Growth Failure After Treatment of Pediatric Brain Tumors

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ABSTRACT. *Objectives.* **Primary brain tumors are the most common solid tumors that occur in childhood. With improved management of these tumors, there are more survivors with long-term sequelae of radiation and chemotherapy including growth failure. The aim of this study was to assess growth prospectively in children with nonpituitary-related primary brain tumors.**

Methods. **Forty-one children 3.1 to 13.8 years of age diagnosed consecutively between 1989 and 1992 with a primary nonpituitary-related brain tumor were studied.**

Results. **Of 34 prepubertal children, 14 (41%) were diagnosed as having growth hormone (GH) deficiency. All 14 children were treated with cranial irradiation. During the first year from completion of brain tumor therapy, the annual height velocity of those children confirmed subsequently as being GH-deficient was 3.06 ± 1.19 cm compared with 5.29 ± 2.21 cm for those who were not GH-deficient. During the second year, the annual height velocity was 3.29 ± 1.14 cm per year for the GH-deficient group compared with 5.48 ± 1.24 cm per year for the non-GH-deficient group. All children with GH deficiency received cranial irradiation and chemotherapy. Two of 34 children developed precocious puberty. Primary hypothyroidism was diagnosed in 6 of 41 children (12%).**

Conclusion. **We conclude that GH deficiency and primary hypothyroidism are common after cranial irradiation and chemotherapy for nonpituitary-related brain tumors. Linear growth appears to reflect GH status accurately in children with brain tumors. Precise auxologic evaluation is simple and noninvasive and may reflect more accurately GH status than provocative GH testing. These findings reflect the need for prospective growth monitoring of children with nonpituitary-related brain tumors treated with cranial irradiation and chemotherapy. Early diagnosis of GH deficiency facilitates early initiation of GH therapy and optimization of final height.** *Pediatrics* **1999;103(3). URL: http://www.pediatrics.org/cgi/content/full/103/3/e37;** ***brain tumors, cranial irradiation, growth, growth hormone deficiency, hypothyroidism.***

ABBREVIATIONS. GH, growth hormone; TSH, thyroid-stimulating hormone; HV, height velocity; SDS, standard deviation score.

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Primary brain tumors are the most common solid tumors that occur in childhood and the second most common form of malignant disease in children under the age of 15, being superseded only by leukemia.[1,2] The incidence of brain tumors in children is ~1/50 000 children.[3] There has been progressive improvement in survival rates of children treated for brain tumors during the past 25 years as a result of improved management.[4,5] With increased survival, it has become evident that these children may have significant long-term effects, the most notable of which are growth failure with reduced adult height and decreased cognitive function.[6–8]

Multiple factors contribute to poor growth after treatment of childhood brain tumors. A radiation dose of ≥27 Gy to the hypothalamic pituitary axis is known to result in growth hormone (GH) deficiency and growth impairment.[9] Spinal irradiation also may contribute to poor growth by decreasing spinal growth, and the younger the child is at treatment, the greater the loss in final height. The average loss in height from spinal irradiation is 5 to 7 cm, and this is not ameliorated by GH therapy.[10] Chemotherapy also may affect growth of children treated for brain tumors adversely, possibly by a direct effect on bone or by blunting growth in puberty as well as directly causing GH deficiency.[11–13] Children who have received cranial irradiation with a dose of >25 Gy are vulnerable to early puberty, the age of onset of puberty being related to the age at irradiation. The decreased duration of the pubertal growth spurt also may contribute to a reduced final height.[14]

It is standard clinical practice to assess endocrine function perioperatively and prospectively in children with primary brain tumors directly affecting the hypothalamic pituitary axis. However, children with nonpituitary-related brain tumors may be referred for endocrine evaluation at a later stage when endocrine dysfunction, specifically short stature, is clinically evident. The aim of this study was to assess growth prospectively from brain tumor diagnosis in children treated with cranial irradiation for nonpituitary-related brain tumors.

METHODS

Forty-one children with a primary brain tumor, not involving any part of the hypothalamic pituitary axis, diagnosed consecutively between 1989 and 1992 were studied. Thirty-five children had a posterior fossa tumor, and 18 of these were medulloblastomas (Table 1). The treatment of these children consisted of surgery only (n = 12); surgery and chemotherapy (n = 6); and surgery, chemotherapy, and cranial irradiation (n = 23); 20 of those treated with cranial irradiation also received spinal irradiation. The me-

TABLE 1. Brain Tumor Diagnosis

	n
Posterior fossa tumors	**35**
Medulloblastoma	18
Pilocytic astrocytoma	11
Cerebellum (9)	
Brainstem (2)	
Ependymoma	3
Others	3
Choroid plexus papilloma (2)	
Pineocytoma (1)	
Supratentorial tumors	**6**
Anaplastic astrocytoma	4
Primary neuroectodermal tumor	1
Oligodendroglioma	1
Total	**41**

dian craniospinal irradiation dose was 36 Gy (30 to 54 Gy) in 20 fractions (15 to 30 fractions) for 45 days (28 to 60 days). For those children with medulloblastomas, the cranial radiation was directed to the whole brain and, for all other tumors, was localized to the area of the tumor. All 18 children with medulloblastomas and 3 with posterior fossa ependymomas received a posterior fossa boost of radiation. The median dose was 18 Gy (14 to 24 Gy) in 10 fractions (8 to 12 fractions).

All children were seen within 1 year of diagnosis by the same pediatric endocrinologist and annually thereafter. At each endocrine visit, height was measured using a wall-mounted stadiometer and pubertal status assessed clinically by the method of Tanner.[15] In addition, the serum thyroid-stimulating hormone (TSH) and Free T4 were measured and a radiograph of both hands taken to assess bone age. This was evaluated using the Greulich and Pyle method.[16] Height velocity (HV) was calculated annually from completion of brain tumor treatment. Those patients with an annual HV below the 25th percentile for age at ≥2 years from completion of radiation and chemotherapy had provocative GH testing with insulin-induced hypoglycemia, arginine, L-dopa-propranolol, or exercise. The diagnosis of GH deficiency was made based on a subnormal growth velocity (<25th percentile) and biochemical data, that is, serum GH value <8 μg/L on one physiologic and two pharmacologic tests. Synthetic GH therapy was initiated based on these criteria at ≥2 years from completion of brain tumor therapy. Provocative GH testing was not conducted before 2 years from completion of brain tumor therapy because the recurrence rate for many tumors decreases significantly at 2 years from completion of therapy, and we were not prepared to initiate GH therapy before that time.[7,17]

Statistical Analysis

Height was expressed as a standard deviation score (SDS) according to the method of Tanner and associates to compare heights at different ages and genders.[18] The height SDS at first assessment and at the end of the first and second years from completion of brain tumor therapy were calculated, as well as the HV in centimeters per year for both years. The results are expressed as mean ± SD. One child was excluded from the auxologic analysis because of a tumor recurrence. Two children with rapid growth associated with precocious puberty (ie, onset of breast development before age 8 years in girls and onset of testicular enlargement before age 9 years in boys), 2 girls with a bone age >12 years, and 2 boys with a bone age >14 years were excluded from the auxologic analysis because of limited growth potential. The 34 remaining children, 18 of whom received cranial irradiation, were prepubertal or Tanner stage II at 2 years from completion of therapy. The data at first endocrine assessment of the 23 children who received cranial irradiation were compared with data from a group of 8 children diagnosed before 1988 whose endocrine function was not monitored prospectively.

Comparisons of HV and height SDS were determined by using analysis of variance with subsequent multiple comparison testing. Multiple regression analysis was performed to determine correlation coefficients. Values of $P < .05$ were considered significant.

RESULTS

The median follow-up time for the total study group of 41 children was 5 years (4 to 8 years) from brain tumor diagnosis. Fourteen of the 34 children who were Tanner stage I or II at 2 years from completion of brain tumor therapy had confirmed GH deficiency on biochemical testing. The growth data are presented in Table 2 and Fig 1. There was no significant difference in height SDS between the two groups at first assessment (year 0) of growth (Table 2). The height SDS was significantly lower for the GH-deficient group compared with the non-GH-deficient group at the end of both years 1 and 2. The growth velocity in the GH-deficient group was significantly less than that in the non-GH-deficient group for both years 1 and 2 ($P < .002$ and $P < .0001$) The primary brain tumor diagnosis in those with GH deficiency was anaplastic astrocytoma (1), a primary neuroectodermal tumor (1), and medulloblastoma in the other 12 children. All 14 children with confirmed GH deficiency received cranial and spinal irradiation, and all but one had chemotherapy. Of the 20 children who were not GH-deficient, 6 received spinal irradiation. There was no difference in height SDS or HV between those who received spinal irradiation and those who did not.

Of the 41 children, 6 were diagnosed as having primary hypothyroidism, with TSH values ranging from 7.5 to 32.8 mIU/l (<5 mIU/L). Free T4 values were all within the normal range. The primary brain tumor diagnosis in 5 of these children was medulloblastoma, and all 6 received cranial and spinal irradiation and chemotherapy. Two children developed precocious puberty and were treated with a gonadotropin-releasing hormone analog. The 14 children with GH deficiency have been treated with synthetic GH, and the growth velocity during the first year on GH therapy ranged from 7.5 to 10.2 cm. To date, there have been no adverse effects of GH therapy, including brain tumor recurrence.

The growth velocity of the 12 children treated with surgery alone and the 6 children who were treated with chemotherapy after surgery was normal for both years 1 and 2 and, therefore, none of these individuals have undergone provocative GH testing. No other endocrine problems have been documented in this group.

The mean interval from diagnosis to first endocrine assessment for the study group was less than 1 year and >6 years (4 to 12 years) for the late-referred group (Table 3). For the study group, the mean height SDS at first assessment was significantly

TABLE 2. Height and HV

n	GH-Deficient 14	Non-GH-Deficient 20	*P*
Height SDS			
Y 0	−0.25 ± 1.16	−0.02 ± 0.73	NS
Y 1	−1.31 ± 1.15	−0.26 ± 0.95	$P < .01$
Y 2	−1.73 ± 1.09	−0.23 ± 0.74	$P < .0001$
HV cm/y			
Y 1	3.06 ± 1.19	5.29 ± 2.21	$P < .002$
Y 2	3.29 ± 1.14	5.48 ± 1.24	$P < .0001$

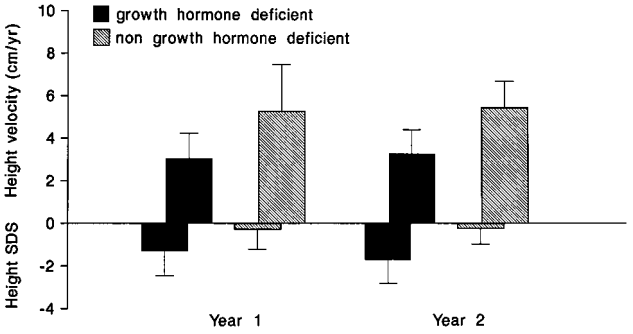

Fig 1. Height and HV in GH-deficient and non-GH-deficient children.

TABLE 3. Interval From Brain Tumor Diagnosis to Endocrine Assessment

	Prospective	Referred Late	
Patients with brain tumor treated with cranial irradiation	23	8	*P*
Interval to first endocrine assessment (y)	0.8 ± 0.2	6.6 ± 3.2	$P < .001$
Height SDS at first assessment	−0.6 ± 1.3	−2.9 ± 1.6	$P < .005$

closer to the mean height for age and sex than that for the group referred late ($P < .005$). The growth chart of one of the children in the study group is illustrated in Fig 2. This boy was diagnosed as having a medulloblastoma at the age of 4 years in 1991 and received standard therapy. His first endocrine assessment was 2 months after diagnosis, and he was followed prospectively. His growth velocity decelerated from the 75th percentile close to diagnosis to the 25th percentile 2 years from completion of brain tumor therapy. GH deficiency was confirmed at the age of 6.5 years, and he was started on GH therapy. His height subsequently accelerated to the 50th percentile, and he continues to grow well between the 25th and 50th percentiles, with a predicted height of 175 cm, which is 5 cm less than his target height. In contrast, Fig 3 illustrates the growth chart of a boy also diagnosed with a medulloblastoma at the age of 6 years in 1980. His first endocrine assessment was at the age of 11 years when his height was well below the 3rd percentile, with a height age of 7 years. He was diagnosed with GH deficiency and primary hypothyroidism and treated with GH and thyroid hormone replacement. At the age of 16 years, he reached a final height of 146 cm, which is well below his target height.

DISCUSSION

We found a significant incidence of GH deficiency in children treated with both cranial irradiation and chemotherapy for nonpituitary-related brain tumors. Fourteen of these 18 prepubertal or early pubertal children had confirmed GH deficiency. We did not detect GH deficiency in any individuals treated with only chemotherapy or cranial and/or spinal irradiation alone. Most of those children who received irradiation without chemotherapy and did not develop GH deficiency received radiation localized to the tumor area rather than to the whole brain, resulting in a lower radiation dose to the hypothalamic–pituitary area. However, the small numbers in the study did not permit analysis of the independent effects of chemotherapy or cranial irradiation. We found that linear growth appears to reflect GH status accurately in children with brain tumors. Those children confirmed subsequently as GH-deficient clearly grew more slowly from soon after brain tumor diagnosis. We did not test those children with a normal growth velocity and therefore did not confirm their GH status. However, because these children were growing normally, provocative GH testing would be neither necessary nor ethical in this group.

At this time, no adverse effects of GH therapy including recurrence of brain tumor have been observed, but initiation of GH therapy was delayed in all children until 2 years from completion of brain tumor therapy. Primary hypothyroidism was detected only in those children who received cranial and spinal irradiation. We did not conduct thyroid-releasing hormone testing to evaluate central hypothyroidism; however, the serum Free T4 assayed by a fully automated chemiluminescent method is minimally affected by protein binding abnormalities and provides an accurate measure of free thyroid hormone levels, which, if depressed, are reflective of central hypothyroidism. The serum Free T4 was not depressed below normal in any patient with a normal TSH.

It is well documented that children with brain tumors treated with cranial irradiation are at increased risk for endocrine dysfunction in particular GH deficiency.[19–21] Because most treatment regimes for brain tumors involve chemotherapy as well as cranial irradiation, the separate impact of chemotherapy on GH status has not been clear. However, recent studies also have implicated chemotherapy alone as being associated with an increased risk of GH deficiency.[13,22] In most studies, patients were evaluated years after the initial brain tumor diagnosis, whereas in our study, endocrine function, in particular growth, was monitored prospectively. It is evident that delayed diagnosis of GH deficiency and late initiation of GH therapy is likely to contribute to the decreased final height reported in survivors of childhood brain tumors. Short stature in childhood as well as reduced adult height may be associated with significant morbidity.[23] Assessment of GH status in children treated with cranial irradiation may be delayed until the height has decelerated below the 3rd percentile. Prospective monitoring of growth as conducted during our study facilitates early identification of the child with a subnormal growth velocity before the height has decelerated below the normal range. It may be valid to consider making the diagnosis of GH deficiency in this group based on auxologic data rather than on provocative GH testing, because their subnormal growth rate is clearly reflective of GH deficiency and significantly lower than the growth rate of those without GH deficiency. In addition, provocative GH testing may not reflect accurately GH status in this group. Cranial irradia-

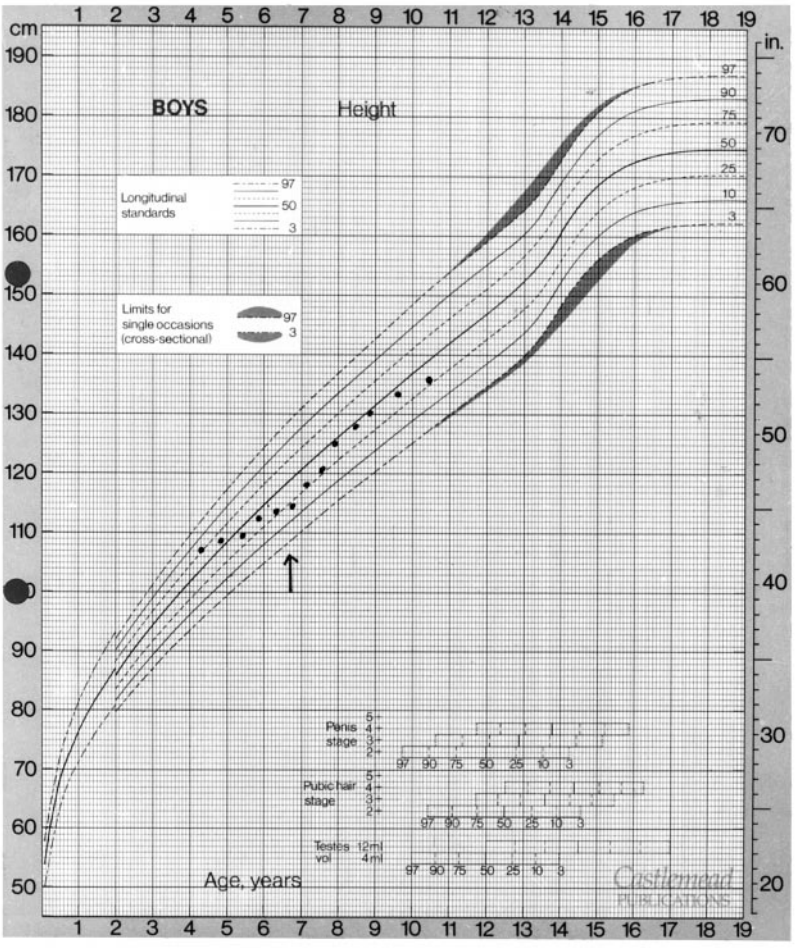

Fig 2. Growth chart: first endocrine assessment 2 months after brain tumor diagnosis.

tion probably affects the hypothalamus more than the pituitary, resulting in neurosecretory dysfunction, which may be associated with a normal GH response to provocative testing.

Timing of initiation of GH therapy impacts on final height. A prolonged untreated interval of GH deficiency is likely to be associated with significantly reduced final adult height. In our experience, those children whose growth was first evaluated >4 years after brain tumor diagnosis already were significantly short, whereas those children followed prospectively had heights close to the mean at their initial endocrine assessment. The average time interval from brain tumor diagnosis to initiation of GH therapy in the study group was 2.5 to 3 years. Others have reported an increased time interval from brain tumor diagnosis to initiation of GH therapy averaging 4 to 5 years.[24,25] Although GH therapy does not appear to affect the late relapse rate of brain tumors, it seems reasonable to delay initiating GH therapy until 2 years after completion of brain tumor therapy because the contribution of exogenous GH to relapse would be difficult to interpret.[26,27] One patient with a medulloblastoma in our study recurred during this 2-year period.

It is of note that 26% (6 of 23) of children who received cranial irradiation developed primary hypothyroidism. Five of these children had a medulloblastoma. The spinal irradiation or the posterior fossa radiation boost or the combination of the two may have affected the thyroid gland directly. These children all had chemotherapy as well as cranial and spinal irradiation, and there are data indicating that radiation plus chemotherapy is associated with a higher incidence of thyroid dysfunction than is radiation alone.[28] Because hypothyroidism may be associated with significant clinical disturbance, it is of value to diagnose early and initiate treatment, thus

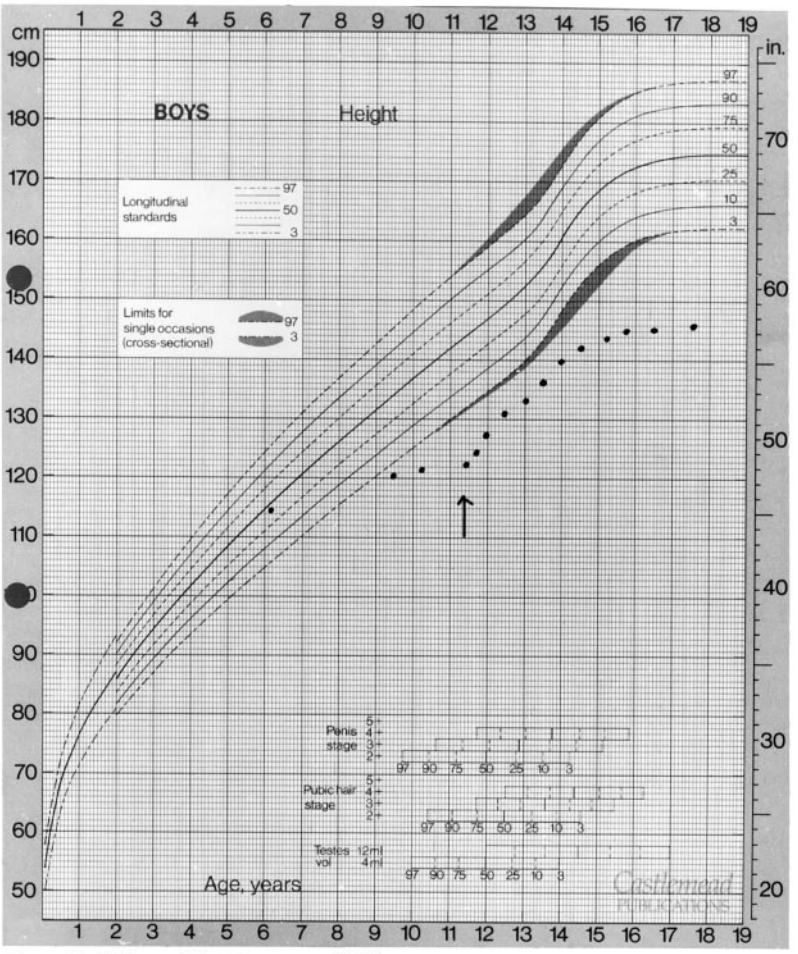

Fig 3. Growth chart: first endocrine assessment 5 years after brain tumor diagnosis.

minimizing symptomatology. In addition, the risk of thyroid carcinoma is increased when the thyroid gland is included in the radiation field.[28–30] It is possible that children treated for medulloblastomas also may be at long-term risk for development of thyroid carcinoma. Long-term endocrine monitoring is therefore essential.

In clinical practice, GH therapy usually is discontinued once growth is complete. However, adults with GH deficiency have been reported to have significant changes that may respond to administration of GH. These include abnormal body composition, altered lipid metabolism, increased cardiovascular disease, and reduced quality of life.[31–33] Although adults with GH deficiency are not offered replacement therapy routinely in North America, in some countries GH deficiency is a recognized indication for therapy. Recently, an increased mortality rate has been described in a large population of children with GH deficiency.[34] In view of the multiple endocrine risks for these patients and changing treatment patterns, it is clear that effective transfer to adult centers and long-term monitoring is important.

Because many of these patients were treated with both radiation and chemotherapy, it is not possible to assess their effects independently, although it appears that radiation therapy may be the more significant factor contributing to poor linear growth. In our study, we documented GH deficiency and primary hypothyroidism only in those children receiving cranial irradiation as well as chemotherapy. Recent data support the efficacy of chemotherapy alone in controlling progressive low-grade gliomas in young children.[35] An added advantage of this therapeutic approach is the possible minimization of long-term endocrine problems.

We conclude that there is a high incidence of GH deficiency and primary hypothyroidism after cranial

irradiation and chemotherapy for the treatment of nonpituitary-related brain tumors, particularly medulloblastomas. Linear growth appears to reflect GH status accurately in children with brain tumors, and it may be that provocative GH testing is unnecessary in this high-risk group. Therefore, rather than delaying intervention until growth failure is evident in children with nonpituitary-related brain tumors, we recommend routine prospective monitoring of growth with annual height measurements as well as serum TSH measurements. Prospective monitoring is relatively simple and not labor-intensive, and facilitates identification and treatment of GH deficiency that may improve final height in this group.

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