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Hypothalamic-Pituitary Dysfunction after Irradiation of Nonpituitary Brain Tumors in Adults

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Context: Hypothalamic-pituitary (HP) dysfunction is common in children treated with cranial radiotherapy (RT) for brain tumors, but there is little known about the risk of HP dysfunction in adults treated with RT for primary nonpituitary brain tumors.

Objective: The objective was to study the frequency of HP dysfunction in adults after RT for nonpituitary brain tumors.

Method: We studied 56 adult patients who received external beam RT for primary nonpituitary brain tumors at time intervals of 12–150 months after RT. The control group consisted of 20 RT-naive patients with primary brain tumors. GH and adrenal axes were assessed using the insulin tolerance test or the glucagon stimulation test. Gonadotroph, thyrotroph, and lactotroph function were assessed using baseline blood measurements. The biological effective dose (BED) to the HP axis was calculated in the RT patients.

Results: Hypopituitarism was present in 41% of patients. The frequency of GH, ACTH, gonadotropin, and TSH deficiencies, and hyperprolactinemia was 32, 21, 27, 9, and 32%, respectively. Any degree of hypopituitarism and GH deficiency was significantly associated with longer time interval from RT and greater BED. However, gonadotropin deficiency and hyperprolactinemia were only related to BED, whereas ACTH deficiency was only significantly associated with the time interval from RT. One RT-naive patient was GH deficient.

Conclusion: Adult patients treated with cranial irradiation for primary nonpituitary brain tumors are at high risk of hypopituitarism, which is time and dose dependent. Long-term surveillance and periodic evaluation are needed. We recommend that adult late effect clinics, similar to those for children, should be established. **(*J Clin Endocrinol Metab* 90: 6355–6360, 2005)**

THERAPEUTIC CRANIAL IRRADIATION has long been recognized to cause hypothalamic-pituitary (HP) dysfunction. Traditionally, high-risk groups for postirradiation hypopituitarism were patients with preexisting pituitary disease (mainly pituitary tumors) (1), survivors of childhood cancer (2–8), and patients who received high-dose radiotherapy (RT) to treat nasopharyngeal cancers (9, 10). However, the potential for cranial RT to cause significant pituitary dysfunction in adult patients with nonpituitary brain tumors has received little attention. The assumption has been that, in adult subjects, the HP axis is more resistant to the effect of cranial RT than in children. This hypothesis has been supported by the finding that adults who received low-dose total body irradiation (TBI) show normal pituitary function after a mean of 2.4 yr (11), whereas 50% of children who received the same TBI schedule show evidence of GH deficiency at the same time interval (12). However, it is possible that higher doses of RT used to treat primary brain tumors in adult patients may cause significant HP dysfunction.

Recent advances in the diagnostic and therapeutic interventions for primary brain tumors in adult patients are likely to result in a reduced rate of recurrence and improved survival. Therefore, more attention should be focused on late sequelae of treatment, including the potential for postirradiation hypopituitarism. In this paper, we report the results of a study of postirradiation HP function in adult survivors of primary nonpituitary brain tumors.

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Abbreviations: AST, Arginine stimulation test; BED, biological effective dose; BMI, body mass index; CT, chemotherapy; CV, coefficient of variation; FT_4, free T_4; GHD, GH deficiency; GST, glucagon stimulation test; HP, hypothalamic-pituitary; ITT, insulin tolerance test; RT, radiotherapy; SDS, SD scores; SST, short synacthen (corticotropin) test; TBI, total body irradiation; ULN, upper limit of normal.

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Patients and Methods

Patients

Fifty-six patients (28 males) who received cranial RT for primary brain tumors between 1991 and 2003 were included in the study. Patients were identified and recruited from the RT clinic at St. Luke's Hospital in Dublin. Patients were eligible for the study if they were older than 16 yr of age at the time of RT, if they had a primary brain tumor that was distant from the HP axis, and if at least 1 yr had elapsed since the last dose of irradiation. Exclusion criteria were as follows: patients with known HP dysfunction, patients with malignant astrocytic tumors (World Health Organization grades III or IV), patients who received glucocorticoid treatment in the preceding 6 months, and patients who were too ill to undergo testing. In all, 79 patients were initially identified to be eligible, but 19 declined to participate and four could not be contacted. Patients' baseline characteristics are shown in Table 1.

Controls

Twenty radiation-naive patients (12 males) with primary extrasellar brain tumors were also studied. The control patients were randomly selected from admission records at Neurosurgical Department in Beaumont Hospital. The control and RT patients were matched for their baseline characteristics (Table 1), and similar exclusion criteria were applied.

TABLE 1. Basic demographic and clinical characteristics of patients and controls

Characteristic	Patients (n = 56)	Controls (n = 20)
Age at RT (yr)	33.3 ± 12.0	NA
Age at testing (yr)	39.3 ± 11.9	36.5 ± 10
Male sex	28 (50)	12 (60)
Interval between radiotherapy and testing (months)	38 (12–150)	NA
BMI (kg/m^2)	26.1 ± 5	26.4 ± 3.6
Tumor type		
Gliomas	43 (77)	16 (80)
Meningliomas	5 (9)	1 (5)
Pinealomas	3 (5)	2 (10)
Medulloblastomas	2 (4)	0
Others	3 (5)	1 (5)
Surgical procedure		
Resection	36 (64)	13 (65)
Biopsy only	18 (32)	7 (35)
None	2 (4)	0
BED (Gy) [median (range)]	54 (4–97)	NA

Results are presented as number (percentage), mean ± SD, or median (range). *P* values were nonsignificant for any of the characteristics. NA, Not applicable.

RT

Cranial irradiation was delivered by linear accelerators of 6–8 MV in fractionated doses that included all or part of the hypothalamus and pituitary gland in its field. The radiation dose to the HP axis was estimated by either dose-volume histograms (using planning computerized tomography, after the year 2000) or by manual calculation from simulation films (before the year 2000). To allow for direct comparison of different RT fractionation schedules, the dose was transformed to the biological effective dose (BED), which has been shown previously to be a predictor of late adverse endocrine effects (13). The BED was calculated using the quadratic model, as follows: $BED = D \times [1 + d/(\alpha/\beta)]$, where D is the total dose, d is the fraction size, α represents is the linear nonreparable component of cell killing, and β represents quadratic component of cell killing. $\alpha/\beta = 3$ for late responding tissue such as nerve tissues. Two patients with medulloblastomas also received fractionated spinal irradiation and local irradiation to the posterior fossa.

Chemotherapy (CT)

Five patients with gliomas received a combination of procarbazine, lomustine, and vincristine, and one patient received temozolomide. The two patients with medulloblastomas received a combination of carboplatin and etoposide (VP16).

Endocrine assessment

GH and adrenal axes (Fig. 1). Twenty-five RT patients (45%) and seven radiation-naive controls (35%) who had no history of seizures were studied using the insulin tolerance test (ITT) (14–17). The remaining patients and controls with seizures were initially screened using the glucagon stimulation test (GST) (18–21). Because the GST has occasionally been associated with false-positive (false-fail) results (18, 22), subjects who failed the test were subsequently reassessed using a second provocative test: the arginine stimulation test (AST) for GH axis (23, 24) and the standard-dose short synacthen (corticotrophin) test (SST) (25–27) for adrenal function (Fig. 1). Basal plasma ACTH concentration was measured in all cases.

For the ITT, GH deficiency (GHD) was defined as a peak response less than 5 μg/liter and severe GHD as a peak response less than 3 μg/liter (16, 17), and ACTH deficiency was defined as a peak cortisol response less than 500 nmol/liter (18 μg/dl). For the GST, we have previously defined GHD in lean young adults in our unit as a peak GH response less than 5 μg/liter and ACTH deficiency as a peak cortisol response less than 450 nmol/liter (16 μg/dl) (22). Because GH response to the ITT and the AST in post-RT adults was found to be equivalent (24), we used the same cutoff to define GHD for the AST and the ITT. For the SST, secondary hypoadrenalism is defined in our laboratory as a 30-min response less than 500 nmol/liter (18 μg/dl). Patients were regarded as GH or ACTH deficient if they failed the ITT alone or, alternatively, both the GST and the AST or the SST as applicable.

Other anterior pituitary hormones. Baseline morning serum samples were withdrawn for measurements of FSH, LH, free T_4 (FT_4), TSH, prolactin, IGF-I, and testosterone in males or estradiol levels in females. In all females, menstrual history was obtained.

In males, gonadotropin deficiency was defined by a low serum testosterone with inappropriately low (below or within normal range) gonadotropin level, in premenopausal females, by oligo-amenorrhea in the presence of low serum estradiol level without a rise in gonadotropin level, and, in postmenopausal females, by serum gonadotropin concentration in the premenopausal range (28, 29). TSH deficiency was defined by low serum FT_4 level (after excluding artifactual causes) without appropriate elevation in serum TSH (28, 29). Hyperprolactinemia was defined as a basal level greater than the locally derived normal assay reference range.

Analytical methods

Serum GH was assayed using a noncompetitive immunoradiometric method (DiaSorin, Vercelli, Italy), with an intraassay coefficient of vari-

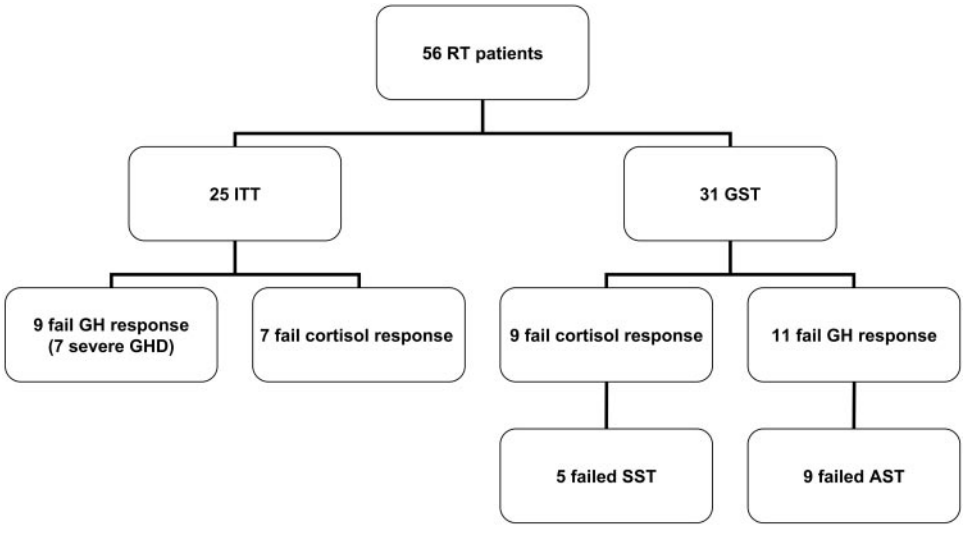

FIG. 1. Assessment of GH and adrenal axes in the 56 patients after RT.

ation (CV) of 1.9, 1.9, and 3.9% at GH means of 18.4, 8.2, and 1.71 μg/liter, respectively. The interassay CV was 5.5, 4.5, and 2.3% at GH means of 17.5, 7.7, and 1.69 μg/liter, respectively. Conversion factor was 1 μg/liter = 2.5 mIU/liter. Serum cortisol was measured using a fluoroimmunoassay (AutoDELFIA; PerkinElmer, Turku, Finland) with an intraassay CV of 3.6, 2.7, and 3% and an interassay CV of 1.6, 1.1, and 1.5%, at serum cortisol concentrations of 210, 517, and 781 nmol/liter, respectively. All GH and cortisol samples from any single individual were assayed in the same batch.

Serum IGF-I was measured using HCl^- ethanol extraction radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA). Serum testosterone, LH, FSH, FT_4, TSH, prolactin, and estradiol were measured using a fluoroimmunoassay (AutoDELFIA; PerkinElmer). Plasma ACTH was measured using a two-site immunoradiometric assay (ORIS Group, Gif-sur-Yvette, France). Plasma glucose was measured using the hexokinase method.

Normal reference ranges were as follows: testosterone, males, 10.3–34.5 nmol/liter (300–1000 ng/dl); premenopausal estradiol, more than 100 pmol/liter (27ng/liter); FT_4, 8–21 pmol/liter (0.62–1.62 ng/dl); TSH, 0.5–4.2 mIU/liter; prolactin, males, 83–414 mIU/liter (2.3–11.5 ng/ml); females, 90–523 mIU/liter (2.5–14.6 ng/ml); plasma ACTH, 10–65 ng/liter.

Statistical analysis

Age, body mass index (BMI), and IGF-I SD scores (SDS) were log transformed before testing for significance using a two-sample *t* test. However, for descriptive purposes, data are expressed as untransformed mean ± SD. The BED and time interval from RT to testing were significantly skewed and were compared using the Wilcoxon's rank-sum test for nonparametric measurements. Categorical data were compared using the Fischer's exact test. Multifactorial logistic regression models were developed to assess the effect of appropriate variables in the presence of other confounding variables in the development of pituitary hormones abnormalities. The dependent variables for the models were any degree of hypopituitarism; GH, ACTH, and gonadotropin deficiencies, and hyperprolactinemia, whereas the independent variables were age, gender, BMI, BED, time interval from RT, and the presence or absence of adjuvant CT. Correlation between variables was made using the Spearman's coefficient (r_s). Serum IGF-I SDS were calculated according to the following formula: IGF-I SDS = In (IGF-I) − [5.92 − (0.0146 × age in years)]/0.272 (30). Significance of results was determined according to the two-tailed alternative hypothesis, and results were deemed significant for P values <0.05. All of the analysis was performed using the statistical software package STATA (version 8; StataCorp, College Station, TX).

Ethics

The study was approved by the ethics section of Beaumont Hospital Medical Research Committee. The purpose of the study was explained carefully to patients who were provided with written information on the background to the study. After an interval of 1 wk, patients who agreed to participate signed written consent for inclusion in the study.

Results

Patients

Evidence of hypopituitarism was present in 23 patients (41%). Nine patients (16%) had single hormone deficiency, whereas 14 patients (25%) had multiple deficiencies, including four (7%) with panhypopituitarism. The breakdown pattern of anterior pituitary hormones deficiency is shown in Fig. 2.

GH and adrenal axes. Nine of the 25 patients who had the ITT achieved a GH response to adequate hypoglycemia less than 5 μg/liter (median, 1.84; range, 0–4.6 μg/liter), including seven with a response less than 3 μg/liter (Fig. 1). Among the 31 patients who had the GST, 11 had GH response less than 5 μg/liter (median, 0.5; range, 0–3.3), and nine failed the AST (median GH response, 0.8; range, 0–3.1 μg/liter) including eight with GH response to AST less than 3 μg/liter. Therefore, 18 patients (32%) had GHD, including 15 (27%) with severe GHD. IGF-I SDS were significantly lower in GHD (−1.3 ± 1.2) compared with non-GHD patients (+0.5 ± 1.5; $P < 0.001$).

Seven patients failed the ITT (peak cortisol response, 46–481 nmol/liter). Nine patients failed the GST (peak cortisol response, 33–448 nmol/liter), of whom five also failed the SST (30-min cortisol response, 41–476 nmol/liter) (Fig. 1). Therefore, 12 patients (21%) were defined as glucocorticoid deficient. All 12 patients had inappropriately low basal serum ACTH concentration.

Other abnormalities. Fifteen patients (27%, seven males) had gonadotropin deficiency, which was associated in three patients with mild hyperprolactinemia [prolactin levels one to

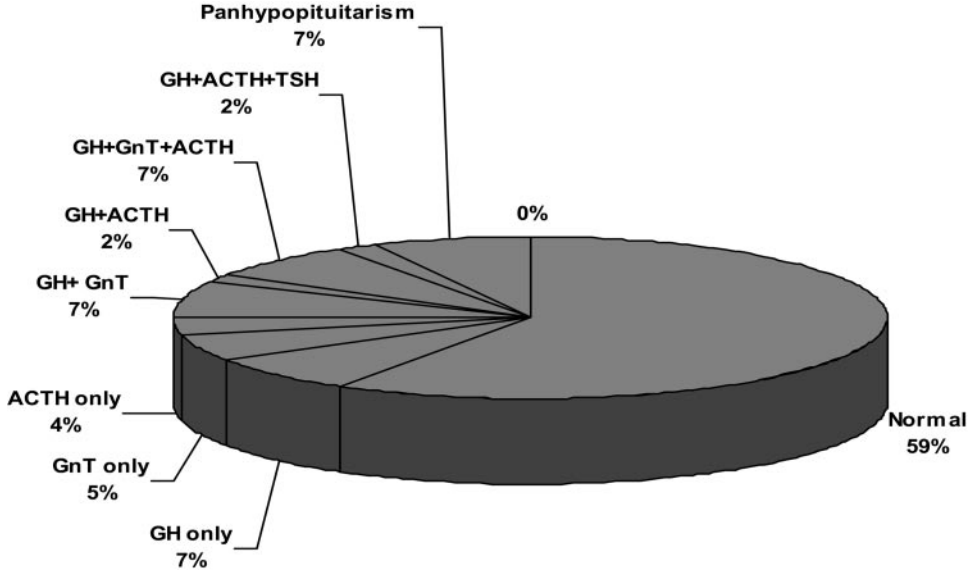

FIG. 2. The frequency and pattern of different anterior pituitary hormone deficiency after RT. GnT, Gonadotropins.

two times the upper limit of normal (ULN)] and in five patients with moderate hyperprolactinemia (prolactin level two to four times the ULN). Four male patients had evidence of primary testicular failure (three received CT); one had low testosterone with raised LH and FSH, one had low-normal testosterone with raised LH and FSH, and one had isolated raised FSH with normal testosterone and LH levels. The fourth patient who did not receive CT had isolated raised FSH with normal serum LH and testosterone concentrations.

Five patients (9%) had evidence of central hypothyroidism. One of the two patients who had spinal irradiation had subclinical primary hypothyroidism, and another patient had thyroid-peroxidase antibodies-positive primary hypothyroidism. Hyperprolactinemia was present in 18 patients (32%), eight had prolactin levels between one and two times the ULN, and 10 had prolactin levels more than two times ULN. One patient who had panhypopituitarism had low serum prolactin level.

Control subjects

All controls who had the ITT and 11 of 13 controls who had the GST achieved normal GH response more than 5 μg/liter. One control subject failed the GST (GH response, 3.25 μg/liter) but passed the AST (GH response, 7.22 μg/liter). Another, lean 33-yr-old control subject who had extensive debulking of a right-sided parietal astrocytoma failed both the GST (undetectable GH response) and the AST (GH response, 1.82 μg/liter; IGF-I SDS, −1.1). Two control subjects failed the GST but passed the SST.

All control subjects had normal gonadal and thyroid function and normal prolactin levels.

Risk factors for postradiation hypopituitarism (Tables 2 and 3)

Logistic regression analysis showed that any degree of hypopituitarism and GHD was significantly associated with the time interval from RT and the BED (Table 2). However, gonadotropin deficiency and hyperprolactinemia were only related to BED, whereas ACTH deficiency was only significantly associated with the time interval from RT (Table 2). Age at time of RT, gender, BMI, or adjuvant CT were not predictors of the development of hypopituitarism.

There was an inverse correlation between peak stimulated GH and both the BED and the time interval from RT (Table 3 and Fig. 3) and between basal testosterone and FT_4 and the time interval from RT. A weak inverse correlation was seen between peak stimulated cortisol concentration and the time interval from RT (Table 3).

TABLE 3. Correlation (r_s) between hormone measurements and BED (Gy) and the time interval between RT and testing (months)

	Time interval from RT	BED
Peak stimulated GH	−0.54	−0.53
P value	<0.001	<0.001
Peak stimulated cortisol	−0.27	−0.17
P value	0.04	0.22
FT_4	−0.31	−0.16
P value	0.02	0.25
Testosterone	−0.54	−0.29
P value	0.004	0.13
Prolactin	−0.03	0.19
P value	0.84	0.15

Discussion

Our results show that adult patients who have received cranial irradiation for primary nonpituitary brain tumor are at high risk of developing hypopituitarism. Although the prevalence of hypopituitarism is lower than that reported for survivors of childhood cancer (5, 8, 13, 31) or after high-dose irradiation for nasopharyngeal tumors (9, 10), the 41% of our patients who showed evidence of hypopituitarism represent a considerable clinical problem that is probably unrecognized. The risk of post-RT hypopituitarism was time and dose dependent, and the hierarchy of anterior pituitary hormone deficiency was similar to that documented previously in other subgroups of patients who received cranial irradiation for pituitary and nonpituitary tumors, with GHD being the commonest, followed by gonadotropin, ACTH, and TSH deficiency (6). However, our study showed a much lower frequency of GHD at 32% compared with the 80–100% prevalence of GHD reported in children treated with cranial RT for brain tumors (5, 8, 13, 31). This may be explained by the notion that the GH axis is more sensitive to the effect of RT in children than in adults, a hypothesis that has also been supported by the finding that adults who received low-dose TBI show normal pituitary function after a mean of 2.4 yr (11), whereas 50% of children who received the same TBI schedule show evidence of GHD at same time interval (12). However, comparing our finding of ACTH deficiency in 21% of our adult patients with the frequency of postirradiation ACTH deficiency in children is complicated by a significant inconsistency among published studies. Although some authors reported low likelihood of ACTH deficiency in only

TABLE 2. Results of multivariate regression models examining the relationship between hypopituitarism and the time interval from RT and BED

Hormone abnormality	Time interval from RT (months)			BED (Gy)		
	Present	Absent	*P* value	Present	Absent	*P* value
Any degree of hypopituitarism	78 (38–120)	28 (14–42)	0.02	71 (59–80)	43 (34–58)	0.012
GHD	100 (47–130)	28 (15–45)	0.001	72 (62–80)	44 (37–65)	0.029
Gonadotropin deficiency	100 (48–130)	31 (17–51)	0.10	78 (71–85)	44 (37–62)	0.004
ACTH deficiency	100 (50–128)	32 (18–60)	0.02	72 (57–80)	50 (38–75)	0.26
Hyperprolactinemia	33 (16–80)	39 (21–87)	0.22	72 (43–80)	50 (39–69)	0.02

Results are expressed as median (interquartile range). Independent variables in the model were age, gender, BMI, BED, time interval from RT, and the presence or absence of adjuvant CT.

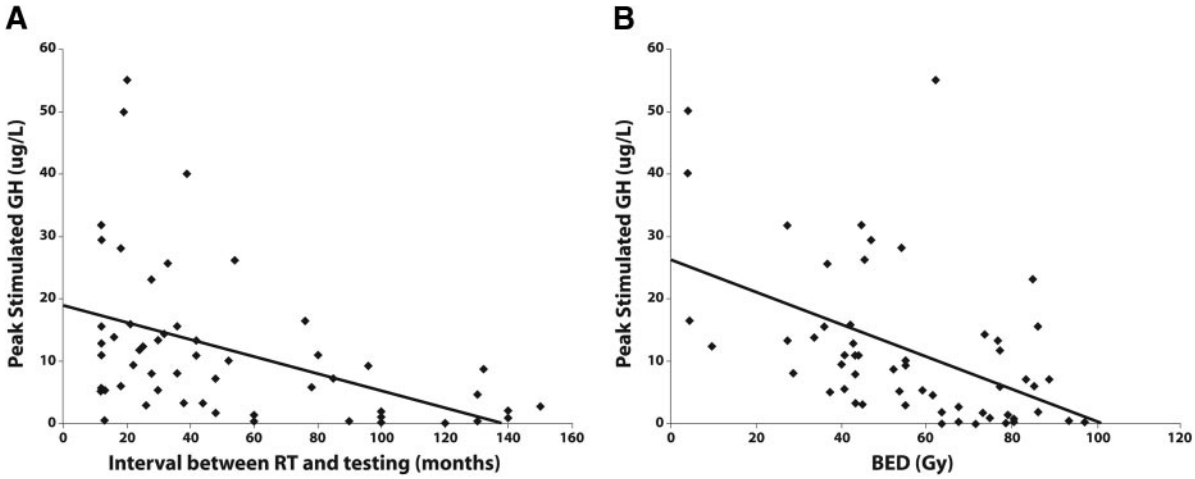

FIG. 3. Relationship between peak stimulated GH (after ITT or glucagon) and the interval from RT ($r_s = -0.54$; $P < 0.001$) and the BED ($r_s = -0.53$; $P < 0.001$).

4–6% of children treated with RT for brain tumors (8, 31), others reported childhood RT to be associated with convincing evidence of ACTH deficiency (failing both the ITT and the SST) in 19% of subjects (32). In the last study, 48% of subjects failed the ITT alone (32). The discrepancy between these studies may reflect differences in the RT doses and schedules that prevent direct comparisons between groups and different durations of follow-up but also the difficulty in diagnosing milder cases of ACTH deficiency, particularly in children in which the diagnostic utility of different stimulation tests and normal responses are not well established.

We have also been able to show that the insult to the HP axis is primarily caused by RT, because only one of the radiation-naive patients had GHD. This would strongly suggest that neither the original tumor nor the subsequent neurosurgery was responsible for the development of pituitary dysfunction in the vast majority of patients. It has been speculated that CT could potentiate the damaging effect of RT on the HP axis (33). We did not, however, find an association between the use of CT and HP axis dysfunction, although the small number of patients who received CT precludes definitive conclusion about this speculative relationship.

The effect of cranial irradiation on HP function in adults treated for nonpituitary disease has only received limited attention. Harrop *et al.* (34) studied nine patients who were irradiated for primary brain tumors that were remote from the HP axis, six of whom were older than 16 yr at the time of RT. Five patients showed impaired GH, two impaired gonadotropin, and one impaired TSH secretion. Adrenal function appeared normal in all patients. Littley *et al.* (35) evaluated pituitary function in seven adults who were studied 5–13 yr after RT for gliomas (30 Gy in eight fractions) and reported GH, gonadotropin, ACTH, and TSH deficiencies in six, five, three, and two patients, respectively. The higher rate of pituitary dysfunction in this study probably reflected the longer interval between RT and evaluation. In contrast to these studies, Constine *et al.* (36) evaluated 32 patients aged 6–65 yr who received cranial RT for primary brain tumors at 2–13 yr before the study and found a strikingly high frequency of central hypothyroidism in 65% of patients, but the frequency of hypothyroidism among children and adults was not separately reported. Sixty-one percent of the postpubertal patients had hypogonadism, but there was inconsistency in the reported frequency of adrenal insufficiency between the metyrapone test (35% fail) and the CRH test (all normal). GH axis was not assessed in that study.

One particular difficulty in assessing GH and ACTH reserves in adult patients with brain tumors is the high frequency of seizure disorders associated with tumors of astrocytic origin, which precludes the use of the gold-standard ITT (14–17). The alternative test, the GST, assesses the entire GH and adrenal axes and has been shown to be reliable (18–21), although it is occasionally associated with false-positive results (18, 22). For this reason, we reassessed patients who failed the GST with another stimulus and only accepted the patients to be GH or ACTH deficient if they failed the second test also. Therefore, we feel confident that we did not overestimate the prevalence of GH and ACTH deficiency in our cohort. It is, however, possible that some of our RT patients who showed normal stimulated GH response may have GH neurosecretory dysfunction, a state that is characterized by diminished spontaneous or physiological GH secretion but normal response to provocative stimuli (37).

The insult causing pituitary dysfunction after cranial irradiation is believed to be primarily hypothalamic in origin because the hypothalamus is more sensitive to the effect of radiation than the pituitary (33, 38). The exact mechanism of radiation damage to the hypothalamus is not known, but both vascular etiology and direct damage to the cell nuclei have been proposed. The latter hypothesis may explain the delayed onset of hormone deficiency until the cells of the slowly dividing tissue die during mitosis (38).

Our findings have important implications for clinicians looking after this group of patients. Adult patients who received cranial irradiation for nonpituitary brain tumors should be screened for the late effects of hypopituitarism. Replacement therapy with sex steroids, glucocorticoids, and T_4 have well-established value, but the benefit (39) and safety (40) of GH replacement in this subgroup of hypopituitary

patients is less well established and requires additional studies.

Current 5-yr overall survival rates for patients who were treated for low-grade gliomas are estimated to be between 60 and 70% (41), whereas treatments for other more benign tumors such as meningiomas are highly effective. Therefore, more attention should be focused on the slow effect of cranial RT on the HP axis, necessitating long-term surveillance and periodic clinical and biochemical evaluation to detect evolving hypopituitarism. We recommend that adult late effects clinics, similar to those for children, should be established for adult RT patients. In this context, prospective longitudinal studies are needed to establish the appropriate timing and frequency of post-RT pituitary assessment.

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