Physiologic Growth Hormone–Replacement Therapy and Craniopharyngioma Recurrence in Pediatric Patients: A Meta-Analysis

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Key words
- Craniopharyngioma
- Growth hormone
- Growth hormone–replacement therapy
- Pediatrics
- Recurrence

Abbreviations and Acronyms
CI: Confidence interval
GHD: Growth hormone deficiency
GHRT: Growth hormone–replacement therapy
IGF-1: Insulin-like growth factor 1
NOS: Newcastle-Ottawa Scale

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OBJECTIVE: **A systematic review and meta-analysis were conducted to examine the effect of growth hormone–replacement therapy (GHRT) on the recurrence of craniopharyngioma in children.**

METHODS: **PubMed, Embase, and Cochrane databases were searched through April 2017 for studies that evaluated the effect of GHRT on the recurrence of pediatric craniopharyngioma. Pooled effect estimates were calculated with fixed- and random-effects models.**

RESULTS: **Ten studies ($n = 3487$ patients) met all inclusion criteria, including 2 retrospective cohorts and 8 case series. Overall, 3436 pediatric patients were treated with GHRT after surgery and 51 were not. Using the fixed effect model, we found that the overall craniopharyngioma recurrence rate was lower among children who were treated by GHRT (10.9%; 95% confidence interval 9.80%–12.1%; $I^2 = 89.1\%$; P for heterogeneity <0.01; $n = 10$ groups) compared with those who were not (35.2%; 95% confidence interval 23.1%–49.6%; $I^2 = 61.7\%$; P for heterogeneity $= 0.11$; $n = 3$); the P value comparing the 2 groups was <0.01. Among patients who were treated with GHRT, subgroup analysis revealed that there was a greater prevalence of craniopharyngioma recurrence among studies conducted outside the United States ($P < 0.01$), single-center studies ($P < 0.01$), lower impact factor studies ($P = 0.03$), or studies with a lower quality rating ($P = 0.01$). Using the random-effects model, we found that the results were not materially different except for when stratifying by GHRT, impact factor, or study quality; this led to nonsignificant differences. Both Begg's rank correlation test ($P = 0.7$) and Egger's linear regression test ($P = 0.06$) indicated no publication bias.**

CONCLUSIONS: **This meta-analysis demonstrated a lower recurrence rate of craniopharyngioma among children treated with GHRT than those who were not.**

INTRODUCTION

Craniopharyngiomas are histologically benign neuroepithelial tumors found near the pituitary gland that are observed most commonly in children between the ages of 5 and 10 years.[1] These tumors may cause compression of adjacent neural structures of the brain and impact the normal functioning of the pituitary gland's growth hormone–producing tissue. Growth hormone deficiency (GHD) stands out as the most common endocrinologic disturbance that occurs as a result of a craniopharyngioma.[2]

GHD results from the destruction of the normal functioning of the pituitary and hypothalamic tissues,[3] which can stem from mass effect, surgical manipulation, or radiosurgery. Pediatric GHD occurs when the body is unable to produce enough growth hormone or when end-organs are unable to respond to growth hormone normally.[4] Low levels of growth hormone in the body of a child may have significant effects on the child's long-term growth and well-being. Growth hormone–replacement therapy (GHRT) involves the use of somatotropin, a growth hormone of recombinant DNA origin, to replace the body's natural pituitary-derived growth hormone.

An important concern for clinicians caring for children who have undergone resection of craniopharyngioma is whether GHRT contributes to the recurrence of these tumors. A conclusive study exclusively analyzing the effect of GHRT on the recurrence of pediatric craniopharyngiomas has yet to be conducted, and the issue remains somewhat of a clinical dilemma. Therefore, we sought to undertake a systematic review and meta-analysis to analyze whether physiologic GHRT increases the risk of craniopharyngioma recurrence among the pediatric population.

MATERIALS AND METHODS

Literature Search

The search for related articles was conducted with PubMed, Embase, and

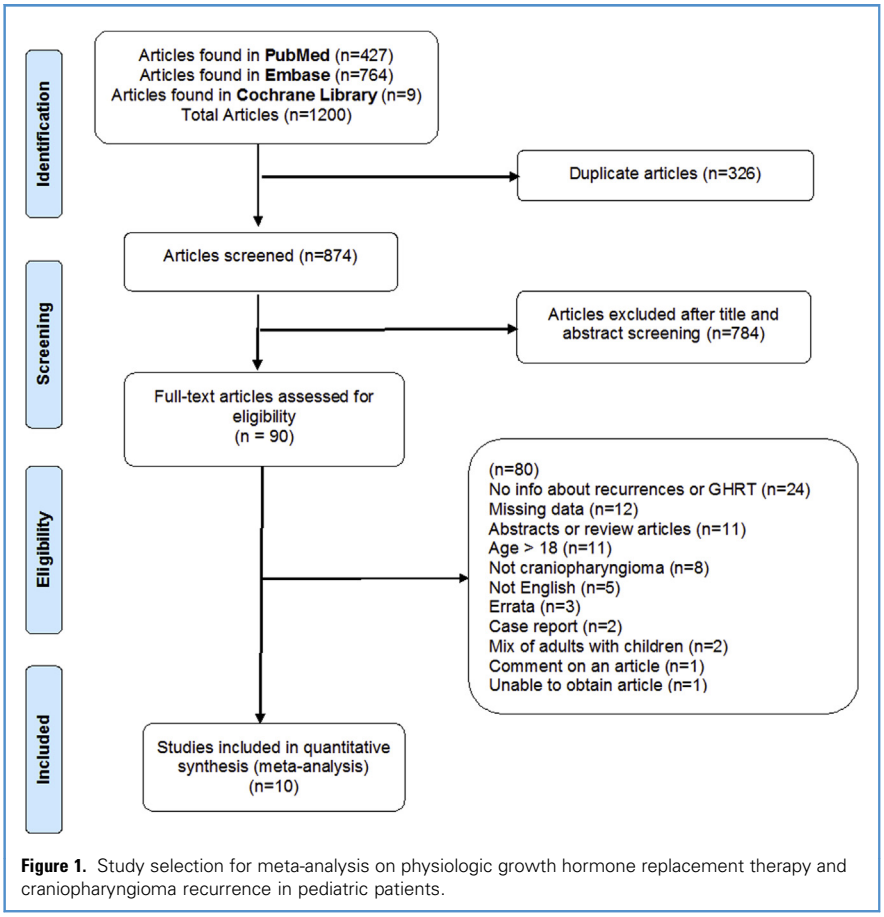

Figure 1. Study selection for meta-analysis on physiologic growth hormone replacement therapy and craniopharyngioma recurrence in pediatric patients.

Cochrane Library from their creation date through April 23, 2017, for studies evaluating the effect of GHRT on the recurrence of pediatric craniopharyngiomas. The search strategy joined several search terms for growth hormone (e.g., growth hormone, somatotrophic hormone, and hormone-replacement therapy), and craniopharyngioma (e.g., pediatric craniopharyngioma, craniopharyngioma*) (Appendix 1).

Study Eligibility

Studies were included in the current meta-analysis if they met the following criteria: 1) studies of recurrence of craniopharyngiomas in pediatric patients who did or did not receive GHRT; 2) studies with patient populations ranging from newborn to 18 years who were diagnosed with craniopharyngiomas; 3) studies that included 5 or more patients; 4) studies in which the measurable outcome was recurrence or nonrecurrence of craniopharyngioma; and 5) sudies in which the intervention was GHRT. Articles that did not meet the inclusion criteria, were not in English, or did not report recurrence were excluded. Titles and abstracts were screened and selected for the full-text evaluation if it met the inclusion criteria. This screening was performed independently in duplicate. Discrepancies were resolved by consulting a senior author (H.Z.).

Data Extraction

The following data were extracted from the selected studies, when available: participants' characteristics (age, sex); intervention characteristics (surgery type; GHRT, dose, frequency); study characteristics (authors, publication year, journal impact factor, center, continent, sample size, and study design); and outcome results (number of recurrences in each group, total number). In studies in which the median and range were given instead of the mean, the mean was then estimated.[5] Data extraction was performed independently in duplicate. Discrepancies were resolved by consulting a senior author (H.Z.).

Statistical Analysis

Comprehensive Meta-Analysis version 3 (Biostat, Englewood, New Jersey, USA) was used to perform the data analysis. The overall recurrence prevalence estimate and its 95% confidence intervals (CIs) among patients with craniopharyngioma with or without GHRT was obtained by using the fixed-effect model, which only accounted for the within-study variance. In addition, variation between and within studies was evaluated for comparison via a random-effects model.[6] The individual and summary estimates were visualized with the use of forest plots. Cochran's Q test ($P < 0.10$) and I^2 were used to evaluate the heterogeneity among studies. An I^2 was considered high if its value was >50%. Subgroup analyses by categorical covariates such as growth hormone—replacement therapy (GHRT; no GHRT), continent (studies in the United States; outside the United States), international journal impact factor (median value ≤3.7; >3.7), Newcastle-Ottawa Scale (NOS) (median value of ≤3; >3), and center (single; multiple) were used to explore potential sources of heterogeneity. Covariates such as age range, surgery type, treatment duration, length of follow-up, and timing of initiation of GHRT after surgery were not always specified and hence were not used to assess for heterogeneity. Funnel plots, Egger's linear regression test, and Begg's and Mazumdar rank correlation test were used to assess potential publication bias at the P value of <0.05 level of significance. The number of missing studies in a meta-analysis was evaluated by the trim and fill method if publication bias was indicated.

Quality Assessments

The nature of the available studies was noncomparative. Therefore, we modified the NOS to assess the quality of included studies by removing the comparability criteria.[7] The selection and outcome criteria were used to assess the quality of the study. Studies with a score ≤3 (median value) were considered low quality, whereas those with a score >3 were considered high quality.