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Reduced Thyroid Volume and Hypothyroidism in Survivors of Childhood Cancer Treated with Radiotherapy

Cassiane Bonato, Romulo França Severino and Regina Helena Elnecave

Endocrinology Division, Hospital de Clinicas de Porto Alegre, Brazil

ABSTRACT

Aim: **Children treated for cancer may have sequelae due to the treatment. The aim of this study was to assess the frequency of hypothyroidism and the thyroid volume of patients treated with radiotherapy for cancer during childhood.**

Patients: **Fifty-nine patients treated with external beam radiation to different areas of the body during childhood.**

Methods: **Cross-sectional study of patients assessed for late effects of external beam radiation treatment for childhood cancer. General and anthropometric characteristics, time from radiotherapy, family history of thyroid dysfunction, radiotherapy report, thyroid function tests, anti-thyroperoxidase antibodies and thyroid ultrasound were analyzed.**

Results: **Hypothyroidism was found in 23 (39%) patients, 3.5 ± 1.9 years after radiotherapy carried out at the mean age of 7.6 ± 3.4 years. Site of irradiation had the greatest association with hypothyroidism. Anti-thyroperoxidase antibodies were normal in all patients. Thyroid volume was significantly lower in irradiated patients with hypothyroidism than in those with normal thyroid function (p <0.001).**

Conclusions**: Hypothyroidism is very common in survivors of childhood cancer treated with external beam radiation. Primary thyroid damage is suggested because of the smaller thyroid volume.**

Reprint address:
Regina Helena Elnecave, M.D., Ph.D.
Endocrinology Division
Hospital de Clinicas de Porto Alegre
Rua Ramiro Barcelos, 2350, predio12, 4° andar
90035-903 - Porto Alegre, RS, Brazil
e-mail: rhelnecave@gmail.com

KEY WORDS

hypothyroidism, thyroid volume, children, malignancy/radiotherapy

INTRODUCTION

The life-expectancy of patients treated for childhood cancer by surgery, chemotherapy and radiotherapy has significantly increased[1]. At the same time, the risk of survivors developing disorders secondary to treatment has also increased[2]. Despite the use of protective shields during radiotherapy, dispersion to other tissues often occurs, directly related to their distance from the source.

The thyroid is a highly radiosensitive organ and it is often close to or included in the radiotherapy fields. Thyroid dysfunction is a fairly common complication of the exposure of the gland to ionizing radiation. The most frequently found thyroid dysfunction in association with radiotherapy for the treatment of childhood cancer is primary hypothyroidism[3-5], which appears within 2-7 years after treatment in half of the patients, the incidence declining thereafter[4,6,7]. Hypothyroidism is directly related to the radiation dose reaching the thyroid[6].

The aim of this study was to assess the frequency of hypothyroidism related to thyroid volume in patients treated for childhood cancer with radiotherapy in different body areas.

PATIENTS AND METHODS

This was a retrospective, cross-sectional study of the charts of 68 consecutive patients with no prior history of thyroid disorders, who underwent external beam radiation during childhood or adolescence for the treatment of cancer, and were followed at the Hospital de Clínicas de Porto Alegre endocrine outpatient clinic for the detection of late complications. Of these, six with tumors in the hypothalamic-pituitary region and three with no complete information about radiotherapy were excluded. The final sample was composed of 59 patients who underwent radiotherapy between 1985 and 2004.

Age, gender, anthropometric data (weight [kg], height [cm] and body surface [m^2]) at the time of radiation therapy were recorded. Body surface was determined by Mosteller's equation[8,9]. Thyroid volume (ml) was assessed from the ultrasound used for nodule identification (Aloka, Pro sound 4000 with linear 15 Hz transducer). The ecobody index was calculated as the ratio of thyroid volume (ml)/body surface (m^2)[10]. Thyroid volume and the ecobody index were compared between hypothyroid and euthyroid patients.

Measurements of serum thyroid stimulating hormone (TSH), thyroxine (T4), free T4 (fT4), anti-thyroperoxidase antibodies (anti-TPO) and thyroid ultrasound are part of the routine evaluation. At the time the serum determinations were made, the method used was chemiluminescence (Roche, Mannheim, Germany). In the age group assessed, the reference values (RV) for these tests are: TSH: 0.27-4.2 μIU/ml, T4: 65.6-181.4 nmol/l (5.1-14.1 μg/dl), fT4: 11.9-21.8 pmol/l (0.93-1.7 ng/dl).

By definition, primary thyroid hypofunction is diagnosed when the TSH levels are higher than 4.2 μIU/ml with low (clinical) or normal (subclinical) T4 or fT4. More stringent criteria, with TSH cut-off levels of 10.0 μIU/ml, were used in a separate analysis.

Anti-TPO antibodies levels lower than 35 IU/ml were considered normal.

The time elapsed since radiotherapy, the fields and the doses of radiation were assessed. The fields irradiated were classified according to the expected risk for thyroid injury: 1 - high risk: neck, mantle, spine (C2-T2), brainstem (posterior-anterior), Waldeyer's ring and neck, supraclavicular and nasopharyngeal regions and total body irradiation (TBI); 2 - intermediate risk: Waldeyer's ring, brain to C2, brainstem (lateral), and lungs; 3 - low risk: skull, orbital, frontal lobe, parietal lobe, abdominal, testicular[11]. The patients were classified by the area of highest risk to which they were exposed. As the number of patients in the low risk group was small in the present study (four patients), these were added to those irradiated in intermediate risk regions. Thus, only two categories - low/intermediate and high risk - were used.

The time interval between radiotherapy and detection of thyroid dysfunction was determined, the use of chemotherapy was recorded, and family history of hypothyroidism was sought in the records.

This study was approved by the Ethics in Research Committee of the Hospital de Clínicas de Porto Alegre.

Statistical analysis

Logarithmic transformation of the serum TSH levels and the total radiation dose received by the patients was done for normalizing the data. As the total dose is an asymmetric variable, medians and interquartile range were used, and compared between the two groups using the Mann-Whitney test. In the logistic regression analysis, hypothyroidism was the dependent variable, and age, gender, total radiation dose and risk categories of thyroid injury, the independent variables. Thyroid volume and the ecobody index were expressed as means ± SD, and compared between the groups with and without hypothyroidism by Student's t-test for independent samples. The chi-squared test was used for comparing qualitative variables. The magnitude and direction of the association between quantitative variables were determined by Pearson correlation. The adopted significance level was 5%.

The SPSS (Statistical Package for Social Sciences) packet, version 13.0, was used for all the analyses.

RESULTS

The patients' mean age at the time of radiotherapy was 7.62 ± 3.42 years (range: 2.66-16.33 years). Forty-one patients (69.5%) were male. Mean follow-up time was 7.3 ± 3.62 years (range: 0.9-20.5 years). The median total irradiation dose received by the patients was 42 Gy (25^{th} percentile = 26.8 Gy and 75^{th} percentile = 72 Gy). The disorders treated by radiotherapy were quite variable and are listed in Table 1.

Primary thyroid hypofunction (TSH >4.2 μIU/ml) was found in 23 patients (39%) and secondary (central) hypofunction in three (5.1%). Of those 23 patients, four (17.3%) had clinical hypothyroidism and 17 (73.9%) subclinical hypothyroidism. In two patients, treatment with levothyroxine was started at the demonstration of high TSH levels, with no concomitant T4 or fT4 measurements available. Hypothyroidism was detected 3.5 ± 1.9 years (range: 0.91-7.08 years) after radiotherapy. Hypothyroidism occurred more frequently in males: 18/23 patients (78.2%).

Regarding the type of malignancy, the highest frequency of hypothyroidism was found in patients treated for medulloblastoma (61.5%), as shown in Table 1.

At the time of diagnosis, 16 patients (69.5%) with primary hypothyroidism had serum TSH levels between 4.2 and 10.0 μIU/ml, and seven (30.4%), above 10.0 μIU/ml. The mean time interval post-radiotherapy in patients displaying serum TSH levels between 4.2 and 10.0 μIU/ml was 7.69 ± 4.82 years (range: 1.16-20.5 years), and in those with TSH levels >10.0 μIU/ml, 4.73 ± 3.79 years (range: 0.91-9.75 years). The time interval difference was not significant ($p < 0.92$). All the patients with TSH levels >10.0 μIU/ml were irradiated in high risk areas. Of the patients with serum TSH levels between 4.2 and 10.0 μIU/ml, one (6.25%) had been irradiated in a low risk area, two (12.5%), in intermediate risk areas, and 13 (81.25%) in high risk areas. The total radiation dose and the age at the time of radiotherapy were similar in the two groups.

In patients with hypothyroidism, TSH levels and the time from radiotherapy were negatively correlated ($r = -0.45$, $p < 0.03$) (Fig. 1).

Anti-TPO antibodies were negative in all patients, regardless of the presence of hypothyroidism. Family history of hypothyroidism was positive in 2/13 patients with hypothyroidism and in 3/20 patients without hypothyroidism.

The 'high risk' area was the only variable significantly associated with hypothyroidism, with odds ratio (OR) of 9.6 (95% confidence interval [CI] = 1.7-51.8, $p < 0.01$). The high confidence interval is probably due to the small sample size. Total radiation dose, age at the time of radiotherapy, gender and time from radiotherapy had no significant effect on the appearance of hypothyroidism (Table 2).

Negative correlation was observed between thyroid volume and TSH levels ($r = -0.56$, $p < 0.001$) (Fig. 2). In the patients with TSH levels between 4.2 and 10.0 μIU/ml, the mean thyroid volume was 3.1 ± 2.1 ml (range: 0.7-8.76 ml), whereas in those with TSH levels >10.0 μIU/ml, it was lower, mean 1.36 ± 0.97 ml (range: 0.4-2.89 ml) ($p < 0.04$).

DISCUSSION

A high prevalence (39%) of primary hypothyroidism in external beam radiation-treated survivors of childhood cancer was found in this cross-sectional study, similar to that found in other series[4,12,13]. This disorder was recognized 3.57 ± 1.91 years after radiotherapy, also consistent with what was found in other studies[4,6,14,15]. As this study analyzed cross-sectional data, it is unknown whether thyroid function will improve, stabilize or worsen with time.

The upper normal values of TSH in children and adolescents have not been determined in Brazil; however, large scale studies have established that the normal range for TSH in this age group is similar to that of adults[16-18]. The importance of treating subclinical hypothyroidism in children is not established, but improved atherogenic profile[19] and improvement of growth velocity[20] after treatment with levothyroxine have been reported. In 69.5% of patients with hypothyroidism the TSH levels were between 4.2 and 10.0 μIU/ml. Of note, the highest TSH levels were found earlier in time from radiotherapy ($p < 0.03$).

Most studies have looked at thyroid changes in children treated with radiotherapy for Hodgkin's lymphoma, due to the inclusion of the thyroid gland in the field irradiated. In the present study, the tumor types associated with a higher proportion of hypothyroidism were medulloblastoma, Hodgkin's lymphoma, central nervous system tumors and acute lymphoblastic leukemia. As in the study by van Santen *et al*[11], the frequency of hypothyroidism was significantly higher in patients irradiated in areas of 'high risk' than in those irradiated in areas

TABLE 1

Frequency of radiation-treated malignancy type and primary hypothyroidism

Disorder	No. of patients (%)	No. of cases of hypothyroidism (%)
Acute lymphoblastic leukemia	23 (39)	7 (30.4)
Medulloblastoma	13 (22)	8 (61.5)
Hodgkin's lymphoma	6 (10.2)	3 (50)
CNS tumors	6 (10.2)	3 (50)
Parapharyngeal rhabdomyosarcoma	3 (5.1)	1 (33.3)
Lymphoblast lymphoma	2 (3.4)	0 (0)
Retinoblastoma	2 (3.4)	1 (50)
Wilms' tumor	2 (3.4)	0 (0)
Orbital rhabdomyosarcoma	1 (1.7)	0 (0)
Ewing's sarcoma	1 (1.7)	0 (0)
Total	59 (100)	23 (38.9)

TABLE 2

Logistic regression analysis of the factors with likely association with the appearance of post-radiotherapy hypothyroidism

Factor	β	Significance (p)	Odds ratio	95% confidence interval
Total radiation dose	0.53	0.36	1.70	0.53-5.38
Age at radiotherapy	-0.07	0.46	0.92	0.75-1.13
Male gender	1.32	0.07	3.74	0.86-16.27
High risk area	2.26	<0.01	9.60	1.77-51.87
Time from radiotherapy	0.01	0.89	1.01	0.84-1.21
Constant	-4.38	0.07	0.01	

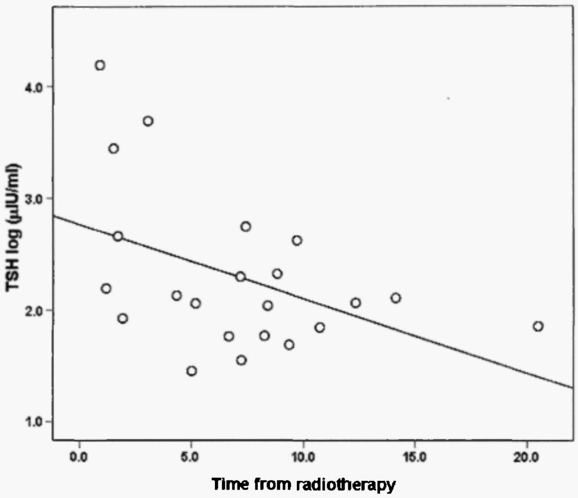

Fig. 1: TSH levels (log) and time from radiotherapy in patients treated for non-thyroid childhood cancer.

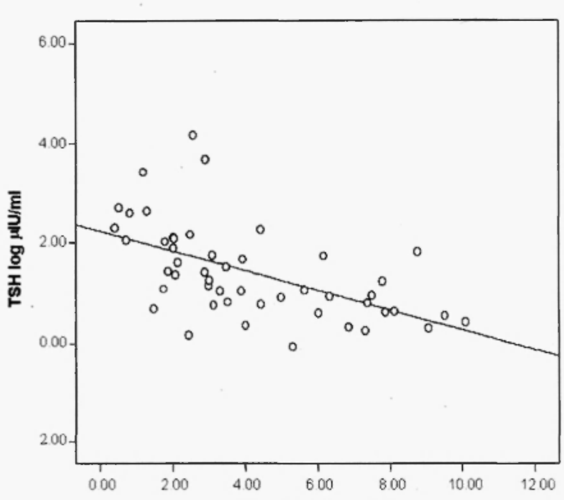

Fig. 2: TSH levels (log) and thyroid volume of patients treated with external beam radiation for non-thyroid cancer during childhood.

of 'low/intermediate risk' ($p < 0.003$), likely because of the higher radiation dispersed to the thyroid. 'High risk' area was the factor with greatest association with hypothyroidism ($p < 0.09$). Schmiegelow *et al.*[13] found primary hypothyroidism in 24% of patients treated with radiotherapy for brain tumors, 29% of whom had cranial and 71% craniospinal irradiation ('high risk' area). It can never be stated that full protection to the thyroid exists, even in patients receiving radiotherapy in 'low risk' areas. Dosimetry studies in children with leukemia, even after prophylactic irradiation, have shown that a significant proportion of radiation reaches the thyroid[21,22].

The influence of age at the time of radiotherapy was not clear in this study, and it is conflicting in different series[4,12,23,24]. Gender was not a risk factor in this study, as well as in other series[7,12,25-28]. The influence of chemotherapeutic agents may not be dismissed, but the number of patients in each of nine categories of chemotherapy was insufficient. Other studies found no additional damaging effect of chemotherapy on the thyroid of radiation treated children[11].

In patients with subclinical hypothyroidism, secondary or tertiary hypothyroidism cannot be ruled out. The TRH test may not be helpful in such cases, as a high proportion of patients with central hypothyroidism display a normal TRH test or similar to patients with primary hypothyroidism[29-32]. Other proposed strategies to differentiate these conditions require hospitalization and are thus not practical[33]. In the present study, a negative correlation between thyroid volume and TSH levels was found, suggesting that the lesion is primary. The secretory capacity of the thyroid could perhaps be assessed using recombinant TSH stimulation.

The mechanisms of radiation induced thyroid dysfunction are multifactorial[34]. Histopathological examination of the thyroid after external beam radiation has shown vascular and follicular cell injury after doses as little as 1.5 Gy[35-37]. Thyroid hypofunction seems to be directly related to follicular cell number reduction after radiotherapy and not with auto-antibody activation, as suggested by some authors[38-40]. In the present study, the anti-TPO antibody levels were normal in all patients, in agreement with other studies[24,41]. In the present study, there was a significant difference in thyroid volumes of patients with TSH levels >4.2 μIU/ml (hypothyroid) and <4.2 μIU/ml (euthyroid).

Thyroid volumes of irradiated children with normal thyroid function may also be different from those of normal children. Studies determining normal thyroid volumes in children were done with the aim of assessing goiter[42]. A prospective study assessing thyroid volume by ultrasound before and after radiotherapy is necessary, as is its correlation with thyroid function parameters. Such studies of thyroid volume could assess whether radiotherapy has injured the thyroid.

CONCLUSIONS

Patients treated with radiotherapy for childhood cancer have a high prevalence of primary hypothyroidism, which is correlated with reduced thyroid volume. The fact that this is a small cross-sectional study may be a limitation for generalizing these findings, but does not invalidate these preliminary results. Prospective studies are needed to assess the immediate and late effects of non-targeted external beam radiation on thyroid volume and function of children. Ultrasound may be a good test to assess the damaging effect of radiotherapy on the gland.

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