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Predicting the Probability of Abnormal Stimulated Growth Hormone Response in Children After Radiotherapy for Brain Tumors

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Abstract

Purpose—To develop a mathematical model utilizing more readily available measures than stimulation tests that identifies brain tumor survivors with high likelihood of abnormal growth hormone secretion after radiotherapy (RT), to avoid late recognition and a consequent delay in growth hormone replacement therapy.

Methods and Materials—We analyzed 191 prospectively collected post-RT evaluations of peak growth hormone level (arginine tolerance/levodopa stimulation test), serum insulin-like growth factor 1 (IGF-1), IGF-binding protein 3, height, weight, growth velocity, and body mass index in 106 children and adolescents treated for ependymoma ($n = 72$), low-grade glioma ($n = 28$) or craniopharyngioma ($n = 6$), who had normal growth hormone levels before RT. Normal level in this study was defined as the peak growth hormone response to the stimulation test > 7 ng/mL.

Results—Independent predictor variables identified by multivariate logistic regression with high statistical significance ($p < 0.0001$) included IGF-1 z score, weight z score, and hypothalamic dose. The developed predictive model demonstrated a strong discriminatory power with an area under the receiver operating characteristic curve of 0.883. At a potential cutoff point of probability of 0.3 the sensitivity was 80% and specificity 78%.

Conclusions—Without unpleasant and expensive frequent stimulation tests, our model provides a quantitative approach to closely follow the growth hormone secretory capacity of brain tumor survivors. It allows identification of high-risk children for subsequent confirmatory tests and in-depth workup for diagnosis of growth hormone deficiency.

Keywords

Pediatric brain tumor; Radiotherapy; Growth hormone; Insulin-like growth factor; Stimulation test

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Conflict of interest: none.

Introduction

Growth hormone deficiency (GHD) is a common disorder in pediatric cancer survivors who received radiotherapy to sellar or parasellar tumors. Using a peak growth hormone cutoff of $<5 \mu\text{g/L}$ for the arginine–insulin tolerance test, the prevalence of radiation-induced GHD was estimated to be 35% in a recent pooled study with a hypothalamic–pituitary dose ranging from 13 to 65 Gy (1). Without being detected and treated, GHD can cause short stature, truncal obesity, loss of strength and musculature, psychological symptoms, and lower quality of life. For pediatric brain tumor survivors prone to GHD after radiotherapy, routine surveillance and early detection allowing prompt intervention with growth hormone replacement is crucial.

In clinical practice, growth hormone stimulation tests are the mainstay for ascertaining the status of GHD. Test-specific peak growth hormone cut points are carefully chosen, owing to the variability of growth hormone response according to pharmacologic agent and assay (2). Despite the primacy of growth hormone stimulation tests in diagnosing GHD, these tests are expensive and time-consuming, and the stimulation agents can be in short supply. In addition, serial blood sampling is unpleasant for children. These undesirable characteristics limit frequent use of stimulation tests for GHD screening in pediatric patients after radiotherapy.

Measuring serum levels of insulin-like growth factors (IGF) and their binding proteins (IGFBP) has been suggested as an alternative to growth hormone stimulation testing in children (3). Insulin-like growth factor 1 (IGF-1) and IGFBP-3 are the most growth hormone–dependent peptides of their respective family groups. As an indirect means of assessing growth hormone secretion, measuring the concentrations of IGF-1 and IGFBP-3 is less expensive and more reproducible than growth hormone stimulation testing based on single samples, because of minimal diurnal variation (4). Normal reference ranges adjusted for age and sex are available. Despite the fact that pituitary growth hormone secretion is the predominant hormonal variable regulating serum IGF-1 concentrations, many variables also affect its level, including nutritional status, genetic factors, and insulin. On the basis of their diagnosis of GHD according to the results of growth hormone stimulation tests, most studies suggested that IGF-1 and IGFBP-3 may not have sufficient precision to be used as a stand-alone test in the diagnosis of GHD (5–8). However, growth factor measurements may be useful in excluding patients who are unlikely to have GHD or to identify patients in whom an expedited workup should be performed (3, 9).

In this study we investigated the feasibility of using serum levels of IGF-1 and IGFBP-3 to predict the presence of abnormal stimulated growth hormone response in pediatric brain tumor patients after radiotherapy. To improve prediction accuracy we also included relevant clinical, auxologic, and dosimetric factors. Our unique contribution is that we developed a prescreening strategy utilizing more readily available measures that identifies patients with a high likelihood of abnormal growth hormone secretion during follow-up for subsequent confirmatory stimulation tests. This alleviates the need to perform frequent stimulation tests in all brain tumor survivors while still allowing timely diagnosis of GHD in those who need it most.

Methods and Materials

Patients

Included in this research are 106 patients (59 male and 47 female) with 191 sets of concurrent measurements of growth hormone, serum IGF-1, and IGFBP-3 levels after radiotherapy. Measurement data were included for analysis only if their age at the time of

testing was 17.5 years for males and 14.5 years for females, the approximate ages reaching the end of puberty. All study patients had localized primary brain tumors with normal baseline growth hormone secretion and enrolled in an institutional review board–approved Phase II trial of conformal radiotherapy between 1997 and 2008. The median age of these patients at the start of radiotherapy was 5.6 years (range, 1.1–16.6 years). The median follow-up for growth hormone secretion was 3 years (range, 0.4–5.8 years). Diagnoses included low-grade glioma (28 cases), ependymoma (72 cases), and craniopharyngioma (6 cases). Tumor locations were divided into supratentorial (41 cases) and infratentorial (65 cases).

Radiotherapy treatment planning and delivery

To assist in delineation of tumor and normal tissue volumes, including pituitary and hypothalamus, magnetic resonance images of T1- and T2-weighted and balanced sequences were spatially registered to simulation computed tomography images for treatment planning. Prescribed tumor doses were 54–55.8 Gy for craniopharyngioma, 54 Gy for low-grade glioma, and 54–59.4 Gy for ependymoma at 1.8 Gy per fraction. Either three-dimensional conformal or intensity-modulated radiotherapy with X-rays was delivered. Because of the small size of the pituitary and hypothalamus, we used their mean dose to represent the delivered dose. Normal tissue delineation, treatment planning, and delivery have been described in detail previously (10, 11).

Growth hormone and growth factor assays

Growth hormone secretion was prospectively evaluated with the arginine plus levodopa (L-dopa) stimulation test before radiotherapy and at 6, 12, 36, and 60 months after therapy. Test results of growth hormone and growth factor were excluded from analysis if they were collected during or after the period when patients received growth hormone replacement therapy, during steroid treatment, or after tumor progression. Patients fasted the night before the arginine plus L-dopa stimulation test. After the baseline serum sample was obtained, arginine HCl (0.5 g/kg to a maximum of 30 g) was administered intravenously (i.v.) over a 30-min period. Levodopa (10 mg/kg to a maximum of 500 mg) was administered orally 90 min after the baseline blood sample. A total of 11 blood samples were drawn over a 210-min period for each stimulation test. Abnormal stimulated growth hormone response was defined as the peak response <7 ng/mL, a frequently used cutoff. Measurements of serum IGF-1 and IGFBP-3 levels were performed separately and typically before the growth hormone stimulation test. To account for the normal variation by age, sex, and pubertal stage, IGF-1 and IGFBP-3 levels were converted into standardized z scores using the reference ranges published by Elmlinger *et al.* (12). The z score indicates how many standard deviations an observation is above or below the population mean.

Auxologic measurements

We recorded height, weight, growth velocity, and body mass index (BMI) of each patient at each follow-up examination. These auxologic measurements except growth velocity were converted into z scores using the normal growth data for age 2 to 20 years provided by the Centers for Disease Control and Prevention (http://www.cdc.gov/growthcharts/percentile_data_files.htm). For growth velocity, we adopted age-related reference ranges published by Tanner and Davies (13). Growth velocity was calculated in two ways. It was expressed in z scores for chronological age and also for bone age, to adjust for pubertal status. The bone age was determined from the radiological study of a patient's hand and wrist (14). When data on height, weight, BMI, and IGF-1 and IGFBP-3 levels were not available from the day of the growth hormone stimulation test, they were collected from a clinic visit occurring no more than 1 week before or after the stimulation test.

Statistical analysis

Multi-time-point measurements of a patient were treated as independent samples and were not averaged over time. Individual time-point data from all patients were grouped together for modeling. A mathematical model was derived to produce a probability for each single time point given observations at that time point rather than assigning only one probability to a patient for the entire follow-up period. We first performed univariate logistic regression analysis to assess the association of peak stimulated growth hormone levels and serum levels of growth factors. We also tested clinical, dosimetric, and auxologic variables to identify additional predictor variables that may improve the model predictability. To prevent including co-dependent variables in multivariate regression modeling, Pearson correlations were calculated for continuous variables and *t* tests for categorical variables. Peak growth hormone levels were log transformed to approximate a normal distribution and allow being fitted with a linear model. Backward elimination was performed to remove variables found no longer statistically significant. A logistic regression model allows one to predict the probability of abnormal stimulated growth hormone response given the outcomes of predictor variables that are easier to measure. Model performance was assessed by evaluating the receiver operating characteristic (ROC) curve against the original test data. All statistical analyses were performed using SAS/STAT software version 9 (SAS Institute, Cary, NC).

Results

Variation of patient data

For data analyzed in this research, Fig. 1 shows the variation in peak stimulated growth hormone level, *z* scores of IGF-1, IGFBP-3, height, weight, BMI, and growth velocity, as well as pituitary and hypothalamic doses. All measurements taken at various time points after radiotherapy were combined for display here and for subsequent regression analysis. The plots indicate that measurement data are distributed widely across all variables, which makes our regression model applicable to a wide range of situations.

Univariate logistic regression analysis

Table 1 lists the *p* value, estimated odds ratio, and 95% confidence interval for variables tested in the univariate analysis. As expected, IGF-1 and IGFBP-3 *z* scores were strongly associated with the peak stimulated growth hormone level. Other significant variables include BMI *z* score, weight *z* score, radiation dose to pituitary and hypothalamus, and tumor location. *Z* scores of IGF-1 and IGFBP-3 were weakly correlated (Pearson correlation coefficient $r = 0.3174$, $p < 0.0001$), whereas doses to pituitary and hypothalamus were strongly correlated ($r = 0.8822$, $p < 0.0001$). The latter reflects the proximity of these two organs. The literature suggests a lower threshold and earlier effect for radiation-induced damage in hypothalamic tissue than in pituitary (15). Therefore, we have selected hypothalamic dose instead of pituitary dose for the subsequent multivariate analysis.

Multivariate logistic regression analysis and model evaluation

Table 2 lists maximum likelihood estimates of a multivariate logistic regression function that best fits the data sets included in the study. During the variable selection process, IGFBP-3 *z* score, tumor location, and BMI *z* score subsequently lost their statistical significance and were eliminated from the final model. The remaining highly significant variables are IGF-1 *z* score, weight *z* score, and hypothalamic dose. Results in Table 2 can be converted to the logistic regression equation for peak stimulated growth hormone level: $P = 1/(1 + e^{-x})$, where $x = -3.9965 - (0.8651 \times \text{IGF-1 } z \text{ score}) + (0.9813 \times \text{weight } z \text{ score}) +$

$(0.0541 \times \text{hypothalamic dose in Gy})$, where P is the probability of the stimulated peak level being <7 ng/mL.

Figure 2 shows the ROC curve corresponding to the regression model in Table 2. The model demonstrated fairly reasonable discriminatory power with the area under the ROC curve (AUC) being 0.883. At a potential cutoff point of $p = 0.3$ near the shoulder of the curve, the sensitivity was 80% and specificity was 78%.

The logistic regression modeling was also performed separately using IGF-1 z score or IGFBP-3 z score as the only predictor variable. The AUC was low (0.651 for IGF-1 and 0.617 for IGFBP-3), which confirms that neither IGF-1 nor IGFBP-3 alone has sufficient precision in predicting the abnormality of growth hormone secretion.

General trends

A scatter plot of all 191 measurements is shown in Fig. 3 using predictor variables identified from multivariate analysis as three axes. The dose effect was easily seen. When the dose to hypothalamus was low (<20 Gy), the measured stimulated growth hormone level was likely to be normal (>7 ng/mL) unless the weight z score was high (8 in 13 or 62% abnormal for patients with weight z score >2 vs. 3 in 78 or 4% abnormal for those with weight z score ≤ 2). When the hypothalamic dose was >20 Gy, the growth hormone level was likely to be abnormal when either the weight z score was high (>2) or the IGF-1 z score was low (<-2). The corresponding raw incidences were 92% and 71%, respectively.

Discussion

Predictive models for longitudinal change and normality of growth hormone secretion

We previously developed a linear mixed-effects model that predicts the peak growth hormone response within 12 months after conformal radiotherapy (10). A new model fitting data from a larger patient cohort with 5 years of follow-up was recently published (16). The model allows estimation of the rate of decline in the peak growth hormone response given the baseline growth hormone level, the presence of cerebrospinal fluid shunting, the mean dose to hypothalamus, and the time from radiotherapy. Our present study further expands the growth hormone research in radiotherapy. The logistic regression model calculates the probability of abnormal stimulated growth hormone response according to simple measures acquired at a time point during follow-up. The model may serve as a practical prescreening tool for monitoring growth hormone secretion after radiotherapy in a particularly vulnerable pediatric population.

Association of obesity with abnormal stimulated growth hormone response

In healthy adults and short-stature children, obesity has been demonstrated to be associated with diminished growth hormone response (17, 18). The risk of overdiagnosis of GHD due to this confounding effect is well known. Our present study confirmed this association in a unique population of children with prior cranial irradiation. The developed model provides a means to estimate the contribution of obesity to the overall likelihood of abnormal growth hormone response. Because obesity can result from severe GHD, guidelines utilizing auxological, biochemical, and radiological evaluations should still be followed to avoid late recognition of GHD in obese patients (19).

Lack of predictive power of growth velocity

Our univariate analysis found that growth velocity was not predictive of the normality of stimulated growth hormone response at the same measurement time point. We speculate that the decline in stimulated growth hormone response may occur before the manifestation of

growth failure. The confounding factor of obesity may contribute to the disassociation (20). However, our finding should not be misinterpreted to discourage the use of growth velocity as one of the clinical criteria to initiate immediate investigation for GHD, particularly when low growth velocity is sustained over 1 to 2 years (19).

Effect of disease progression on IGF-1 level

There is a concern whether serum levels of IGF-1 would rise in patients who experienced disease progression, which may diminish the association between growth hormone and IGF-1 levels. Eighteen patients in this study experienced disease progression during the follow-up period. At the time of disease progression, the mean IGF-1 *z* score was -1.14 ± 1.07 in 12 patients with available IGF-1 measurements. When including evaluations at all time points, the mean IGF-1 *z* score was not statistically different ($p = 0.25$, two-sample *t* test) between patients with (-0.43 ± 1.01) and without disease progression (-0.69 ± 1.25). The same phenomenon was also observed for IGFBP-3 *z* score (-0.65 ± 0.98 with progression vs. -0.63 ± 1.23 without). In this unique population, disease progression did not seem to be a confounding factor in the use of IGF-1 or IGFBP-3 for predicting the growth hormone level.

Strengths and limitations of the study

This research is based on prospectively collected data in a unique population of children and adolescents receiving radiotherapy for brain tumors. All patients were consistently treated on an institutional protocol and tested for growth hormone secretion throughout the entire follow-up. Although we presented results using the threshold of 7 ng/mL for determining the normality of growth hormone response, additional testing using another common cutoff (10 ng/mL) identified the same predicting variables and showed a similar model performance. The predictive model developed in this research was evaluated using original data sets. External validation using independent data sets is needed in the future.

Conclusions

We have developed a model predicting the probability of abnormal stimulated growth hormone response based on measures of IGF-1 level, body weight, and radiation dose to the hypothalamus. As a rule of thumb, patients who received low-dose irradiation (<20 Gy) to the hypothalamus and maintained normal body weight during follow-up are highly likely to have normal stimulated growth hormone response. For patients receiving high-dose irradiation, the stimulated growth hormone response is likely to be abnormal if they are obese or have low IGF-1 level, which warrants close follow-up and in-depth workup for diagnosis of GHD.

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Summary

On the basis of prospectively collected data from 106 pediatric brain tumor patients, a multivariate logistic regression model was developed to predict the presence of abnormal stimulated growth hormone response after radiotherapy. Incorporating insulin-like growth factor 1 level, body weight, and radiation dose to hypothalamus, the model demonstrated a strong discriminatory power and provides a means to follow and identify survivors at risk of low growth hormone secretion, without frequent stimulation tests.

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Fig. 1.

Box plots of biochemical, auxologic, and dosimetric variables of study evaluated after radiotherapy. The bottom and top of the box are lower and upper quartiles, respectively. The band inside the box is the median. Ends of the whiskers are the lowest and highest data within 1.5 times the interquartile range. Outliers are displayed with a plus sign. IGF-1 = insulin-like growth factor 1; IGFBP-3 = IGF binding protein 3; BMI = body mass index.

Fig. 2. Receiver operating characteristic plot of the logistic regression model. AUC = area under the receiver operating characteristic curve.

Fig. 3. Scatter plot of peak stimulated growth hormone level of 191 measurements from 106 patients. Empty and solid circles represent those with the growth hormone level ≥ 7 and <7 ng/mL, respectively. IGF1 = insulin-like growth factor 1.

Table 1

Univariate logistic regression of potential predictor variables

Variable	<i>p</i>	Odds ratio	95% confidence interval
Sex (female vs. male)	0.0921	0.643	0.385–1.075
Tumor location (infratentorial vs. supratentorial)	0.0002	0.368	0.219–0.620
Pre-RT chemotherapy (no vs. yes)	0.0535	0.553	0.304–1.009
Age at RT start (y)	0.5256	1.022	0.955–1.095
Age at test (y)	0.9828	1.001	0.935–1.071
Years from RT start at test	0.1581	0.886	0.749–1.048
IGF-1 z score	0.0005	0.585	0.433–0.791
IGFBP-3 z score	0.0066	0.691	0.530–0.902
Height z score	0.4291	0.903	0.700–1.163
Weight z score	<0.0001	1.695	1.367–2.102
BMI z score	<0.0001	1.854	1.513–2.272
Growth velocity z score of chronological age	0.7466	1.003	0.986–1.020
Growth velocity z score of bone age	0.5877	1.001	0.996–1.007
Pituitary mean dose (Gy)	<0.0001	1.067	1.050–1.084
Hypothalamus mean dose (Gy)	<0.0001	1.047	1.033–1.061

Abbreviations: RT = radiotherapy; IGF-1 = insulin-like growth factor 1; IGFBP-3 = IGF binding protein 3; BMI = body mass index.

Table 2

Maximum likelihood estimates of multivariate logistic regression function

Variable	Regression coefficient	Standard error	Wald χ^2	<i>p</i>	Odds ratio	95% confidence interval
Intercept	-3.9965	0.5696	49.2272	<0.0001	–	–
IGF-1 z score	-0.8651	0.2081	17.2859	<0.0001	0.421	0.280–0.633
Weight z score	0.9813	0.1901	26.6431	<0.0001	2.668	1.838–3.873
Hypothalamic dose (Gy)	0.0541	0.0105	26.6256	<0.0001	1.056	1.034–1.078

Abbreviation as in Table 1.