Physiological growth hormone replacement and rate of recurrence of craniopharyngioma: the Genentech National Cooperative Growth Study

Timothy R. Smith, MD, PhD, MPH, David J. Cote, BS, John A. Jane Jr., MD, and Edward R. Laws Jr., MD

Departments of Neurosurgery, Brigham and Women’s Hospital, Boston, Massachusetts; and Department of Neurosurgery, University of Virginia, Charlottesville, Virginia.

OBJECTIVE The object of this study was to establish recurrence rates in patients with craniopharyngioma postoperatively treated with recombinant human growth hormone (rhGH) as a basis for determining the risk of rhGH therapy in the development of recurrent tumor.

METHODS The study included 739 pediatric patients with craniopharyngioma who were naïve to GH upon entering the Genentech National Cooperative Growth Study (NCGS) for treatment. Reoperation for tumor recurrence was documented as an adverse event. Cox proportional-hazards regression models were developed for time to recurrence, using age as the outcome and enrollment date as the predictor. Patients without recurrence were treated as censored. Multivariate logistic regression was used to examine the incidence of recurrence with adjustment for the amount of time at risk.

RESULTS Fifty recurrences in these 739 surgically treated patients were recorded. The overall craniopharyngioma recurrence rate in the NCGS was 6.8%, with a median follow-up time of 4.3 years (range 0.7–6.4 years). Age at the time of study enrollment was statistically significant according to both Cox (p = 0.0032) and logistic (p < 0.001) models, with patients under 9 years of age more likely to suffer recurrence (30 patients [11.8%], 0.025 recurrences/yr of observation, p = 0.0097) than those ages 9–13 years (17 patients [6.0%], 0.17 recurrences/yr of observation) and children older than 13 years (3 patients [1.5%], 0.005 recurrences/yr of observation).

CONCLUSIONS Physiological doses of GH do not appear to increase the recurrence rate of craniopharyngioma after surgery in children, but long-term follow-up of GH-treated patients is required to establish a true natural history in the GH treatment era.

http://thejns.org/doi/abs/10.3171/2016.4.PEDS16112

KEY WORDS craniopharyngioma; growth hormone; recurrence; oncology

Craniopharyngiomas are histologically benign tumors first described over 150 years ago. They are thought to arise from squamous cells resulting from partial involution of the embryonic vestigial hypophysial-phyaryngeal duct, also known as the “craniopharyngeal duct.” They may represent one end of a spectrum of diseases spanning Rathke’s cleft cysts, arachnoid cysts, colloid cysts, cystic pituitary adenomas, epidermoid cysts, and dermoid cysts. Although benign histologically, their anatomical location, physical characteristics, biological behavior, and associated morbidity and mortality make craniopharyngiomas one of the most destructive lesions of the sellar region.

Craniopharyngiomas comprise approximately 1.2%–4% of all intracranial tumors in children. They can be detected at any age, with peak incidence rates in children 5–14 years old and adults 50–74 years of age. Approximately 340 cases are diagnosed and treated annually in the United States. The management of craniopharyngiomas continues to be an area of intense controversy in pediatric endocrinology, neurosurgery, and radiation oncology. Major questions exist regarding the optimal surgical goals (for example, gross-total resection vs subtotal resection followed by adjuvant therapy), the ideal timing and modality of radiation therapy, and the role of pituitary hormone replacement therapy. Some studies have reported that physiological growth hormone (GH) replacement after resection of craniopharyngioma may increase the recurrence rate of these lesions, while others indicate that GH replacement is safe and effective.

ABBREVIATIONS GH = growth hormone; NCGS = National Cooperative Growth Study; rhGH = recombinant human GH.

SUBMITTED February 24, 2016. ACCEPTED April 5, 2016.

INCLUDE WHEN CITING Published online June 10, 2016; DOI: 10.3171/2016.4.PEDS16112.
The Genentech National Cooperative Growth Study (NCGS) was designed to monitor the efficacy and adverse event profile of recombinant human GH (rhGH) therapy in pediatric patients receiving rhGH manufactured by Genentech, Inc. Included in the patients enrolled in the NCGS were those with a history of GH deficiency secondary to surgical treatment for craniopharyngioma. This report is an analysis of the correlation between the recurrence rate of surgically treated craniopharyngiomas in children treated with postoperative physiological rhGH replacement therapy whose data were entered into the NCGS.

Methods

Description of the NCGS

The NCGS core study (registered with the ClinicalTrials.gov database, registration no. NCT00097539) is a multicenter, open-label, observational, postmarketing surveillance study of the Genentech rhGH products Protropin, Nutropin, Nutropin AQ, and Nutropin Depot, which were marketed at different times in the United States and Canada. The study includes male and female patients treated, between 1986 and 2005, with one or more of the aforementioned products for pediatric growth disorders for which GH is indicated. Subjects initiating or receiving therapy with one of these products could be voluntarily enrolled in the study and followed up throughout the course of their treatment. Subjects were excluded from study entry if they were being treated with a non-Genentech rhGH product, had closed epiphyses, or had active neoplasia. Intracranial lesions were required to be inactive (without progression either clinically or radiologically), and antitumor therapy must have been completed for a period of 12 months prior to the institution of rhGH therapy in all included patients. Data for children enrolled in the NCGS with a diagnosis of preexisting craniopharyngioma were extracted for analysis in our study.

Patients

A total of 739 patients who had a craniopharyngioma prior to the initiation of rhGH therapy and who also had follow-up information in the NCGS database were included in this analysis. The data cutoff for the analysis was May 2005. Patients were divided into 3 age groups for study: < 9 years, 9–13 years, and > 13 years. This analysis was restricted to the first 7 years from enrollment because the data were too sparse after this time period. The average dose of rhGH in this patient group was 0.253 ± 0.07 mg/kg/wk. As part of the NCGS follow-up of the children while on rhGH, investigators at the Genentech Department of Medical Information reported adverse events; one of the adverse events reported for patients enrolled with a craniopharyngioma diagnosis is recurrence of the craniopharyngioma—defined as clinical progression, tumor growth on imaging, or both. Reporting tumor recurrence was mandated by the study protocol. Therefore, the NCGS data provide a reasonable assessment of children diagnosed with craniopharyngioma who are treated with rhGH and subsequently experience recurrence of the craniopharyngioma.

Results

The overall incidence of recurrence in this analysis of 739 patients with craniopharyngioma treated with rhGH replacement was 6.8% (50 recurrences), with a median follow-up of 4.3 years (range 0.7–6.4 years) after initiation of GH therapy (Table 1). Age at the time of study enrollment was statistically significant according to both Cox proportional-hazards (p = 0.0032) and multivariate logistic regression (p < 0.001) models, with patients under 9 years of age more likely to develop recurrence (30 [11.8%], 0.025 recurrences/yr of observation) than those ages 9–13 years (17 [6.0%], 0.017 recurrences/yr of observation) and those older than 13 years (3 [1.5%], 0.005 recurrences/yr of observation; p = 0.0097; Fig. 1). When monitored longer on GH therapy, all age groups were found to be more likely to develop recurrence.

Discussion

After the resection of craniopharyngiomas, many patients retain or develop new endocrine dysfunction. There is some evidence that the most frequent hormone deficiency in all types of central nervous system tumors, regardless of the treatment received, is GH. Often these patients—particularly pediatric patients—require hormone replacement to restore normal physiology. For pediatric patients, GH is perhaps most important to their healthy growth and development, yet its use remains controversial. There is continuing concern that long-term GH replacement could increase the recurrence rate of craniopharyngioma.2,4,8,10,12,26,33,37,39

It is well known that GH has both mitogenic and antiapoptotic functions.4,48 Several studies have independently shown that GH can exert direct antiapoptotic effects on human cancers of various kinds, including breast, brain, colon, and prostate.2,4,28,37–39,48 The mitogenic and antiapoptotic properties of GH have led to some concern that long-term GH replacement could increase the recurrence rate or decrease the time to recurrence in patients who have undergone resection of craniopharyngioma. In 1998, an analysis of 488 patients (median follow-up 3.7 years) from the Kabi Pharmacia International Growth Study (KIGS)
database and Upjohn International Growth database demonstrated recurrence rates similar to those reported in the present study (54 patients [11.1%], 0.045 recurrences/yr of observation).31 Using the same database in 2006, Daren-deliler et al. reported similar recurrence rates in 1038 patients treated with rhGH after a median treatment duration of 2.8 years (121 patients [11.6%], 0.036 recurrences/yr of observation).10 An overview of literature rates of craniopharyngioma recurrence after conventional surgical and adjunctive care is presented in Table 2.6,7,11,13,14,18,19,23,32,34,36,41,44,46 Yet recurrence is not the only concern when GH is replaced. A recent study from France described a possible association between GH therapy during childhood among “low-risk patients” (isolated GH deficiency, idiopathic short stature, and small for gestational age) and increased risk for hemorrhagic stroke in young adulthood, though its conclusions have been contested.29

Growth hormone replacement is an effective therapy that often restores normal physiological conditions in patients who otherwise would have severe endocrine deficiencies. In 2003, Gleson et al. reported that, over the last 25 years, GH therapy in childhood survivors of brain tumors improved final height for patients undergoing both cranial (r = 0.5, p = 0.03) and craniospinal (r = 0.6, p < 0.001) operations.16 Also in 2003, Monson reported that GH replacement helps reduce the significant morbidity associated with GH deficiency by improving central fat mass and reducing serum total and low-density lipoprotein cholesterol.26 He also pointed to GH replacement as an important contributor to psychological well-being that helps resolve some of the psychosocial issues that GH-deficient pediatric patients face.26 Geffner et al. reported excellent linear growth in a series of 199 prepubertal patients undergoing rhGH therapy after resection of a craniopharyngioma; however, they noted that it had no ameliorative effects on morbid weight gain, a common side effect of resection of tumors in the region of the hypothalamus.15 Careful dosing and monitoring of rhGH is crucial to the success of GH replacement therapy, as the elevation of GH above physiological levels can have adverse effects.1,9,31,33,35,45

The major limitation of this study is its inclusion criteria. Children followed in this study clearly do not represent all potential GH-treated patients with craniopharyngiomas; one would suspect that patients who fare poorly after surgery or other forms of therapy or who have significant residual tumor after resection might never be considered candidates for GH replacement therapy. Additionally, the timing of the initiation of GH replacement certainly varies from one child to another. The NCGS protocol follows the guidelines of the 2003 Lawson Wilkins Pediatric Endocrine Society by stating that “prudence would dictate waiting one year after completion of tumor therapy with no evidence of further tumor growth before initiating GH therapy.”55 Although craniopharyngiomas are not truly malignant, the majority of NCGS patients were treated after at least 1 year from primary therapy; therefore, the rate of recurrence in the 1st year is unlikely to have been captured. Most recurrences have been reported to occur in the first 3 years after surgery.42 The actual length of exposure to GH must be considered as one of the factors influencing recurrence in these patients. If there is a relationship between GH replacement and recurrence rates, it would be important to calculate the outcome according to length of exposure and doses of GH. Additional limitations due to the nature of the NCGS relate to missing data, including absent data on possible differences in postoperative adjuvant treatment rates among each cohort, extent of initial resection, and frequency of postoperative MRI monitoring.
Despite these limitations, this report encompasses the largest group of children with craniopharyngiomas ever analyzed for recurrence and provides a valuable resource to assess recurrence specifically in a GH-treated population. The recurrence rates in these children were as low or lower than those seen in other careful studies of children who have undergone surgical removal of craniopharyngiomas.\(^2\)\(^{12,27}\) Specifically, the rate of recurrence of craniopharyngioma after rhGH therapy reported here, 6.8% over 4.3 years of follow-up, compares favorably with the contemporary literature rates of 11%–16%, though a limitation of our study was its relatively shorter median follow-up period.\(^10\)\(^{27}\) While there is some cell culture evidence showing that craniopharyngioma cell growth is promoted by GH exposure in vitro, perhaps related to the expression of GH receptors and insulin-like growth factor-I receptors on the tumor, clinical studies do not support this correlation.\(^25\)\(^{27}\) Long-term rhGH replacement therapy does not appear to affect the progression-free survival rate in patients with craniopharyngiomas.\(^25,27,37,43\)

Conclusions

This analysis provides evidence that there is very low, if any, risk that physiological rhGH replacement therapy given to children who have undergone craniopharyngioma resection facilitates tumor recurrence. This evidence may allow for more systematic and effective GH replacement therapy in these children, for whom the psychosocial aspects of GH deficiency can significantly impede their quality of life.

Acknowledgments

We thank Barbara Lippe, MD; Bert Bakker, MD, PhD; Tom Maneatis, MD; Kevin Connelly; Sumeet Brar; Robert Masi; Joan Jacobs; Winifred Werther; and Jim Frane (Genentech, San Francisco, California) for their contributions to this study.

References


TABLE 2. Overall craniopharyngioma recurrence rates in the neurosurgical literature

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Recurrence Rate</th>
<th>Mean Time to Recurrence (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz, 1975</td>
<td>40</td>
<td>12%</td>
<td>48</td>
</tr>
<tr>
<td>Shapiro et al., 1979</td>
<td>60</td>
<td>23%</td>
<td>29</td>
</tr>
<tr>
<td>Thomsett et al., 1980</td>
<td>42</td>
<td>29%</td>
<td>43</td>
</tr>
<tr>
<td>Richmond et al., 1980</td>
<td>32</td>
<td>38%</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Carmel et al., 1982</td>
<td>45</td>
<td>50%</td>
<td>67</td>
</tr>
<tr>
<td>Clayton et al., 1988</td>
<td>2</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Weiss et al., 1989</td>
<td>31</td>
<td>14%</td>
<td>25</td>
</tr>
<tr>
<td>Yaşargil et al., 1990</td>
<td>144</td>
<td>7%</td>
<td>—</td>
</tr>
<tr>
<td>Fischer et al., 1990</td>
<td>37</td>
<td>57%</td>
<td>—</td>
</tr>
<tr>
<td>Hetelekidis et al., 1993</td>
<td>52</td>
<td>25%</td>
<td>45</td>
</tr>
<tr>
<td>Fahibush et al., 1999</td>
<td>148</td>
<td>11%</td>
<td>&lt;71</td>
</tr>
<tr>
<td>Duff et al., 2000</td>
<td>121</td>
<td>17%</td>
<td>—</td>
</tr>
<tr>
<td>Gupta et al., 2006</td>
<td>116</td>
<td>13%</td>
<td>16</td>
</tr>
<tr>
<td>Schoenfeld et al., 2012</td>
<td>122</td>
<td>25%</td>
<td>12</td>
</tr>
</tbody>
</table>

--- = not reported.


42. Zeitler P, Siriwardana G: Antagonism of endogenous growth hormone-releasing hormone (GHRH) leads to reduced proliferation and apoptosis in MDA231 breast cancer cells. *Endocrine* 18:85–90, 2002

**Disclosures**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Laws, Smith, Jane. Acquisition of data: Smith, Cote. Analysis and interpretation of data: Cote. Drafting the article: Laws, Cote. Critically revising the article: Laws, Smith, Jane. Reviewed submitted version of manuscript: Laws. Approved the final version of the manuscript on behalf of all authors: Laws. Statistical analysis: Smith. Administrative/technical/material support: Laws, Smith, Cote. Study supervision: Laws, Jane.

**Correspondence**

Edward R. Laws, Department of Neurosurgery, Brigham and Women’s Hospital, Harvard Medical School, 75 Francis St., PBB3, Boston, MA 02115. email: elaws@partners.org.