Growth Hormone and Prolactin Secretion after External Cranial Irradiation for Extrasellar Tumours

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Abstract

Background : Deficiency of one or more anterior pituitary hormones may follow treatment with external radiation when hypothalamo-pituitary axis lies within the field of radiation. Patients with brain tumours who are treated with radiation frequently have growth hormone (GH) deficiency, other neuro-endocrine abnormalities are presumed to be uncommon. The present study has been undertaken with the aim to study GH and prolactin secretion, their relationship with dose of radiotherapy and duration after radiotherapy in patients who have received extracranial radiation for extrasellar tumours.

Method : In this study, 96 patients who underwent cranial radiation before 12 months, were evaluated. Basal 8 a.m. venous blood samples were taken for estimation of prolactin and GH. Insulin tolerance test was performed for stimulated GH levels.

Result: GH deficiency was present in 59% patients. Isolated GH deficiency was present in 12 (21%) cases, whereas others had associated hormone deficiency. Height percentiles of prepubertal and pubertal patients were 10th to 25th (-1.5 to -0.5SD). Patients with isolated GH deficiency had received significantly higher radiation dose than normal pituitary function (5795 ± 24 vs 4908 ± 71 , $p=0.001$). Proportion of patients with GH deficiency increased with increasing dose of radiation ($p=0.12$), fractional dose of radiation ($p=0.08$) and increasing duration after radiotherapy ($p=0.038$). GH levels among all decreased significantly with increasing dose of radiation ($p=0.02$). Hyperprolactinemia was present in 21% of cases. GH deficiency is more common with lower ($<5\text{ng/ml}$) and higher ($>15\text{ng/ml}$) prolactin levels.

Conclusion: GH deficiency is common after extracranial radiation for extrasellar tumours. GH deficiency is related to dose of radiation, fraction of radiation, and duration after radiotherapy. All prepubertal and pubertal patients with GH deficiency had their height percentile within normal range. Relation of prolactin and GH deficiency indicates that radiation affects both hypothalamus and pituitary.

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Key Words : Cranial radiation; Growth hormone deficiency; Hyperprolactinemia

Introduction

Deficiency of one or more anterior pituitary hormones may follow treatment with external radiation when hypothalamo-pituitary axis lies within the field of radiation. The radiobiologic impact of an irradiation schedule is dependent on the total dose, number of fractions and duration [1]. With the better prognosis of certain types of brain tumours, chronic damage following external irradiation of the normal pituitary, delivered during radiotherapy of the neoplasms of head, is more commonly appreciated than in the past [2-6]. Patients with brain tumours who are treated with radiation frequently have GH deficiency, other neuro-endocrine abnormalities are presumed to be uncommon [2]. Clinical damage to the pituitary gland is usually manifested months to years after treatment and is preceded by a long subclinical phase. The present study has been undertaken with the aim to study GH and prolactin secretion, their relationship with dose of radiotherapy and duration after radiotherapy in patients who have received extracranial radiation for non-pituitary pathology.

Material and Methods

In this prospective study, 96 patients who underwent cranial radiation by (Theratron 870 E Cobalt 60 Teletherapy unit), at least 12 months before, at the radiotherapy department of the Malignant Diseases Treatment Centre (MDTC), Pune, 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 haematological, renal and hepatic functional parameters were assessed. GH and prolactin assessment was done the following way:

Growth Hormone : Basal 8 a.m. venous blood samples were taken for estimation of basal GH. Insulin tolerance test was performed after overnight fast unless contraindicated (history of ischemic heart disease, cerebrovascular accident or convulsions). A serum level of $>5\text{ng/ml}$ in adults and $>10\text{ng/ml}$ in children of less than 18 years was taken as normal.

Prolactin : Basal 8 a.m. 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 female less than 20 ng/ml was considered normal [8]. Other hormonal assays were also performed to assess pituitary function.

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 $\pm$ standard error.

Results

Mean age of the patients was 32 ± 0.10 years (8-60 years). Male to female ratio was 3:1. The commonest cranial tumour was astrocytoma (63%), followed by oligodendroglioma (17%), and others (20%). Most of the patients (63 patients - 66%) received chemotherapy within 6 months of radiotherapy. Among all 84 (88%) patients had evidence of pituitary dysfunction. GH deficiency was the commonest, present in 57 (59%) of cases. All the patients below 15 years and above 45 years showed evidence of GH deficiency. Isolated GH deficiency was present in 12 (21%) cases. 19 cases of GH deficiency (33%) were associated with hypoadrenalism (12 cases), hypogonadism (5 cases) or hypothyroidism (2 cases). All 26 cases of panhypopituitarism (46%) had GH deficiency along with two other hormone deficiencies. Most of the patients (63 patients - 66%) received chemotherapy within 6 months of radiotherapy. There was no significant difference in basal (0.61 ± 0.01 vs 0.91 ± 0.04 , $p=0.16$) or stimulated peak (5.60 ± 0.10 vs 6.68 ± 0.19 , $p=0.56$) GH level in recipient and non recipient of chemotherapy.

There were 6 patients ranging from 8-15 years, who were evaluated between 20 to 48 months after radiotherapy. There was no record of previous height parameters. However, at the time of evaluation, their height parameters were between 10th to 25th percentiles (-0.5 to -1.5 SD).

Patients with GH deficiency received higher radiation dose and fraction. Patients with isolated GH deficiency received significantly higher radiation dose than those with normal pituitary function (5795 ± 24 vs 4908 ± 71 , $p=0.001$). Proportion of patients with GH deficiency increased with increasing dose of radiation (Table 1), fractional dose of radiation (Table 2) and increasing duration after radiotherapy (Table 3). GH levels among all decreased significantly with increasing dose of radiation ($p=0.02$) (Table 1). Patients with GH deficiency received significantly higher fractional doses of radiation than those without GH deficiency (188 ± 0.30 vs 181 ± 0.46 rads, $p=0.042$).

Fig. 1 : Effect of radiation dose on mean prolactin levels

Table 1

Radiation dose and GH deficiency

Dosage of radiation	No of patients	GH deficiency	Peak GH (ng/ml)
Upto 5000 rads	24 (25%)	10 (42%)	8.56 ± 0.35
5001-6000 rads	63 (65%)	41 (65%)	5.12 ± 0.09
More than 6000 rads	9 (10%)	6 (67%)	4.99 ± 0.46
p value		0.12	0.02

Table 2

Radiation dose fraction and GH deficiency

Dose fraction	No of patients	GH deficiency*
Upto 150 rads	12 (12.5%)	4 (33%)
151-2000 rads	82 (85.5%)	51 (62%)
More than 200 rads	2 (2%)	2 (100%)

*Chi-square 5.01, $p = 0.08$

Table 3

Duration after radiation and GH deficiency

Duration	No (%)	GH deficiency*
< 18 months	30 (31%)	16 (53%)
19-36 months	32 (33%)	21 (66%)
> 36 months	34 (36%)	20 (59%)

*Chi-square 6.52, $p = 0.038$

Table 4

Relation between prolactin level and GH deficiency

Prolactin level (ng/ml)	No (%)	GH deficiency*
1-5	21 (22%)	17 (81%)
5.1-10	25 (26%)	11 (44%)
10.1-15	28 (29%)	13 (46%)
> 15	22 (23%)	16 (73%)

*Chi-square 10.08, $p = 0.018$

Hyperprolactinemia was present in 21% of cases. It was more frequent in males than females (25% vs 8%). Cases were evenly distributed among the age group between 5-45 years. Serum prolactin levels also decreased significantly with increase in dose of radiation from <5000 rads to 6000 rads, however there was no further decline with increase in dose above 6000 rads (Fig 1). GH deficiency was more common with lower (<5ng/ml) and higher (>15 ng/ml) prolactin levels (Table 4).

Discussion

GH deficiency is often the first and most frequently noted deficiency after cranial radiation [4,7-9]. 57 patients (59%) had GH deficiency in this study. GH deficiency among survivors after cranial radiotherapy has ranged from 26-100% depending upon age of patients, radiation dose, radiation fraction and time lag after radiation [4,10-12].

In the present study, there were four pre-pubertal

(age 8-12 years) and two pubertal (13 years) patients. Their pre-operative, pre and post radiotherapy height measurements were not available. At the time of evaluation, their height percentiles were 10th to 25th (-1.5 to -0.5 SD). However, all these patients had evidence of GH deficiency on stimulation test. Growth failure has been reported in many small studies after radiotherapy in children with nasopharyngeal carcinoma [10,13]. However, in this study, one prepubertal patient of nasopharyngeal carcinoma was evaluated 4 years after radiotherapy. Though he had subnormal response to insulin-induced hypoglycaemia, his height parameter remained within normal range (-1.5 SD). Further follow-up may reveal subtle growth failure in this child. Normal growth has been described despite abnormalities in GH secretion in recipient of cranial irradiation in childhood [5,9,14,15].

Among patients with GH deficiency 12 cases (21%) had isolated GH deficiency. Isolated hormonal deficiency after cranial irradiation is common [4,7,8]. Patients with isolated GH deficiency had received significantly higher radiation dose than patients with normal pituitary function. Proportion of patients with GH deficiency increased with increasing dose of radiation. GH levels decreased significantly with increasing dose of radiation. Patients with GH deficiency received significantly higher fractional doses of radiation than those without GH deficiency. Proportion of patients with GH deficiency significantly increased with increasing fractional dose of radiation. GH deficiency can occur after doses as low as 18 Gy, whereas other hormone deficiency is observed with doses more than 40 Gy [9]. Adult patients given total body radiation of 1000-1300 rads revealed normal growth hormone response to provocative stimuli [16]. At lower doses (20-24 Gy) the only effect may be altered GH secretory pattern and subnormal response to insulin-induced hypoglycaemia [17]. With intermediate and higher doses, GH response to arginine is impaired, and the frequency and amplitude of pulsatile GH secretion is decreased [5,6].

GH deficiency was the commonest pituitary hormone deficiency in present study, which is similar to that observed with many cases of pituitary macroadenoma [18]. However, there were no local pituitary abnormalities in patients of this study. Hence, GH deficiency could be due to high radiosensitivity of GHRH neurons in the hypothalamus or the pituitary somatotrophs. It seems that various cells of pituitary gland show differential radiosensitivity depending upon their mitotic potential. Pituitary somatotrophs have faster doubling time in tissue culture after lactotrophs; hence somatotrophs and lactotrophs are more likely to be

sensitive to radiation damage. In this study, most patients developed GH deficiency within 36 months after radiation. Furthermore, GH deficiency was observed more frequently with lower (<5 ng/ml) and higher prolactin level (>15 ng/ml). Lower prolactin level suggests direct radiation damage to lactotrophs and higher level hypothalamic dysfunction. Hence, result of this study suggests that GH deficiency is due to both hypothalamic and pituitary damage. Similar views have been expressed by other authors [4,6].

Hyperprolactinemia occurs commonly after head and neck irradiation. In this study, 20 patients (21%) had hyperprolactinemia. Amongst these, 18 were males and 2 were females. 66% of male patients complained of decreased libido and impotence. Amenorrhoea without galactorrhoea was present in females with hyperprolactinemia. In other series, the incidence of hyperprolactinemia ranged from 20% to 87% [8,11,19]. Hyperprolactinemia was more common in females in other studies [11,12]. Radiation damage to the hypothalamus leading to loss of the normal inhibition of PRL secretion is the proposed mechanism for this effect. Hyperprolactinemia occurred less frequently than expected in this study, which indicates high sensitivity of lactotrophs to direct radiation damage. There was no relationship observed between serum prolactin concentration and radiation dose, fraction and duration after radiotherapy, but serum prolactin declined with increasing dose of radiation.

This study highlights that GH deficiency is common after cranial radiation for tumours remote from hypothalamo-pituitary axis and may not develop for many years. GH deficiency is related to effect of radiation of hypothalamus and pituitary. GH deficiency in prepubertal and pubertal patients does not correlate with current height measurement and may require long term follow up for height velocity to assess the requirement of growth hormone therapy. As radiation therapy and chemotherapy for patients with tumours of the brain and surrounding structures improve, follow-up evaluation will need to focus less on the possibility of tumour recurrence and more on delayed effects of therapy, certainly including the endocrine effects. Such patients should therefore have annual assessment of hypothalamic-pituitary function.

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Transpired in Court

Q : Doctor, before you performed the autopsy, did you check for a pulse

A : No

Q : Did you check for blood pressure?

A : No

Q : Did you check for breathing?

A : No

Q : So, then it is possible that the patient was alive when you began the autopsy?

A : No

Q : How can you be so sure, Doctor?

A : Because his brain was sitting on my desk in a jar.

Q : But could the patient have still been alive nevertheless

A : It is possible that he could have been alive and practising law somewhere.