ORIGINAL ARTICLE

Hypopituitarism following external cranial irradiation for extrasellar tumors

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ABSTRACT

Introduction: Cranial irradiation has significant long-term deleterious effects, in the form of endocrinopathies. With better prognosis of certain types of brain tumors, chronic damage following external irradiation of the normal pituitary, is more commonly appreciated than in the past.

Objectives: This retrospective analysis was to assesses the effects of radiation on pituitary function and relate them to the dose and time since radiation, in a cohort of patients treated with cranial radiotherapy for non pituitary brain tumors.

Material & Methods: In this study, 96 patients, who underwent cranial radiation at least 12 months earlier were evaluated. Pituitary function was assessed with basal levels of T3, T4, TSH, LH, FSH, PRL, GH, and cortisol GH and cortisol levels following insulin induced hypoglycemia were also done.

Results: Pituitary dysfunction was present in 84 (88%) of cases. GH, gonadotrophin, ACTH, and TSH deficiency was documented in 59, 54, 46, and 13% respectively while 21% had hyperprolactinemia. Panhypopituitarism was present in 27% cases. Patients without pituitary dysfunction (12%) received significantly less radiation than those with pituitary dysfunction (4908 ± 70 vs. 5519 ± 6 rads, $p = 0.0005$). Percentage of patients developing hypopituitarism increased with increasing dose of radiation (p 0.0015).Single hormone deficiency was more common in those studied within 18 months while multiple hormone deficiency were more common in those studied more than 36 months after irradiation. Total T3 and testosterone were negatively correlated with the total radiation dose and time since radiotherapy.

Conclusions: Pituitary dysfunction is common after cranial radiation for extrasellar tumours. Pituitary dysfunction is related to dose of radiation, fraction of radiation, and duration after radiotherapy. All patients who receive external cranial radiation for extrasellar tumour should undergo endocrine evaluation yearly.[IJEM 2007;11(1&2):3-9]

Key Words: Cranial radiation, pituitary function, hypopituitarism

INTRODUCTION

Cranial irradiation has significant long-term deleterious effects, in the form of endocrinopathies. With the better prognosis of certain types of brain tumors, chronic damage following external irradiation of the normal pituitary, during radiotherapy of the neoplasms of head, is more commonly appreciated than in the past(1-9). Patients with brain tumors who are treated with radiation frequently have growth hormone deficiency, but other neuro-endocrine abnormalities are presumed to be uncommon(10). Acute radiation effects occur largely in rapidly renewing or proliferating cells. The late effects are really the dose-limiting factor in radiation therapy. Clinically late effects appear to depend much more on the total dose of radiation and the size of the radiation fraction(11). Clinical damage to the pituitary gland is usually manifested months to years after treatment and is preceded by a long sub clinical phase. The paucity of data on the effects of radiation on pituitary function from India prompted this study.

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MATERIAL AND METHODS

In this prospective study, 96 patients who underwent cranial radiation (Theratron 870 E Cobalt 60 Teletherapy unit), at least 12 months before, at the radiotherapy department of the Malignant Diseases Treatment Centre (MDTC), Pune-40, were evaluated. The diagnosis and radiation profile details, including the total dose, dose fraction, duration and the year were retrieved from the MDTC files.

After detailed clinical examination the hematological, renal and hepatic functional parameters were assessed. Endocrine evaluation included assessment of:-

1. *Thyroid and Gonadal Function:* Basal 8 AM venous blood samples were taken for serum triiodothyronine (T3), thyroxine (T4), and thyrotropin stimulating hormone (TSH) estimation. Pooled samples (Three samples taken 20 minutes apart and pooled together) were taken for LH, FSH, and testosterone (TE) estimation. The serum was separated and stored at -20°C until the time of assay.
2. *Adrenal Function:* Basal 8 AM venous blood samples were taken for estimation of basal cortisol. Insulin tolerance test was performed after overnight fast unless contraindicated (history of ischemic heart disease, cerebrovascular accident or convulsions). The test and symptoms of hypoglycemia were explained in detail to the patient. A heparin lock venous cannula was place in the morning. Blood was drawn at 0 minutes for glucose and cortisol estimation. Then 0.1 unit per kg body weight of regular insulin was injected intravenously. Pulse and blood pressure were measured at base line and at the time of blood sampling at 30, 60, 90, and 120 minutes. Clinical signs of hypoglycemia and blood glucose less than 40 mg/dl or drop in 50% of basal glucose were taken as evidence of adequate hypoglycemia, which was then reversed with intravenous 10% dextrose solution. A peak serum cortisol of 18 mg/dl or more was taken as an adequate response. Serum was separated and stored at –20°C until the time of the assay.
3. *Growth Hormone (GH):* Basal 8 AM venous blood samples were taken for estimation of basal GH. Insulin tolerance test was performed as above. A serum level of more than 5 ng/ml in adults and more than 10 ng/ml in children of less than 18 years were taken as normal.
4. *Prolactin:* Basal 8 AM venous blood samples were taken for serum prolactin estimation. The serum was separated and stored at -20°C until the time of assay. A serum prolactin level in male less than 15 ng/ml and females less tan 20 ng/ml were considered normal.

Hormonal Assays

The serum T3, T4 and leutinising hormone (LH) were estimated by radioimmunoassay (RIA) by kits supplied by Bhabha Atomic Research Centre, Mumbai (BARC). The normal range of T3, T4 and LH were 80-200 ng/dl, 5.5-13.5 mg/dl and 5-15 mIU/ml respectively. Serum TSH and prolactin was estimated by an immunoradiometric assay, using a commercial kit supplied by BARC. Normal range of serum TSH and prolactin were 0.2-4.05 mIU/litre and 0-15 in male & 0-20 in females respectively. Serum cortisol was estimated by Gammacoat cortisol 125I RIA kit by Diasorin, Stillwater, Minnesota, USA. Normal morning cortisol ranged from 5-25mg/dl. Serum GH and testosterone were estimated by RIA using commercial kits supplied by Diasorin, Stillwater, Minnesota, USA. For all assay interassay coefficient of variation was less than 15% and intra-assay variation was less than 10%.

Statistical Methods

Statistical analysis was done by ANOVA test using computer programme EPI-6. Chi-square test was used for analysis of nonparametric data. Results were expressed in mean ± standard error.

Criteria For Deficiency

Hypothyroidism: Hypothyroidism was defined when T4 levels were < 5.5 μg/dl with normal or low TSH. However in the literature secondary hypothyroidism was defined as T4 <4.0 μg/dl(12), but in our study we defined hypothyroidism as T4 levels <5.5 μg/dl because lowest level defined by BARC for the Indian population was > 5.5 μg/dl.

Hypogonadism: In post-pubertal male was defined by serum testosterone levels < 3.0 ng/ml, by presence of amenorrhoea with normal or low FSH levels in premenopausal women, and by normal or low FSH in postmenopausal women.

Hypoadrenalism: Adrenal insufficiency was defined by either basal cortisol levels < 5.0 μg/dl or peak cortisol levels < 18.0 μg /dl after insulin induced hypoglycemia.

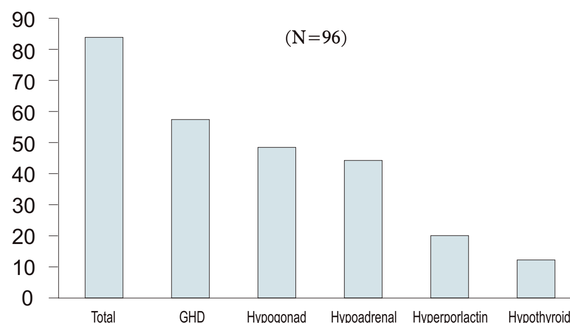
Growth Hormone deficiency: Growth hormone deficiency was defined by post insulin induced hypoglycemia growth hormone levels < 5.0 ng/ml in adult and levels < 10.0 ng/ml in prepubertal and pubertal patients.

Hyperprolactinemia: Hyperprolactinemia was defined as prolactin levels > 15 ng/ml in Male and > 20 ng/ml in Female(8).

RESULTS

The 96 subjects (72 males and 24 females) had a mean age of 32 ± 0.10 years (range 8–60 years); most (88%) were 16-45 years old. The tumors treated were (63%), oligodendroglioma (17%), glioma (6%), nasopharyngeal carcinoma (5%), meningioma (3%), rhabdomyosarcoma (2%), glioblastoma (2%), and hemangioblastoma (2%). Most of the patients (63; 66%) received chemotherapy with agents, vincristine, carmustine, methotrexate, and prednisolone, within 6 months of radiotherapy.

Eighty four patients (88%) had evidence of pituitary dysfunction involving one or more pituitary hormones. Deficiency of GH, gonadotrophins, ACTH, and TSH was found in 59, 54, 46, and 13% respectively and hyper-prolactinemia in 21% (Figure-1). Deficiency of one, two, and more than two hormones was present in 34, 26, and 27% respectively. The commonest single hormone deficiencies noted were gonadotrophin (39%) and GH (34%) deficiencies. In 80% of those with two hormone



* Six prepubertal and pubertal patients were excluded in from Hypogonadism.

Fig. 1: Distribution of pituitary dysfunction components

deficiency GH deficiency occurred with TSH, gonadotrophin, or ACTH deficiency. All patients with panhypopituitarism had GH deficiency. Most commonly observed combination was GH deficiency along with gonadotrophin and ACTH deficiency.

Chemotherapy had no statistically significant effect on hormone levels, except LH and FSH. Though basal GH was lower in patients who received chemotherapy, the difference was not statistically significant. However, this difference was not evident in stimulated GH levels (Table-1).

Table 1: Effect of chemotherapy on hormone levels

Hormone	Chemotherapy received 63 (66%)	Not received 33 (34%)	*p* value
T-4 (μg/dl)	8.05±0.04	8.16±0.06	0.20
T3 (ng/dl)	123±0.46	119±0.79	0.52
TSH (mIU/L)	2.17±0.04	1.82±0.04	0.56
LH (mIU/ml)	11.32±0.08	15.34±0.16	0.001
FSH (mIU/ml)	10.83±0.25	5.05±0.12	0.04
Testosterone (ng/ml	3.83±0.06	2.98±0.06	0.10
Cortisol			
Basal (μg/dl)	9.07±0.07	9.77±0.16	0.69
Peak (μg/dl)	16.48±0.11	17.33±0.25	0.60
GH			
Basal (ng/ml)	0.61±0.01	0.91±0.04	0.16
Peak (ng/ml)	5.60±0.10	6.68±0.19	0.56
Prolactin (ng/ml)	10.42±0.12	12.80±0.21	0.14

The mean dose of radiation was 5442 ± 6 rads (range 3000-6600 rads). Patients who had no hormonal deficiency received significantly less radiation than those had any hormonal deficiency (4908 ± 70 vs 5519 ± 6, p = 0.0005). Percentage of patients developing hypopituitarism increased with increasing dose of radiation, which was statistically significant. All patients with radiation dose of more than 6000 rads developed hypopituitarism (Table-2). There was no statistically significant effect of total radiation dose on the hormone levels except T3. However, total T3, testosterone, peak GH and prolactin were negatively correlated with the total radiation dose(Table-3 & Fig. 2).

Table 2: Relation of radiation dose and hypopituitarism

Dosage of radiation	No. of patients	Hypopituitarism*
Upto 5000 rads	24 (25%)	16 (67%)
5001-6000 rads	63 (65%)	59 (94%)
More than 6000 rads	9 (10%)	9 (100%)

*Chi-Square 12.99, *p* value = 0.0015

Table 3: Correlation of hormone levels with radiation dose

Hormone	Confidence Limits	*f* statistics	*p* value
T4 (μg/dl)	0.04 (-0.16 – 0.24)	0.17	0.69\
T3 (ng/dl)	-0.19 (-0.38 – 0.01)	3.68	0.05
TSH (mIU/L)	0.07 (-0.13 – 0.22)	0.53	0.49
LH (mIU/ml)	0.12 (-0.09 – 0.31)	1.27	0.24
FSH (mIU/ml)	0.01 (-0.19 – 0.21)	0.02	0.92
Testosterone (ng/ml)	-0.14 (-0.37 – 0.11)	1.20	0.26
GH			
Base (ng/ml)	0.17 (-0.03 – 0.36)	2.73	0.09
Peak (ng/ml)	-0.11 (-0.31 – 0.09)	1.20	0.28
Cortisol			
Base (μg/dl)	0.05 (-0.15 – 0.25)	0.21	0.62
Peak (μg/dl)	0.09 (0.12 - 0.28)	0.72	0.38
Prolactin (ng/ml)	-0.05 (-0.24 – 0.16)	0.19	0.62

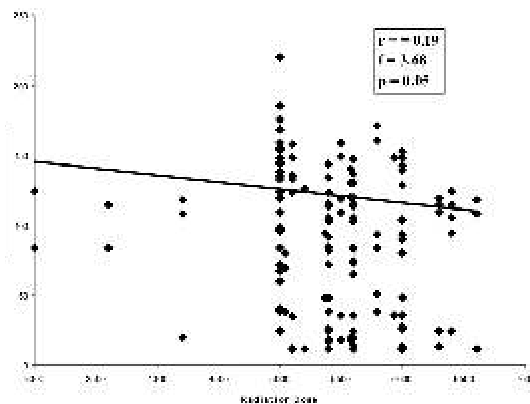


Fig. 2: Correlation of T3 with radiation dose

Most of the patients (85.5%) received a daily dose fraction between 150-180 rads. Sixty seven percent of patients who had received dose fraction of 150 rads/day revealed endocrine abnormality. Proportion of endocrine abnormalities increased steeply (92%) with dose fraction of 151-200, reaching 100% with dose fraction of more than 200. Patients who had received fractional dose up to 150 rads had one hormone deficiency more often than those who received more than 200 rads (Table-4).

Total T3 levels were negatively correlated with time since radiotherapy (*p* 0.05) (Figure-2). Total T4, FSH and testosterone were also negatively correlated with duration after radiotherapy, but could not reach statistical significance level (Table-5). Pituitary dysfunction revealed significant variation with duration between radiotherapy

Table 4 : Relation of radiation dose fraction and hypopituitarism

Dose Fraction	No. Of patients	No Hormone deficiency	One Hormone deficiency	Two Hormone deficiency	> Two Hormone deficiency	Total
150 rads	12 (12.5%)	4 (33%)	4 (33%)	2 (17%)	2 (17%)	8 (67%)
151-200 rads	82 (85.5%)	8 (10%)	29 (35%)	23 (23%)	22 (27%)	74 (92%)
> 200 rads	2 (2%)	0	0	0	2 (100%)	2 (100%)
Total	96	12	33	45	26	84
Chi-square	-	-	1.09	1.42	6.05	5.61
p value	-	-	0.58	0.49	0.048	0.06

and endocrine evaluation. Ninety percent of patients were already showing at least in one hormone deficiency by 18 months, which increased to 97% by 36 months. Among patients evaluated within 18 months of radiation (n 30) less than a half had deficiency of more than one hormone while this fraction was a little over three fourths in the 34 patients studied more than 36 months after radiation (Table-5). Similarly single hormone deficiency was more common with lower prolactin level and multiple hormone deficiency was more common with higher prolactin level (Table-6).

Table 5: Duration between radiation and onset of endocrinological evaluation

Duration	No (%)	One Hormone	2 hormone	3 hormone	Total*
< 18 months	30(31)	11 (37%)	8 (27%)	8 (27%)	27 (90%)
19-36 months	32(33)	16 (50%)	7 (22%)	8 (25%)	31(97%)
> 36 months	34(36)	6 (18%)	10 (38%)	10 (38%)	26 (76%)

* Chi-square 6.52, $p = 0.038$

Table 6: Relation between prolactin level and endocrine deficiencies

Prolactin	No (%)	One Hormone	2 hormone	3 hormone	Total*
1-5 (ng/ml)	21	7 (33%)	8 (30%)	4 (19%)	19 (90%)
5-10 (ng/ml)	25	12 (48%)	8 (32%)	3 (12%)	23 (92%)
10-15 (ng/ml)	28	10 (36%)	5 (18%)	9 (32%)	24 (86%)
>15 (ng/ml)	22	4 (18%)	4 (18%)	10 (45%)	18 (82%)
p value		0.19	0.29	0.05	0.79

Table 7: Comparison of our study with published series showing magnitude of endocrine deficiency

Author	No. of patients	Endocrine Deficiency
Samaan *et al*(13)	15	93%
Fernandez *et al*(3)	7	71%
Danoff *et al*(4)	23	26%
Lam *et al*(18)	8	100%
Woo *et al*(5)	11	100%
Constine *et al*(8)	32	91%
Pai *et al*(21)	107	84%
Present Study	96	88%

DISCUSSION

Close to 90% of the subjects in our study had some degree of pituitary dysfunction. The reported frequency of pituitary hormone abnormalities in patients given high dose radiation in head and neck tumors has ranged from 26 to 100%3-5,8,13-15 reflecting variations in age, radiation dose, time since irradiation, and protocols employed for endocrine evaluation in different studies(1,3,5,7-9,13, 14-16).

Variation in Age: The threshold for radiation-induced damage to the hypothalamic-pituitary axis differs between children and adults. The central nervous system of a very young child may be more radiosensitive than that of an older child. Some authors have studied only prepubertal children(1-4,9,16) and others only adult(7,13). Among adults treated with 1000 to 1300 rad (10 to 13 Gy) of total-body irradiation, GH secretion was normal two to four years later(7), whereas a high proportion of children so treated became GH-deficient after a similar interval(16). An overwhelming majority (92%) patients in our study were adults.

Variation in Radiation Dose: The total dose of radiation delivered to the hypothalamic-pituitary region is a major determinant of the speed of onset as well as the incidence and severity of anterior pituitary hormone deficiencies(11). The greater the dose of radiation, the earlier the onset and greater the extent of hypopituitarism. Radiation dose delivered to patients varied from 1000-8700 rads in various studies(1,3,5,7-9,13,14-18).

Variation in Duration after Radiotherapy: Endocrine evaluation has been undertaken from 3 months to 5 years after radiotherapy in various studies(5,7,8,17). In the present study endocrine evaluation was done at least 12 months after radiation to avoid the effect of acute radiation and steroid therapy. Pituitary gland is usually affected late by radiation therapy because of slow turnover of its cells(10,11,19).

Variation in Endocrine Evaluation: Many earlier studies have not assessed all hormones and mainly concentrated on growth hormone(16,17,18), while others have not assessed growth hormone assessment(6,8). Adrenal function was assessed by basal cortisol level(5) whereas stimulation is essential to exclude adrenal insufficiency.

Some studies have assessed only thyroid hormone abnormalities(6). In our study all patients were assessed for target gland dysfunction along with abnormalities in growth hormone and prolactin secretion. Limitations of our study were that we could neither measure free T4 and free testosterone level nor perform various stimulation tests with hypothalamic releasing factors. However our results were similar to earlier studies(3,8,13). In earlier studies involving nasopharyngeal carcinomas, Samaan *et al*(13), Fernandez *et al*(3) and Woo *et al*(5) reported endocrine dysfunction in 93%, 71% and 91% respectively. Constine *et al*(8) reported endocrine dysfunction in 29 out of 32 (91%) of patients. Though results of endocrinal abnormalities are similar to ours, all these studies had small number of patients ranging from 7 to 32. Because of the similarity between the present study and those reported in patients with head or neck tumours, we surmise that endocrine dysfunction occurs frequently when patients with brain tumours are aggressively treated with large doses of radiation that encompasses the hypothalamus and pituitary gland.

The frequency, the severity (in terms of number and combinations of hormone abnormalities) and time profile of pituitary dysfunction in our study are comparable to those reported in literature(2,3,5,7-9,13).

Tissue injury caused by radiation is generally related to the dose of radiation, fraction of radiation per day, and duration after radiotherapy. Hence an increase in severity or frequency of pituitary dysfunction with an increasing dose might be expected(11,19). Patients in this study had received cranial irradiation of doses ranging from 3000 rads to 6600 rads (5442±6) over 24 to 42 days. In comparable studies undertaken earlier dose ranged from 3000 to 8300 rads for nasopharyngeal carcinomas (2,3,5,13,14) and 3960 to 8700 rads for brain tumours(1,8,9). In present study 65% patients received radiation dose of 5000-6000 rads. Patients who had no hormonal deficiency received significantly less radiation than those had any hormonal deficiency (4908 ± 70 vs 5519 ± 6 rads, $p = 0.0005$). Percentage of patients developing hypopituitarism increased with increasing dose of radiation, which was statistically significant. All patients with radiation dose of more than 6000 developed hypopituitarism. In this study total T3, testosterone, and peak GH were negatively correlated with total radiation dose. Sheline *et al*(2) and Schmiegelow *et al*(9) observed significant inverse correlation between radiation dose and peak GH response. Constine *et al*(8) found conflicting results with negative correlation of total T4 and T-3 with dose of radiation, where as no correlation with serum free T4 concentration.

The same total dose given in higher fractions over a shorter period is likely to cause a greater incidence of pituitary hormone deficiency than if the schedule is spread over a longer time interval with lower fractions(20). In this study, fraction of radiation per day ranged from 150 to 250 rads. Sixty-seven percent of patients who had received dose fraction of 150 rads/day revealed endocrine abnormality compared to 92 and 100% of those who had received 150-200 and more than 200 rads per day respectively. Moreover patients given the lower fractional dose per day had one hormone deficiency more often than multiple hormone deficiencies (33% vs 17%), whereas those with higher fractional dose had significantly more chances of developing multiple hormone deficiencies (17% vs 100%, p value 0.048) (Table 4). Shalet *et al*(14) found that the number of patients with GHD was significantly greater in those who received 2400 rads over 2.5 weeks in 10 fractions than patients who received 2500 rads in 20 fractions over 4 weeks. The timing of the second dose of a fractionated scheme may be critical because cells desynchronize rapidly and redistribute themselves according to the original cell age distribution. This phenomenon seems to be important unless there is incomplete redistribution between fractions(11).

One of the determinants of endocrine abnormality is duration after radiotherapy. The detection of chronic radiation damage in tissues depends on the rate of mitotic divisions occurring in the irradiated tissues, and on the duration of observation period(2,11). Endocrine tissues, including pituitary are classified as "slow renewal tissues" in which mitosis is normally an infrequent event. Those tissues, which undergo slow turnover, respond very slowly to radiation effects(11,19,20). Though this study was cross sectional in nature, endocrine abnormalities revealed significant variation with duration after radiotherapy in this study (p 0.038).Hypopituitarism was less severe in those evaluated within 18 months of radiotherapy than in those evaluated more than 36 months following radiotherapy. There was negative correlation between duration after radiotherapy and total T3, T4, FSH and testosterone. Constine *et al*(8) observed significant negative correlation between serum free T4 concentration and duration after radiotherapy. However in their study more patients were evaluated long after radiotherapy (59% after five years), whereas only 17% patients were evaluated after five years in our study. Peak GH was negatively correlation with length of follow up in one study(9), which was not observed in present study. However all patients were children in that study, who were irradiated at age of 0.8-14.9 years unlike adult patients in this study and follow up period was more than this study (2-29 years).

Many studies have highlighted the effect of chemotherapy on pituitary dysfunction(6,21). Sixty-three patients (66%) received chemotherapy in this study. There was no statistically significant difference in the various hormone levels between patients who received and who did not receive chemotherapy. However, LH levels were significantly lower in patients who received chemotherapy and can contribute to hypogonadism in some patients.

Though the basal GH level was lower in patients who received chemotherapy, there was no significant difference in stimulated GH level. Several combinations of adjuvant chemotherapy (vincristine, lomustine, cisplatinum, and methotrexate) have been reported to potentiate the adverse effects of radiation on growth in prepubertal children with medulloblastoma(21).

Most of the patients with brain tumour complained of vague nonspecific symptoms after cranial radiation (Data no shown). These symptoms are usually attributed to after effects of tumour or radiation. Importantly even patients with panhypopituitarism lacked signs and symptoms; similar findings have been reported by others(5,8,9) underscoring the importance of periodic endocrine evaluation in patients given cranial radiation even in the absence of signs and symptoms suggestive of pituitary dysfunction. Early detection and treatment of endocrine deficiency may have significant impact on quality and duration of life of a cancer survivor.

Pathogenesis of radiation hypopituitarism remains unknown. Normal pituitary is said to be radioresistant and brain and neurons are more sensitive to radiation damage(11,19,20). Hence the changes in the pituitary function seen could be attributed to the indirect effects of radiation to the hypothalamus. But evidence for such a mechanism is inconclusive. Hypopituitarism can result from direct injury to the cells responsible for hormonal secretion, or injury to the stroma or its microvasculature, or an injury to the vascular channels that transfer the hypothalamic hormones to the pituitary, or direct injury to hypothalamic cells responsible for synthesis of various stimulatory and inhibitory factors. Hyperprolactinemia occurred less frequently than expected in this study ; more than a fifth had in fact low prolactin (<5 ng/ml) levels.) Hyperprolactinemia is considered as indicative of hypothalamic damage(4,8) and lower prolactin level may indicate direct damage to lactotroph cells(12). This higher frequency of single rather than multiple hormone deficiency in patients with low prolactin and the opposite in those with hyperprolactinemia suggests isolated hormone deficiency after radiation is more often due to direct damage to adenohypophyseal cells and panhypopituitarism is due to radiation effect on hypothalamus. The correlation between the frequency of hypopituitarism and interval between radiotherapy and evaluation is compatible with both vascular injury (hypothalamic) and damage to parenchymal cells (pituitary), which have a slow turn over rate(8,11,19).

CONCLUSION

This study highlights that pituitary hormone deficiencies are common after cranial radiation for tumors remote from hypothalamo-pituitary axis and may not develop for many years. Growth hormone deficiency is the commonest, followed by gonadotrophin, ACTH, and TSH deficiency. As radiation therapy and chemotherapy for patients with tumors of the brain and surrounding structures improve, follow-up evaluation will need to focus less on the possibility of tumor recurrence and more on the delayed effects of therapy, certainly including the endocrine effects. Such patients should therefore have annual assessments of hypothalamic-pituitary function for the rest of their lives. Anterior pituitary hormones can be assessed by measuring serum concentrations of gonadotropins, prolactin, testosterone, TSH, and thyroxin. Dynamic tests are required to assess corticotropin and GH secretion.

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