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Energy expenditure in obesity associated with craniopharyngioma

Roy J. Kim¹, Rachana Shah¹, Andy M. Tershakovec², Babette S. Zemel³, Leslie N. Sutton⁴, Adda Grimberg¹, and Thomas Moshang¹

Roy J. Kim: kimr@email.chop.edu

¹ Division of Endocrinology, Children's Hospital of Philadelphia, 34th and Civic Center Blvd, Philadelphia, PA 19104, USA

² Merck & Co., Inc., North Wales, PA, USA

³ Division of Gastroenterology and Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA, USA

⁴ Division of Neurosurgery, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Abstract

Background and purpose—Obesity is a common yet incompletely understood complication of childhood craniopharyngioma. We hypothesized that craniopharyngioma is associated with specific defects in energy balance compared to obese control children.

Methods—Eleven craniopharyngioma patients were recruited for a study on body composition and energy balance. Eight subjects were obese. The obese craniopharyngioma patients had a mean age ($\pm$ SD) of 11.2 ± 1.7 years. The average body mass index z score was $2.33 (\pm 0.32)$. A previously studied group of obese children (BMI z score 2.46 ± 0.46) served as controls. Resting energy expenditure (REE) was determined by indirect calorimetry and body composition by dual energy X-ray absorptiometry in all children.

Results—Obese craniopharyngioma patient subjects had increased mean ($\pm$ standard error) fat-free mass compared to obese controls ($57\% \pm 0.88\%$ vs $50.0\% \pm 0.87\%$, $p=0.02$). The obese craniopharyngioma patients had a 17% lower REE compared to values expected from the World Health Organization equation ($1,541 \pm 112.6$ vs $1,809 \pm 151.8$ kcal; $p=0.01$). In contrast, the obese control children had measured REE within 1% of predicted ($1,647 \pm 33.2$ vs. $1,652 \pm 40.2$; $p=0.8$). In a linear regression model, REE remained significantly lower than predicted after controlling for FFM.

Conclusions—Lower REE may be a factor contributing to obesity in children with craniopharyngioma. Further study is needed into the mechanisms for reduced energy expenditure in patients with craniopharyngioma.

Keywords

Obesity; Craniopharyngioma; Energy expenditure; Hypothalamic obesity

Correspondence to: Roy J. Kim, kimr@email.chop.edu.

Roy J. Kim and Rachana Shah are first coauthors.

Conflicts of interest The authors declare that they have no conflict of interest.

Introduction

Craniopharyngioma is an important type of childhood brain tumor. Although histologically benign, its propensity to develop near important brain structures can cause significant morbidity. Treatment consists usually of surgery and radiation. Following treatment, endocrine deficiencies are common, and more than half will develop obesity [1,2]. The obesity is often severe and can be accompanied by adverse changes in metabolism [3].

The pathogenesis of the obesity in craniopharyngioma has not been completely elucidated. Hyperphagia, though frequently reported, is not a universal feature of obesity in craniopharyngioma and may not fully explain the magnitude of weight gain. One study of 27 craniopharyngioma patients found a decrease in physical activity rather than greater energy intake to be associated with obesity [4]. A potential mechanism which has not been explored is a disturbance in resting energy expenditure (REE) which could occur as a consequence of craniopharyngioma. Even a small decrease in REE could, over time, result in significant weight gain. To test whether obesity occurring in craniopharyngioma subjects is associated with a unique change in resting energy expenditure, we compared REE in obese craniopharyngioma patients with REE in control obese subjects.

Methods

Eligible subjects were aged 4 years and older and treated for craniopharyngioma over a 5-year period at the Children's Hospital of Philadelphia. All subjects were under the care of an endocrinologist, had regular monitoring of endocrine function, and treated with hormone replacement as necessary. Exclusion criteria included weight greater than 136 kg (the capacity of the dual energy X-ray absorptiometry scanner), non-ambulatory status, and other systemic illness other than hypopituitarism that could affect the assessments.

Craniopharyngioma patients were admitted overnight to the Children's Hospital of Philadelphia. After a standardized dinner and 12-h overnight fast height, weight, and skinfold measurements were obtained. REE was then determined by open-circuit indirect calorimetry (SensorMedics 2900; SensorMedics Corp, Yorba Linda, CA). To ensure that they were truly at rest, subjects were wheeled to the calorimeter and remained supine for the entire hour while oxygen and carbon dioxide measurements were taken. Because it was an assessment of resting energy expenditure, measurements collected during nonresting conditions (i.e., when the subject moved) were omitted according to a standard protocol. Body composition was determined by dual energy X-ray absorptiometry (DEXA) using a Hologic QDR-2000 whole-body scanner (Hologic, Wortham, MA) in pencil beam mode. Brain MRI results were reviewed to determine the location of the craniopharyngioma and the presence of hypothalamic involvement. Control subjects were obese children, aged 7 or older, who were previously studied [5] at our center using the same protocols for DEXA to assess body composition and indirect calorimetry for REE, except that control subjects were not admitted overnight prior to their studies.

For each subject, a predicted REE was calculated using the World Health Organization formula [6]. This formula is widely accepted as a means for predicting REE, although it has recognized limitations. For each subject, the difference between REE measured by calorimetry was compared to REE predicted by the WHO equation. This difference was defined as Δ REE. Our primary outcome was the Δ REE in obese craniopharyngioma patients versus obese control subjects. Statistical significance of the differences between the two groups was tested using the unpaired Student's *t* test. Linear regression modeling was used to examine the relationship between the difference in REE and body composition parameters. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. BMI is

reported as a *z* score, defined as the standard deviation score specific for the age and gender (obtained using the online calculator at <http://stokes.chop.edu/web/zscore/>). Statistical analyses were performed using Stata (StataCorp, Texas, USA). The study was approved by the Institutional Review Board of the Children's Hospital of Philadelphia and complies with the standards of the 1964 Declaration of Helsinki.

Results

Eleven subjects were enrolled. Eight subjects were obese (mean BMI *z* score $2.33 \pm \text{SD } 0.32$); three were normal weight (BMI *z* score $0.16 \pm \text{SD } 1.4$). Height *z* scores were similar. All patients underwent surgery and 45% (four obese, one non-obese) received radiation. All eight obese subjects, and none of the normal weight subjects, had suprasellar involvement. All obese subjects were on adrenal and thyroid hormone replacement, and 38% were on growth hormone therapy. Diabetes insipidus was present in seven of eight obese subjects. Three of eight subjects were on sibutramine as a weight loss agent, and one was on methylphenidate for attention deficit. Because our analysis focused on differences in obese craniopharyngioma patients compared to obese controls, the normal weight craniopharyngioma patients were omitted from further analyses.

Obese children with a history of craniopharyngioma had greater percentage fat-free mass (FFM) compared to obese controls (mean $\pm$ standard error, SE $57.2\% \pm 0.088\%$ vs. $50.0\% \pm 0.87\%$) as shown in the Table 1. There was no significant difference observed between obese craniopharyngioma patients and obese controls with respect to age, height, weight, body mass index, fat mass, or fat mass percentage.

In obese craniopharyngioma patients, measured REE was significantly lower than WHO-predicted REE (mean $\pm$ SE $1,541 \pm 112.6$ vs $1,809 \pm 151.8$ kcal; $p=0.01$; Fig. 1). This represented a Δ REE of 268 kcal or a daily kcal deficit of 17% (Fig. 2). In obese control subjects, there was no significant difference between measured and predicted REE ($1,647 \pm 33.2$ vs $1,652 \pm 40.2$ kcal, $p=0.8$; Fig. 1).

To determine whether body composition mediated the relationship between REE and craniopharyngioma status, we performed linear regression analysis using fat mass and FFM as independent variables. As expected, in obese controls, REE was dependent on FFM ($R^2=0.65$ $p<0.001$). In obese craniopharyngioma patients, the relationship between FFM and REE showed a lower *R*-squared value that did not reach statistical significance ($R^2=0.38$, $p=0.09$; Fig. 3). The regression coefficients (28.0 for obese control, and 17 for craniopharyngioma subjects) were not significantly different ($p=0.4$).

Discussion

Obesity occurring after craniopharyngioma is common, often severe, and can be refractory to treatment. Our results, while preliminary, show that resting energy expenditure is diminished in craniopharyngioma patients in comparison to obese controls. A decreased REE is observed in spite of a relative increase in fat-free mass in craniopharyngioma patients. Indeed, regression modeling in our small population suggests that the typical close association between fat-free mass and energy expenditure, observed in control obese subjects, may be reduced in the setting of craniopharyngioma.

Regulation of resting energy expenditure depends on many factors, such as fat-secreted and pituitary hormones. For example, leptin and adiponectin can act centrally to increase energy expenditure [7]; this action can be dampened by adipose inflammation that can result from obesity itself [8], high-fat diet [9], or hormone deficiencies [10–12]. Sympathetic tone may be decreased in craniopharyngioma patients which could be a factor leading to decreased REE

[13]. Multiple signaling pathways involving the hypothalamus, including leptin [14] and adiponectin [15] from adipocytes, ghrelin from the gastrointestinal tract [16], and the endocannabinoid pathway [17] are implicated in appetite control and metabolic rate. Notably, all obese craniopharyngioma subjects (versus none of the non-obese) had suprasellar tumor involvement, suggesting hypothalamic dysfunction as a factor in the observed differences in REE.

Several medications used by our subjects can affect energy balance. Three subjects were taking sibutramine which promotes weight loss by increasing satiety and energy expenditure [18]. One of these three was also taking methylphenidate for attention-deficit disorder. Methylphenidate is reported to increase REE and suppress food intake [19,20]. In spite of this, our patients still had a lower than expected REE indicating that these medicines were unlikely to be confounders in our analysis.

Under-treatment of endocrine deficiencies could also contribute to weight gain. Growth hormone can increase resting energy expenditure [21] and modulates thyroid hormone metabolism by increasing activation of thyroxine to tri-iodothyronine [22]. It increases lean mass and reduces body fat [23]. Hypothyroidism is associated with increased fat mass and low resting energy expenditure which improve with thyroid hormone replacement [24]. Conversely, thyroid hormone in excess is catabolic to muscle. Thus, an untreated deficiency of growth hormone or thyroid hormone could contribute to weight gain and body fat increase. Cortisol increases resting energy expenditure; however, it also increases appetite [25] and, therefore, tends to favor a positive energy balance. Overall, untreated deficiencies of these hormones are unlikely to entirely explain our main observation given the close monitoring of hormone replacement these subjects received.

Surprisingly, though they had a deficit in REE, the craniopharyngioma patients were in fact not lower in FFM. This combination suggests that the fat-free mass in patients with craniopharyngioma had a lower intrinsic metabolic activity. Other mechanisms could play a role in the observed alteration in REE. Derangements in the hypothalamic endocannabinoid pathway, which controls appetite and food intake by central and peripheral effects, may affect skeletal muscle energy balance. Of particular therapeutic interest, overactivation of the endocannabinoid system has been associated with obesity, making antagonists of the hypothalamic receptor (CB1) novel candidates for treatment [26]. Uncoupling proteins, important in thermogenesis and resting metabolism [27], are found in human adipocytes and skeletal muscle and found to be expressed in the hypothalamus and pituitary of primates [28]. Theoretically, damage to these structures may lead to decreased levels of the proteins and thus reduced metabolic activity.

Our control subjects were not hospitalized the night before their indirect calorimetry study. However, their resting energy expenditure as determined by indirect calorimetry was, on average, very close to that predicted by the WHO equation (Figs. 1 and 2). Therefore, they appear to be valid comparison subjects for the purposes of testing the applicability of the WHO prediction model to measured energy expenditure in craniopharyngioma patients.

Given our small sample size, these results must be validated by larger-scale studies. It is possible that differences in body composition that did not reach statistical significance in our subjects may do so when larger numbers are evaluated. Similarly, a larger study might also reveal unexpected associations between overweight and endocrine deficiency and medication usage. However, our preliminary results outline an interesting area for future study and clinical intervention.

Clinical experience indicates that hormone replacement to minimize metabolic derangements, and counseling on diet and exercise are by themselves not sufficient to prevent or reverse life-

threatening obesity in all craniopharyngioma patients. New interventions will require additional studies directed at determining the specific pathways leading to abnormal energy homeostasis in these patients.

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Fig. 1.
REE measured by indirect calorimetry (*white*) versus REE predicted by the WHO formula (*gray*) in obese control subjects and obese craniopharyngioma patients. *NS* nonsignificant; * $p=0.01$

Fig. 2.
ΔREE or the difference between predicted REE and measured REE in obese control children and children with obesity and craniopharyngioma

Fig. 3.
Association between fat-free mass and measured REE in obese craniopharyngioma patients (filled squares, solid line) and obese controls (unfilled circles, dashed line)

Table 1

Auxologic characteristics and body composition

	Craniopharyngioma [<i>n</i> =8]	Obese controls [<i>n</i> =90]	<i>P</i> value
Age, years	11.2 (1.7) ^a	10.3 (1.4)	0.11
Height, cm	145.9 (9.6)	148.2 (12.2)	0.58
Weight, kg	69.2 (23)	68.8 (17.5)	0.95
BMI, kg/m ²	32.0 (8.2)	31 (5.1)	0.53
Fat mass, kg	30.0 (10)	33 (11.3)	0.20
Fat mass, %	42.8 (2.5)	47.0 (7.5)	0.15
Fat-free mass, kg	39.6 (12)	34.4 (9)	0.14
Fat-free mass, %	57.2 (2.5)	49.5 (5.9)	0.02

^aMean value shown with standard deviation in parentheses