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RESEARCH ARTICLE

Evaluation of radiation-induced thyroid disorders in non-thyroid head and neck cancers in childhood

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ABSTRACT

Background: The thyroid gland constantly regulates many body functions that help in the growth and metabolism, so any thyroid hormone disorder will affect these functions. However, treating cancer in the head and neck (HAN) region with radiotherapy may potentially harm the healthy cells of the thyroid gland. **Aim:** Hence, the current study aimed to evaluate radiation-induced thyroid disorder of head-and-neck cancer in children (≤18 years old, with normal TSH). **Methods:** The radiation-induced thyroid disorders were monitored by measuring the changes in TSH, FT3, FT4, Anti-TPO Ab and IGF-1 serum levels using ELISA kits in children. These biomarkers were measured at the baseline, after ten RT sessions (15–18 Grays) and after the radiotherapy (21–60 Grays). Three patient groups represent before, during and after the radiotherapy were compared with the control (healthy). **Results:** The results showed that TSH, IGF-1, and Anti-TPO Ab levels significantly decreased in the treated groups compared with the controls. However, FT4 increased significantly, and these changes weren't in a dose-dependent pattern. There was no significant difference in FT3 between the treated groups and the control. The TSH level in the patients after therapy (dose from 21 to 60 Grays) showed a significant negative correlation with the D_{mean} and $D_{50\%}$ of the thyroid, while the FT4 level showed a positive correlation. **Conclusion:** Radiotherapy of the head and neck region in children (≤ 18 years) may result in changing euthyroid to hyperthyroidism, which could be mainly attributable to the thyroid gland rather than the pituitary gland.

Keywords: Radiotherapy; Head and Neck cancers; TSH; FT3; FT4; Anti-TPO Ab; IGF-1; Pituitary gland; Thyroid gland

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INTRODUCTION

In the human body, the largest endocrine gland is the thyroid gland. Thyroid hormones (thyroxine and triiodothyronine) are essential for the development, metabolism, growth, overall energy expenditure, and the functioning of many organs in the human body. Radiation can cause thyroid disorders such as hypothyroidism and hyperthyroidism. These diseases are significant and sometimes life-threatening (Blasko et al., 2000).

The thyroid gland is irradiated during the radiotherapy of HAN cancers which are aggressive epithelial tumors and are recognized as being particularly challenging to treat (Xu et al., 2021). The primary damage caused by the thyroid gland's irradiation is thyroiditis (Bakhshandeh et al., 2012). Apart from that, autoimmune reactions including thyroid atrophy, and hypothyroidism may be induced via radiation exposure (Reiners et al., 2020). The probability and severity of such complications depend on a variety of factors, such as the dose of radiation delivered, duration, and which sites of the head and neck obtained radiation, e.g., Hodgkin Lymphoma (HL), Rhabdomyosarcoma (RMS), and nasopharyngeal carcinoma (Stubblefield, 2017).

Thyroid dysfunction has been observed when the head and neck region was irradiated, even by small doses of radiotherapy. In contrast,

multiple anterior pituitary hormone deficiencies are frequently observed following irradiation (> 60 Gy) in the treatment of nasopharyngeal and skull base tumors (Foo et al., 1993; Pai et al., 2001).

TSH interaction with other growth factors, especially Insulin-like growth factor-1 (IGF-1), and its effects on thyroid proliferation have been extensively studied (Kimura et al., 2001). IGF-1 is a small peptide hormone (Alpay et al., 2007). Circulating IGF-1 is bound to a family of insulin-like growth factor-binding proteins (IGFBPs) (Jones and Clemmons, 1995). IGFs affect the thyroid gland and its hormones. Further, thyroid hormones and TSH can influence the biological effects of IGF-I and growth hormone on target tissues. The results of this two-way interplay can affect many metabolic and immunologic processes in the long term (Inukai et al. 1999; Smith, 2021)

The human thyroid peroxidase (TPO), the vital accelerator that is responsible for the synthesis of thyroid gland hormones, catalyses the chemical process and coupling of aminoalkanoic acid residues in thyroglobulin that ends up in the synthesis of triiodothyronine and thyroxine. The suppression of thyroid hormone synthesis due to TPO reduction could contribute to the early development of thyroid dysfunction (Blasko et al., 2000).

The present study analyzed thyroid and pituitary parameters in children before, during and immediately after head and neck cancers radiotherapy to monitor the abnormalities and their relation to the radiation dose.

SUBJECTS AND METHODS

Subjects

This study included 39 children (≤18 years old): 19 with non-thyroid head and neck cancer and 20 healthy children as a control group. The current study included a control group of matched age and sex individuals who were free of any malignancy and did not have any chronic health problems.

All participants were randomly enrolled from the National Cancer Institute, Egypt (NCIE) and Borg el-Arab children's hospital, Alexandria University, Alexandria, Egypt. They freely volunteered to participate in the study. The study was conducted following the Declaration of Helsinki and approved by the Ethical Committee of the Medical Research Institute, Alexandria University, Alexandria, Egypt (IOROH: IORG 0008812). All treated patients (≤ 18 years old) were cancer patients treated with primary or postoperative radiotherapy for various cancers (non-thyroid) in the head and neck region with normal TSH before radiotherapy. These requirements were designed to ensure that participants were not influenced by known factors that could affect the study scope.

Methods

After written informed consent from patients' parents, three fresh blood samples (5 mL/ sample) were collected from each patient. The first sample was before the radiotherapy. Another blood sample was obtained at the end of the 10^{th} fraction (during therapy). The third sample was collected after RT (after radiotherapy). Venous blood was collected in a serum separating tube. The blood sample was allowed to clot for 30 min and then centrifuged at 3000 rpm for 10 min to isolate serum. The serum was stored at -20 °C freezer for one month until used to assay circulating levels of thyroid-stimulating hormone [TSH] (REF: EIA-1782), free triiodothyronine [FT3] (REF: EIA-2385), free thyroxine [FT4] (REF: EIA-2386), thyroid peroxidase antibody [Anti-TPO Ab] (REF: EIA-3561), and Insulin-Like Growth factor-I [IGF-I] (REF: EIA-4140) by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (DRG International, Inc., USA). Thyroid dose parameters such as maximum dose (D_{max}), minimum dose (D_{min}), mean dose (D_{mean}), and 50% volume dose ($D_{50\%}$) were obtained from the dose volume histogram (DVH) generated by the treatment planning system using 3D conformal and IMRT techniques as appropriate.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD) or median and Inter quartile range (IQR). The difference between the groups was assessed by using a student t-test, Mann-Whitney test or Chi-square test, based on normality. A value of $p < 0.05$ was considered statistically significant. A Spearman coefficient

was calculated to evaluate the correlation between relevant parameters. Statistical analyses were conducted using the statistical software package SPSS version 20 (SPSS Inc., Chicago, USA).

RESULTS

Demographic parameters of the subjects and tumor types

This study included 39 children (≤ 18 years); 19 head and neck region cancer patients (non-thyroid), and 20 healthy children representing the control group of matched age (U=196.0, P=0.925) and sex (χ^2=0.143, *P*=1.00) as illustrated in Table 1. Also, this table shows that the Median (IQR) age of the patients and control groups was 7.0 (5.0-13.0) and 8.0 (5.0-13.0), respectively. 75-80% of this study participants were males and the rest was females. Hodgkin Lymphoma (HL) and Acute Lymphoblastic Leukemia (ALL) represented about 42% of this research patient group. Medulloblastoma, Ependymoma, Rhabdomyosarcoma (RMS) on the back of the neck, and Myoblastoma represented 10.5% for each. The rest of the cases were Neuroblastoma, Multiple skull osteolytic lesion and Astrocytoma as shown in Table 2.

The parameters measured (TSH, FT3, FT4, Anti-TPO Ab, and IGF-I)

Table 3 shows the pattern and behavior of the five parameters in the two studied groups (including the different time intervals: before, during, and after radiotherapy). In comparison with the control group, TSH levels significantly reduced (P=0.004, and 0.007) due to irradiation during (15–18 Gy) and after (21–60 Gy) groups respectively compared with the control. Insignificance difference was observed in FT3 before, during, or after radiotherapy groups when compared to the healthy control group (P=0.618, 0.191, and 0.376 respectively). FT4, IGF-1, and TPO showed statistically significant differences when comparing the patient groups to the control group. FT4 level raised significantly in patient groups (before, during, and after radiotherapy) (P=0.001, 0.007, and 0.001, respectively). On the other hand, IGF-1 and TPO significantly declined in patient groups when compared with the control. As there has been no effect on FT3, the observed changes in TSH and FT4 could be due to the radiation, and not due to a feedback mechanism.

The Correlation between the parameters and the dose quantities

Table 4 shows the mean dose (D_{mean}) parameter that was obtained from the dose volume histogram (DVH) generated by the treatment planning system using 3D conformal and IMRT techniques as appropriate.

Table 5 TSH showed a significant negative correlation with the D_{mean} and $D_{50\%}$ of the thyroid (P = 0.043, and P = 0.019 respectively) in the patients' group who received a total dose ranging from 21 to 60 Grays, while FT4 showed a positive correlation with the D_{mean} and $D_{50\%}$ (P= 0.021, and P=0.006 respectively).

DISCUSSION

Head and neck region cancer is the eighth most common cancer worldwide (Xu et al., 2021). Albright et al. (2002) reported that 12 percent of all children with cancer have a malignancy of the head or neck. Radiation therapy is a curative treatment modality, which could be applied alone or in combination (Foo et al., 1993). Although radiotherapy is carefully planned in HAN region cancers in children, it is difficult to keep away from exposing the thyroid gland (partially or totally) to radiation (Bittermann et al., 2013). In fact, because of the relatively low proliferative index of the adult thyroid gland cells, it is resistant to radiation (Hall and Giaccia, 2006). However, it is known that radiation affects the morphology of the thyroid gland and induces thyroid dysfunction, so radiation induced hyperthyroidism, adenoma, hypothyroidism, Graves' disease, and thyroid cancer may occur (Jereczek-Fossa et al., 2004). Other variables such as age, gender, and thyroid volume all play a role in the probability of these dysfunctions occurring (Miller and Agrawal, 2009). Furthermore, it is believed that concomitant chemotherapy causes hypothyroidism by increasing the sensitivity of the thyroid gland to radiation (Alterio et al., 2007).

This study aimed to evaluate radiation-induced thyroid disorders during radiotherapy of head and neck region cancer in children (≤18 years old).

Table 1. Comparison between the patient and control groups according to demographic data

	Control (n=20)		Patients (n=19)		Test of Sig.	P
	No.	%	No.	%		
Gender						
Male	16	80	14	73.6	χ^2=0.143	FE p=1.00
Female	4	20	5	26.3		
Age (years)						
Min. – Max.	1.60 – 18.0		1.0 – 18.0		U=196.0	0.925
Mean ± SD.	8.96 ± 4.87		8.78 ± 4.96			
Median (IQR)	8.0 (5.0 – 13.0)		7.0 (5.0 – 13.0)			

IQR: Inter quartile range, SD: Standard deviation, U: Mann-Whitney test, χ^2: Chi-square test, FE: Fisher Exact, p: p-value for comparing the studied groups

Table 2. Tumor types in the patients' group

Type of tumor	No.	%
Hodgkin Lymphoma (HL)	4	21
Acute Lymphoblastic Leukemia (ALL)	4	21
Medulloblastoma	2	10.5
Ependymoma	2	10.5
Rhabdomyosarcoma (RMS) on the back of the neck	2	10.5
Myoblastoma	2	10.5
Neuroblastoma	1	5.3
Multiple skull osteolytic lesion	1	5.3
Astrocytoma	1	5.3

Table 3. Pituitary and thyroid parameters at three-time intervals, before, during, and after radiotherapy of head and neck cancer patients compared with the control group

	Control (n = 20)	Patient group at different time intervals		
		Before (n = 19)	during (n = 19)	After (n = 10)
TSH				
Min. – Max.	1.10 – 6.30	0.30 – 4.80	0.10 – 3.90	0.40 – 3.80
Mean ± SD.	2.48 ± 1.36	2.22 ± 1.45	1.47 ± 1.03	1.43 ± 0.96
Median (IQR)	1.85 (1.69 – 2.80)	1.92 (0.85 – 3.50)	1.50 (0.71 – 1.70)	1.12 (0.80 – 1.70)
U (p)		170.50 (0.588)	89.0 (0.004*)	40.0 (0.007*)
FT3				
Min. – Max.	1.80 – 4.10	1.0 – 4.87	0.90 – 5.37	1.23 – 4.95
Mean ± SD.	3.23 ± 0.63	3.10 ± 0.98	2.86 ± 1.09	2.88 ± 1.15
Median (IQR)	3.44 (2.80 – 3.65)	3.40 (2.57 – 3.79)	2.90 (2.21 – 3.38)	2.67 (2.03 – 3.52)
t (p)		0.503 (0.618)	1.331 (0.191)	0.920 (0.376)
FT4				
Min. – Max.	0.45 – 1.35	0.55 – 2.25	0.40 – 2.60	0.80 – 1.90
Mean ± SD.	0.92 ± 0.26	1.34 ± 0.42	1.26 ± 0.45	1.31 ± 0.32
Median (IQR)	1.0 (0.68 – 1.10)	1.40 (0.95 – 1.55)	1.20 (1.08 – 1.49)	1.35 (1.05 – 1.45)
t (p)		3.726 (0.001*)	2.872 (0.007*)	3.555 (0.001*)
IGF-1				
Min. – Max.	50.0 – 600.0	95.0 – 350.0	90.0 – 440.0	95.0 – 425.0
Mean ± SD.	340.8 ± 172.7	191.6 ± 70.79	178.42 ± 86.01	193.50 ± 100.86
Median (IQR)	285.0(242.5 –495.0)	200.0(132.5 –230.0)	155.0(130.0 –185.0)	167.5(115.0 –235.0)
U (p)		76.00 (0.001*)	70.0 (<0.001*)	45.0 (0.015*)
Anti-TPO Ab				
Min. – Max.	35.0 – 39.0	32.0 – 38.0	32.0 – 39.0	32.0 – 40.0
Mean ± SD.	36.95 ± 1.10	34.11 ± 1.70	34.32 ± 2.11	35.0 ± 2.67
Median (IQR)	37.0 (36.0 – 38.0)	33.0 (33.0 – 35.0)	33.0 (33.0 – 33.0)	34.0 (33.0 – 37.0)
t (p)		6.181 (<0.001*)	4.853 (<0.001*)	2.220 (0.049*)

IQR: Inter quartile range, t: Student t-test, U: Mann Whitney test, p: p-value for comparing between patient in each period and the control, * : refers to significant differences at $p \leq 0.05$. The difference in the number of the after-radiotherapy group resulted from patients who didn't complete their radiotherapy.

Table 4. Description of D_{Mean} received to thyroid and pituitary in head and neck cancer patients during and after RT.

During group (n = 9)	
Thyroid	
D_{Mean} (Mean ± SD)	13.86 ± 7.5
Pituitary	
D Mean (Mean ± SD)	18.95± 30.6
After group (n = 9)	
Thyroid	
D Mean (Mean ± SD)	20.99 ±12.39
Pituitary	
D Mean (Mean ± SD)	29.38±17.8

The difference in the number resulted from missed data.

Table 5. Correlation between Thyroid and Pituitary D_{Mean} and different parameters in irradiated patient groups

		Thyroid				**Pituitary**			
		D_{mean}		**$D_{50\%}$**		**D_{mean}**		**$D_{50\%}$**	
		r_s	**P**	**r_s**	**P**	**r_s**	**p**	**r_s**	**P**
Within group	TSH	0.067	0.854	0.176	0.626	-0.371	0.291	-0.383	0.275
	FT3	-0.261	0.467	-0.188	0.603	-0.309	0.385	-0.370	0.293
	FT4	-0.413	0.235	-0.243	0.498	-0.340	0.336	-0.267	0.455
	IGF-1	0.134	0.713	0.085	0.815	-0.486	0.154	-0.541	0.106
	TPO	-0.235	0.513	-0.242	0.501	-0.483	0.157	-0.483	0.157
After group	TSH	-0.648	0.043*	-0.721	0.019*	-0.285	0.425	-0.139	0.701
	FT3	-0.042	0.907	0.091	0.803	-0.188	0.603	0.212	0.556
	FT4	0.713	0.021*	0.799	0.006*	0.268	0.454	0.085	0.815
	IGF-1	0.273	0.446	0.442	0.200	0.212	0.556	0.055	0.881
	TPO	-0.056	0.877	0.025	0.945	-0.313	0.379	-0.206	0.567

r_s: Spearman coefficient, *: Statistically significant at $p \leq 0.05$

Those children had normal TSH hormone levels before the radiotherapy. Radiation-induced thyroid disorder was monitored by measuring the changes in TSH, FT3, FT4, Anti-TPO Ab, and IGF-1 using ELISA kits. These biomarkers were measured at the baseline, after 10 fractions of radiotherapy (15–18 Grays), and after the radiotherapy sessions (21–60 Grays).

The vascular and functional thyroid indicators of patients treated with radiotherapy for head and neck cancers were evaluated prospectively and longitudinally by Bakhshandeh (2012). With a threshold of 12 Grays, significant changes in serum T4, T3, and TSH, echo levels, and coloration Doppler parameters were observed during radiotherapy. These tests evaluate radiation thyroiditis as an event that may lead to hypothyroidism or hyperthyroidism later on and they concluded that patients with head and neck cancers, radiation-induced thyroiditis is a primary thyroid gland damage indicator (Bakhshandeh et al., 2012).

Bernát and Hrušák (2014) reported that there are no differences in hormone levels were observed between subjects with early follow-up (0-60 months) and the control group, while patients with follow-up longer than 60 months (60+) had different hormone levels from the control group. These findings are somewhat different from our results, may be because the current study's results showed significantly reduced TSH levels and raised FT4 levels in (15–18 Gy) and after (21–60 Gy) groups. So that, this difference may be due to the differences in the subjects, as their control was patients with less advanced disease who were treated surgically. However, our thyroid parameters determined were consistent with the results of Bernát and Hrušák (2014) as there was an insignificant difference in the 3 parameters (TSH, FT3, and FT4) when comparing the three studied patient groups (before, during and after radiotherapy), which illustrates that radiation could change these parameters but not immediately after irradiation.

On the other hand, in 2018, Lin and his colleagues concluded that the radiation-induced thyroid volume shrinkage and FT4 reduction trends were similar. They showed a decreasing drift from zero to thirty months. After 36 months, the thyroid volume and function became in a reasonably stable state (Lin et al., 2018). These results disagree with ours, may be due to the different patient's ages. Their mean age was 48.5 years, while we found it is very important to screen the radiation-induced thyroid abnormalities in childhood (≤18 years, M±SD=8.78 ± 4.96).

The thyroid dose parameters, such as mean dose (D_{mean}), maximum dose (D_{max}), minimum dose (D_{min}), and dose of 50% volume ($D_{50\%}$), were obtained from the treatment planning system's dose-volume histogram (DVH) (Lin et al., 2018). The size of the thyroid gland and the dose of radiation exposure to the gland are the two most important factors in the improvement of radiation-induced hypothyroidism (RIHT). Both of these factors must be taken into account when assessing thyroid dose constraints. Furthermore, routine assessment of the function of the thyroid gland after radiotherapy in the neck region is necessary. Xu et al. (2018) proved that RIHT is related to radiation dose, mainly with D_{mean} and $D_{50\%}$ of the thyroid gland. Their results are consistent with ours, as shown in table (4) that illustrates TSH and FT4 (function indicators) are correlated to D_{mean} and $D_{50\%}$. Particularly, the TSH level of the patient group after radiotherapy (the patient's group who received a total dose of 21 to 60 Grays) showed a significant negative correlation with the D_{mean} and $D_{50\%}$ of the thyroid, while the FT4 level showed a positive correlation with the D_{mean} and $D_{50\%}$ of the thyroid. Since FT3 did not demonstrate a significant difference due to radiation, the changes in TSH and FT4 could be attributed to radiation, not the feedback mechanism.

IGF-1 significantly decreased in the patient group when compared with the control group, as shown in table (3). This result is consistent with that of Völzke et al. (2007) who investigated the possible associations between serum IGF-I level and thyroid disorders (Völzke et al. 2007). Also, our results are in agreement with Inukai et al. (1999) and Smith (2021) who concluded the two-way interplay between IGF-1 and the thyroid gland.

Thyroid peroxidase, also called thyroperoxidase (TPO), or iodide peroxidase, is considered the key to the synthesis of thyroid hormones. TPO works to oxidise the ions of iodide to create iodine atoms to synthesize T4 and T3. Moreover, TPO is stimulated by TSH. Reduced TPO expression, along with the resulting suppression of thyroid hormone synthesis, should help to boost thyroid dysfunction sooner after irradiation. As a result, thyroid function testing seems to be indicated, even early after external radiation therapy of the head and neck region or after whole-body irradiation (Ruf and Carayon, 2006).

In thyroid autoimmune disorders, the immune system produces antibodies that mistakenly attack normal and healthy tissue. Inflammation and impaired thyroid function will be a result of targeting the thyroid gland by antibodies. TPO antibodies in the blood indicate that thyroid disease is caused by an autoimmune disorder such as Hashimoto's disease or Graves' disease (chronic thyroiditis) (Inukai et al., 1999). TPO Ab is additionally positive in a lesser number of people with other thyroid diseases (Blasko et al., 2000). About three percent of people with a positive Anti-TPO Ab test did not complain of any abnormality. However, the presence of Anti-TPO Ab may additionally amplify the risk of chronic thyroid disorders. The chance of having a positive Anti-TPO Ab test is greater in females and increases with age (Blasko et al., 2000). Our study did show that Anti-TPO Ab level was significantly decreased when comparing patient groups (before, during, and after radiotherapy) with the control group. Also, Anti-TPO Ab is negatively correlated with radiation total dose in the patient group after radiotherapy (who received from 21 to 60 Gy) ($p=0.045$), but since TSH level changed after radiotherapy, the Anti-TPO Ab change could be attributed to TSH levels.

From the overall results of the current study, we could conclude that radiotherapy to the head and neck region in children aged less than 18 years could result in changing euthyroid to hyperthyroidism. Moreover, the pattern of thyroid gland changes after radiotherapy in

head and neck cancer patients could be attributable to the thyroid gland rather than the pituitary gland. So, we recommend following up on the five parameters in these target groups of children for 5-10 years and implementing the same experimental design on a larger number per cancer type.

LIST OF ABBREVIATIONS

- TSH: Thyroid Stimulating Hormone.
- FT3: Free Triiodothyronine.
- FT4: Free Thyroxine.
- Anti-TPO Ab: Anti-Thyroid Peroxidase antibodies.
- IGF-1: Insulin-like growth factor 1.
- DVH: dose-volume histogram.
- D mean: mean dose.
- D max: maximum dose.
- D min: minimum dose.
- D50%: dose of 50% volume.
- AITD: Auto Immune Thyroid Diseases.
- RIHT: radiation-induced hypothyroidism.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All participants were randomly and freely volunteered to participate in the study and informed written consent from the patient's parents was gathered before inclusion. The study was approved by the Ethical Committee of the Medical Research Institute, Alexandria University (IOROH: IORG 0008812).

AVAILABILITY OF DATA AND MATERIALS

The datasets and/or analyses of the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

SN & MM: Conception, laboratory investigations, interpretation of data, preparation of the manuscript, and revision for important intellectual content. MA: laboratory investigations, and interpretation of data. SF: patient communication, interpretation of data, and revision of important clinical content. All authors have read and approved the manuscript.

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