The Use of Dextroamphetamine to Treat Obesity and Hyperphagia in Children Treated for Craniopharyngioma

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**Background:** Obesity and attention difficulties are known complications following surgical treatment for craniopharyngioma. Treatments to date have been largely disappointing.

**Objective:** To examine the use of the central nervous system stimulant dextroamphetamine sulfate to regulate appetite and subsequent weight gain in children treated for craniopharyngioma.

**Setting:** A multidisciplinary clinic specializing in pediatric brain tumors.

**Patients:** Five consecutive patients with significant weight gain and poor attention following surgical treatment for craniopharyngioma were selected for the study.

**Intervention:** Children enrolled in the study were treated with dextroamphetamine, and growth, laboratory, and behavioral assessments were conducted for 24 months.

**Results:** Mean ± SD body mass index (weight in kilograms divided by height in meters squared) increased from 21 ± 3.5 before the operation to 32 ± 2.8 by the start of the protocol. Body mass indices remained stable throughout the protocol. No changes were observed in insulin levels or caloric intake, but the children were more active when taking dextroamphetamine. Parents noted a significant improvement in hyperactivity (mean ± SD, 1.2 ± 0.4 to 0.6 ± 0.2; P = .05), scored with the Conners Parent and Teacher Rating Scales. Teachers noted a similar improvement.

**Conclusions:** During dextroamphetamine treatment, weight gain stabilized in children who had experienced obesity following surgical resection for craniopharyngioma. In addition, parents and teachers noted significant improvements in children’s overall activity and attention. Further studies are needed to determine if the improvements are stable and if earlier intervention can prevent the initial obesity.

Arch Pediatr Adolesc Med. 2002;156:887-892

**CRANIOPHARYNGIOMA** is the third most common cranial tumor in children and the most common tumor involving the hypothalamus and the pituitary gland. Neurosurgical resection remains the main therapy for craniopharyngioma, yet after the procedure, virtually all children have some degree of hypothalamic-pituitary dysfunction, including growth hormone (75%), gonadotropin (40%), corticotropin (25%), and thyrotropin (25%) deficiencies. In addition to hormonal abnormalities, hyperphagia, unrelenting weight gain, and subsequent life-threatening obesity have been found in up to 50% to 80% of all children surgically treated for craniopharyngioma. Control of hyperphagia and obesity has been difficult to achieve, and most attempts at behavior modification have been unsuccessful.

In our clinical practice, we observed that many children exhibit hyperphagia, obesity, poor attention, and difficulties with impulse control postoperatively. We now report the effect of taking dextroamphetamine sulfate for 24 months on hyperphagia, weight gain, and behavior in children who had previously undergone surgical therapy for craniopharyngioma.

**PATIENTS AND METHODS**

**Patients**

Five children who had undergone surgical resection for craniopharyngioma and had significant weight gain postoperatively were enrolled in our study (Table 1). Each child demonstrated weight gain of more than 75% during an average of 10 months after the operation and before being evaluated in our clinic. To better determine the impact of dextroamphetamine on weight gain, each child served...
as his or her own internal control; this allowed us to compare pretreatment and posttreatment weight gain. A crossover arm of this protocol allowing each patient to serve as his or her own control was entertained as a comparison group but was not used because of concerns that rebound weight gain after treatment could influence outcomes.

Traditional therapies, including intensive dietary counseling with a nutritionist, caloric restrictions, behavioral modification, and inpatient treatment in the medical-psychiatric unit (for patient 1), were ineffective, and weight gain for the group was 2 kg/mo from surgical treatment until the onset of dextroamphetamine therapy. Each child had been found to have multiple pituitary deficiencies that were corrected and monitored throughout the protocol. Postoperative magnetic resonance images were evaluated using the scoring criteria described by De Vile et al; the floor of the third ventricle was completely absent in all our patients (grade 2). The study was approved by the Institutional Review Board of Emory University, Atlanta, Ga, and informed consent was obtained for each child prior to the initiation of the protocol.

Treatment with dextroamphetamine sulfate was initiated at 5 mg each morning and was titrated upward by 2.5 mg weekly until either a decrease in appetite, significant improvement in behavior, or an adverse reaction occurred (Table 1). Additional doses, including prelunch and predinner doses, were added when needed to inhibit the child’s appetite further and modulate unwanted behaviors. Discussions occurred between the investigators, parents, and teachers to assess any positive and negative impacts on children’s overall behaviors. The mean ± SD maximum daily dosage of dextroamphetamine sulfate was 16 ± 2 mg, which was divided into 3 doses.

GROWTH AND LABORATORY ASSESSMENT

Growth data, including height, weight, and body mass index (weight in kilograms divided by height in meters squared) (BMI), were obtained for each child at the tumor diagnoses, the start of the study, and at each visit during the protocol (1, 3, 6, 9, 12, 18, and 24 months of therapy). A 72-hour diet and exercise log was maintained by each family and collected at the clinical visit. Laboratory studies including insulin, insulinlike growth factor I, insulinlike growth factor–binding protein 3, total protein, and albumin levels were conducted at 6-month intervals throughout the protocol.

All hormone assays were performed by the Nichols Institute, Quest Diagnostics (San Juan Capistrano, Calif). Height SD score, weight SD score, and weight vs height percentile were calculated using the Anthro portion of the Epi Info program, version 6.0 (Centers for Disease Control and Prevention, Atlanta).

Statistical analysis was performed using Statistical Product and Service Solutions software, version 9.0 (SPSS Inc, Chicago, Ill). Growth variables, including height and weight SD scores, weight vs height, height velocity, and BMI were reported as mean ± SD. The results were compared over the course of the study using analysis of variance, and, when significant, data were pairwise analyzed with the Tukey test. Change in height per visit and selected variables were correlated using linear regression analysis. Associations were reported as r values, and P < .05 was considered significant.

BEHAVIORAL EVALUATION

To determine if dextroamphetamine therapy was affecting overall attention and behavior, each child’s parents were contacted regularly for comments about his or her behavior, and both the parents and a teacher were asked to routinely complete Conners Parent or Teacher Rating Scales. If the child had multiple teachers, the primary teacher was asked to complete a questionnaire. Each question was scored, and the sum of all scores was determined. Parents were asked 48 questions, and the questions were scored and compared with the normal values reported by Goyette et al. Each teacher was asked 39 separate questions, and the answers were scored and compared with normal values. An answer of “not at all” was scored as 0; “just a little,” 1; “pretty much,” 2; and “very much.” 3. Parent questionnaires were analyzed by 6 categories: conduct problems, learning problems, psychosomatic problems, impulsivity-hyperactivity, anxiety, and a hyperactivity index. Values for each of the 6 categories were compared at the start of the protocol and at 3, 6, 12, 18, and 24 months of therapy. Teacher responses were analyzed using the categories conduct problems, hyperactivity, inattention-passivity, and a hyperactivity index. Values were determined at the start of the protocol and at 3, 6, 12, 18, and 24 months of therapy.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No./ Age, y/Sex</th>
<th>Time From Surgery to Protocol, mo</th>
<th>Hypothalamic Scale*</th>
<th>Hormonal Deficiencies</th>
<th>Maximum Daily Dosage of Dextroamphetamine Sulfate/Time of Day Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/8.5/M 1</td>
<td>9</td>
<td>Grade 2</td>
<td>Thyroid, adrenal, and diabetes insipids</td>
<td>7.5 mg/AM</td>
</tr>
<tr>
<td>2/6.0/F 2</td>
<td>7</td>
<td>Grade 2</td>
<td>Thyroid, adrenal, and diabetes insipids</td>
<td>7.5 mg/AM</td>
</tr>
<tr>
<td>3/9.8/F 3</td>
<td>14</td>
<td>Grade 2</td>
<td>Thyroid and growth hormone</td>
<td>5 mg/AM</td>
</tr>
<tr>
<td>4/9.0/M 4</td>
<td>10</td>
<td>Grade 2</td>
<td>Thyroid, adrenal, and diabetes insipids</td>
<td>7.5 mg/AM</td>
</tr>
<tr>
<td>5/8.2/M 5</td>
<td>12</td>
<td>Grade 2</td>
<td>Thyroid, adrenal, and diabetes insipids</td>
<td>2.5 mg/AM</td>
</tr>
</tbody>
</table>

*The extent of hypothalamic damage was scored using the system by De Vile et al. Grade 0 indicates no visible damage by magnetic resonance imaging and minimal risk of obesity; grade 1, disruption of the floor of the third ventricle and some risk of obesity; and grade 2, absence of the floor of the third ventricle with the greatest risk of obesity.
The parents of one child (patient 1) were not compliant and, despite repeated requests, did not bring in the teacher’s questionnaire. However, they did complete the parent questionnaire during their office visits.

RESULTS

GROWTH AND LABORATORY ASSESSMENT

Five patients (3 boys and 2 girls) were enrolled in this protocol because their weight significantly increased from prior to surgical treatment until they were evaluated for our protocol (Table 1). The mean age at the start of the protocol was 8.3 years. All subjects had multiple pituitary hormone deficiencies postoperatively, which were treated and stable throughout the protocol (Table 1). Growth hormone stimulation tests were not performed because of the normal growth rate and insulinlike growth factor binding protein 3 levels of the children, as well as our practice of delaying growth hormone administration after surgical treatment for craniopharyngioma. The children were enrolled in the protocol at a mean of 10.4 months postoperatively and were found to be gaining weight at a mean ± SD rate of 2±0.3 kg/mo in this interval (Figure). This resulted in a significant rise in their overall BMI from 21±3.5 when the tumor was diagnosed to 32±2.8 at the start of the protocol (P= .01; Table 2).

After initiation of dextroamphetamine therapy, overall weight gain changed significantly. The BMIs stabilized by 1 month after therapy began (data not shown) and remained stable throughout the protocol (Table 2); BMI values went from 32±2.8 at the start of treatment to 31±3.3 by the end of the protocol at 24 months. Weight velocity showed a significant slowing; the rate of monthly weight gain decreased to 0.4±0.2 kg/mo (P = .009; Figure). Despite the weight stabilization, there was no significant change in height velocity while on dextroamphetamine, with the velocity increasing slightly from a pre-treatment rate of 6.5±1.9 cm/y to 7.3±0.5 cm/y after 24 months of therapy (P = .69).

Fasting insulin levels did not significantly change during dextroamphetamine therapy, increasing slightly from a pretreatment value of 43.8±6.4 µU/mL (314±33 pmol/L) to 49.4±11.8 µU/mL (359±85 pmol/L) at the completion of therapy (P = .32). Despite the normal growth observed, there was a significant decrease in insulinlike growth factor 1 levels during treatment from 99.8±43.5 ng/mL to 49.8±38.4 ng/mL at 24 months of treatment (P = .005). Insulinlike growth factor–binding protein 3 values, however, did not significantly change after 24 months of therapy, decreasing from 1.8±0.3 mg/L to 1.7±0.4 mg/L (P = .91).

Weight stabilization appeared to be sustained throughout the protocol. Despite this, there was no significant change in reported caloric intake according to the diet logs (mean daily calories, 1189±69 pretreatment to 1335±137 posttreatment; P = .33). No significant changes were noted in electrolyte profiles, protein levels, or albumin concentration throughout the 24 months of treatment.

A review of exercise logs, as reported by the parents, showed that the children had become more active. Prior to the dextroamphetamine protocol, parents reported that their children were rather sedate, exercising less than 1 hour per day, and parents generally reported extreme difficulty and resistance to exercise on their child’s part. With dextroamphetamine therapy, parents reported that their children were much more active and often increased their play to more than 2 hours per day with significantly less prompting. Parents reported that their children were more willing to play and participate in activities throughout the protocol than they had been prior to the initiation of therapy.

BEHAVIORAL EVALUATION

Prior to the initiation of therapy, parents and teachers reported significant problems with each child’s attention. In addition to anecdotal reports from parents and teachers, scores on the Conners questionnaires showed improvements in overall behavior and attention (Table 3 and Table 4). The mean hyperactivity index, as reported by the parents at diagnosis, was 1.15±0.42 (scale, 0, “not at all” to 3, “very much”) or 0.6 more than age- and sex-matched normal values for each child. This represents an increase, or worsening, of hyperactive symptoms compared with normal children. The parents reported an overall improvement in their child’s activity as reflected by a decrease in the hyperactivity index to 0.57±0.21 after 24 months (mean age and sex norm, 0.54). Parents also noted significant problems with learning, with a pretreatment mean learning index of 1.69±0.66, which is 1.1±0.6 greater than age- and sex-matched normal values. With time, there was a slight improvement in parental perception of learning problems, as seen by an overall decrease in the learning index to 0.83±0.63 after 24 months.

Teachers noted more problems with conduct (1.36±1.04) and hyperactivity (1.26±0.98) prior to the dextroamphetamine therapy. This represented a mean increase, or greater problems, compared with age- and sex-matched normal values of 1.1±1.0 and 0.8±1.0, respectively. With treatment, the teachers reported an improvement in the child’s level of hyperactivity, and the hyperactivity index decreased from 1.26±0.98 at the start of dextroamphetamine therapy to 0.50±0.57 at 24 months. There were
also improvements in conduct and inattention indices from 1.36 ± 0.94 and 1.06 ± 0.72, respectively, at the start of therapy to 0.79 ± 0.83 and 0.50 ± 0.71 at 24 months.

ADVERSE EFFECTS

Children had no reported adverse effects from or reactions to dextroamphetamine. There were no significant changes in blood pressure, fasting cholesterol levels, or fasting glucose values throughout the protocol (data not shown). One child complained of headaches after a dosage increase of 5 mg. The dosage was lowered to the level prior to the increase, and the headaches improved.

The dosage was then increased by 2.5-mg increments without complaints. There were no recurrences of tumors during dextroamphetamine therapy. One child had enlargement of a cyst, which initially required a shunt to attempt drainage and ultimately was treated with radiation. Children ultimately required medication 3 times per day, with the last dose occurring near dinnertime (around 6 PM). Despite this, there were no reports of sleeping problems with any of the children. Parents actually reported that their children were more active during the day and slept better at night than they had prior to the initiation of the protocol.

Hyperphagia and life-threatening obesity are adverse effects often encountered by children who undergo surgical removal of a craniopharyngioma. Several studies have observed significant weight gain in between 50% and 80% of children following surgical treatment, and slowing the rapid gain in weight has proven difficult. The weight gain appears to be unrelenting. One of 2 patients described by Costin et al continued to demonstrate weight gain of more than 7 kg/y for up to 4 years postoperatively. In a series of 21 patients, Curtis et al noted significant weight gain 3 years postoperatively. A review of our patients prior to this study found that many had prolonged weight gain, and 3 children had gained more than 10 kg/y over 2 years postoperatively (data not shown).

We describe 5 children who were referred to our multidisciplinary neuro-oncology clinic for possible intervention. The children were near normal in size prior to their operations, with a mean BMI of 21 ± 3.5. Following surgical treatment, the parents all reported great difficulty controlling their child’s appetite and significant problems with lack of activity. There was a dramatic increase in their overall weight, with an average weight gain of 2 ± 0.3 kg each month from surgical treatment until they were evaluated in our clinic and enrolled in the study.

Two theories have been proposed to explain the etiology of the weight gain and to ultimately design therapeutic approaches to control or prevent it. The...
first theory suggests that the weight gain is driven by hyperphagia that occurs following hypothalamic insult by either the tumor location or surgical intervention. Clinical reports of hyperphagia following surgical treatment are similar to animal studies, in which destruction of the ventromedial nucleus of the hypothalamus also causes hyperphagia and morbid obesity. Each of our patients had extensive surgical resection, including removal of the floor of the third ventricle. De Vile et al had previously demonstrated a correlation between the extent of surgical resection and the risk of hyperphagia and obesity. The mechanism by which hypothalamic damage influences the loss of satiety is not completely understood. It has been suggested that direct damage of the satiety centers induces hyperphagia, resulting in obesity. Roth et al recently examined potential mediators of the loss of appetite suppression following hypothalamic damage by examining the effect of surgical damage of the hypothalamus on leptin levels. They noted significant elevation of leptin levels with respect to BMI following surgical treatment for craniopharyngiomas, which suggests that the observed rise in leptin levels following surgery may be due to the loss of feedback inhibition on neuropeptide Y and appetite. The loss of appetite control thus may be related to the lack of feedback regulation by leptin at the hypothalamic receptor.

A second theory proposed to explain the rapid weight gain following surgical treatment is that the weight gain is mediated through damage to the hypothalamus, resulting in disinhibition of vagal tone at the pancreas and leading initially to hyperinsulinism, which in turn induces obesity. Through inhibition of insulin release with a somatostatin analogue, Lustig et al demonstrated weight loss in 8 older children. Despite significant weight stabilization, we have not been able to demonstrate a change in insulin values. We feel that the increase in insulin concentrations is caused by the increased insulin resistance inherent in obesity. In addition, we have examined a child (data not shown) who began to gain weight immediately following surgical treatment yet has maintained normal insulin concentrations. This would suggest that the weight gain was not driven by increased insulin concentrations but that the increased insulin levels occurred as a function of obesity. However, we clearly have not demonstrated definitively the active or passive role of insulin in the observed weight changes following surgical treatment. Further studies will be needed to better understand the pathophysiologic characteristics of the weight gain.

Given the proposed model that ventromedial nucleus damage leads to hyperphagia and subsequently to obesity, our therapeutic intervention was selected to address the initial hyperphagia. We had originally chosen the sympathomimetic amine dextroamphetamine to help a patient with attention problems that developed postoperatively. However, we noted that his weight stabilized while he was taking the medication. We elected to expand this study and take advantage of the known anorectic effects of dextroamphetamine to determine its ability to control the dramatic weight gain seen in patients surgically treated for craniopharyngioma. In addition, there is a widespread history of the beneficial effects of central nervous system stimulants, such as dextroamphetamine, on children with behavioral problems caused by impulsivity and attention-deficit/hyperactivity disorder. In short-term clinical trials, dextroamphetamine, in conjunction with dietary modifications, has also been shown to induce a greater weight loss in adult obese subjects than was seen in those treated with diet and placebo alone. It is possible that an element of the hyperphagia seen in these children is impulsive eating and that dextroamphetamine leads to a decrease in impulsive activity, thereby improving schoolwork and decreasing rash food consumption.

The etiology of our patients’ observed weight stabilization while taking dextroamphetamine is not completely understood. Although the parents reported that mean daily calories consumed went from 1189±69 prior to dextroamphetamine therapy to 1335±137 after 24 months of treatment, the numbers of calories reported are extremely low and likely represent a significant underreporting. Indeed, there may have been a change in the calories consumed, but we were unable to detect the differences because of the inaccuracies of diet logs. Parents had consistently noted that their children’s diets were much easier to control during the dextroamphetamine therapy. Parents previously had difficulty limiting the number of servings consumed by their children at meals and noted a marked improvement during treatment with dextroamphetamine. We had observed an increase in overall activity for each of the children, which may have accounted for the weight stabilization or slowed weight gain. Prior to the start of the protocol, each parent had difficulty encouraging his or her child to exercise. Parents reported that their children were much more willing to participate in activities during dextroamphetamine treatment, and this increase in activity was maintained throughout the protocol.

One consistent finding at the start of the protocol was children’s difficulty maintaining attention. The problems were noted both in school and by the parents at home. The Conners profiles demonstrated impaired conduct as reported by both the parents and teachers. This is similar to previous studies that demonstrated a significant increase in attention problems postopera-
tively.\textsuperscript{15,16} We elected to treat children with dextroamphetamine to alleviate the attention difficulties reported postoperatively. Both parents and teachers reported an improvement in the child’s overall performance. We observed a decrease in the parent-reported hyperactivity index as well as in the teacher-reported conduct and hyperactivity indices during the dextroamphetamine protocol. There were no other significant changes in the Conners indices. Both parents and teachers made repeated comments that the children were more “focused” and were more likely to participate in activities during treatment.

Overall, we demonstrated that weight gain stabilized in children taking dextroamphetamine. This was the first such period noted for each child since surgical treatment. The weight changes are likely related to increases in activity, although we could not definitively exclude changes in calories consumed. We also noted a marked increase in the overall activity of each child, improved performance in school, and much more manageable and agreeable behavior in the home. The long-term stability of these changes has yet to be determined, and future studies are needed to determine if the changes remain constant or if additional therapies are required. In addition, it has yet to be determined if intervention earlier in the time course, such as immediately after surgical treatment, could prevent the initial weight gain and the need for subsequent weight stabilization after obesity has occurred.

Accepted for publication April 25, 2002.

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REFERENCES