Magnetic resonance imaging–graded hypothalamic compression in surgically treated adult craniopharyngiomas determining postoperative obesity

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Object. Obesity as a consequence of management of pediatric craniopharyngioma is a well-described phenomenon related to the degree of hypothalamic involvement. However, weight change and obesity have not been analyzed in adult patients. Therefore, the purpose of this study was 1) to evaluate the pattern of postoperative weight gain related to preoperative body mass index (BMI), 2) determine if postoperative weight gain is an issue in adult patients, and 3) develop an objective MR imaging grading system to predict risk of postoperative weight gain and obesity in adults treated for craniopharyngioma.

Methods. The authors retrospectively screened 296 patients with known craniopharyngioma for the following inclusion criteria: pathologically confirmed craniopharyngioma, index surgery at the authors’ institution, and operative weight and height recorded with at least 3 months of follow-up including body weight measurement. Patients aged 18 years or younger were excluded, yielding 28 cases for analysis. Cases of craniopharyngiomas were compared with age- and sex-matched controls (pituitary adenoma patients) to evaluate the pattern and significance of perioperative weight changes.

Results. Mean age was 46 ± 17 years at surgery, and 64% of the patients were male. Complete resection was achieved in 71% of cases. There was no correlation of preoperative BMI and postoperative weight gain testing in a linear model. Sixty-one percent and 46% of patients had postoperative weight gains greater than 4 and 9%, respectively.

Comparing craniopharyngioma patients (cases) to age- and sex-matched controls, the preoperative BMIs were similar (p = 0.93) between cases (mean 28.9 [95% CI 30.9–26.9]) and controls (mean 29.3 [95% CI 31.9–26.7]). However, there was a trend to a greater mean postoperative weight change (percentage) in cases (10.1%) than in controls (5.6%) (p = 0.24). Hypothalamic T2 signal change and irregular contrast enhancement correlated and predicted higher-grade hypothalamic involvement. Furthermore, they can be used to objectively grade hypothalamic involvement as the authors propose. Progressive hypothalamic involvement correlated with larger postoperative weight gains (p = 0.022); however, hypothalamic involvement did not correlate with preoperative BMI (p = 0.5).

Conclusions. Postoperative weight gain in adult patients undergoing surgery for craniopharyngioma is a significant problem and correlates with hypothalamic involvement, as it does in pediatric patients. Finally, objective MR imaging criteria can be used to predict risk of postoperative weight gain and aid in grading of hypothalamic involvement. (DOI: 10.3171/2010.1.FOCUS09303)

Key Words • craniopharyngioma • weight gain • hypothalamus • obesity • body mass index

PERIOPERATIVE weight gain is a substantial issue in pediatric patients undergoing surgery for craniopharyngioma for a plethora of reasons including increased morbidity and poor patient self-perception.²²,²⁴ Through the pediatric craniopharyngioma literature, it is becoming clearer that increased morbidity and poor patient self-perception are associated with increased weight gain. However, weight change and obesity have not been analyzed in adult patients. Therefore, the purpose of this study was 1) to evaluate the pattern of postoperative weight gain related to preoperative body mass index (BMI), 2) determine if postoperative weight gain is an issue in adult patients, and 3) develop an objective MR imaging grading system to predict risk of postoperative weight gain and obesity in adults treated for craniopharyngioma.

Abbreviations used in this paper: BMI = body mass index; NIH = National Institutes of Health.
Furthermore, it is unknown whether there is a difference between higher-grade patients, but preliminary reports suggest that a difference does exist. Therefore, if this grading system is to be used to prognosticate postoperative weight gain, additional objective MR imaging findings should be evaluated as additional criteria to define Grade 1 and Grade 2 cases.

Here, we have undertaken a review of data obtained in adult patients with craniopharyngioma to determine the following: 1) the pattern of postoperative weight gain related to preoperative BMI, 2) if postoperative weight gain is an issue in adult patients, and 3) if MR imaging can be used to predict development of postoperative weight gain and obesity in adults treated for craniopharyngioma.

Methods

Inclusion and Exclusion Criteria

We searched the clinical, surgical, and pathological databases of the Mayo Clinic in Rochester for the keyword craniopharyngioma in all available fields with a cutoff of January 2009. This search yielded 296 patients. These patients were then screened for this study with the following inclusion criteria: 1) pathologically confirmed craniopharyngioma; 2) first surgery performed at Mayo Clinic; 3) operative weight and height recorded; and 4) at least 3 months of follow-up including body weight measurement.

Age 18 years or younger was an exclusion criterion. Utilizing these criteria, 28 cases treated between August 1998 and January 2009 were identified for analysis. During this period, there were 131 patients overall, and of these there were 94 adult patients undergoing resection. Therefore, 30% of the cases treated from August 1998 to January 2009 were analyzed. The reasons for exclusion were: 165 treatments occurred either before MR imaging was available or did not have preoperative MR imaging; of the 131 patients with MR imaging, 37 were 18 or younger, and 66 either underwent revision surgery or did not have adequate perioperative weight assessments. This study was approved by our institutional review board (study number 05–004448).

Control Individuals

Control individuals were matched for sex and age by searching our surgical database for patients with pathologically confirmed pituitary adenomas undergoing surgery between January 2004 and December 2006. Pituitary adenoma was used as a control because of its sellar location, furthermore it mimics perioperative endocrine
Perioperative weight change in adult surgical craniopharyngiomas

Weight Recordings

All patients were reviewed for height (cm) and weight (kg). Height was measured using a stadiometer. Body mass index was calculated with the following formula (BMI = [kg weight]/[height in meters]^2) for the initial visit. Weights were recorded for all visits available, but data acquired at 3-, 6-, 9-, and 12-month follow-up were used for analysis. Weights up to 24 months were recorded. After this point, the assumption was that recurrence or adjuvant therapy effects might interfere with this analysis. For initial analysis, preoperative weight categories were subdivided into normal (BMI < 25), overweight (BMI 25–30), and obese (BMI > 30). For simple binary analysis of prognostic outcomes, obesity was defined as a BMI greater than 27.3 kg/m^2 per NIH consortium guidelines.1

Interpretation of MR Imaging Findings

Tumor size (cm^3) was calculated using the maximal tumor diameters in 3 dimensions based on the results of MR imaging as documented by the radiologist. Hypothalamic involvement was graded as described by Meuric et al.20 and modified by Puget et al.22 under the guidance of Dr. Sainte-Rose and colleagues.24 Hypothalamic involvement was graded progressively as none (Grade 0), compression (Grade 1), and severe involvement or unidentifiable hypothalamus (Grade 2) (1, 2, and 3 in earlier publication). We assessed the following to make this determination: hypothalamic involvement according to side (right vs left hypothalamus), T2-weighted signal change in the hypothalamus, enhancement (smooth vs indistinct), and invasion (blinded interpretation independently given by F.B.M.). Figure 1 demonstrates examples of these features.

Statistical Analysis

We used JMP 8.0 (SAS Institute, Inc.) and Prism 4.03 for Windows (GraphPad Software, Inc.) to process raw data. A 2-tailed Student t-test (Mann-Whitney analysis) using the assumptions of nonparametric and nonpaired data was used to determine differences between 2 means. One-way ANOVA was used to determine differences between more than 2 means, and the Wilcoxon test was used to estimate the probability value in multiple group analysis.

Results

Demographics

The mean age at surgery for the 28 patients with craniopharyngioma was 45.8 ± 16.7 years; 64% (18 patients) were male. Surgical approach included 23 frontotemporal (either subfrontal or pterional), 3 transnasal-transsphenoidal, 1 interhemispheric, and 1 transcortical. Excluding transnasal procedures, 22 were right sided and 3 were left sided. Complete resection was achieved in 20 patients (71%). One patient presented with preoperative hydrocephalus.

Weight and BMI

Currently, there are no data to define a significant weight gain in patients treated for craniopharyngiomas, especially in adults. Pediatric cases of excessive weight gain are based on 2 SDs above normal child weights for age. While there are extant pediatric papers detailing perioperative weight gain as a problem, they use an arbitrary cutoff to assess this end point. Therefore, in our 28 patients, we have set up gradients according to maximal weight gain in the first 2 postoperative years (Table 1). Furthermore, we subcategorized postoperative weight gain according to preoperative BMI (Table 1). No correlation exists between preoperative BMI and postoperative weight gain. Sixty-one percent and 46% of patients had postoperative weight gains greater than 4 and 9%, respectively (Table 1). Using the NIH consortium guideline to define obesity at a BMI of 27.3 kg/m^2, or 17, of our patients had preoperative BMIs greater than this.1 There was no association between preoperative BMI and postoperative weight gain (p = 0.9337); this, again, is evident when looking at the distribution of these patients in Table 1.

To better understand the significance of preoperative BMI and postoperative weight gain, the patients with craniopharyngioma (cases) were compared with age- and sex-matched control patients undergoing pituitary surgery for pituitary adenomas and fitting the other inclusion criteria. The preoperative BMIs were similar (p =

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TABLE 1: Weight distribution of preoperative BMI and postoperative weight gain in adult patients with craniopharyngioma*

<table>
<thead>
<tr>
<th>Preop BMI</th>
<th>&lt;4%</th>
<th>4.01–6%</th>
<th>6.01–8%</th>
<th>8.01–9%</th>
<th>9.01–10%</th>
<th>10.01–15%</th>
<th>15.01–20%</th>
<th>&gt;20.01%</th>
<th>BMI Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–30</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;30</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>total</td>
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<td>1</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>28</td>
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<tr>
<td>cumulative percentage</td>
<td>36</td>
<td>39</td>
<td>43</td>
<td>54</td>
<td>61</td>
<td>71</td>
<td>82</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

* The BMI was calculated as described in Methods.
0.93) between cases (mean 28.9 [95% CI 30.9–26.9]) and controls (mean 29.3 [95% CI 31.9–26.7]) (Fig. 2). However, there was a trend to a greater mean postoperative weight change in cases (10.1%) than in controls (5.6%) (p = 0.24). The pattern of postoperative weight gain is represented in Fig. 3; here we defined an event as the follow-up date in which there was a greater than 9% weight gain. There was no difference between cases and controls on Kaplan-Meier analysis (p = 0.2). However, notice that approximately 35% of patients achieved a 9% weight gain at 6 months postoperatively. In all cases in which a 9% weight gain was achieved, the weight was gained by 12 months in this study.

Endocrine Data

Patients with craniopharyngioma required postoperative endocrine replacement more frequently than controls; 57% of the patients and 18% of controls required posterior pituitary replacement (vasopressin). Cortisol replacement, usually provided with hydrocortisone (10 mg twice daily), was required in 68% of cases and 36% of controls. Thyroid and sex hormone replacement were needed in 61 and 50% of craniopharyngioma patients, respectively, and 39% for both in controls (Table 2). No patient received postoperative growth hormone therapy.

Magnetic Resonance Imaging and Hypothalamic Involvement

Progressive hypothalamic involvement (as defined by Sainte-Rose Grade 0–2) correlated with postoperative weight gain (Fig. 4; p = 0.04, Wilcoxon test); however, hypothalamic involvement did not correlate with preoperative BMI (p = 0.5). Left-sided hypothalamic compression correlated with postoperative weight gain (p = 0.006), but right-sided compression did not (p = 0.15). Furthermore, total volume of the tumor correlated with hypothalamic involvement (Fig. 5). Hypothalamic T2 signal change correlated with hypothalamic involvement (p = 0.0008) (Table 3). Invasion, as defined by enhancement without a smooth interface with the hypothalamus was also associated with hypothalamic involvement (p = 0.0009). All patients with Grade 0 hypothalamic involvement had absent T2 signal change and absent invasion, and all patients with Grade 2 hypothalamic involvement had the presence of T2 signal change and invasion. Therefore, the absence of T2 signal change and the absence of invasion were both 100% sensitive in predicting a Grade 0 lesion (Fig. 6). Similarly, the presence of T2 signal change and the presence of invasion were both 100% sensitive in predicting a Grade 2 lesion (Table 3). We then assigned a point for either T2 signal change in the hypothalamus (+1) or
hypothalamic invasion defined by irregular enhancement into the hypothalamus (+ 1); the addition of these points (0, 1, or 2) correlated strongly with hypothalamic grade (p < 0.0001).

**Discussion**

Obesity associated with or caused by craniopharyngiomas is among the most difficult to treat in medicine and has significant health and long-term impact for the patient.12,23,25,27,28 The most commonly accepted cause for obesity in these cases is neural injury to the ventromedial hypothalamus, which in animals regulates appetite, satiety, and body fat composition and is thought to do the same in humans.15–19 In children, there is ongoing debate as to the cause of craniopharyngioma-associated postoperative obesity. It is known that pediatric patients undergoing surgery for craniopharyngioma are shorter both at the time of surgery and thereafter.8 Thus, one possible cause for postoperative obesity in children with normal eating habits is lack of growth leading to obesity.8 In an attempt to probe this hypothesis, Geffner et al.8 treated children postoperatively for 3 years with growth hormone to improve their height; despite statistically significant gains in height, their postoperative obesity was not corrected. Further evidence that this hypothesis is not correct is supported by our present findings. In adults, in whom growth is presumably relatively stable, our data showed that postoperative obesity continues to be a problem for patients with surgically treated craniopharyngiomas where 61 and 46% of patients had a greater than 4 and 9% postoperative weight gain, respectively. We found that postoperative severe obesity was greater than 40%, which is very similar to that in published pediatric case series.4,5,13,21 Furthermore, postoperative weight gain is a common occurrence after management of craniopharyngioma and has been described in 35–58% of patients in previous studies.4,6,11,27

Hypothalamic involvement by tumors and postoperative weight gain do not represent a new concept in pediatrics; however, this has never been shown in adults. The St. Jude experience demonstrates that among an assortment of tumors (astrocytoma, ependymoma, or craniopharyngioma), hypothalamic involvement correlates radically with postoperative weight gain in this pediatric cohort and was independent of pathology.18 Although not assessed with this study, it may be logical to approach adults as pediatric neurosurgeons do. Although controversial, some authors believe that, in cases of severe hypothalamic involvement, subtotal resection with decompression of the optic apparatus may be a reasonable approach compared with unwavering pursuit of gross-total resection.3,20,29,30 While it is becoming well accepted that there is an association with hypothalamic compression and perhaps sur-

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**TABLE 2: Percentage of patients receiving postoperative endocrine replacement**

<table>
<thead>
<tr>
<th>Replacement Therapy</th>
<th>Patients w/ Craniopharyngioma (%)</th>
<th>Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vasopressin</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>cortisol</td>
<td>68</td>
<td>36</td>
</tr>
<tr>
<td>thyroid</td>
<td>61</td>
<td>39</td>
</tr>
<tr>
<td>sex hormone</td>
<td>50</td>
<td>39</td>
</tr>
</tbody>
</table>

**TABLE 3: Magnetic resonance imaging prediction of hypothalamic grade**

<table>
<thead>
<tr>
<th>Hypothalamic Involvement (Sainte-Rose Grade)</th>
<th>T2 Signal Change (%)</th>
<th>Invasion/Irregular Enhancement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1</td>
<td>57</td>
<td>50</td>
</tr>
<tr>
<td>Grade 2</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

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**Fig. 4.** Maximum postoperative weight change as a function of the hypothalamic compression. Markers represent individual patients, midline represents mean, and brackets represent SEM. First column in each group (0, 1, and 2) represents data for the combined group, followed by distribution for right and left hypothalamic compression, respectively. Overall, compression of the hypothalamus correlated with total postoperative weight gain (p = 0.04, Wilcoxon test), as did left-sided compression (p = 0.006); however, right-sided compression did not (p = 0.15). Means and 95% CIs for combined compression are: Grade 1 (2.7, −2.0 to 7.4), Grade 2 (10.6, 3.4–17.8), and Grade 3 (18.7, 4.2–33.1).

**Fig. 5.** Spherical volume as a function of the hypothalamic compression. Markers represent data points, midline represents mean, and brackets represent SEM. Means and 95% CIs are: Grade 0 (2.2, 0.5–3.8), Grade 1 (9.0, 3.2–14.0), and Grade 2 (28.8, 5.3–52.3).
gical management, both may contribute to postoperative obesity in patients with tumors of this region, and this assumption cannot be directly drawn to include adults, as growth and development are accompanied by significant changes in the hormone milieu in children, in contrast to adults. Unfortunately, we have found in adult patients at risk for postoperative obesity that this perioperative morbidity is a real concern. Furthermore, as we become more aware of this complication, it becomes increasingly important that we focus some of our postoperative care on counseling our patients about its occurrence, detecting this complication, and preventing it.

Importantly, we have attempted to further develop objective grading criteria for hypothalamic involvement, thereby quantifying a descriptive classification proposed by Drs. Sainte-Rose and colleagues, which is summarized in Fig. 7. Meuric et al. introduced the concept of grading hypothalamic involvement with a proposed grade of 1–3, later modified to the 0–2 system, reflecting progressive hypothalamic involvement. Using this grading system, Drs. Puget and Sainte-Rose et al. were prospectively able to avoid any inappropriate postoperative weight gain by performing subtotal resection and avoiding associated operative hypothalamic damage in children. This may or may not be the case in adults; however, this study represents the first step toward this determination, recognizing that hypothalamic involvement is associated with the same complications as in children. Furthermore, objective criteria to differentiate Grade 1 from Grade 2 may be additionally useful in the prognostication of postoperative obesity. First, peritumoral edema can be evaluated preoperatively with T2-weighted and FLAIR imaging. Previously this has been suggested as a significant harbinger of complications and was named “moustache appearance” by Higashi et al. in a description of perifocal hypothalamic edema in 2 patients with craniopharyngioma. The existence of hypothalamic edema in this study was strongly associated with progressive hypothalamic involvement. Furthermore, irregular enhancement suggestive of invasion was associated with more severe hypothalamic involvement. This concept has not been previously described; however, Shi et al. have discussed the importance of maintenance of the tiny perforating vessels that supply the hypothalamic nuclei, and perhaps irregular enhancement suggests that these vessels are parasitized or congested and therefore at risk.

Our results have provided a rather curious finding, in that it appears in this small group that left-sided hypothalamic compression statistically is more important than right-sided compression in relation to postoperative weight gain. We recognize, given our limited data, that this is inconclusive; however, the brain in most circum-

**Fig. 6.** Scatterplot showing the distribution of cases (individual markers) as segregated by T2-weighted MR imaging hyperintensity in the hypothalamus (left y axis, Yes is hypothalamic T2 change) and enhancement pattern (smooth vs irregular border) in relation to hypothalamic compression. Note no Grade 0 case has either MR imaging characteristic whereas all Grade 3 cases have both irregular enhancement and hypothalamic hyperintensity.

**Fig. 7.** Flow diagram of hypothalamic compression grading system, as described by Drs. Meuric, Puget, and Sainte-Rose (see text), compared with this study’s proposed objective MR imaging criteria.
stances is organized with dominant and nondominant paired structures. Further, the endocrine consequences in these patients may also influence postoperative weight gain. Growth hormone deficit and consequent low levels of insulin-like growth factor are a well-known complicating factor of weight gain in patients with anterior pituitary origin and hypothalamic involvement. Although growth hormone deficiency appears to be important, Kendall-Taylor et al. have implicated hypothalamic involvement, in patients with combined hypothalamic involvement and growth hormone failure, as the major cause of obesity in these patients. None of our patients received postoperative growth hormone replacement. Therefore, because the effects of treatment with growth hormone on adult patients are unknown it may be reasonable to attempt this as a treatment to prevent postoperative obesity in these patients.

The inclusion criteria used in this study may impose a bias in relation to patients at risk for developing postoperative obesity. The assumption here is that those at risk for weight gain were the ones that were followed with weight recordings. Therefore, 39% (> 9% change) to 57% (> 4% change) of these patients with significant postoperative obesity may not represent the true percentage of all presenting patients because, in the present study, this represents only 30% of the patients in that time period. Consequently, the external validity of this study is poor. However, to evaluate our initial study questions we believed that our excessive inclusion criteria were important to analyze the impact of hypothalamic involvement and weight changes in adult patients undergoing surgery for craniopharyngioma. Furthermore, although there was no statistically significant difference in postoperative weight gain between craniopharyngioma patients and pituitary adenoma patients, it is likely that one does exist. Due to the variability of weight recordings, a standardized effect of likely 0.4 could be used, coupled with a power of 80% and alpha of 5%; we would need approximately 148 patients in each group to detect a difference between cases and controls.

Conclusions

Although this has been long recognized in children, this series suggests that we must consider postoperative obesity an important morbidity in adult patients undergoing surgery for craniopharyngioma. Furthermore, we are then obligated to consider alterations in established therapies and interventions for these patients. In preoperative counseling, it will be vital to inform the patient of the real risk of obesity postoperatively if certain imaging findings are present. We conclude here, as has been concluded in pediatric cases, that the degree of hypothalamic involvement, as evaluated preoperatively by MR imaging, may predict postoperative obesity. As surgeons, we need to continue to improve patient outcomes, and this study serves as a starting point to do so in adult patients with craniopharyngiomas.

Disclosure

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References


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