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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

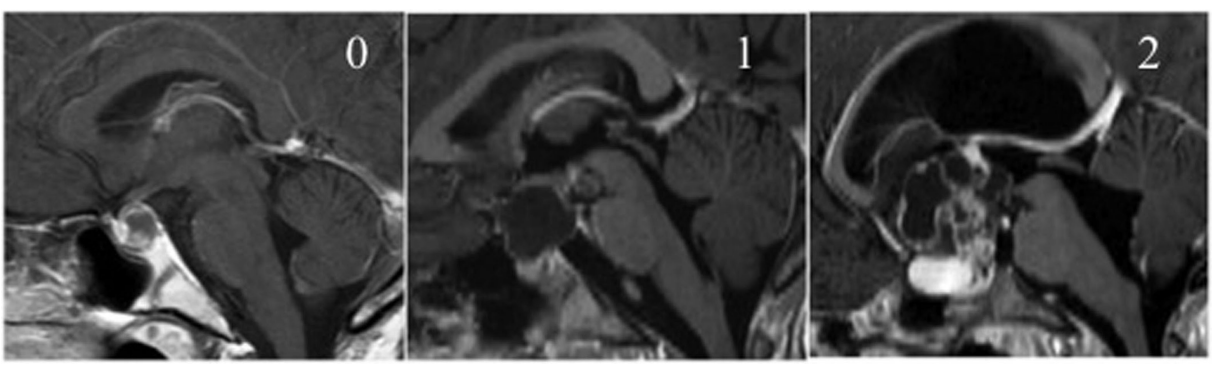

FIGURE 1 | Pre-operative MRI classification according to hypothalamic involvement. Type 0 pre-op: no involvement of the hypothalamus, Type 1 pre-op: distortion/elevation of the hypothalamus, Type 2 pre-op: the hypothalamus is not visible due to tumor invasion.

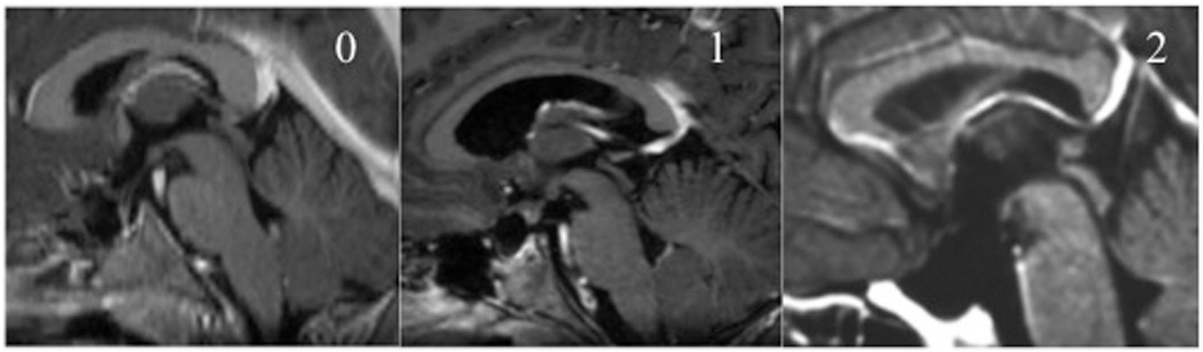

FIGURE 2 | Post-operative MRI classification according to hypothalamic injury. Type 0 post-op: intact hypothalamus, Type 1 post-op: breech/residue on the hypothalamus, Type 2 post-op: severe hypothalamic injury.

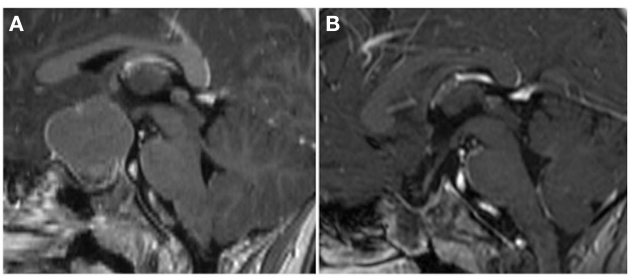

FIGURE 3 | Surgical strategy grade 0/1 pre-op. (A) On the pre-operative MRI, the hypothalamus appeared to be more displaced than invaded by tumor (Type 1 pre-op). **(B)** This was confirmed during surgery and a complete removal preserving the hypothalamus could be achieved (Type 0 post-op).

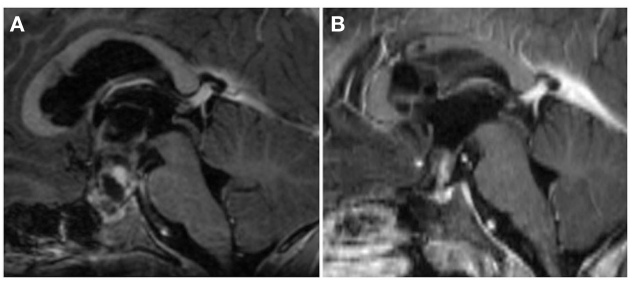

FIGURE 4 | Surgical strategy grade 2 pre-op. (A) At referral, the patient had severe intracranial hypertension secondary to obstructive hydrocephalus from a large intraventricular cyst of the third ventricle. An Ommaya reservoir was placed within the cyst as a matter of urgency. The tumor clearly invaded 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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