diagnosed with fibromyalgia and symptomatic hyperuricemia, which were treated with regular analgesia and allopurinol. She also required ongoing treatment for depression. In addition, she developed a dumping-type syndrome (pallor, diaphoresis, and shakiness following meals) without associated hypoglycemia. The second patient was a 15-year-old male, diagnosed with CP at age of 4 years, also with panhypopituitarism and rapid weight gain following gross total resection. Comorbidities included dyslipidemia, hepatosteatosis, and hyperinsulinism. At the age of 14 years, a trial of octreotide led to no reduction of weight gain. At the time of bariatric surgery, his BMI was 42 kg/m^2. Given that the underlying cause of obesity was biological and would be present life-long, the surgeons involved felt that a diversionary surgical procedure would be a better option than LAGB. Following a BPD with duodenal switch, his BMI decreased to 32 kg/m^2 over the 2-year follow-up. The post-operative course was complicated by bradycardia requiring pacemaker placement, and stenosis of the distal surgical anastomosis requiring several laparoscopic repairs. Overall, both patients exhibited robust, sustained weight loss with resolution of metabolic comorbidities.

The efficacy of bariatric surgery for weight loss has also been examined in other HyOb patient populations. Scheimann et al. recently reported a retrospective critical analysis of bariatric procedures in PWS. PWS is a complex genetic disorder that results in marked hyperphagia and obesity felt to be secondary to hypothalamic dysfunction. The critical analysis revealed that a number of procedures, including BPD, RYGB, VBG, and endoscopic intragastric balloon placement have been used in this population. A review of 60 PWS patients highlighted the limited effectiveness and concerning safety profile of operations for weight loss in this unique population (Scheimann et al., 2008). In the short term, there appears to be some limited weight loss that is variable across different procedures. For RYGB, average weight loss was 4.2% for PWS patients after 6 months. Twelve month and 24 month follow-up revealed 6.5 and 2% weight loss, respectively. This weight loss is far less than the 35% reduction in BMI we see 1 year after RYGB for adolescents who do not have PWS. Five year follow-up, while limited, showed only a 2.4% weight loss in PWS patients after RYGB ($n = 9$). Long term weight loss was worse with VBG, with PWS patients experiencing a 3.5% weight gain after 5 years ($n = 2$). Patients undergoing BPD had higher weight loss of 27.6% at 12-months, but nearly half regained weight within 2–5 years. In addition, the report highlights what appears to be a high post-operative complication rate, with 47% requiring surgical revision after RYGB and 27% experiencing acute gastric dilation (Scheimann et al., 2008).

Bariatric surgery has also been reported in an adolescent patient with BBS. Patients with BBS demonstrate hyperphagia and obesity which have been linked to disruption of primary cilia in POMC neurons in the hypothalamus and possibly to altered leptin receptor functioning. In this 16-year-old with a BMI of 53 kg/m^2, RYGB resulted in a 33% reduction in BMI 3 years following surgery (Daskalakis et al., 2010). Improvement in hypertension and hyperuricemia was also observed.

Finally, as melanocortin 4 receptor (MC4R) variants represent the most common monogenetic form of HyOb in humans, it is relevant to assess the outcome of bariatric surgery in individuals with documented MC4R mutations. Surgical experience in this special group of HyOb patients is very limited. A group of investigators at the University of California San Francisco (UCSF) described surgical outcomes in an adolescent patient with a complete loss of function mutation at MC4R. This 18-year-old male presented with a preoperative weight of 166 kg and BMI of 54 kg/m^2 and underwent bilateral truncal vagotomy and laparoscopic adjustable GB. In this patient, the surgical intervention did not result in successful weight loss. Indeed, after an initial modest weight reduction of 12 kg over the first 4 months, the patient regained weight and by 1 year was 6.5 kg over his preoperative weight. Several features of the case however are relevant to interpretation of the outcome. First, the patient had moved away to college 4 months prior to the operation, and had in that time experienced a 66-kg weight gain. Also, the patient returned for only two band adjustments in the 1-year period of time, which is markedly less than the typically recommended post-operative adjustment schedule. Finally, the authors described an insatiable hunger 1 year after the operation, which was almost certainly a factor contributing to weight gain (Aslan et al., 2011b).

In a more recent publication from the same group at UCSF, the first report of an experience with gastric bypass in the setting of mutant MC4R contrasts with the results obtained after GB. Aslan et al. analyzed 1 year outcomes of four adults with heterozygous MC4R mutations in comparison to matched controls with normal MC4R gene sequences. Excess weight loss (EWL) in these four subjects was identical to the 60–70% EWL seen in matched controls. There was no mention of changes in post-operative appetite in these patients, nor any changes in metabolic features in this cohort (Aslan et al., 2011a).

DISCUSSION AND FUTURE DIRECTIONS

Hypothalamic obesity is observed in a high percentage of patients with CP, resulting in significant comorbidities and negatively impacting quality of life. Unfortunately, few treatments have

proven effective in this patient population. First line therapy for HyOb should include aggressive lifestyle modification including appropriate caloric intake and activity. Pituitary hormone deficiencies, if any, should be replaced and doses optimized. As mentioned previously, glucocorticoid replacement should be targeted at replacement doses (8–10 mg/m^2/day hydrocortisone equivalent) and patients should be given the lowest dose possible that is adequate to avoid symptoms of adrenal insufficiency. Thyroid replacement should generally target the fT4 at the upper third of the normal range and patients should be clinically and biochemically monitored for signs/symptoms of hyper- and hypothyroidism (Rose, 2010). The decision to replace GH should be made in consultation with the patient, family, and other team members such as their oncologist and neurosurgeon. If done, GH doses should be titrated to keep IGF-1 levels within the median range. Ideally, other medical treatments aimed specifically at ameliorating weight should be pursued through approved protocols at centers capable of collecting outcomes data on a sufficiently large number of patients so that risks and benefits of treatment can be more precisely defined. This is especially important with respect to bariatric surgery in this population.

Here, we have reviewed the current body of published research on bariatric surgery in CP–HyOb. We have also included several published reports of bariatric surgery in other populations of HyOb, including PWS, BBS, and patients with MC4R mutations. While the limited scope of these reports makes comparison difficult, the experience in PWS patients demonstrates that all cases of HyOb should not be treated equally. Likely as a result of the multisystemic nature of their disorder, PWS patients have a significantly increased incidence of complications following bariatric surgery without the benefits of sustained weight loss. In addition, it appears that early dietary interventions are able to partially abrogate weight gain this population (Schmidt et al., 2008). Thus, the risk–benefit ratio of bariatric surgery in PWS does not appear to be favorable.

The initial reports of bariatric surgery in CP–HyOb and patients with MC4Rappear more promising, but again, their limited scope makes it difficult to draw any substantial conclusions as to the long term safety and efficacy of these procedures in this population. The limited number of cases inhibits comparison among various procedures. For instance, how does RYGB compare to LAGB with regard to long term, sustained weight loss, or with regard to safety and side-effects? In addition, more work is needed to understand the hormonal alterations that occur in CP–HyOb following bariatric surgery. Are such alterations similar to those seen in diet-induced obesity? If not, why? If so, do CP–HyOb patients derive the same benefits given their underlying hypothalamic damage? If hyperinsulinism is an underlying factor in the development of HyOb, will patients benefit or be harmed from increased levels of the insulin secretagogues such as GLP-1. Will potentiating insulin secretion place these patients at higher risk of hypoglycemia secondary to the mismatch of insulin secretion and carbohydrate absorption? These and other questions remain unanswered by the current body of research in this population and should be the subject of future work.

In addition, as 50% of patients diagnosed with CP are children, there are serious medical, psychological, and ethical concerns regarding bariatric surgery that must be considered in this population (Inge et al., 2004). Generally, adolescent candidates for bariatric surgery must meet more conservative patient selection criteria than are acceptable in adults. However, exact criteria are still of some debate. In 2008, the Endocrine Society, in conjunction with the Pediatric Endocrine Society, published a Clinical Practice Guideline on the Prevention and Treatment of Pediatric Obesity, wherein the task force recommended limiting bariatric surgery to adolescents with a BMI $\geq$ 50 kg/m^2 or a BMI $\geq$ 40 kg/m^2 with significant, severe comorbidities. In addition, the task force recommended that candidates have attained Tanner 4 or 5 pubertal development and near-final adult height, experienced continued weight gain despite following a formal program of lifestyle modification, and belong to a stable, medically competent family unit. The patient and family should understand that bariatric surgery is not a cure for obesity, but rather an adjunct to a continued commitment to lifestyle modifications in diet and activity. The surgery should be performed by an experienced surgeon in a medical center employing a team capable of long term follow-up and participating in a study of bariatric surgery outcomes. These recommendations largely agree with guidelines previously published and advocate the priority of avoiding unforeseen complications associated with life-long exposure to anatomical and functional alterations above the value of weight loss and amelioration of obesity-related complications provided by bariatric surgery (August et al., 2008).

More recently, Pratt et al. (2009) suggest that adolescents with a BMI $\geq$ 35 kg/m^2 and serious comorbidities including Type 2 diabetes, moderate to severe OSA, and/or pseudotumor cerebri or those with BMI $\geq$ 40 kg/m^2 with less serious comorbid conditions such as hypertension, dyslipidemia, gastroesophageal reflux disease, and/or psychosocial stress should be considered as candidates for bariatric surgery. While concurring with the other physical, lifestyle, and psychosocial criteria previously published, they use several lines of evidence to defend the lower BMI criteria. First, they cite data to indicate that patient safety and weight loss outcomes for extremely obese adolescents who undergo bariatric surgery are comparable to, or better than, those seen in adults. Second, even with the lower BMI criteria of 35 kg/m^2, candidates under the age of 18 would still be above the 99th BMI percentile and be at substantially increased risk for short and long term medical comorbidities. Third, they stress that selection for bariatric surgery during adolescence should be closely linked to obesity-related comorbidities. The less severe comorbidities and/or fewer risk factors for long term disease, the higher the BMI cut point should be before considering bariatric surgery. Finally, some have suggested that because younger patients will generally have fewer advanced comorbidities, early bariatric surgery may decrease the risk of future perioperative mortality, assuming the needed surgery is delayed until adulthood (Garcia and DeMaria, 2006).

Importantly, none of the guidelines for bariatric surgery directly addresses the use of bariatric surgery in HyOb generally or CP–HyOb in particular. In general, we believe that most criteria from the published guidelines can be applied to the HyOb patients, especially in adults. Whether one or more of the published criteria should be modified in the context of children and adolescents is subject to ongoing debate. Given what is known

about the natural history of HyOb, its resistance to diet and lifestyle modification, and the extreme and progressive weight gain involved, some may consider bariatric surgery appropriate at ages currently considered too young in patients with exogenous obesity. However, in general, the younger the patient the more compelling and serious the comorbidities must be to justify surgical intervention. Because of the need for life-long medical support, optimal care of HyOb patients will be best met in the setting of tertiary care centers where they can receive treatment in a coordinated, multidisciplinary fashion. Team members should include the primary care physician and as needed subspecialists in neurosurgery, neurology, oncology, endocrinology, bariatric surgery, and mental health. Ideally, ancillary support by nutrition, physical therapy, nursing, and social work should also be available. Patients and families choosing to undergo bariatric surgery should be properly informed regarding specific risks and benefits associated with surgical weight loss and age appropriate consent or assent obtained. To facilitate needed research in this area, patients should be encouraged to enroll in available databases and research protocols.

These early reports of outcome of surgical weight loss treatment of HyOb are limited in scope and number, but give us a glimpse of the possible role of surgery in treatment of these conditions. They also make evident the need for more robust, controlled, prospective studies with long term follow-up in order to better define the role of medical as well as surgical therapies in the treatment of HyOb. In order to ultimately understand the outcome of surgical therapy for HyOb, sufficiently long follow-up of sufficient numbers of similar patients who undergo surgery as well as non-surgical controls will be required. Non-human surgical models might also in the future permit a better understanding of the mechanisms of obesity, and the importance of tailoring specific operative elements to each unique population.

Research in this important area is hampered by the difficulty of assembling a sufficiently large cohort of CP–HyOb patients. Given the relative rarity of the condition, it would take a single institution many years to put together a study large enough to reach valid, persuasive conclusions regarding the treatment of HyOb – surgical or otherwise. In order to increase public awareness of HyOb, facilitate future research and ultimately improve the management of HyOb, the International Registry for HyOb Disorders (www.IRHOD.org) has been established. The web-based interface will permit both healthcare providers and patient/families to easily enter basic information regarding their HyOb case. The systematic accumulation of a large world-wide cohort of patients with HyOb will facilitate recognition of individuals eligible for participation in studies of HyOb and its treatment. This registry, therefore, has potential to fill many of the numerous knowledge gaps around pathogenesis, coexisting disease, and treatment outcomes for this debilitating form of obesity.

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