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Growth and Endocrine Disorders Secondary to Cranial Irradiation

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ABSTRACT. External cranial radiation for the treatment of malignant diseases has become a frequent cause of growth hormone deficiency (GHD). The timing of occurrence and the frequency of GHD were related to the hypothalamic-pituitary radiation dose. Frequency varied from 50% in leukemia (2400 cGy) to 75% in face and neck tumors or medulloblastoma (2500–4500 cGy) and up to 100% in optic glioma (>4500 cGy). The significantly more severe growth deficit in patients with GHD given higher radiation doses suggests different levels of residual GH secretion according to radiation dosage. The minimum harmful radiation dose is probably close to 1800–2000 cGy. Our data show that stimulation tests remain a useful means of defining GHD and predicting growth. A fair agreement between GH secretion and growth was found in most cases, regardless of the radiation dose. The only exception was a group of leukemic children (2400 cGy) who achieved normal prepubertal growth despite a low GH response. The 24-h spontaneous plasma GH profiles and IGF-I measurements may add information if growth is retarded despite a normal GH response. We showed that growth retardation occurring after some schedules of total body irradiation was not due to GH deficiency but rather to radiation-induced skeletal lesions. Early or true precocious puberty, generally associated with GHD, was another cause of height loss. As the role of GH deficiency in the final height reduction was demonstrated in all groups of patients after cranial radiation, we suggest that hGH therapy should be considered in any child with proven GH deficiency and significant growth retardation after such radiation. (*Pediatr Res* 25: 561–567, 1989)

Abbreviations

GH, growth hormone
TBI, total body irradiation
GHSP, GH secretory profile
ALL, acute lymphoblastic leukemia
GHRH, GH releasing hormone
TSH, thyroid-stimulating hormone
AIST, arginine-insulin stimulation test

External cranial irradiation has proven to be a major tool in the treatment of various malignant diseases. Many treatment protocols incorporate cranial irradiation; these protocols differ according to the causal disease. High radiation doses are used to treat brain tumors such as optic gliomas, ependymomas, medulloblastomas, and face and neck malignant tumors such as nasopharyngeal sarcomas or retinoblastomas. The protocols used for more than a decade to treat acute lymphoblastic leukemia (ALL) involve lower radiation doses. The newer technique of bone marrow transplantation preconditionning by TBI was first applied to leukemic children but has now extended to nonmalignant conditions, including hematologic, metabolic, and immunologic disorders.

Although these therapies have significantly improved the survival rate in a large number of children, the growth retardation resulting from radiotherapy has become a matter of concern. All cranial radiation protocols included the hypothalamic-pituitary axis, and it has been clear, since the earliest studies (1–3), that such radiation impaired GH secretion. Other endocrine disorders have been described depending on the initial disease and the total radiation dose delivered to the hypothalamic-pituitary area (Table 1). Growth retardation is considered to be mainly due to GH deficiency, although other factors, including impaired skeletal growth and precocious puberty, may also have an impact on final height.

GROWTH HORMONE DEFICIENCY

Frequency. The first case of induced hypopituitarism and growth retardation in children after cranial radiation for a tumor distant from the hypothalamic-pituitary region was reported in 1966 (4), and was followed quickly by several other reports (5–12). It soon became apparent that irradiation of the hypothalamus and the pituitary gland resulted in a high incidence of GH deficiency and growth retardation. The frequency of GH deficiency was reported to vary according to the initial disease and the effective biologic dose of radiation reaching the hypothalamo-pituitary region. An inverse correlation was found between that dose and the plasma GH response to pharmacologic stimulation (3, 13). We have found that 56% of a group of children given 2400 cGrays (Gy or rad) as prophylactic irradiation for ALL had GH deficiency, with a GH peak response to the arginine-insulin stimulation test (AIST) less than 8 ng/ml (Table 1). Complete GH deficiency with two consecutive GH peak responses less than 5 ng/ml was observed in 30% of the same population. The GH response to AIST of eight children more recently treated with a radiation dose of 1800 cGy remained normal at least 4 y after irradiation (Fig. 1). This radiation schedule is presently more frequently used and deserves further evaluation. We also found normal GH secretion in another group of children treated for retinoblastoma when the radiation dose delivered to the pituitary region was less than 2000 cGy (14). The frequency of GH deficiency is much higher in children given cranial doses above 2400 cGy; we found a frequency of about 75% in children treated with up to 4500 cGy. All of a group of children irradiated for optic glioma with doses above 4500 cGy had GH deficiency (15). Thus, the total radiation dose is an important variable for the risk of pituitary dysfunction, as are the fractionation schedule

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Table 1. *Endocrine abnormalities after external cranial irradiation**

Etiology	Radiation cGy	Cases (*n*)	Percentage of cases with endocrine abnormality				
			GH peak (ng/ml)				
			<5	5–8	Thyroid†	ACTH	Puberty‡
Leukemia	1800 –2400	8	0	0	0	0	0
		86	30	22	2	0	3
Face and neck tumors	2500 –4500	56	46	22	35	7	16
Medulloblastoma	2500 –4500	59	52	24	47	8	20
Optic glioma	4500 –5500	39	77	23	46	3	40

* All patients were evaluated at least 4 y after irradiation.

† Includes high plasma TSH values when the neck had also been exposed to irradiation.

‡ Frequency evaluated in patients with pubertal age. We have not included chemotherapy or radiation induced primary gonadal failure.

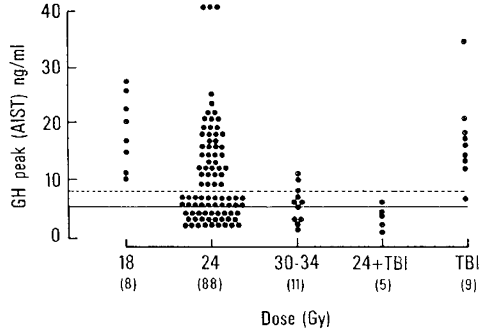

Fig. 1. GH responses to an AIST in 121 children treated for acute lymphoblastic leukemia according to their therapeutic protocol. They were studied at least 4 y after irradiation except for those given TBI, who were followed for shorter intervals. The TBI groups received 1000 cGy in a single exposure. The *dotted* (8 ng/ml) and the *solid* (5 ng/ml) *lines* represent the conventional values of the GH peak in partial and complete GH deficiency.

and the duration of the radiation therapy (16). In children treated with low range radiation doses the apparent frequency of GH deficiency may also depend on the type of stimulation testing: impairment of GH response to insulin-induced hypoglycemia but not to arginine stimulation was reported after 2400 cGy by some (17, 18) but not other investigators (19).

The age at time of cranial irradiation is another important risk factor for GH deficiency because it has been shown that younger children are more vulnerable than older ones (13, 20). Furthermore, according to two prospective studies of patients given radiation doses of more than 3000 cGy, children (21, 22) appeared to develop GH deficiency more rapidly than adults (23).

The issue of the harmful radiation dose is also quite critical in children given TBI as conditioning for bone marrow transplantation. Early reports indicated that complete or partial GH deficiency was a frequent complication (24, 25). However, GH deficiency would be expected in many of these children who had already received cranial irradiation with 1800 to 2900 cGy. Partial GH deficiency could be attributed to TBI itself in only a few cases (24). The effect of the radiation dose in TBI was further evaluated by comparing different radiation protocols. We observed only one child of the 25 with a low GH response to AIST within 1½ and 7 y after irradiation with up to 1000 cGy given in a single exposure, or 1200 cGy given as fractionated doses (26). We concluded that the radiation doses presently used as conditioning for bone marrow transplantation did not impair GH secretion.

The timing of occurrence of GH deficiency also is related to the radiation dose. Deficiencies may appear during the first year after radiation in patients irradiated with doses above 4500 cGy (15, 22) and most of these children were GH deficient within 2 or 3 y. A prospective study of patients given 3100–4200 cGy doses for medulloblastoma, revealed that the first significant decrease in GH response to stimulation occurred at the 12-mo evaluation, and 60% of the cases had GH deficiency at the 24-mo follow-up (21). In our experience with a group of patients irradiated for brain tumors, GH deficiency almost always appears within 5 y. It should be added that no child has spontaneously recovered from GH deficiency. An early transient reduction in nocturnal GH secretion after prophylactic cranial radiation with 2000–2400 cGy has been reported for a small number of patients (27).

Diagnosis. Most of the reported data on GH secretion in irradiated children have been based on the GH response to stimulation tests. Another approach to diagnosis of GH deficiency is the 24 hour spontaneous plasma GHSP on the assumption that such a diurnal pattern provides a better diagnostic tool of GH deficiency (28). A low GHSP has been observed in leukemic patients given prophylactic cranial radiation treatment (29) and in experimental studies on irradiated monkeys (30). However, the relative diagnostic value of an abnormal GHSP as compared with stimulated levels of GH remains controversial according to a recent study in normal short prepubertal children (31). Using the AIST we found that only 56% of a group of 86 prepubertal children irradiated with 2400 cGy had a low GH response (32) (Fig. 1). In that group a normal GH response to stimulation was associated with normal or minimally impaired growth before puberty. Moëll *et al.* (33), in contrast, have observed GHSP to be substantially blunted in all cases of a group of 13 girls irradiated for ALL and studied before or during puberty.

The GH data for children who have been irradiated with doses in excess of 2400 cGy probably are easier to interpret. We found that the spontaneous GH night peaks and peak responses to AIST of a group of 34 prepubertal children were significantly correlated (Fig. 2). Only five children had reduced spontaneous peaks despite normal responses to stimulation (34). Similarly in another study, all children with a blunted GH response to insulin-induced hypoglycemia were found to have a reduced GHSP (35). Thus, pharmacologic tests of GH secretion remain a useful means of obtaining biochemical evidence of traditionally defined GH deficiency in these patients, and to predict growth retarda-

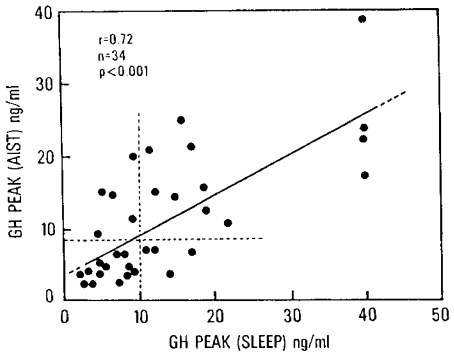

Fig. 2. Comparison between the GH response to an AIST and the spontaneous night peak GH values in 34 children given cranial radiation doses of 3200 to 4000 cGy (34). They were studied at least 2 y after irradiation. The *dotted lines* represent the conventional lower limit of normal in prepubertal children for each test. Reproduced with permission (34).

tion. It has not been shown that GHSP is a more reliable technique to identify children at risk for growth retardation after cranial irradiation.

Plasma IGF-I values might be another useful parameter for evaluating GH secretion after cranial radiation. The plasma IGF-I values of patients irradiated with 3100 to 4200 cGy were in agreement with the GH response to provocative tests (21). We performed a similar comparison 4 y or more after a 2400 cGy irradiation for ALL. The IGF-I values in this group tended to be at the lower limit of the normal range for age before puberty and more severely decreased during puberty, irrespective of the GH response to AIST (Fig. 3). A similar trend for low IGF-I was reported in one recent study (36) but not found in another (33). From our data, it is tempting to suggest that the low IGF-I values found in the leukemic patients reflected a decreased GH secretion before and during puberty. However, the cytostatic chemotherapy may have played a role in reducing the circulating IGF-I concentration: this possibility is currently being investigated.

Possible mechanisms. Reduced GH secretion has been considered to be the result of GHRH deficiency due to damage to the hypothalamus. Earlier experimental studies in rats and monkeys provided pathologic evidence that the hypothalamus and higher neural centers were more radiosensitive than the pituitary gland (37, 38). However GHRH stimulation of GH production after cranial irradiation has produced results, which varied with the radiation dose, time interval since radiation and the etiology of the underlying disease (39–41). All the patients irradiated with high doses (5000 cGy or more) had a very low response to GHRH, whereas children treated with 2400 cGy were still able to secrete GH in response to GHRH, although the response was lower than that of short-stature control children (33, 42). These data provide evidence for both pituitary and hypothalamic damage. Other evidence for hypothalamic damage includes the observations that 1) plasma prolactin levels may be elevated (43), *2*) the rise in TSH after thyrotropin-releasing hormone stimulation is elevated and delayed, *3*) adrenocortical function is subnormal although the corticotropin response to corticotropin releasing factor is normal (44), *4*) there is a discrepancy between GH secretion responses to insulin and arginine (see above), and *5*) physiologic GH secretion is severely blunted despite a normal GH response to arginine and L-dopa in irradiated monkeys (30) and in some patients (29). The positive growth response to long-term GHRH 1-29 therapy also is consistent with a predominant hypothalamic lesion (45). However, a pituitary lesion cannot be excluded by the GHRH stimulation test as a single pulse cannot demonstrate the ability of pituitary cells to produce new GH. Also there is a negative relationship between the GHRH-stimulated GH response and the time after radiotherapy, which may indicate late pituitary failure.

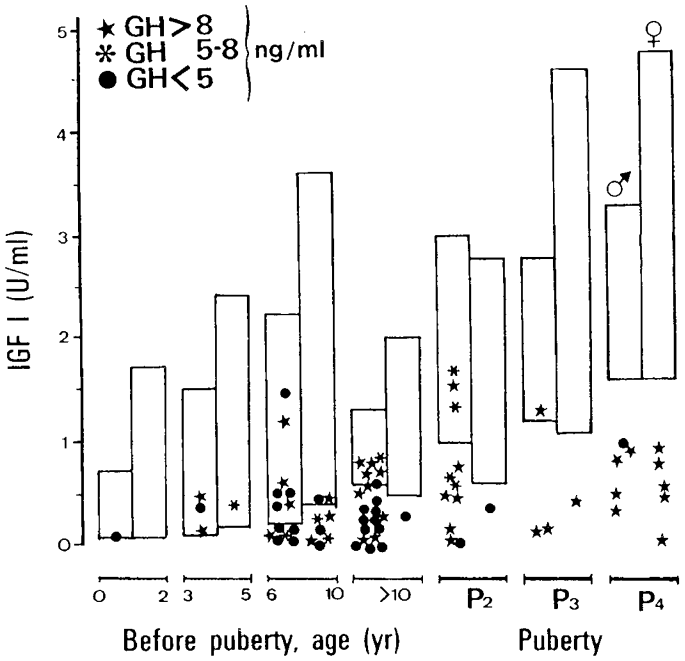

Fig. 3. Plasma IGF I (Sm-C) values in 74 children prophylactic 2400 cGy of cranial irradiation for acute lymphoblastic leukemia (*stars, asterisks* and *dots*). IGF I measurements were made in unextracted plasma samples as previously published (21). GH peak responses were obtained after an arginine-insulin stimulation test. The *open bars* show the range of values for age in normal children.

PUBERTAL DEVELOPMENT

Cranial radiation may alter gonadotropin secretion in different and opposite ways. It may produce gonadotropin deficiency with a loss or pertubation of pubertal development (43, 46, 49) or may cause precocious puberty (50). Hyperprolactinemia also may alter normal reproductive physiology at a later age (43). The risk of gonadotropin deficiency also depends on the radiation dose. Only five of 45 children treated with 2500–5000 cGy doses before or during puberty showed a complete gonadotropin deficiency at pubertal age, and two children presented evidence of partial gonadotropin deficiency. Documented gonadotropin deficiency usually was associated with GH deficiency (43, 46, 47). Until more extended follow-up studies are performed, the true frequency of hypogonadism in these children may be underestimated.

The LH and FSH responses to LHRH in children treated with 2000–2500 cGy for ALL were found to be normal (51). These data are consistent with the normal pubertal progression observed in most of these girls. Those few exceptions that occurred could be accounted for by chronic illness or wt loss (48). Only hypergonadotropic hypogonadism was reported in the group of children treated with TBI, indicating the lack of hypothalamic and pituitary failure (52). Elevated plasma prolactin levels have been reported in adults given high doses of cranial irradiation (43, 46). But, similar changes have been infrequent in children or adolescents (47, 48). True precocious puberty initially was reported in children given high radiation doses (more than 2500 cGy) for brain tumors (50). We have now extended this group to 11 children, three boys and eight girls. Three of them had received 2400 cGy as prophylactic irradiation for ALL. Precocious puberty was associated with GH deficiency in all but two children. Premature puberty also occurred in children treated with radiation doses as low as 1800 cGy (53). Other than overt true precocious puberty, there also is a trend toward an earlier onset of puberty and first menses in girls (51). Premature activation of puberty may indicate a primary hypothalamic defect which would be in agreement with the suppressive effect of

luteinizing hormone-releasing hormone analog treatment in these cases.

OTHER ENDOCRINE DISORDERS

Other anterior pituitary endocrine functions are much less frequently impaired than GH secretion, and multiple endocrine deficiencies are more prevalent in patients who have received high radiation doses (Table 1). Interestingly, diabetes insipidus has not been reported after cranial irradiation. Hypothyroidism with low serum thyroxin and low TSH levels is quite infrequent. In such a patient a lack of TSH response to thyroid-releasing hormone would be due to pituitary failure, whereas a delayed response is more compatible with a primary hypothalamic lesion. However, very few of the patients presenting with these changes are hypothyroid. The elevated basal TSH seen in some patients with medulloblastoma or face and neck tumors is due to primary hypothyroidism secondary to direct irradiation of the thyroid (54). Corticotropin deficiency with clinical symptoms also is a rare complication. Almost all of the children we have investigated had a normal cortisol response to insulin-induced hypoglycemia and it appears that only a few patients among those irradiated with high cranial doses required hydrocortisone replacement therapy.

GROWTH AFTER CRANIAL RADIATION

The effect of cranial radiation on growth has been recently reviewed (2, 3). Most studies have attempted to correlate growth with GH secretion, and there is fair agreement between the two in children given high radiation doses. The problem is more complex in children treated with low doses of radiation; these children may show moderate growth retardation, but only a few are really at risk for short stature. Growth also involves factors unrelated to GH secretion. Spinal irradiation in children with medulloblastoma impairs growth as does diffuse cartilage plate exposure during TBI.

Growth after high-dose cranial radiation. Radiation treatment for brain or head and neck tumors, which results in hypothalamic-pituitary radiation doses in excess of 3000 cGy, will reduce final height in most children (41). Most of these patients develop GH deficiency and, as discussed, the time of onset of the GH deficiency will vary. Also the time interval between irradiation and the onset of growth deficiency varies. In a prospective study, we found a minimal but significant decrease in height after 2 y with a mean loss of 0.4 height SD; individual values ranged from +0.4 to −1.2 SD. As 60% of the children had developed GH deficiency by that time it was concluded that GH deficiency remained largely asymptomatic during that early post irradiation interval (21). The mean height loss came close to 1.1 SD when the prepubertal follow-up was extended to 7 y. This resulted in an average final height loss of 1.6 SD in patients who had not been treated with exogenous hGH. Patients with optic glioma given even higher radiation doses (4500 cGy or more), developed growth retardation more rapidly and a mean height loss of 1.1 SD was observed 2 y after therapy. A total of 100% of these children manifested GH deficiency at that time. In children who had received additional spinal irradiation, as for the treatment of medulloblastoma, growth was more severely impaired (21).

Growth after low dose cranial radiation. Low radiation doses (ranging from 1800–2400 cGy) are prescribed for children with ALL as prophylactic therapy for CNS recurrence. The reports on the occurrence of growth retardation in these patients are conflicting and the issue has probably been confused by the difficulty in sorting out the influence of many factors, such as age at irradiation, pubertal status during the evaluation of growth, type of chemotherapy, and perhaps duration and severity of the initial disease. Furthermore, some of the reported differences may have been due to the heterogeneity of the patient population in terms of their total cranial radiation dose and fractionation schedule. The long-term effects of a total radiation dose of 2400 cGy have been most comprehensively investigated. A moderate height reduction occurred during the first 2 y after diagnosis, followed, after completion of chemotherapy, by a slight catch-up growth (55). Thereafter, either a normal growth rate (55) or a persistent growth retardation (19) were observed. The mean height loss was close to 1 SD after a 10-y follow-up. This mean height loss, as estimated mostly in prepubertal patients, results from a wide range of individual height losses.

As growth hormone deficiency remains the prime candidate for etiology of the growth retardation, we investigated the significance of GH responses to stimulation in relation to prepubertal growth. The growth of 38 children was followed over a 4-y prepubertal period, after completion of their chemotherapy (Fig. 4). Those who had a normal GH response ($n = 14$) had all maintained a normal growth rate. Therefore the response of GH to AIST appears to provide reliable information for predicting growth in normal responders. In contrast, the growth patterns of the children who were low responders (GH peak less than 5 ng/ml) varied greatly. One group ($n = 13$), including children who had lost 1 SD or more in height after therapy, experienced a mean height loss of 1.5 SD after 4 y. In contrast, 11 patients maintained a normal growth rate, and therefore did not differ in this respect from the normal GH responders.

It was somewhat surprising, as already mentioned (62), that so many children remained asymptomatic. This paradoxical growth was observed only in patients treated with low radiation doses. We therefore extended our study and compared the prepubertal height changes of this group (treated with 2400 cGy) with the heights of GH-deficient patients given higher radiation doses. As shown in Figure 5 the height loss of patients treated for face and neck tumors and for optic gliomas was significantly more severe than in the leukemic group (63). These data suggest that despite a similarly low GH response to AIST children with low dose cranial radiation had varying levels of residual GH secretion and some of these children had adequate GH secretion to maintain normal height velocity.

Role of puberty. The pubertal growth of irradiated children has been less well documented. Most of the data have been obtained by comparing the figures for irradiated children with the prepubertal and final heights of untreated patients. It seems that growth retardation during puberty accounts for a total final height loss of 0.5 to 1 SD in leukemic children (64), and probably slightly more in other patients if they are GH deficient. Although not demonstrated, it is likely that the height deficit during puberty would be aggravated by the severity of GH deficiency. This issue is quite critical in GH-deficient patients presenting a true precocious puberty. They experience accelerated bone maturation that is not accompanied by an appropriate height gain and may end up with severely reduced final height (50). As a consequence of these rapid changes, all irradiated children should be monitored for their bone age progression and for signs of early puberty.

Other factors influencing growth. Many of the patients given cranial radiation receive other treatment as part of their initial treatment protocols. They are therefore exposed to additional factors which may interfere with the growth response to GH replacement therapy. The growth retardation due to spinal irradiation involving radiation doses above 2000 cGy has been well documented in children suffering from medulloblastoma. An effect on sitting height, independent of GH deficiency and resulting in very short trunk length, has been observed (65–67). Spinal irradiation accounted for most of the growth retardation observed in the 2 y after irradiation with a mean height loss of 1.3 SD as compared to only 0.3 SD in the cranial irradiated children (21). We estimated that a final height loss of 1.4 SD could be attributed to the lack of spinal growth. Spinal growth was more impaired if the patients were less than 6 y old when irradiated (68).

Some patients given TBI also are at risk for growth retardation unrelated to GH deficiency (26). Growth can be impaired due

to diffuse radiation-induced skeletal lesions; patients given a single 1000 cGy radiation dose had retarded growth despite their normal GH secretion. A more extensive evaluation of growth after TBI currently is under way to assess the impact of different radiotherapy schedules on growth and pituitary function. Chemotherapy, as used in leukemic patients not given radiotherapy, has been reported to allow normal growth (57, 58, 69). However, there is some question as to the adverse effect on growth of more recent intensive chemotherapy regimens (19, 55). They may have independent effects on growth and eventually play a role in the lack of sufficient catch-up growth observed in some leukemic patient. For leukemic patients our experience to date is summarized in Table 2 which shows the frequency of growth retardation and GH deficiency as observed in relation to treatment.

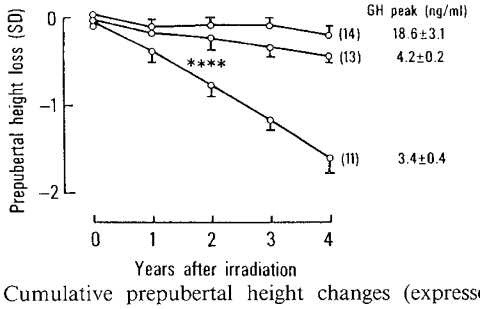

Fig. 4. Cumulative prepubertal height changes (expressed in SD score), in children treated with 2400 cGy for acute lymphoblastic leukemia. The upper group (n = 14) included normal GH responders (GH peak > 8 ng/ml). Patients in the two lower groups were GH deficient (GH peak < 5 ng/ml). They were separated according to their height loss. (*middle line* < *1SD* n = 13; *lower line* > 1 SD n = 11.) See text. **** $p < 0.001$ comparing the > 1 SD group with < 1 SD group.

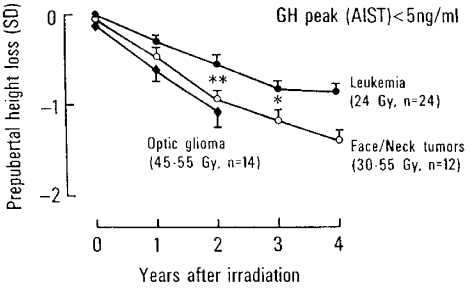

Fig. 5. Cumulative prepubertal height loss from irradiation according to their hypothalamic-pituitary radiation dose in three groups of children. All were GH deficient (GH peak response to arginine-insulin < 5 ng/ml). The mean ages at irradiation were similar in the three groups. Then 4 y after irradiation a height loss of more than 1 SD was found in 11 of 24 cases and 10 of 12 cases in leukemic and face or neck tumors group, respectively. The patients given 30–55 Gy for face or neck tumors were significantly growth retarded as compared to the leukemic group (* $p < 0.05$, ** $P < 0.01$). The optic glioma patients had slightly more severe and more rapid growth retardation.

GROWTH HORMONE TREATMENT

There are very few data on the final heights attained after spontaneous growth in cranial-irradiated children (41). We therefore performed a retrospective study to evaluate the height losses between irradiation and time of final height in children grouped according to their GH secretion (Fig. 6). The mean height losses in the untreated GH-deficient patients as compared to normal GH responders, were greater by 1.2 SD (leukemic patients) and 1.0 SD (face or neck tumor patients). These data, despite the small number of patients studied, emphasize the need to consider GH treatment in irradiated children with GH deficiency.

Presently most agree that hGH treatment of children after cranial radiation produces annual height gains between 6 and 10 cm during the first year of treatment (70–72). These height gains are similar to those observed with treatment of children with idiopathic GH deficiency (73). However, this initial catch-up growth does not persist in subsequent years, leading to poor final height results. A mean decrease in standard height SD score of 0.2 SD between the onset of hGH therapy and the final height in cranial irradiated patients (74), and of 0.9 SD in craniospinal patients was reported recently (75). Our data (unpublished) confirm that prolonged hGH therapy does not significantly improve the mean height SD scores of patients given cranial or craniospinal irradiation. The differences in mean height gain in hGH-treated patients were only 0.6 and 0.3 final height SD in cranial and craniospinal-irradiated patients, respectively, as compared to the untreated groups. There might be several reasons why the catch-up growth of these patients is less than that of children with idiopathic GH deficiency: *1*) the cranial-irradiated patients have been GH-deficient for a shorter period, *2*) their first year response, although significant, may already be lower than in idiopathic hypopituitarism (72), *3*) their bone age was less retarded at the onset of GH therapy, *4*) some had an earlier puberty, which accelerated the skeletal maturation faster than the increase in growth rate.

As a rule, it is essential to commence hGH therapy as soon as growth velocity declines, except for the initial post-radiation period when growth retardation is unlikely to be related to GH deficiency. We consider for hGH therapy any child with a height loss of 1 SD or more since the time of irradiation, with proven GH deficiency and a follow-up period after radiation of 2 y or more. Appropriate therapy of thyroid deficiency also is necessary to optimize growth. Precocious puberty is an additional risk factor in some children and LHRH analog therapy should be considered in association with hGH administration. We are investigating whether this treatment schedule should be extended to patients with early onset of puberty alone. Final results may be improved if hGH treatment is started at an appropriate time and if current hGH dosages are employed with daily subcutaneous injections. An alternative approach has been proposed using daily GHRH treatment; encouraging short-term results on growth have been observed (45).

In summary, most, if not all, the children given high doses of cranial radiation should be treated with hGH. Despite the reported poor results, cranio-spinal irradiated patients also should be treated, preferably before puberty to assure maximum growth

Table 2. *Growth retardation in relation to GH deficiency before puberty in patients treated for acute lymphoblastic leukemia with cranial radiation (CR) or total body irradiation (TBI) as conditioning for bone marrow transplantation (n cases)**

	CR 1800 cGy (n = 8)	CR 2400 cGy (n = 88)	TBI 1000 cGy (n = 9)	TBI 1000 cGy + CR 2400 cGy (n = 5)
Peak GH AITT < 8 ng/ml	0	46	1	5
Height loss > 1 SD	0	32	9	5

* All patients were evaluated >4 yr after irradiation except for the TBI group (1000 cGy given in a single exposure) studied 1.5 to 7 y after irradiation.

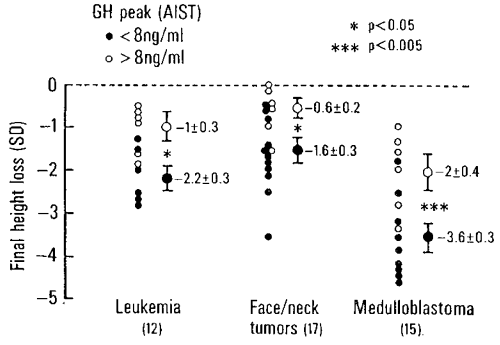

Fig. 6. Final height loss expressed as the difference between height SD score values at irradiation and at time of final height in untreated irradiated patients. Normal and low GH responders to stimulation (GH peak < 8 ng/ml) were compared in each group. The mean height loss was significantly greater in the GH-deficient patients in each group.

of the lower body segment. Children irradiated for ALL are less frequently candidates for GH therapy as their potential height loss generally is moderate. However, we have shown that some of these children do develop GH deficiency and will have a height loss of 1 SD or more even before puberty. If these patients also are constitutionally short they are at risk of severe short stature if their growth and pubertal development are not adequately monitored in order to decide hGH treatment at the appropriate time. The possibility that hGH might stimulate relapse of the original malignancy is a concern in hGH-treated patients. Two separate studies (76, 77) have suggested that hGH therapy does not increase the recurrence of disease or the development of other malignancy.

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