Growth hormone deficiency following radiation therapy of primary brain tumors in children

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The medical records of 123 patients treated for brain tumors at Children’s Hospital and Medical Center, Seattle, Washington, between 1985 and 1987 were reviewed. The endocrinological complications of radiation therapy and the effectiveness of growth hormone (GH) replacement therapy were assessed. These were the first 2 years after synthetic GH became available. The disease pathology was confirmed at craniotomy or biopsy in 108 patients. Ninety-five children completed radiation therapy and 65 of these were alive at the time of review; these 65 children represent the study population. The most common tumor types were medulloblastoma, craniopharyngioma, and ependymoma. Endocrine evaluation was initiated with changes in the patients’ growth velocity. Patient workup included skeletal x-ray films for determination of bone age, and analysis of thyroxin, thyroid-stimulating hormone, and somatomedin-C levels. Following L-dopa and clonidine stimulation, provocative studies of GH levels were performed.

Growth hormone failure and short stature were observed in 26 children, most commonly in the 2nd year after tumor treatment. Eight patients with GH failure were also hypothyroid. Hormone replacement therapy was initiated with recombinant GH, 0.05 mg/kg/day, and all children so treated showed an increase in height, with eight patients experiencing catch-up growth. There were no complications of therapy or tumor recurrence.

Studies of baseline bone age and somatomedin-C levels on completion of radiation therapy are recommended. Comprehensive endocrine studies should follow changes in the patients’ growth velocity. With early GH replacement, catch-up growth is possible and normal adult heights may be achieved.

Key Words • growth hormone • panhypopituitarism • radiation therapy

Endocrinological complications of cranial radiation therapy, including short stature and panhypopituitarism, have been recognized for many years.18 Comprehensive endocrinological studies have demonstrated radiation dose-dependent changes in pituitary and hypothalamic function. Growth hormone (GH) is the most sensitive component of the endocrine axis to the effects of cranial irradiation delivered for the treatment of hematological malignancies and primary brain tumors and before bone marrow transplantation.20 Prior to 1985, GH replacement required the use of postmortem pituitary preparations; complications associated with this treatment included documented cases of Creutzfeldt-Jakob disease.10,11 Recombinant biosynthetic GH became available in late 1985 and has facilitated widespread hormone replacement in cases of secondary and idiopathic deficiencies.

The overall mortality rate in children with primary brain tumors has steadily decreased. The survival rate in medulloblastoma 5 and 10 years after resection and radiation therapy is now approaching 60% to 70%.1,12 As the prognosis for pediatric brain tumors improves, and more aggressive irradiation and adjuvant chemotherapy protocols are utilized, greater attention must be focused upon the long-term sequelae of treatment.

We have reviewed the medical records of brain-tumor patients treated between 1985 and 1987 at Children’s Hospital and Medical Center in Seattle, Washington. An assessment of the endocrinological complications of radiation therapy and effectiveness of GH replacement is presented.

Clinical Material and Methods

Between 1985 and 1987, 123 patients with brain tumors were referred to the Neuro-Oncology Service at Children’s Hospital and Medical Center for surgery and comprehensive adjuvant therapy. This type of patient is treated by a multidisciplinary team of pediatric neurosurgeons, hematologist-oncologists, radiation therapists, endocrinologists, neurologists, and nurses.
Patient Population

In 108 patients, tumor histology was confirmed at craniotomy or by computerized tomography (CT)-assisted stereotactic biopsy. A presumptive diagnosis of intrinsic brain-stem and optic pathway tumors followed magnetic resonance (MR) imaging or CT scanning in 15 patients. The families of five children refused all treatments offered to them. Chemotherapy was the only treatment used in six children less than 18 months of age, who were too young to undergo radiation therapy, and in two older children with optic pathway tumors. In 17 patients, no additional therapy was given after complete tumor resection. Radiation therapy was completed in 95 children with 40 patients receiving craniospinal field dosage. The average whole-brain exposure was 3750 cGy with a posterior fossa boost to 5200 cGy. The average spinal axis dose was 3500 cGy. Thirty-one patients had supratentorial fields averaging 5100 cGy, whereas focal infratentorial radiation portals averaging 5300 cGy were utilized in 24 patients.

The overall survival rate was 78% in our series and 96 patients were alive at the time of this review. The 65 patients who received radiation therapy (68% of the survivors) represent our study population. The tumor histology in these patients is outlined in Fig. 1. Patient age at the time of diagnosis ranged from 6 months to 18 years. There were 37 boys and 28 girls for a male:female ratio of 1.34:1.

Postoperative Evaluation

Postoperative follow-up examination for each child included serial CT or MR studies and a comprehensive team evaluation every 3 months. Patient height in both the standing and sitting positions and weight were measured on each clinic visit and recorded on standard growth charts. Endocrinological evaluation and laboratory studies were initiated when height measurements revealed a growth velocity less than 4 cm/yr in patients over 4 years of age. In younger children, endocrinological evaluation followed any drop in their height percentile.

Endocrinological studies included x-ray films for determination of bone age and laboratory tests for triiodothyronine, thyroxine, thyroid-stimulating hormone (TSH), somatomedin-C, and prolactin levels. Provocative tests for GH levels were performed when somatomedin-C was depressed below normal age-specific values. Serial assay of GH followed provocative oral stimulation with l-dopa, 10 mg/kg body weight at 30, 60, and 90 minutes, and clonidine, 0.15 mg/sq m (up to a maximum dose of 0.1 mg) at 60, 90, and 120 minutes. Other studies included serial TSH and prolactin assays following intravenous stimulation with thyrotropin-releasing hormone (TRH, 7.5 ìg/kg) and adrenalin axis evaluation after administration of oral metyrapone (30 mg/kg).

Our criteria for GH replacement included the following: 1) a fall off in stature and growth velocity; 2) delayed bone age (determined by skeletal x-ray films); 3) depressed levels of somatomedin-C; and 4) failure of provocative hormone stimulation with GH values less than 10 ng/ml.

Replacement therapy was initiated with recombinant GH (Protropin),* administered as three subcutaneous injections/wk of 0.1 mg/kg each, or daily injections of 0.05 mg/kg. Dosage was increased in relation to current body weight at the time of follow-up examination every 3 months. Serial thyroid studies were obtained on a similar schedule. When hypothyroidism was confirmed, oral l-thyroxine replacement of 0.05 to 0.10 mg was initiated. Patients on GH and/or thyroid hormone replacement underwent endocrinological evaluations every 3 months. The studies included sitting and standing heights, weight, inspection of injection sites, gonad measurement, and Tanner stage examination. Skeletal x-ray films were repeated every 6 to 12 months for analysis of bone age.

* Protropin manufactured by Genentech, Inc., South San Francisco, California.
Results

Clinical Characteristics

Twenty-six (40%) of the 65 patients who received radiation therapy developed GH failure (Fig. 1). These included 18 boys and eight girls; the mean age at tumor diagnosis was 5.5 years in boys and 7 years in girls (Fig. 2). The mean interval from tumor diagnosis until confirmation of GH failure was 26 months in boys and 17 months in girls (Fig. 3). At that time, the height of each child was 1 standard deviation (SD) below initial stature and 18 children had fallen below 2 SD's. The oldest patient with short stature and GH deficiency was 13 years of age when his tumor was diagnosed. One male and one female patient had entered puberty by the time of their tumor diagnosis.

Seventeen children completed craniospinal radiation therapy and five patients had focal supratentorial fields. The remaining four children received focal infratentorial radiotherapy. Chemotherapy was administered in 15 patients (Table 1); GH failure was twice as common after focal infratentorial and craniospinal radiation therapy when adjuvant chemotherapy was involved (Fig. 4).

Endocrinological Studies

The bone age of each patient was delayed by a mean of 18 months (range 6 to 46 months). After confirmation of normal thyroid function, somatomedin-C was found to be depressed below normal age-specific values in 24 patients. Twelve patients had flat GH responses to provocation with levels of less than 2.0 ng/ml, while peak hormone levels in the other 14 children were 8.6 ng/ml after clonidine and 7.2 ng/ml after l-dopa stimulation (Table 1).

Prolactin secretion was studied in five children and found to be normal in all; two of these patients had GH deficiency and three had normal GH axis. Eight patients with GH deficiency also developed hypothyroidism at a mean interval of 26 months after tumor diagnosis. Following surgery and radiation therapy, panhypopituitarism was present in three patients with craniopharyngioma and in two patients with suprasellar germinoma. Each patient developed GH deficiency which had not been present at the time of tumor diagnosis, and each was hypothyroid. Diabetes insipidus was found in one patient at the time of diagnosis of a suprasellar germinoma, and was discovered in three other patients following subfrontal craniopharyngioma resection.

Hormone Replacement

Twenty-five patients were started on GH therapy; hormone replacement was refused by the family of one child. Sixteen children received three injections/wk and the other nine were given daily hormone replacement. All patients with craniopharyngioma and germinoma required prednisone treatment; 0.15 to 0.30 cc intranasal desmopressin (DDAVP) was required for control of diabetes insipidus in four patients.

After the start of GH therapy, 12 patients had limited growth with a height velocity of less than 0.4 cm/mo, whereas five patients had normal growth parallel to the percentile curve to which their stature had fallen. Eight patients demonstrated catch-up growth with improvement in their height percentile and a growth velocity ranging from 0.8 to 1.1 cm/mo. Superior growth velocity of 0.9 to 1.1 cm/mo was achieved in three of eight patients after they began thyroid replacement. Two of 25 patients started hormone therapy within 1 year of completing radiation therapy. Their growth velocities exceeded 1.0 cm/mo and catch-up growth to their original height percentile was completed in 18 months. The success of GH replacement was independent of sex, portals of radiation therapy, chemotherapy, and onset of puberty.

Patients with medulloblastoma reached the highest growth velocities. The lowest growth velocities were

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found in patients receiving prednisone. Advancement of bone age occurred in each child receiving GH replacement with a mean of 9 months for each year of therapy. The mean growth velocity in children receiving daily GH injections (0.7 cm/mo) was greater than for those who had three injections per week (0.42 cm/mo).

Three male patients had normal onset of puberty after radiation therapy and no precocious sexual maturation was observed. There were no complications of GH replacement. At the time of this analysis, no tumor recurrence or progression of residual disease has developed in patients receiving GH treatment.

Discussion

Review of the Literature

Growth hormone deficiency following radiation therapy for brain tumors in children has been documented since the 1970’s. Shalet, et al., demonstrated a 50% incidence of GH failure in 14 patients who underwent endocrinological studies. The two most common tumors in their patient series were medulloblastoma and ependymoma. Brown, et al., investigated 13 patients after surgery and craniospinal radiation for medulloblastoma. Four of their patients received chemotherapy. Poor growth was confirmed in all 13 children, and partial or complete GH deficiency was documented in four boys and five girls. All of their patients were studied at least 16 months after radiation therapy was completed.

Park, et al., found patient height fell below the third percentile in 47% of their surviving patients treated for medulloblastoma. Comprehensive endocrine studies confirmed panhypopituitarism in 11 patients and hypothyroidism and GH deficiency in four. Bloom, et al., reported GH deficiency in 65% of their medulloblastoma patients with long-term survival. In another study, Lannering, et al., observed a decreased GH secretion level in 16 patients; 10 of their children received GH replacement and had a mean growth velocity of 8.3 cm/yr without acceleration of bone age. Only two patients experienced catch-up growth. Recently, Shalet, et al., evaluated the effectiveness of GH therapy after completion of cranial radiation in seven patients with brain tumors; two of these patients were hypothyroid. Of the seven children, 43% had final height above the third percentile and growth velocity was 5.6 to 7.4 cm/yr during hormone treatment.

Table 1: Summary of therapy data and results of endocrinological studies in 26 patients with GH deficiency

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Tumor Histology</th>
<th>Chemo-therapy</th>
<th>Somato-medin-C Level (U/ml)</th>
<th>Clonidine-Stimulated Peak GH Level (ng/ml)</th>
<th>L-Dopa-Stimulated Peak GH Level (ng/ml)</th>
<th>Peak Growth Velocity During GH Therapy (cm/mo)</th>
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<tr>
<td>1</td>
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<td>VINC/CCNU</td>
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<td>1.6</td>
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<td>0.50</td>
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<td>1.9</td>
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<td>0.90</td>
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<td>0.18</td>
<td>1.5</td>
<td>1.0</td>
<td>0.95</td>
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*GH = growth hormone; VINC/CCNU = vincristine/lomustine; 8-1 = protocol utilizing methylprednisolone, vincristine, CCNU, procarbazine, hydroxyurea, cyclophosphamide or imidazole carboxamide, cisplatin, and cytosine arabinoside.
Growth hormone deficiency following irradiation

Analysis of Present Results

In our patients, we demonstrated GH failure in 40% of tumor survivors following radiation therapy. The most common tumor types associated with GH failure were medulloblastoma and ependymoma, confirming the previous findings of Shalet et al., Duffner, et al. The male predominance among children with GH deficiency exceeded the male/female ratio in the overall surviving population and that reported in other series. We conclude that this striking result is most likely related to the lower mean age of males at the time of tumor diagnosis. Eight of 18 males were younger than 4 years of age when radiation therapy was initiated.

Our study confirms that somatomedin-C is a useful laboratory screen for GH deficiency with only two false negative values resulting. Somatomedin-C is a polypeptide with insulin-like properties, synthesized by liver and chondrocytes. Serum levels will be depressed by GH deficiency, decreased caloric intake, steroid use, and thyroid deficiency. The reliability of somatomedin-C screening may therefore be limited during adjuvant chemotherapy, and normal thyroid function must be present for accurate results.

All patients in our series received hypothalamic-pituitary radiation doses exceeding 2700 cGy. Shalet, et al., demonstrated a threshold exposure of 2500 to 3000 cGy as a prerequisite for the development of an endocrinopathy. Sanders et al., reported a 43% incidence of GH failure in 25 patients who received 1000 to 1700 cGy of total body irradiation prior to bone marrow transplantation, suggesting that the endocrine axis sensitivity is even lower than previously thought.

Growth hormone deficiency was rare following supratentorial radiation therapy for hypothalamic and parasellar tumors, despite a restricted radiation field encompassing the hypothalamic-pituitary axis. Endocrine failure is common in patients with craniopharyngioma; many of these patients present with short stature or develop panhypopituitarism following tumor treatment. Three of eight patients in our series with craniopharyngioma had GH failure after subtotal tumor resection and radiation therapy. The other five patients were treated with surgery only, and GH replacement was required in four of these cases. We conclude that direct injury to the hypothalamic or pituitary stalk by the tumor or the effects of resection is the most likely etiology of endocrine failure, rather than the direct effects of radiation therapy.

Growth hormone failure was most commonly seen following irradiation to the posterior fossa and craniospinal fields, independent of tumor histology. A full dose to these fields encompasses the posterior hypothalamus, suggesting that the hypothalamus has a greater radiation vulnerability than the pituitary gland. Prolactin levels are frequently elevated and normal pituitary secretion may follow stimulation with hypothalamic trophic hormones such as GH-releasing hormone and TRH.

The time of GH deficiency occurrence after radiation therapy remains uncertain. A prospective study of 14 patients conducted by Shalet, et al., demonstrated GH failure in six patients at 1 year following radiation therapy; failure developed during the 2nd year in an additional patient. Brauner, et al., found three of seven patients had GH deficiency when studied 2 years after radiation therapy. In our series, the mean interval after tumor diagnosis was 17 months in male patients and 26 months in female patients, and GH deficiency in each patient coincided with an apparent drop in growth velocity. We are now beginning prospective endocrinological evaluations at the conclusion of radiation therapy to determine the exact onset of hormone deficiency in each patient.

The success of hormone replacement in our series was influenced by early treatment with recombinant GH and thyroid hormone replacement. Two patients began GH replacement within 1 year of completing radiation therapy and caught up to their original height percentile within 18 months. During the period of our analysis, no patient receiving GH replacement developed tumor recurrence or progression of residual disease, confirming the conclusion of Clayton, et al., that recombinant GH replacement therapy did not contribute to late tumor relapse of leukemias, medulloblastomas, or gliomas.

The growth velocity associated with daily hormone replacement was superior to that attained with three injections per week and we no longer offer the latter schedule. Similar advantages of daily injection schedules and early GH replacement were noted by Cowell, et al., Nearly one-third of our patients with GH failure were also hypothyroid, noted at a mean interval of 6 months following diagnosis of GH deficiency. Three of eight patients who received l-thyroxine replacement demonstrated accelerated growth velocity after beginning thyroid therapy. We conclude that careful monitoring and maintenance of normal thyroid function is necessary to achieve the maximum effectiveness of GH replacement. New craniospinal radiation protocols with decreased spinal and thyroid dosage should limit thyroid gland exposure and injury.

Effects of Chemotherapy

A recent study by Mulhern, et al., demonstrated decreased growth velocities in brain-tumor patients less than 2 years of age who received preradiation chemotherapy. The competence of GH secretion was not investigated by static or provocative tests. Clayton, et al., demonstrated that, in patients with leukemia, chemotherapy had an effect on growth lasting 2 years after treatment. Catch-up growth was then observed independent of any cranial irradiation. In our patients who only received postoperative chemotherapy, endocrine failure was not found.

In this study, chemotherapy had an enhancing effect on GH failure in patients receiving craniospinal and posterior fossa radiation therapy, which was not proto-
col-specific. The use of chemotherapy did not, however, limit the effectiveness of GH therapy. Further research is required in this area.

Conclusions

Growth hormone deficiency is a common sequela of therapy in patients with craniopharyngiomas and in nearly all survivors of posterior fossa tumors. However, endocrine failure is rare after comprehensive treatment of other tumors of the central nervous system. Careful follow-up studies of patients who receive radiation therapy should include serial measurements of height while sitting and standing and endocrinological evaluation following any change in growth velocity. We recommend baseline assessment of bone age and somatomedin-C levels at the completion of radiation therapy and serial studies during routine neuro-oncology follow-up examinations. Provocative GH studies should follow any change in growth velocity irrespective of the height percentile, advancing delay in bone age, and depression of somatomedin-C levels.

Catch-up growth may be achieved only with early recombinant GH replacement therapy, enabling more children to reach normal adult statures. The use of recombinant GH is safe at any age and it is not associated with tumor recurrence or progression of residual disease.

References


P. M. Kanev, et al.