Growth Hormone Secretion and Hypothalamic-Pituitary-Thyroid Axis Function after Cranial Radiotherapy in Children

Mohammed Abdel-Fadeel Ragab
From the department of Pediatrics, Faculty of Medicine, Alexandria University, Egypt.

Abstract:

Background: *When the hypothalamic-pituitary axis (HPA) is included in the treatment field in children and adults, a variety of neuroendocrine disturbances are more common especially in children than has been appreciated in the past. This study was carried out to evaluate growth hormone secretion and the hypothalamic-pituitary-thyroid axis function in children after cranial radiotherapy.*
Subjects and Methodology*: Twenty children (12 boys and 8 girls) who received cranial/craniospinal radiation therapy were included in this study. Their mean age at the time of therapy was 6 1/2 years (range, 3 to 10 years), and at the time of the study, it was 9 years (range, 5 to 13 years). The mean interval between therapy and testing was 2 years and 4 months (range,1 to 3 years). All the patients were children (<16 years) when tested and the dose of radiation ,delivered to the hypothalamic-pituitary region, ranged from 27 to 45 Gy (1 Gy =100 rads). The serum concentrations of the basal and peak growth hormone, total and free T4, total T3, and basal and peak TSH were measured by radioimmunoassay. A group of 12 age-matched healthy children served as control for estimation of the normal range of these hormones.*
Results: *The mean serum basal and peak GH concentrations after stimulation with clonidine in the included patients were significantly lower than those in the control group. Forty-five percent and 65% of the patients had below-normal basal and peak GH secretion respectively. There was a significant inverse correlation between the serum peak GH concentration and both the dose of radiation and the interval between therapy and testing. The mean serum total T4, free T4, and total T3 concentrations in the patients were significantly lower than those in the healthy subjects. Thirty-five percent, 45%, and 25% of the patients had below-normal serum total T4, free T4, and total T3 respectively. There was no significant difference between the 2 studied groups as regards the mean serum basal and peak TSH concentrations in response to stimulation with thyrotropin-releasing hormone. The most common pattern of abnormality in the hypothalamic-pituitary-thyroid axis function (66.66%) was low serum concentration of free T4 and normal basal and peak serum TSH concentrations which is suggestive of hypothalamic hypothyroidism. Negative significant correlations were found between the dose of radiation and serum concentrations of total T4, free T4, and T3, while inverse significant correlation was observed between the interval between radiation and testing and serum free T4 concentration only. In addition , an inverse correlation was found between the age of the patient when treated and both the serum basal and peak TSH concentrations.*
Conclusion: A *large percentage of children develop growth hormone deficiency (GHD) and hypothyroidism within 2 years after receiving doses of cranial radiation ranging from 27 to 45 Gy. Higher doses of radiation and longer interval between therapy and evaluation are associated with higher incidence of both GHD and hypothyroidism. Younger age children are more susceptible to develop hypothyroidism when they are exposed to cranial/craniospinal radiation than older children. Routine testing for possible GHD and thyroid dysfunction should be included in the follow-up procedures of this population and supplement therapy should start as early as necessary.*

Introduction:

Long-term survival in children with cancer has increased markedly in the past 15 years. Primary brain tumors represent the largest group of malignant solid tumors in children. External cranial and craniospinal radiation has proven to be a major tool in the treatment of various malignant brain tumors.[1] However, a variety of neuroendocrine disturbances are observed following treatment with external radiation therapy when the hypothalamic-pituitary axis (HPA) is included in the treatment field.[2] Clinical damage to the pituitary and thyroid glands usually occur months to years after treatment and is preceded by a long subclinical phase.[3,4] The study of the possible disturbances in both secretion of growth hormone and the function of the hypothalamic-pituitary-thyroid axis after cranial radiotherapy in children and the relation between these changes , if any, and the age of the child at treatment, the dose of radiation , and the

time elapsed since irradiation were the aim of this research.

Subjects and Methods:

The study population consisted of two groups. The first group included 20 children (12 boys and 8 girls) with history of primary brain tumors anatomically distant from the hypothalamic-pituitary axis and treated with cranial/craniospinal irradiation. They were attending the outpatient oncology clinic in K.F.C.H., Kingdom of Saudi Arabia for follow up. The diagnosis was medulloblastoma in 11 children, astrocytoma in 4, fourth ventricular ependymoma in 3 and glioma in 2 children. Seventeen children received only cranial radiation and three had also received radiation to the spinal axis. The calculated dose of radiation delivered to the hypothalamus and pituitary ranged from 27 to 45 Gy (1 Gy = 100 rads). Patients were considered eligible if they had no evidence of tumor recurrence, had not received radiation or chemotherapy for at least one year, had been seizure-free during the last one year, the time elapsed since irradiation did not exceed 3 years and age of the children when tested was less than 16 years. Twelve age-matched healthy children were included as a control group for estimation of the reference ranges for the studied hormones. The selected healthy children were attending the ophthalmology outpatient clinic in K.F.C.H. for correction of errors of refraction. They had no history or clinical findings suggestive of any systemic disease and their weight and height were compatible with their chronological age. Informed consent was obtained from the parents of the patients and the healthy children included in this study.

Endocrinologic evaluation:

The selected patients and healthy subjects were investigated after an over-night fast (12 hours). Venous blood samples were obtained between 8 and 9 A.M for estimation of the basal serum concentrations of growth hormone (GH), total thyroxin (T4), free thyroxin (FT4), total triiodothyronine (T3), and thyrotropin (TSH). After obtaining the basal samples, all included children received thyrotropin-releasing hormone (TRH 7 µg/kg body weight; maximal dose, 200 µg) and an oral dose of clonidine (0.15 mg/m^2). Blood samples were then drawn every 30 minutes for 2 hr, for measurement of the peak serum concentration of thyrotropin (TSH) and growth hormone (GH) respectively. The serum was separated from the formed blood elements by centrifugation and kept frozen at –20^o C until analyzed by radioimmunoassay, using commercial kits provided by Diagnostic Systems Laboratories (DSL), Texas, USA. The tested hormones were assessed in only one occasion thus the data were cross sectional.

Statistical Analysis:

The results are expressed as the mean ± SD. The mean serum concentrations of the basal and peak GH, basal total and free T4, basal total T3, and basal and peak TSH were compared in the 2 studied groups using the un-paired t test when the data were normally distributed and Wilcoxon test when they were not. Statistical significance was accepted when $P < 0.05$. A patient's hormonal secretion was considered abnormal if the basal serum concentration was low or if the patient had a blunted response to provocative testing compared to the control subjects. The relation between the independent continuous variables (the age at irradiation, the time elapsed since irradiation, and the hypothalamic-pituitary axis radiation dose) and the dependent variables (peak GH, peak TSH, basal total and free T4, and total T3 serum concentrations) were analyzed by multiple linear regression.

Results:

The mean age of the patients included in the study at the time of radiation therapy was 6 ½ years (range 3 to 10 years), and at the time of the study, it was 9 years (range 5 to 13 years). The mean interval between therapy and testing was 2 years and 4 months (range 1 to 3 years) and all the patients were children (<16 years of age) when tested.

Growth hormone secretion study:

The mean serum basal and peak concentrations of GH secretion after stimulation using clonidine were significantly lower than those in the control group ($P<0.05$ and $P<0.001$ respectively). Nine (45%) and 13 (65%) of the patients studied had serum basal and peak GH concentration values less than the estimated normal range respectively (table I). There were significant negative correlations between serum peak GH concentration and both the dose of irradiation and the interval between radiation and testing ($P<0.001$ and $P<0.01$ respectively) but not the age of the child when treated (figures 1,2).

Hypothalamic-pituitary-thyroid axis function:

Table II portrays the results of the study done to evaluate the hypothalamic-pituitary-thyroid axis function. Five (25%) of the 20 patients had recent onset of symptoms and signs suggestive of hypothyroidism like lethargy, intolerance to cold, dry skin, constipation, or marked weight gain. The mean serum total T4, free T4, and total T3 concentrations

in the children who received cranial/craniospinal radiation therapy were significantly lower than those in the healthy subjects (P<0.01, P<0.001, and P<0.002 respectively). Seven (35%), nine (45%), and five (25%) patients had serum total T4, free T4, and total T3 concentrations below the estimated normal range respectively. All the patients with below-normal serum total T4 concentration had, as well, below-normal serum free T4 concentration. The mean basal and peak serum TSH concentrations in response to stimulation with TRH in the 20 patients were not significantly different from those in the control group. However, 2 patients had below-normal serum peak TSH concentration and 1 patient had supranormal basal and supranormal peak serum TSH concentrations in response to stimulation with TRH (table II). The 3 patients who received craniospinal radiation therapy had significantly lower mean serum free T4 concentration (P<0.05) and significantly higher mean serum basal and peak TSH concentrations (P<0.05 and P<0.01 respectively) compared to the mean values in the 17 patients who received only cranial radiation. The nine patients who had below-normal serum free T4 had variable results concerning serum basal and peak TSH concentrations. Six patients (66.66%) had normal serum basal and peak TSH concentrations in response to stimulation with TRH which is suggestive of hypothalamic hypothyroidism, two patient (22.22%) had normal serum basal and blunted response of TSH (<5.0 mU/L) to TRH which suggest either hypothalamic or hypopituitary hypothyroidism. The last one patient (11.11%) with below-normal serum free T4 concentration had supranormal basal and supranormal peak serum TSH concentrations after stimulation with TRH, a response reflecting injury to the thyroid gland. It is worth mentioning that this patient had received radiation to the spinal axis in addition to the cranial radiation. There were significant negative correlations between the dose of radiation and the serum concentrations of total T4 (P<0.05), free T4 (figure 3, P<0.01), and total T3 (P<0.05). There was negative significant correlation between the serum free T4 concentration and the interval between radiation and testing (figure 4, P<0.01), but not serum total T4, total T3, and basal and peak TSH concentrations and this interval. Both the basal and peak serum TSH concentrations after stimulation with TRH were negatively correlated with age of the patient at treatment (P<0.05 and <0.01 respectively). No significant correlations were found between other thyroid hormones and age in the patients treated with cranial radiation.

Table I: Serum basal and peak growth hormone concentrations in the patients who received Cranial / craniospinal radiation therapy and in healthy subjects.

	Number	*Basal GH (ng/ml)*	*Peak GH (ng/ml)*
Patients:	20		
Mean ± SD		1.9 ± 0.77*	10.43 ± 5.44**
Range		0.5 – 4.0	1.5 – 20.8
Control:	12		
Mean ± SD		3.2 ± 2.1	18.4 ± 5.0
Range		1.8 – 6.6	10.2 – 28.1

** P<0.05 , ** P<0.001.*

Table II: Hypothalamic-pituitary-thyroid axis function in the patients who received cranial/craniospinal radiation therapy and in healthy subjects.

	Nº.	*S.t.T4 Ug/dl*	*S.FT4 ng/dl*	*S.tT3 ng/dl*	*S.B. TSH mIU/L*	*S.P.TSH mIU/ml*
Patients:	20					
Mean ± SD		5.26 ± 2.07*	0.92 ± 0.3**	124.6 ± 25.3#	2.34 ± .85$	10.37 ±5.6 $
Range		2.1 – 9.6	0.42 – 1.4	78 – 166	1.2 – 4.6	2.2 – 25.4
Control:	12					
Mean ± SD		7.1 ± 1.4	1.18 ± 0.14	151 ± 16.6	1.98 ± 0.94	12.1 ± 3.8
Range		4.76 – 10.4	0.96 – 1.52	126 – 186	0.8 – 3.4	5 - 24

*S.tT4 : serum total T4, S.FT4: serum free T4, S.tT3: serum total T3, S.B.TSH: serum basal thyrotropin, S.P.TSH: serum peak thyrotropin. *P<0.01 , ** P<0.001, # P<0.002, $: Not significant.*

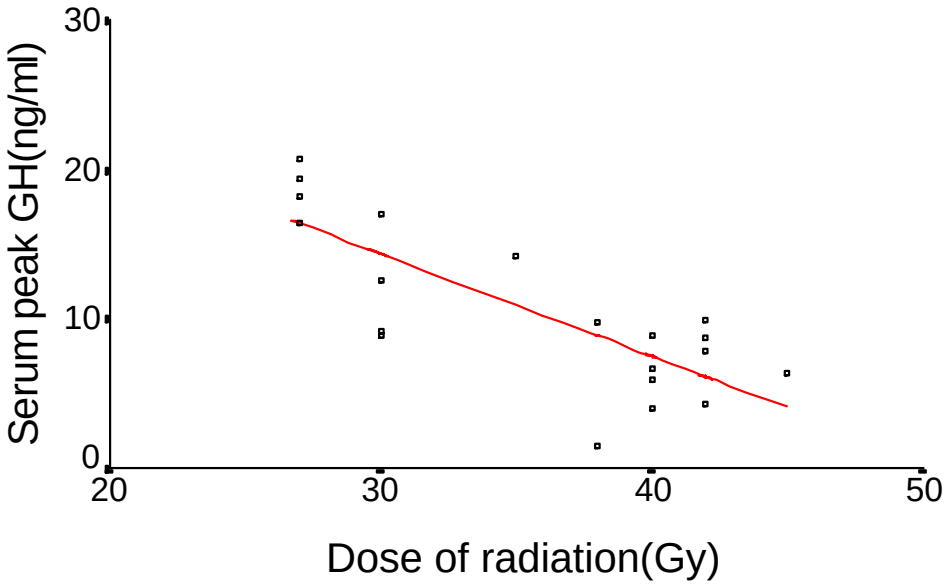

Figure 1: The relation between serum peak GH concentration in response to clonidine and the dose of radiation (r= -0.789, P<0.001)

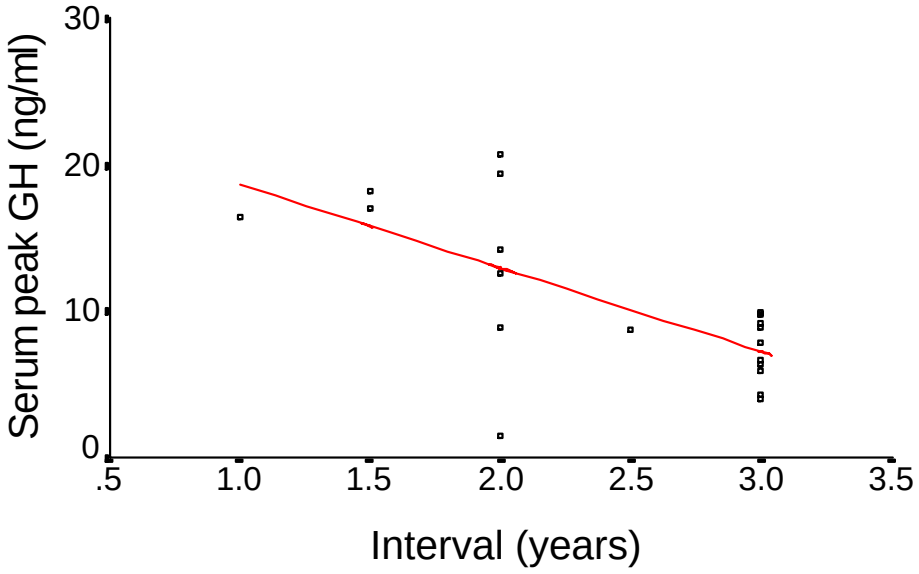

Figure 2: The relation between serum peak GH concentration in response to stimulation with clonidine and the interval between radiation and testing (r = -0.678, P<0.01)

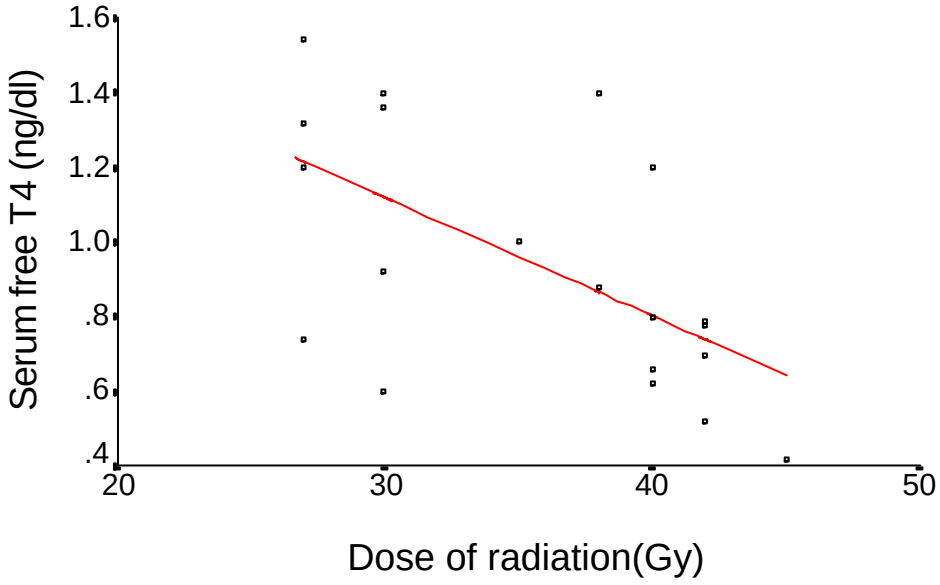

Figure 3: The relation between serum free T4 concentration and the dose of radiation (r = -0.569, P<0.01).

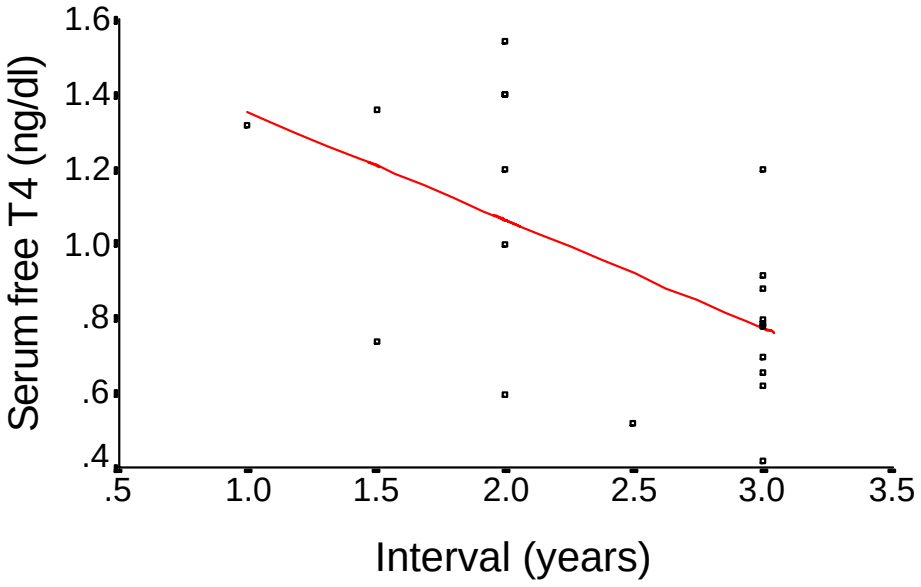

Figure 4: The relation between serum free T4 concentration and the interval between radiation and testing (r = -0.568, P<0.01)

Discussion:

Unfortunately, the dramatic improvement in the survival rates of children with cancer which is attributed, in large part, to the advent of multimodality therapy is associated with severe delayed toxicities that generally are more prevalent and of greater clinical significance when therapy is administered during childhood. The endocrine system seems to be particularly susceptible to damage from radiotherapy. Several retrospective [2,3,5-8] and prospective [9-13] studies have demonstrated that growth hormone deficiency (GHD) is the first and the most frequent pituitary deficiency to occur in children who receive cranial irradiation for tumors distant from the hypothalamus and pituitary region. Our results are consistent with these studies. We found that the mean serum basal

and peak growth hormone concentrations in response to stimulation using clonidine in the children who received cranial irradiation were significantly lower than those in the healthy subjects. Forty-five percent and 65% of our patients had below-normal serum basal and peak GH concentrations respectively. With respect to the mean interval between therapy and testing and the range of the radiation dose in our study, our data suggest that GHD can be diagnosed as early as 2 years after receiving 27 to 45 Gy as cranial radiotherapy for primary brain tumors. In this study, the dose of radiation was an important determinant of the incidence of GHD. This finding is in harmony with the results of other studies[1,2,9,13-17] that found that the total dose of radiation delivered to the hypothalamic-pituitary region is the major determinant of the speed of onset as well as the incidence and severity of anterior pituitary hormone deficiencies. Similar to other studies, [8-10,18-20] the interval between radiation therapy and testing was found to be another major factor in the incidence of GHD as we found a significant negative correlation between this interval and the serum peak GH concentration. While some studies [14,17,21] have demonstrated an age effect on the incidence of GHD, we did not find this relation which was the same conclusion reported by other investigators.[9,20,22] The site of radiation-induced damage leading to GHD might be either the hypothalamus or the pituitary gland. However, the normal serum GH responses to single bolus dose of GH releasing hormone in those with subnormal serum GH responses to the administration of arginine or insulin-induced hypoglycemia, and reduced spontaneous secretion of GH despite normal serum GH responses to pharmacologic stimuli, findings which are characteristic hormonal changes of hypothalamic disease.[18] In addition, the spectrum of endocrinologic abnormalities that occur and the fact that hypothalamus is more radiosensitive than the anterior pituitary indicate that hypothalamic dysfunction is more common than pituitary dysfunction.[2,23] Although the mechanism of radiation damage to the hypothalamus or pituitary is not known, it must involve a direct injury to the stroma or its microvasculature, or an injury to the vascular channels that transfer the hypothalamic hormones to the pituitary. The reported frequency of hypothyroidism in the patients who received cranial/craniospinal radiation therapy is variable from one study to another.[23,24] In this study, the mean serum concentrations of total T4, free T4, and total T3 were significantly lower than those in the healthy subjects. The greater percentage of the patients found to have below-normal free T4 (45%), as compared with low serum total T4 (35%) or total T3 (25%) concentrations, presumably reflects the sensitivity of the free T4 measurement in the assessment of thyroid function. Unlike another study in this field, [23] and consistent with others, [25-27] we found a significant negative correlation between the serum free T4 concentration and the dose of radiation which confirms that the dose of radiation is an important factor in the incidence of hypothyroidism in this population. The most common pattern of abnormality (66.66%) was low concentration of free T4 and normal basal and peak TRH-stimulated serum TSH concentrations, findings suggestive of TRH deficiency. This finding supports the findings of others[23,28,29] who reported that hypothalamic hypothyroidism is the commonest type of hypothyroidism in such study population. The occurrence of primary hypothyroidism in one of the three patients who received craniospinal radiation was expected and could be due to radiation damage to the thyroid follicular cells, the thyroid vasculature or the supporting stroma. The presence of significant inverse relation between serum basal and peak TSH concentrations confirm the conclusion of other investigators that younger age is an added co-factor which increases the risk of hypothyroidism.[20,23]

In conclusion, a large percentage of children develop GHD and hypothyroidism within 2 years after receiving doses of cranial radiation ranging from 27 to 45 Gy. Higher doses of radiation and longer interval between therapy and evaluation are associated with higher incidence of both GHD and hypothyroidism. Children of younger age are more susceptible to develop hypothyroidism when they are exposed to cranial/craniospinal radiation than older children. Routine testing for possible GHD and thyroid dysfunction should be included in the follow-up procedures and supplement therapy should start as early as necessary.

References:

1. Rappaport R, Brauner R. Growth & endocrine disorders secondary to cranial irradiation. Pedia Res 1989; 25(6):561-7
2. Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. Int J Radiation Oncology, Biol, Physics .1995;31(5): 1113-21.
3. Bieri S, Sklar C, Constine I, Bernier J. Late effects of radiotherapy on the neuroendocrine system. Cancer radiother. 1997; 1(6): 706-16.
4. Crom DB, Kaste SC, Tubergen DG, et al. Ultrasonography for thyroid scanning after head and neck irradiation in childhood cancer survivors. Medical Pediatr Oncol. 1997;28 : 15-21.
5. Romshe CA, Zipf WB, Miser A, Miser J, et al. Evaluation of growth hormone release and human GH treatment in children with cranial irradiation-associated short stature. J Pediatr 1984;104:177.
6. Duffner PK, Cohen ME, Voorhess ML, et al. Long-term effects of cranial irradiation on endocrine function in children with brain tumors. Cancer 1985;56:2189.
7. Brauner R, Czernichow P, Rappaport R. Croissance staturale apres irradiation du systeme nerveux central pour medulloblastome de la fosse posterieure. Analyse retrospecteve de 45 observations. Arch Fr Pediatr 1985;42:219.
8. Shalet SM, Beardwell CG, Morris Jones PH, Pearson D. Pituitary function after treatment of intracranial tumors in children. Lancet 1975;2:104-7.
9. Clayton PE, Shalet SM. Dose dependency of time of onset of radiation-induced growth hormone deficiency.J Pediatr 1991;118(2): 226-8.
10. Shalet SM. Irradiation-induced growth failure. Clin Endocrinol Metab 1986: 15: 591-606.
11. Littly MD, Shalet SM, Beardwell CG, Ahmed SR, Applegate G, Sutton ML. Hypopituitarism following external radiotherapy for pituitary tumors in adults. Q J Med 1989;70: 145-60.
12. Lam KSL, Tse VKC, Wang C, Yeung RTT, Ho JHC. Effects of cranial irradiation on hypothalamic pituitary function – a 5-year longitudinal study in patients with nasopharyngeal carcinoma. Q J Med 1991; 78: 165-76.
13. Brauner R, Rappaport R, Prevot C, et al. A prospective study of the development of growth hormone deficiency in children given cranial irradiation, and its relation to statural growth. J Clin Endocrinol Metab 1989;68(2): 346-51
14. Shalet SM, Beardwell CG, Pearson D, Morris-Jones PH. The effect of varying doses of cerebral irradiation on growth hormone production in childhood. Clin Endocrinol (Oxf). 1976;5 : 287.
15. Pomarede R, Czernichow P, Zucker JM, et al. Incidence of anterior pituitary deficiency after radiotherapy at an early age: Study in retinoblastoma. Acta Pediatr Scand 1984; 73: 115.
16. Littley MD, Shalet SM, Beardwell CG, Robinson EL, Sutton ML. Radiation-induced hypopituitarism is dose-dependent. Clin endocrinol (Oxf) 1989;31:363-373.
17. Brauner R. Hypothalamo-hypophyseal function after treatment of cancers. Annales Endocrin 1995;56(2): 127-31.
18. Shalet SM. Radiation and pituitary dysfunction. N Engl J Med 1993; 328(2): 131-3.
19. Shalet SM, Beardwell CG, Aarons BM, Pearson D, Morris-Jones PH. Growth impairement of children treated for brain tumors. Arch Dis Child 1978;63:491.
20. Sklar CA. Growth and neuroendocrine dysfunction following therapy for childhood cancer. Pediar Clin N Am 1997;44(2):489-503
21. Brauner R, Czernichow R, Rappaport R. Greater susceptibility to hypothalamopituitary irradiation in younger children with acute lymphoblastic leukemia. J Pediatr 1986; 108:323.
22. Albertsson-Wikland K, Lannering B, Marky I, et al. A longitudinal study on growth and spontaneous growth hormone secretion in children with irradiated brain tumors. Acta Pediatr Scand 1987; 76:966-73.
23. Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med 1993; 328(2): 87-94.
24. Samaan NA, Schultz PN, Yang KP et al. Endocrine complications after radiotherapy for tumors of the head and neck. J Lab Clin Med 1987: 109; 364-72.
25. Devney RB, Sklar CA, Nesbit ME, et al. Serial thyroid function measurements in children with Hodjkin's disease. J Pediatr 1984; 105: 223.
26. Kapalan MM, Garnick MB, Gelber R et al. Risk factors for thyroid abnormalities after neck irradiation for childhood cancer. Am J Med 1983;74: 272.
27. Oberfield SE, Sklar CA, Allen J et al. Thyroid and gonadal function and growth of long-term survivors of medulloblastoma/PNET. In Green DM, D'Angio GJ (eds): Late effects of treatment for childhood cancer. New York, Wiley-Liss, 1992, p 55.
28. Hajjar RA, Anderson MS, Samaan NA. Thyrotropin-releasing hormone as a pituitary function indicator: a comparison with other tests. Arch Intern Med 1973;132, 836-9.
29. Snyder PJ, Jacobs LS, Rabello MM. Diagnostic value of thyrotropin-releasing hormone in pituitary and hypothalamic diseases; assessment of thyrotropin and prolactin secretion in 100 patients. Ann Intern Med 1974; 81: 751-7

Acknowledgement:: *My great thanks and sincere appreciation to* ***professor Abdullaah-Hedayatullaah****, professor of Radiotherapy, Al-Khartoum University, and head of nuclear medicine department, K.F.C.H. for his unlimited help and support which made the achievement of this research possible.*