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ORIGINAL PAPER

Craniopharyngioma and hypothalamic obesity in children

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Abstract
Background and purpose Obesity is a major concern in children treated for craniopharyngioma and is caused by hypothalamic damage. The role of aggressive surgical removal has been questioned, leading some authors to recommend a minimalist approach. In order to test this hypothesis, we decided to study obesity in craniopharyngioma and the factors related to it.
Materials and methods We reviewed retrospectively our series of pediatric craniopharyngiomas operated since 1981. The body-mass index (BMI) was calculated for each patient pre- and at several intervals postoperatively and expressed as standard deviations (SD) adjusted for age and gender.
Results We operated on 45 cases, which were followed up for a mean duration of 11.0 years. Initial resection was total in 25 cases (55.6%). No patient died because of surgery or tumor progression; two died with delay presumably because of endocrine failure. At last control, 28 patients (62%) had obesity (BMI over +2SD). Hypothalamic involvement was significantly correlated with preoperative and postoperative BMI. Subtotal tumor resection was significantly associated with obesity at last control. Reoperation for tumor recurrence was associated with a significantly higher BMI.
Conclusions Our results suggest that obesity results from hypothalamic lesions caused by the tumor rather than by surgery. The postoperative weight gain appears to result from the continued impact of preoperative hypothalamic damage. The high rate of tumor recurrence in children, with the risk of additional damage to the hypothalamus, incites us to recommend total resection whenever it appears safe during initial surgery.

Keywords Craniopharyngioma · Recurrence · Childhood tumors · Cerebral neoplasms · Hypothalamic dysfunction · Obesity

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Introduction

Craniopharyngioma is a histologically benign, clinically malignant tumor, which has fascinated generations of pediatric neurosurgeons because of its technical difficulties and high stakes in young children. Its management represents a challenge and is the matter of heated debates.

Total resection has long been considered the gold standard for treatment [6, 26, 27]. However, with time, it became evident that in children, the rate of total resection is little higher than 50%, even in experienced hands [3, 11]. In addition, total resection may be associated with a high level of morbidity and mortality, in particular cognitive disorders and obesity resulting from hypothalamic damage caused by dissection of the third ventricle [13]. These considerations have led to consider less aggressive strategies, like subtotal resection followed by irradiation [2, 5, 18], and alternative methods based on stereotactic techniques [8]. This trend from maximalism to minimalism was dubbed "the pendu-

lum of surgical management" by C Sainte-Rose, who favored a cautious approach to these tumors based on preoperative imaging [16].

With a few more years hindsight, however, it may not be so clear whether reduced surgical aggressiveness helps reduce morbidity; in particular, obesity appears not diminished, unlike other postoperative complications [21]. In addition, the oncological aspect should not be forgotten: although histologically benign, recurrences are common in children [1]. These recurrences bear the risk of additional hypothalamic damage and visual loss and a poor vital outcome if the child has been irradiated before [12]; reoperation is generally required, risking additional neurological damage [25]. At this point of our reflection, the question "has the pendulum swung too far back?" should be raised.

The responsibility of total resection in hypothalamic damage, in particular obesity, needs to be substantiated. In a huge and meticulously studied series, Müller et al. documented the body-mass index (BMI) of children with craniopharyngioma, expressed in standard deviations (SD) adjusted for the age and gender, before and after surgery [9]. These authors showed that obesity was often present at the time of diagnosis, especially when the tumor involved the hypothalamus. We decided to apply a similar methodology to study the impact of surgery on the clinical outcome, especially obesity, in children operated for craniopharyngioma.

Materials and methods

We reviewed our database for cases of craniopharyngioma operated at our institution during the last 25 years. The medical and surgical management has been fairly homogenous during that period, with surgery aiming at total removal whenever possible. Stereotactic techniques like intracystic catheter placement for fluid subtraction, intracystic irradiation with β-emitter (Rhenium), and stereotactic irradiation, first with linear accelerator (LINAC) then with gamma-knife, were also developed during that period but generally not used as a first-line treatment. The use of conventional external irradiation was limited to cases of recurrence not amenable to reoperation or stereotactic treatment.

The estimation of hypothalamic involvement was based on imaging and/or operative data; extent of resection was based on operative report and/or imaging. For each patient, the measures of weight and height at the time of surgery; at 1 and 2 years postoperatively; at the age of 20 years when appropriate; and at last control were retrieved from the medical record and follow-up reports. For each of these steps, the BMI was calculated and plotted against the diagram adjusted for age and gender as determined for the French population by Rolland-Cachera et al. [14]. BMI was expressed as a continuous variable in SD from the mean. Each patient was thus represented by a set of five values (or four for those who were aged less than 20 at the time of last control). For statistical analysis, obesity was also expressed as a binary variable defined as BMI above 2SD for the age and gender. Subtotal resection was defined as any resection less than total, including subtotal and partial resection, and biopsy. Functional outcome was evaluated using the Glasgow Outcome Score (GOS) according to the World Federation of Neurological Surgeons (1 = normal activity, 5 = dead); for statistical analysis, we defined the binary variable "poor outcome" as GOS≥3.

Continuous variables were studied with Student's *t* test, regression analysis, and analysis of variance. Discrete variables were studied using Pearson's and Wilcoxon's *Z* tests. Binary variables were studied using the chi-square test or Fisher's exact test. Survival analysis was performed using the Kaplan–Meier method with the log-rank test for statistical significance. Logistic regression analysis was performed for obesity and good outcome as binary endpoints. All statistics were performed using the commercially available software SPSS 13.0 for Windows (SPSS® Inc., Chicago, IL, USA).

Results

We operated on 45 children operated between 1981 and 2006. The mean age at diagnosis was 107 months, (27 months–16.2 years); 21 were male and 24 were female (M/F ratio 0.87). The hypothalamus was involved in 36 cases (80%). Obesity was present at the time of diagnosis in seven cases (15.6%); overall, symptoms of hypothalamic dysfunction were present in 48.9%. Intracranial hypertension was present at diagnosis in 32 cases (71.1%), and 11 patients (24.4%) required shunting initially or during follow-up.

Resection was total in 25 (56.8%), subtotal in ten (22.2%), partial in eight, and limited to a biopsy in two. The mean follow-up after surgery was 11.0 years (16 months to 25 years). No patient died directly because of surgery or tumor progression; two patients died at a distance after surgery without evidence of tumor progression: one because of endocrine imbalance 18 months after surgery; another died abruptly of causes unknown, 5 months after operation for a second recurrence; endocrine failure was suspected in this case also.

The mean follow-up was 11.0 years. Tumor progression occurred in 25 patients (55.6%). The event-free survival (EFS) was 45.5% after 5 years and 42.7% after 10 years. Twenty-one patients underwent 40 tumor resections for recurrence; the maximum number of resections was five.

Other treatments included insertion of a Rickham reservoir for intracystic treatment (seven), radiosurgery (four), and external irradiation (six). At last control, 25 patients were tumor-free, and 18 had stable tumor residue. Extent of tumor resection was the main determinant of EFS (p=0.0011).

The mean age at last control was 20.1 years (7.1 to 38). At last control, two patients were GOS 1 (normal activity), 19 were GOS 2, 22 were GOS 3, and two were GOS 5 (dead), as mentioned earlier. Poor clinical outcome was correlated with hypothalamic involvement (p=0.031), tumor recurrence (p=0.009), reoperations (p=0.002), preoperative BMI (p=0.002), and final BMI (p=0.002). No significant correlation was found between GOS and extent of resection or age at surgery. In logistic regression analysis, preoperative BMI was the only significant and independent variable predicting functional outcome (p=0.043).

At last control, the mean BMI was 30.3; 31 patients (70.5%) were obese (>2SD), 11 (25%) being morbidly obese (>4SD). Univariate analysis showed that obesity at last control was significantly predicted by hypothalamic involvement (<0.001), preoperative BMI (R=0.67, p< 0.001), subtotal resection (p=0.026), tumor recurrence (p=0.02), the number of recurrences (p=0.002), reoperation (p=0.026), the total number of surgeries (p=0.009), and the duration of follow-up (p=0.004). Obesity was also correlated with memory loss (p=0.005) and poor functional outcome (p=0.003). The progression of BMI in relation with hypothalamic involvement, extent of resection, and reoperation is shown in Figs. 1, 2, and 3, respectively. In binary logistic regression analysis, only the preoperative BMI was a significant and independent predictor of obesity at last control.

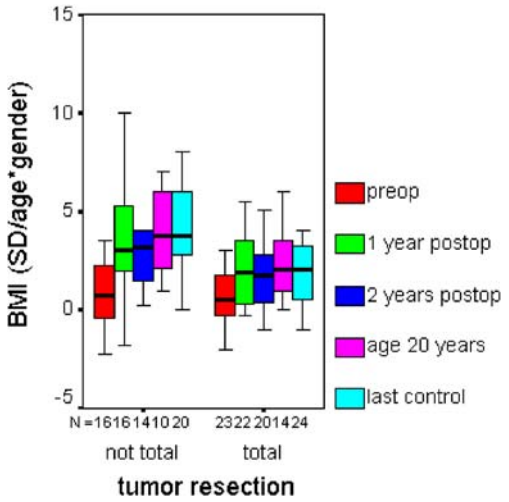

Fig. 2 Comparison of patients with subtotal (*left*) and total (*right*) tumor resection. Evolution of the BMI at the time of diagnosis (*red*); 1 year (*green*) and 2 years (*dark blue*) postoperatively; at 20 years (*pink*); and at last control (*light blue*). Although the BMI showed a marked trend toward higher level in patients undergoing subtotal resection, none of the comparisons (Student's t test) were statistically significant. The number of patients who were obese (>2SD) at last control was, however, significantly higher in the subtotal resection group (chi-square, p=0.026)

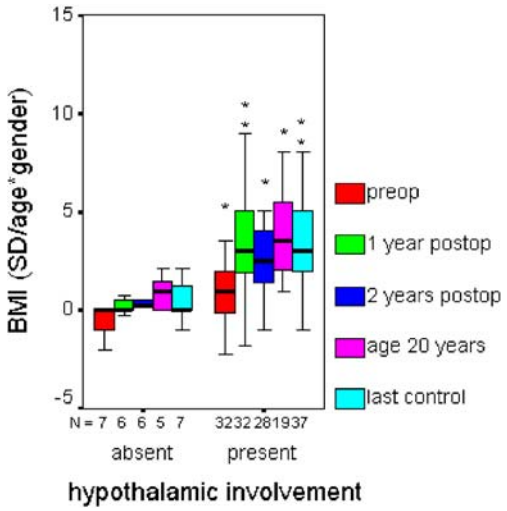

Fig. 1 Comparison of patients without (*left*) and with (*right*) hypothalamic involvement by the tumor. Evolution of body-mass index at the time of diagnosis (*red*); 1 year (*green*) and 2 years (*dark blue*) postoperatively; at 20 years (*pink*); and at last control (*light blue*). The correlation between hypothalamic involvement and obesity was either significant (*p<0.05) or highly significant (**p<0.01) according to the timing relative to surgery

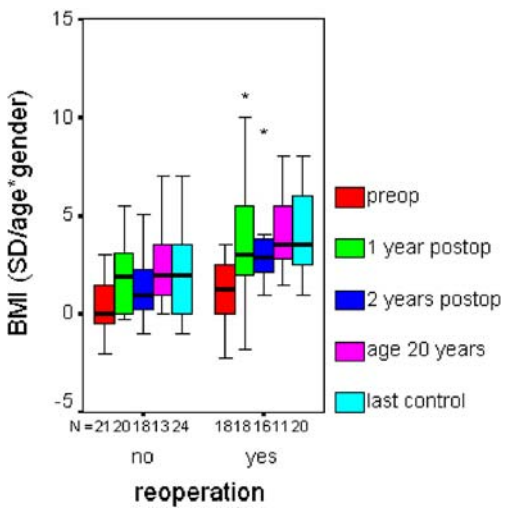

Fig. 3 Comparison of patients not reoperated (*left*) and reoperated (*right*). Evolution of the BMI at the time of diagnosis (*red*); 1 year (*green*) and 2 years (*dark blue*) postoperatively; at 20 years (*pink*); and at last control (*light blue*). In the reoperation group, the BMI was significantly higher (p<0.05) at 1 and 2 years postoperatively. The number of patients who were obese (>2SD) at last control was also significantly higher in the reoperation group (p=0.026)

Discussion

Obesity

The prevalence of obesity in craniopharyngioma has been evaluated at 50% of patients [15, 19], of which "roughly" a third are considered morbidly obese [4]. However, the real prevalence is difficult to evaluate because BMI increases with the duration of follow-up, and values need to be adjusted for age and gender. In our series, after a mean follow-up of 11 years, 70% of patients had become obese, 25% being morbidly obese according to normative values determined in the French population. Obesity has a marked impact on the patient's quality of life and is associated with diminished motility and impaired schooling [17]; our data confirms these previous studies. The pathogenesis of obesity is complex and thought to result from damage to the ventro-median hypothalamus [19]. Hyperphagia can result from hypothalamic resistance to leptin, which is up-regulated [15], and is sometimes part of a severe psychiatric disorder with feeding compulsion, akin to addictive behavior. In most cases, however, caloric intake is considered normal in craniopharyngioma patients, the difference resulting from reduced caloric output caused by altered behavior with hypomobility [9]. This reduction in energetic consumption is to be put in perspective with a decreased nocturnal peak of melatonin, disturbed circadian biorhythm, and the presence of narcolepsia in many patients with craniopharyngioma [10]. The relation of obesity to surgical damage has been debated: Puget found a correlation between obesity and postoperative hypothalamic lesions [11], while Villani found no correlation with the extent of tumor resection [24]. In our series, total resection was associated with absence of obesity, suggesting that the tumors that could not be removed totally were the ones that caused hypothalamic damage and obesity. Müller has also shown that preoperative BMI was the only independent predictor of long-term obesity in craniopharyngioma [9]. Our data confirm these findings, with many patients already markedly obese at the time of presentation (Fig. 4). These data also suggest that surgical resection, when done with restraint, does not necessarily aggravate the hypothalamic lesion caused by the tumor.

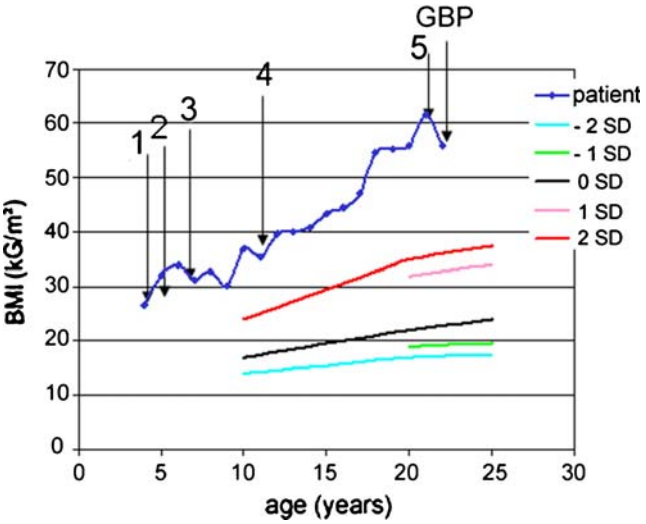

Fig. 4 BMI at diagnosis and during subsequent evolution in a girl who was operated initially at the age of 5, and was reoperated four times for tumor recurrence. At the time of the last recurrence, aged 20, her weight was 204 kg (449 lb), after which she underwent a gastric by-pass (*GBP*). Note that the BMI was highly abnormal from the start and that its progression was initially roughly parallel to the normal and started to spiral out of control at the age of 16, after the third reoperation

Oncological perspective

Although not histologically malignant, pediatric craniopharyngioma is a clinically malignant tumor, which bears a high morbidity, and also a high risk of tumor recurrence. This high rate of recurrence may be ascribed to the adamantinous nature of the tumor and infiltration of brain tissue [26]; however, the extent of tumor resection is the most prominent factor for the risk of recurrence [7]. The first surgery is often regarded as the only good opportunity to cure the patient by performing radical resection [3]. Recurrences have a high functional cost regarding memory, vision, and hypothalamic syndrome [24, 25]. In case of tumor recurrence, the risks are not just functional but vital, especially in irradiated patients [12]. Radiotherapy, radiosurgery, and intracavitary treatments are all part of a growing armamentarium available for the treatment of craniopharyngioma. Irradiation has been proposed as a routine postoperative regimen [2, 5]; however, up to 26% of irradiated patients will present with recurrence, which is difficult to treat and bears a poor prognosis [12]. Often, these recurrences take the form of multicystic lesions, which cannot be efficiently treated with drainage and intracystic treatments. In addition to the classical complications of external irradiation on the developing brain, several cases of malignant radio-induced tumors have also been reported after irradiation for craniopharyngioma [12, 17, 20, 23]. The question with pediatric craniopharyngioma should be: how to manage these children and prevent the tumor from recurring for the rest of their life. Obviously, it is best to keep as many arrows in our quiver and to perform irradiation as late as possible. We think that total resection, when it is feasible, may be the only treatment and appears as the most desirable option; it should remain a therapeutic standard for pediatric craniopharyngioma.

Surgical implications

Radical resection is associated with better clinical outcome as well as better oncological outcome [26]. Again, the absence of hypothalamic infiltration by the tumor accounts for both the better clinical outcome and the possibility of total resection.

Hypothalamic damage, and often obesity, is already present at the time of diagnosis [9]. Interestingly, Thompson has reported that the adoption of a "minimally aggressive" surgical protocol reduced the overall postoperative morbidity but not the prevalence of hypothalamic syndrome [21]; this appears to confirm that "aggressive" surgical resection does not cause additional damage, provided that it is performed cautiously. This is not the case for resection at the time of tumor recurrence [25], and reoperation was associated with increased obesity in our series.

From our data and from the literature, the conclusion that hypothalamic involvement, subtotal resection, tumor recurrence, and obesity are closely correlated tends to impose itself. How can we recognize the good and the bad? Hypothalamic damage can in part be predicted from preoperative magnetic resonance imaging (MRI); Puget has proposed to grade hypothalamic infiltration in a semi-quantitative grading from 0 to 2 [11] and to tailor the extent of resection based on preoperative MRI. MRI is certainly an indication of the operative difficulties; however, we found that it can both overestimate and underestimate surgical difficulties. In an earlier era, Till found that no prediction could be made before surgery and that only operative findings could tell if it is legitimate or not to pursue the goal of total resection; he added that "mature judgment is needed to determine how far to go and when to stop" [22]; these statements remain largely valid in the era of MRI. Maintaining and transmitting the necessary level of expertise required to make that decision is a major challenge for the future and the training of young neurosurgeons.

Conclusion

The problems of postoperative morbidity and of tumor recurrence are connected because both need to be balanced at the time of initial treatment. Viewing this problem as an alternative between subtotal resection on one hand (with the risk of recurrence or the need for postoperative treatment), and inflicting damage to the child on the other hand (with obesity, problems with cognition and memory), may be simplistic and is not supported by facts. Based on our data and reports from the literature, our opinion is that craniopharyngiomas present themselves upfront either with hypothalamic damage, which will develop as obesity whatever is done surgically; or without, in which case surgery done properly will cause no or minimal damage to the hypothalamus. Obesity, like hypopituitarism, is a severe consequence of craniopharyngioma, which surgeons can do little to avert; unlike hypopituitarism, however, obesity generally results from preoperative damage rather than from surgery itself. Whatsoever, the worst complication of craniopharyngioma is blindness; all our efforts to prevent it from happening are warranted, and endocrine complications may be the price for the patient to pay. Looking at an obese self in the mirror is terrible but certainly better than not being able to see oneself in a mirror at all.

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