

## Hypothalamic-Pituitary Dysfunction Following External Cranial Irradiation

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### ABSTRACT

**Background:** Deficiency of one or more anterior pituitary hormones may follow treatment with external radiation when the hypothalamic-pituitary axis falls in the fields of radiation.

**Patients and methods:** Twenty eight patients (12 children with a mean age of  $6.92 \pm 2.78$  years and 16 adults with a mean age of  $36.56 \pm 13.38$  years) were included in the study. The radiation dose received ranged from 28 to 50 Gy in children and 45 to 60 in adults. Serum concentration of GH was measured with insulin, basal serum estimation of thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), prolactin (PRL), luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone were estimated before and after irradiation.

**Results:** Eight patients in the pediatric group (66%) and 2 patients in the adult group had GH deficiency. Fifty percent of the pediatric group and 6.25% of the adult group had low serum TSH. Three patients in the pediatric group had ACTH deficiency. Twenty five percent of the pediatric group and 6.25% of the adult group had low serum LH/FSH. Four patients in both groups had elevated PRL. Testosterone level was low in three patients in the pediatric group and one patient in the adult group. There were significant negative correlation between serum peak GH, ACTH, LH/FSH, testosterone and the dose of irradiation.

**Conclusion:** Patients exposed to high-dose radiotherapy (> 35 Gy) to the hypothalamic-pituitary axis, a variety of endocrine abnormalities may occur, including deficiencies of GH, TSH, ACTH and LH/FSH as well as hypersecretion of prolactin.

**Key Words:** Brain radiation - Hormone deficiency - Hypothalamic-pituitary axis.

### INTRODUCTION

Children and adults with brain tumors who are treated with cranial irradiation may subsequently have abnormal neuroendocrine function [9,13,18,19,28]. Deficiency of one or more anterior

or pituitary hormones may follow treatment with external radiation when the hypothalamic-pituitary axis falls in the fields of radiation [14,27]. Deficiency of growth hormone (GH) is common, but hypothyroidism and gonadal disturbances are reported and are presumed to occur only after particularly high dose of radiation [2,35]. Growth hormone deficiency may develop after cranial irradiation, it is very common following radiation therapy that exposes the hypothalamic-pituitary region to doses in excess of 18 to 20 Gy [23,33]. The greater the dose of irradiation, the higher and the earlier development of GH deficiency [8,31]. Cranial irradiation at a low dose (18-24 Gy) and at a high dose (> 35 Gy) is associated with early and precocious puberty, for unclear reasons girls are affected more than boys [21]. Most patients who experience premature sexual maturation also have been found to be GH deficient [22]. Primary hypothyroidism is a well-established complication of irradiation to the head and neck, it seems to be dose-related with a threshold of 10 Gy at a conventional daily fractions [31]. Clinically significant thyroid hypofunction is seen following irradiation with doses >20 Gy [10]. The aim of this research was to study the remote effect of external cranial irradiation on the function of the hypothalamic-pituitary axis.

### PATIENTS AND METHODS

Twenty-eight patients, 12 children and 16 adults were included in this study, with brain tumors remote from the hypothalamic-pituitary axis. The mean age of the patients included in the study at the time of irradiation in the pediatric

ric group was  $6.92 \pm 2.78$  years (range 3-12 years), 7 were males and 5 were females. In the adult group the mean age was  $36.56 \pm 13.38$  years (range 17-55 years), 12 were males and 4 were females. Treatment consisted of surgery, followed by whole or localized external cranial irradiation. The diagnosis was astrocytoma in 12, medulloblastoma in 7, ependymoma in 3, meningioma in 4 and oligodendroglioma in 2 patients. The radiation dose received ranged from 28 to 50 Gy in children and 45 to 60 in adults.

Medulloblastoma and infratentorial high grade ependymoma in children were treated with irradiation to the craniospinal axis (i.e. whole brain, posterior fossa and spinal cord) received 35 Gy (1.8 Gy/fraction) followed by boost to the posterior fossa to a dose 50 Gy. For low grade cerebral gliomas, local treatment volume were used with a dose of 50 Gy (1.8 Gy/fraction), this localized treatment is 1 cm the beyond the hypodense area on CT or T-1 weighted MRI image. For pediatric group we used wide local volume, based on preoperative tumor extent and reconfiguration of the brain after resection. Margin for wide local volume was typically defined at 2 cm beyond the hypodense area on CT or T-1 weighted image using 50 Gy with conventional fractionation. For adult group we planned to give 2-3 cm margin outside the tumor border and surrounding edema. We gave 45 Gy to the tumor and 2-3 cm margin, then a boost to a total of 60 Gy to 0-2 cm margins. All bilateral and medial cerebral hemispheric tumors were treated with parallel opposed portals. In medulloblastoma, we irradiated the whole subarachnoid space followed by a boost that depends on the tumor size and localization.

Patients were considered eligible if they had no evidence of tumor recurrence, had not received radiation or chemotherapy for at least 2 year, had been seizure-free during the last 1 year and with no previous hormone replacement or steroid therapy. All patients have been studied before external brain irradiation and 2 years after irradiation.

#### *Hormonal assessment:*

Venous blood samples were obtained after an over-night fast (12 hours), at 9 AM and examined using commercial kits by radioimmunoassay, before starting irradiation and 2 years after completion of irradiation. Serum concen-

tration of GH was measured after stimulation with clonidine ( $0.15/\text{m}^2$ ). Values above 1 ng/ml and below 7.0 ng/ml were considered normal response. Basal serum estimation of thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), prolactin (PRL), luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone were estimated. After obtaining the basal samples, all patients received thyrotropin-releasing hormone (TRH)  $7 \mu\text{g}/\text{kg}$  body weight, blood samples were then drawn every 30 minutes for 2 hours for measurement of the peak serum concentration of TSH; no rising in the decreased TSH level denoting a pituitary hypothyroidism. The normal values were as follow: TSH: 0.35-5.5 IU/ml, ACTH: 10-60 pg/ml, PRL: males 2.1-17.7 ng/ml, females 2.8-29.2 ng/ml, LH: children 0.5-4.0 mIU/ml, males 1.3-12.9 mIU/ml, females (mid cyclic) 25-57.3 mIU/ml, FSH: children 0.5-3.7 mIU/ml, males 1.4-18.1 mIU/ml, females (mid cyclic) 3.4-33.4 mIU/ml and testosterone: children 0.06-0.2 ng/ml, males 2.41-8.27 ng/ml and females 0.14-0.76 ng/ml.

The statistical analysis used in the present study included calculation of the mean, standard deviation (SD), analysis of variance (ANOVA) test followed by least significant difference (LSD) test if the F value was significant and the correlation coefficient test. A statistical significant value was considered if the *p*-value was below 5%.

## RESULTS

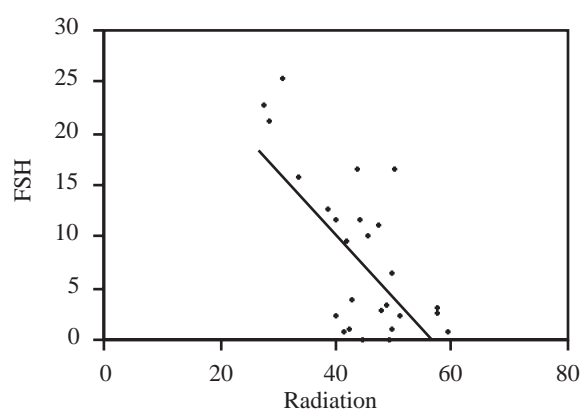
In the present study, we compared the level of hypothalamic-pituitary axis hormones pre-irradiation and 2 years after irradiation. As regards GH, 8 patients in the pediatric group (66%) had GH deficiency. The mean values before and after irradiation were  $4.21 \pm 1.48$  ng/ml and  $1.89 \pm 1.77$  ng/ml respectively. Only 2 patients out of the 16 patients studied in the adult had GH deficiency (12.5%). The mean value before irradiation was  $5.60 \pm 1.67$  ng/ml and after irradiation was  $5.69 \pm 2.23$  ng/ml. A statistically significant difference was found in the pediatric group and not in the adult group (*p* = 0.001, 0.873 respectively). Serum TSH was decreased in 4 patients of the pediatric group (30%), with a mean of  $2.46 \pm 1.45$  IU/ml before irradiation and  $2 \pm 2.09$  IU/ml after irradiation. There was no significant difference before and after radiation (*p* = 0.505). In the adult group,

only 1 patient had low serum TSH (6.25%) after irradiation with a mean value of  $2.8 \pm 1.51$  IU/ml,  $2.45 \pm 1.8$  IU/ml before and after irradiation respectively. Also, there was no significant difference between both levels ( $p = 0.457$ ). The 5 patients with decreased TSH level showed a blunted response ( $< 5$  m $\mu$ /L) to TRH stimulation. Three of the 12 pediatric patients (25%) had lower level of ACTH deficiency after irradiation, their mean value was  $28.71 \pm 11.64$  pg/ml before irradiation and  $20.20 \pm 15.39$  pg/ml after irradiation. In the adult group no one showed ACTH deficiency, the mean serum value was  $34.93 \pm 14.40$  pg/ml and  $32.40 \pm 11.76$  pg/ml before and after irradiation respectively. The mean serum ACTH was significantly different in the pediatric age group before and after irradiation ( $p = 0.029$ ) and there was no significant difference in the adult group ( $p = 0.634$ ). Of the 12 patients studied for LH/FSH in the pediatric group, 3 of them (25%) had deficiency with a mean value for LH of  $2.17 \pm 1.11$  mIU/ml and  $1.39 \pm 1.13$  mIU/ml before and after irradiation respectively and for FSH,  $2.4 \pm 0.88$  mIU/ml and  $1.33 \pm 1.19$  mIU/ml before and after irradiation respectively. There was a significant difference before and after irradiation in both LH and FSH ( $p = 0.049$  and  $0.045$  respectively). One patient in the adult group had low level of LH/FSH (6.25%). The mean value for LH was  $13.61 \pm 13.84$  mIU/ml before irradiation and  $11.10 \pm 8.94$  mIU/ml with no significant difference ( $p = 0.181$ ). The mean value for FSH was  $17.09 \pm 8.18$  mIU/ml and  $12.51 \pm 7.22$  mIU/ml before and after irradiation respectively. There was no significant difference in both hormones

before and after irradiation ( $p = 0.181$  and  $0.07$  respectively). Elevated prolactin level was found in 4 patients of the pediatric group (33%) and 4 patients of the adult group (25%). Their mean values were  $11.55 \pm 7.21$  ng/ml before irradiation and  $16.41 \pm 10.46$  ng/ml after irradiation in the pediatric group and  $15.73 \pm 7.32$  ng/ml before irradiation and  $17.05 \pm 10.35$  ng/ml after irradiation in the adult group. Both groups had no statistical significant difference between their levels before and after irradiation ( $p = 0.203$  and  $0.614$  respectively). Tables (1&2) summarized the result of the study showed to evaluate hormonal deficiency in both pediatric and adult groups.

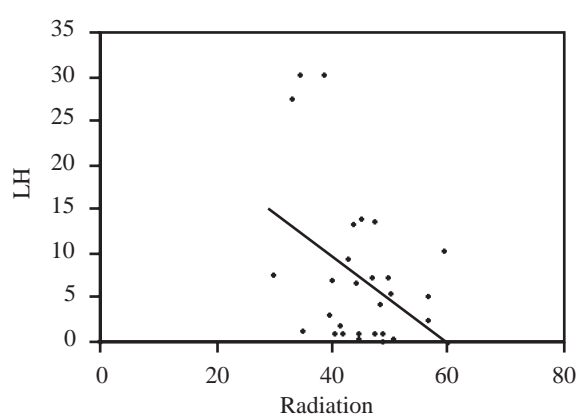
Three patients of the pediatric group had testosterone deficiency (25%), with a mean value for the group before irradiation of  $0.14 \pm 0.06$  ng/ml and  $0.11 \pm 0.07$  ng/ml after irradiation with no statistical significant difference ( $p = 0.202$ ). In the adult group, only one case had testosterone deficiency (6.25%). The mean value of this group before irradiation was  $4.47 \pm 2.90$  ng/ml and after irradiation was  $4.5 \pm 2.81$  ng/ml again with no statistical significant difference ( $p = 0.95$ ). Moreover, there was no significant difference in the hormonal levels before and after irradiation between males and females ( $p > 0.5$ ).

There were significant negative correlation between serum peak GH concentration, ACTH, LH/FSH, testosterone and dose of irradiation, but this significant correlation was not found between TSH and prolactin and dose of irradiation (Table 3, Figs. 1,2).



Correlation between radiation and FSH

Fig. (1): Correlation between dose of irradiation and level of FSH.



Correlation between radiation and LH

Fig. (2): Correlation between dose of irradiation and level of LH.

Table (1): Hormonal functions in the pediatric group.

Hormones	Range		Mean $\pm$ SD		No.	p
	Before XRT	After XRT	Before XRT	After XRT		
GH# (ng/ml)	1.1-6.1	0.6-6	4.21 $\pm$ 1.48	1.88 $\pm$ 1.77	8	0.001*
TSH (IU/ml)	0.39-5.1	0.11-5	2.46 $\pm$ 1.45	2.00 $\pm$ 2.09	4	0.505
ACTH (pg/ml)	11-49	3.7-50	28.71 $\pm$ 11.64	20.2 $\pm$ 15.39	3	0.029*
PRL (ng/ml)	0.7-30.1	2.8-27.8	16.41 $\pm$ 10.46	8.15 $\pm$ 8.2	4\$	0.203
LH (mIU/ml)	0.85-4	0.19-35	2.17 $\pm$ 1.11	1.39 $\pm$ 1.13	3	0.049*
FSH (mIU/ml)	0.8-3.7	0.1-3.1	2.4 $\pm$ 0.88	1.33 $\pm$ 1.19	4	0.045*
Testosterone (ng/ml)	0.06-0.2	0.01-0.2	0.14 $\pm$ 0.06	0.11 $\pm$ 0.07	3	0.202

XRT = External brain irradiation.

No. = Number of hormone deficiency.

\$ = Hypersecretion of PRL.

# = GH level after stimulation.

\* = Significant difference p significant if &lt; 0.05.

Table (2): Hormonal functions in the adult group.

Hormones	Range		Mean $\pm$ SD		No.	p
	Before XRT	After XRT	Before XRT	After XRT		
GH# (ng/ml)	1.9-7	0.1-7.3	5.6 $\pm$ 1.67	5.69 $\pm$ 2.23	2	0.873
TSH (IU/ml)	0.39-5	0.32-5.3	2.8 $\pm$ 1.51	2.45 $\pm$ 1.8	1	0.457
ACTH (pg/ml)	10-58	12-58	34.93 $\pm$ 14.4	32.4 $\pm$ 11.76	0	0.634
PRL (ng/ml)	2.9-28	1.9-38.9	15.73 $\pm$ 7.32	17.05 $\pm$ 10.35	4\$	0.634
LH (mIU/ml)	1.9-47	1.9-29	13.61 $\pm$ 13.84	11.1 $\pm$ 8.94	1	0.181
FSH (mIU/ml)	6.6-33	1.2-26	17.09 $\pm$ 8.18	12.54 $\pm$ 7.22	1	0.07
Testosterone (ng/ml)	0.2-8.2	0.011-8.12	4.47 $\pm$ 2.9	4.5 $\pm$ 2.81	1	0.95

XRT = External brain irradiation.

No. = Number of hormone deficiency.

\$ = Hypersecretion of PRL.

# = GH level after stimulation.

\* = Significant difference p significant if &lt; 0.05.

Table (3): Correlation between irradiation and different hormones.

	Irradiation	
	r	p
GH	0.118	0.551
TSH	0.117	0.552
ACTH	0.413	0.029*
PRL	0.062	0.755
LH	0.400	0.035*
FSH	0.614	0.001*
Test	0.527	0.004*

\* Statistically significant.

## DISCUSSION

Endocrine dysfunction after cranial irradiation have been documented in many retrospective studies, but other factors as type of brain tumor or elevation of intracranial pressure (ICP) on hormone release has not been considered in these studies [7,25,30]. In our prospective

study, all patients had brain tumors remote from the hypothalamic-pituitary axis.

All cases had normal hormonal assay before the study, despite the presence of tumor or increased ICP. Despite the presence of a considerable number of GH deficiency in our study, which indicate that the secretion of GH is always the first to be impaired, other pituitary deficits may be encountered in a well defined order in later years [15]. In this study, the dose of irradiation was an important determinant of the incidence of GH deficiency. This finding is matched with the result of other studies [5,6,8,15,16,23,29,32]. It was found that the total dose of irradiation delivered to the brain particularly the hypothalamic-pituitary region, was the major determinant of the speed of onset as well as the incidence and severity of anterior pituitary hormone deficiency [16]. The greater the dose of irradiation, the more likely the patient will have pituitary deficiency and the earlier the

deficiencies will occur. Other factors of irradiation, such as the fraction size, number of fractions and the duration of treatment, also, are important among adult treated with (10-13 Gy) of total body irradiation [17]. GH secretion was normal, in adult, 2-4 years later. Whereas, a higher proportion of children so treated became GH-deficient after a similar interval. Furthermore, the central nervous system of a young child may be more radio-sensitive than that of an older child [27]. TSH deficiency has been identified in 5 of our patients, whereas 4 of 15 children in another study had either primary, secondary or tertiary hypothyroidism [11]. The threshold dose required to induce TSH deficiency is not known. At hypothalamic-pituitary dose < 40 Gy, TSH deficiency is unusual. In our study, about 18% of patients had TSH deficiency, but in another pediatric series following irradiation of 40 Gy-50 Gy, the incidence of TSH deficiency was < 10% after a mean follow-up of 9-10 years [18,20]. This difference between this study and the other studies is not clear, but other factors may contribute for this difference, as the type of irradiation, fractionation dose, site of irradiation, presence of cranio-spinal irradiation and the age of onset. In another study by Constine et al. [9], he noted a 65% incidence of TSH deficiency in patients treated with a mean dose of 57 Gy. Since our patients were followed for only 2 years, it is possible that hypothyroidism may be a delayed phenomenon and may become evident in later years. The prevalence of primary thyroid dysfunction was 23% compared to 0% for secondary dysfunction in a study by Livesey and Brook [18]. The occurrence of primary hypothyroidism in patients who received cranio-spinal radiation was expected, because their thyroid gland was irradiated directly. Up to 80% of patients with Hodgkin's disease treated with mantle radiation have primary hypothyroidism and the effect is dose-dependent [4,12,34]. This could be due to radiation damage to the thyroid follicular cells, the thyroid vasculature, or the supporting stroma [26]. Limited data concerning the relationship between cranial irradiation and the evolution of ACTH deficiency is present. The interpretation of the data is complicated by the fact that different investigators have utilized different methods of evaluating the ACTH-adrenal axis and the incidence of adrenal insufficiency has varied depending on the testing procedure used [31]. Radiation induced ACTH

deficiency is relatively uncommon at the dose used in our study. Only 25% of our pediatric group tested was found to have an ACTH deficiency. Clinically apparent ACTH deficiency is distinctly uncommon in patients receiving irradiation to the hypothalamic pituitary axis with doses in the range of 35 Gy to 55 Gy [20]. Following doses of more than 50 Gy, the reported incidence of ACTH deficiency varies from 18% to 35% during follow-up periods ranging from 5 to more than 15 years [10,14]. Nevertheless, since this impairment can potentially be life-threatening, it should be ruled out in all children who have had CNS irradiation particularly because these patients are often treated with dexamethasone in addition which might have a prolonged suppressive effect on the hypothalamic-pituitary-adrenal axis [1]. In the present study, 8% of pediatric group who received irradiation < 35 Gy and 16% who received irradiation > 35 Gy and 6.25% in the adult group who received > 45 had LH/FSH deficiency. There is no detailed information on the threshold dose for LH/FSH deficiency. Such deficiency seems to be rare following doses less than 40 Gy to the hypothalamus and pituitary [4,19,24]. There is a progressive increase in the deficiency incidence as the dose exceeds 50 Gy. In the higher dose range, gonadotrophin deficiency has been noted in 20-50% of patients followed for long periods, making it the second most common pituitary abnormality in most series [9,14,24]. Hormonal deficiencies may be treated successfully with replacement therapy, our study confirms that GH deficiency is a common sequela of cranial irradiation and preliminary data suggest that the incidence of tumor recurrence is not higher in GH-treated patients [3]. All patients in the present study who needed hormonal replacement received substitutive treatment and followed after that.

In conclusion, patients exposed to high-dose radiotherapy (> 35 Gy) to the hypothalamic-pituitary axis, may develop a variety of endocrine abnormalities, including deficiencies of GH, TSH, ACTH and LH/FSH as well as hypersecretion of prolactin. These patients are at a high risk for developing endocrine disturbances and require long-term endocrine follow-up.

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