Thyroid Functions and Thyroid Lesions in Children with Hodgkin Lymphoma and Central Nervous System Tumors Who Received Radiotherapy to the Head and Neck Region

Baş Boyun Bölgesine Radyoterapi Uygulanan Hodgkin Lenfoma ve Santral Sinir Sistemi Tümörlü Çocuklarda Tiroid Fonksiyonları ve Tiroid Lezyonları

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ABSTRACT

Objective: The aim of this study was to assess thyroid function and lesions after radiotherapy to the head and neck region in children with Hodgkin lymphoma (HL) or central nervous system (CNS) tumors.

Material and Methods: The study included children diagnosed with HL or CNS tumors who were in complete remission at least one year after completion of chemotherapy (CT) and who had all received radiotherapy (RT) to the head and/or neck. All patients were requested to undergo thyroid function tests and thyroid ultrasonography (USG).

Results: A total of 37 patients were included. The mean age was 13.7±3.8 years. The mean follow-up time was 5.09±2.5 years. All patients had CT and RT. Seven (18.9%) patients had subclinical hypothyroidism, and 7 (18.9%) had thyroid USG abnormalities. None of the patients had thyroid malignancy. Age under 10 years at diagnosis, follow-up time of 3 years or more, and an RT dose of 25 Gy or more were found as effective factors for subclinical hypothyroidism development. Only an RT dose of 25 Gy or more was found to be related to thyroid USG abnormalities.

Conclusion: Thyroid function tests and thyroid imaging should be routinely examined in any patient who has been treated for cancer to evaluate thyroid dysfunction regardless of clinical findings and the follow-up of these patients should be lifelong.

Key Words: Brain tumor, Hodgkin lymphoma, Radiotherapy, Thyroid disease

ÖZ

Amaç: Bu çalışmanın amacı Hodgkin lenfoma (HL) veya merkezi sinir sistemi (SSS) tümörlü çocuklarda baş ve boyun bölgesine uygulanan radyoterapi sonrası tiroid fonksiyonunu ve lezyonları değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya HL veya SSS tümörü tanısı alan, kemoterapi (KT) ve baş boyun bölgesine radyoterapi (RT) tamamlanmasından en az bir yıl sonra tam remisyonda olan çocuklar dahil edildi. Tüm hastalardan tiroid fonksiyon testleri ve tiroid ultrasonografisi (USG) istendi.

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study protocol was approved with the decision of the Education Planning Board of the Turkish Republic Health Ministry, Ankara Child Health Diseases, Haematology Oncology Training and Research Hospital dated 06.11.2014 and numbered 252. Informed consent was obtained from all the participants.

Contribution of the Authors / Yazarların katkısı*: *SANRI E: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***AKÇA G:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***SANRI A:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Reviewing the article before submission scientifically besides spelling and grammar. ***EMİR S:*** Constructing the hypothesis or idea of research and/or article, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Reviewing the article before submission scientifically besides spelling and grammar.

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Bulgular: Çalışmaya toplam 37 hasta dahil edildi. Yaş ortalaması 13.7±3.8'di. Ortalama takip süresi 5.09±2.5 yıldı. Tüm hastalarda BT ve RT mevcuttu. Yedi (%18.9) hastada subklinik hipotiroidi, 7 (%18.9) hastada tiroid USG anormalliği mevcuttu. Hastaların hiçbirinde tiroid malignitesi yoktu. Tanı anında 10 yaşın altında olmak, takip süresinin 3 yıl ve üzerinde olması, RT dozunun 25 Gy veya daha fazla olması subklinik hipotiroidizm gelişimi için etkili faktörler olarak bulundu. Sadece RT dozu 25 Gy veya daha fazlasının tiroid USG anormallikleri ile ilişkili olduğu saptandı.

Sonuç: Kanser tedavisi almış her hastada tiroid fonksiyon bozukluğunu değerlendirmek için klinik bulgulara bakılmaksızın tiroid fonksiyon testleri ve tiroid görüntülemesi rutin olarak incelenmeli ve bu hastaların takipleri ömür boyu yapılmalıdır.

Anahtar Sözcükler: Beyin tümörü, Hodgkin lenfoma, Radyoterapi, Tiroid bozukluğu

INTRODUCTION

With the improvement in the treatment of childhood malignancies, survival rates in childhood cancers have reached 70-80% in recent years. However, due to increased survival rates, there is a marked increase in early and long-term side effects of treatments. Long-term side effects after treatment in childhood malignancies comprise cardiotoxicity, endocrine disorders and neurocognitive impairments (1). Among these, approximately 40% of childhood cancer survivors experience endocrinological side effects (2). Thyroid tissue is one of the most radiosensitive part of human tissue and abnormalities of the thyroid gland following head and neck irradiation have been reported, therefore thyroid functions should be closely monitored in patients receiving RT to head and neck region (3-8).

In the present study, we aimed to assess thyroid functions and lesions after RT to head and neck region in children who were in full remission at least one year after completion of RT and chemotherapy (CT) treatment for Hodgkin Lenfoma (HL) or central nervous system (CNS) tumors.

MATERIAL and METHODS

The study included patients diagnosed with HL or CNS tumors and who have been treated at the Ankara Child Health Diseases, Haematology Oncology Training and Research Hospital and Research Hospital for a period of twelve years. All patients were in full remission at least one year after completion of cancer therapy and all had RT to the head and neck region. The patients with known thyroid disorders before treatment were excluded. Demographic and medical data were obtained from patient files. The study protocol was approved with the decision of the Education Planning Board of the Turkish Republic Health Ministry, Ankara Child Health Diseases, Haematology Oncology Training and Research Hospital dated 06.11.2014 and numbered 252. Informed consent was obtained from all the participants.

Thyroid function studies including thyroid-stimulating hormone (TSH), plasma free thyroxine (fT4), thyroid antibodies [anti-thyroglobulin (TG-Ab) and anti-thyroid peroxidase (TPO-Ab)] were measured in patients. These tests were interpreted according to our hospital's laboratory reference values adjusted for age. Plasma TSH, fT4, and thyroid antibodies levels were measured by electrochemiluminescence immunoassay in a Beckman Coulter dxi 800 device. Overt hypothyroidism was defined as a low fT4 level and an elevated TSH. Subclinical hypothyroidism was defined as a high TSH level with a normal fT4 value. Central hypothyroidism was diagnosed when accompanied by a low serum T4 with low or normal TSH levels. The presence of thyroid antibodies was accepted to indicate autoimmune thyroiditis. Abnormal values were checked at least twice.

Thyroid lesions were assessed with thyroid ultrasonography (USG). Thyroid gland USG was performed with (Toshiba SSA-270-A Powerpace). The terms of hyperechogenicity according to neighboring muscle groups, homogenous echo pattern, having only a few vascular structures, normal anterior-posterior and transverse diameters of the thyroid lobes, and normal thickness of the isthmus according to the age were used to define normal thyroid USG. The thyroid scans other than this definition were accepted as abnormal.

The patients were divided into two groups depending on the diagnosis as HL group and the CNS tumors group. The groups were compared according to sex, mean age, age at diagnosis, duration of follow-up, CT protocols, number of CT cures, RT dosage, RT area, thyroid functions, and thyroid lesions.

Statistical analysis

Statistical analyses were performed using IBM Statiscal Package for the Social Sciences, verison 20.0 (SPSS Inch., Armonk, NY, IBM Corp., USA). Continuous and intermittent numerical variables were defined as mean, standard deviation, minimum and maximum, categorical variables were defined as frequencies and percentages. Kolmogorov Smirnov test was used to detect whether the distribution of intermittent numerical variables was close to normal and homogeneity of the variances was investigated with the Levene test. To compare quantitative data Mann-Whitney U test was used. Qualitative data was compared with the Chi-square test. Statistical significance was considered when the p-value was less than 0.050.

RESULTS

A total of 37 children were included in the study. The total study population consisted of 18 male (48.6%) and 19 female (51.4%). The mean age in the study was 13.7±3.8 years. The mean age at diagnosis was 9±4.2 years. The diagnoses were

Table I: Clinical Characteristics of the HL patients

Sex*	
Male	15 (60)
Female	10 (40)
Stage of the disease*	
I	1 (4)
II	9 (36)
III	10 (40)
IV	5 (20)
Histologic subtype*	
Nodular sclerosis	11 (44)
Mixed cellularity	13 (52)
Lymphocyte rich	1 (4)
Involvement zone*	
Neck	4 (16)
Neck, supradiaphragmatic and infra-diaphragmatic	12 (48)
Neck and supradiaphragmatic	9 (36)
CT protocol*	
ABVD	15 (60)
ABVD-COPP	10 (40)
Current age (yrs)†	13.6±3.7 (7-19.7)
Age at diagnosis (yrs)†	8.6±4.1 (2.9-15.6)
Follow-up time (yrs)†	5.1±2.8 (1.5-11.1)
Number of CT cures†	5.4±2.8 (3-12)
Radiotherapy dosage (Gy) to neck†	23.9±4.9 (15-34)

**n(%), †mean±SD (min-max)*

HL in 25 (67.6%) patients and CNS tumors in 12 (32.4%) patients. The mean follow-up duration was 5.0 ± 2.5 years. All patients had normal thyroid physical examination. Clinical features of the HL and CNS tumor patients are shown in Tables I and II respectively.

Thyroid function abnormalities were detected in 7 (18.9%) patients. All of them had elevated TSH levels and normal fT4 levels. So, these 7 patients were considered as subclinical hypothyroidism. The detailed clinical information of the subclinical hypothyroidism patients is shown in Table III. None of the patients had overt hypothyroidism, central hypothyroidism, and autoimmune thyroid diseases. A comparison of clinic characteristics of subclinical hypothyroidism patients with cases with normal thyroid functions is shown in Table IV. There was no statistically significant difference between the patients with and without subclinical hypothyroidism in terms of gender (p=0.180), age (p=0.277), age at diagnosis (p=0.461), RT dose (p=0.121), number of CT cures (p=0.700), RT area (p=0.254), and CT protocol (p=0.472). The duration of follow-up of patients with subclinical hypothyroidism was longer than that of patients without subclinical hypothyroidism (p=0.003).

Thyroid USG abnormalities were detected in seven (18.9%) patients. four (57.1%) of them were male and three (42.9%) were female. Four (57.1%) of them were diagnosed with HL and three (42.9%) were diagnosed with CNS tumors. The detected USG abnormalities were thyroiditis in three cases, thyroid nodules in three cases, and hypoechoic pattern in one case. Fine needle aspiration biopsy (FNAB) was applied to two of the patients who had nodules, one cytology was a benign follicular nodule and the other one was a hyperplastic adenomatoid nodule. The comparison of clinical characteristics of patients who had thyroid USG abnormalities with cases with normal USG is shown in Table IV.

Table II: Clinical characteristics of the CNS tumor patients

Sex*	
Male	3 (25)
Female	9 (75)
Histologic subtype*	
Medulloblastoma	7 (58.3)
Astrocytoma	3 (25)
Ependymoma	2 (16.7)
CT protocol*	
Cisplatin-Etoposide	10 (83.4)
Carboplastin-Vincristin	1 (8.3)
Temozolomid-Carboplastin-Etoposid	1 (8.3)
Number of patients who RT to the neck region*	2 (16.7)
Number of patients who RT to head region*	12 (100)
Current age (yrs)†	14±4.3 (13.1-21.5)
Age at diagnosis (yrs)†	9.8±4.6 (2.2-17.8)
Follow-up time (yrs)†	5±1.9 (2-8.8)
Number of CT cures†	9.1±1.3 (6-10)
Radiotherapy dosage (Gy) to the neck region†	40.8±10.8 (27-54)
Radiotherapy dosage (Gy) to head region†	36

**n(%), †mean±SD (min-max)*

There was no statistically significant difference between the patients with abnormal thyroid USG and those with normal thyroid scanning in terms of gender (p=0.617), age at diagnosis (p=0.229), duration of follow-up (p=0.130), RT dose (p=0.260), number of CT cures (p=0.072), RT area (p=0.512), and CT protocol (p=0.812), whereas, mean age was higher in patients with thyroid USG abnormalities (p=0.038).

Evaluations of subclinical hypothyroidism patients and patients with thyroid USG abnormalities in terms of possible risk factors are shown in Table V. The age at a diagnosis under 10 years old (p=0.006), follow-up duration of 3 years or more (p=0.010), and RT dose of 25 Gy or more (p=0.014) were related to the development of subclinical hypothyroidism. Only an RT dosage of 25 Gy or more was found to be related to the development of thyroid USG abnormalities (p=0.014).

DISCUSSION

Thyroid disorders that develop due to treatment in cancer patients occur as a consequence of the affected hypothalamus-pituitary-thyroid axis or the thyroid gland. This interaction may be due to CT, RT, or surgery. The risk of thyroid disorder development was found to be 52% and 67% after 20 and 26 years of survival, respectively, in a study including 1787 patients with Hodgkin's lymphoma (9). Demirkaya et al. (10) found thyroid

Table III: Clinical characteristics of the subclinical hypothyroidism patients

Cases	Sex	Age (years)	Diagnosis	CT protocol	Number of CT cures	RT (Gy)	fT4 (ng/dl)	TSH (IU/L)	Thyroid physical examination	Tyroid autoantibodies (TG-Ab, TPO-Ab)	Thyroid USG
1.	M	16	HL	ABVD	6	20	0.7	10.1	Normal	Negative	Nodule
2.	M	18	HL	ABVD	6	30	1.1	7.4	Normal	Negative	Hypoechoic apperance
3.	F	18	HL	ABVD	3	19.8	0.8	7.3	Normal	Negative	Normal
4.	M	16	HL	ABVD-COPP	10	30.6	0.7	6.8	Normal	Negative	Thyroiditits
5.	M	9.1	HL	ABVD	6	26	0.6	9.8	Normal	Negative	Normal
6.	F	9.6	HL	ABVD	3	30.4	0.7	9.2	Normal	Negative	Normal
7.	M	17.8	CNS tumor	Cisplatin-Etoposide	10	36	0.7	9.4	Normal	Negative	Nodule

Table IV: Comparison of clinical characteristics of the patients with subclinical hypothyroidism and USG abnormalities with normals

	Subclinical hypothyroidism	Normal TSH	p	Abnormal USG	Normal USG	p
Current age (yrs)*	14.9±3.8	13.5±3.8	0.277‡	16.3±2	13.2±3.9	0.038‡
Age at diagnosis (yrs)*	8.0±4.8	9.2±4.2	0.461‡	10.5±4.3	8.6±4.2	0.229‡
Follow-up time (yrs)*	7.9±2.6	4.4±2.0	0.003‡	6.7±3.3	4.7±2.2	0.130‡
RT dosage (Gy)*	27.5±5.9	23.8±5.4	0.121‡	27.5±6.8	24.1±5.4	0.260‡
Number of CT cures*	6.2±2.8	6.7±2.7	0.700‡	8.2±2.1	6.2±2.7	0.072‡
Sex†						
Male	5 (27.8)	13 (72.2)	0.180§	4 (22.2)	14 (77.8)	0.617§
Female	2 (10.5)	17 (89.5)		3 (15.7)	16 (82.3)	
RT area†						
Neck	6 (24)	19 (76)	0.254§	4 (16.0)	21 (84.0)	0.512§
Neck±head	1 (8.3)	11 (86.7)		3 (25.0)	9 (75.0)	
CT protocol†						
ABVD	5 (33.3)	10 (66.7)	0.472§	2 (13)	13 (86.7)	0.812§
ABVD-COPP	1 (10.0)	9 (90.0)		2 (20.0)	8 (80.0)	
Cisplatin-Etoposide	1(10.0)	9 (90.0)		3 (30.0)	7 (70.0)	
Carboplastin-Vincristin	0	1 (100.0)		0	1(100)	
Temozolomid-Carboplastin-Etoposide	0	1 (100.0)		0	1(100)	

**: mean±SD, †: n(%), ‡: Mann Whitney U test,§: Chi-square test*

dysfunction in 25.5% of the patients within a mean follow-up duration of 5.54 years. In study of Akca Çağlar et al. (11), 66% of the 79 patients had abnormal thyroid function tests. Eltan et al. (12) found hypothyroidism 12 out of 40 patients (30%) on average 3.1 years after treatment determined. We found a thyroid disorder rate of 25.5% within a mean follow-up duration of 5.09±2.5 years in our study group.

Subclinical hypothyroidism following exposure to radiotherapy has been reported to have a high incidence (13,14). Srikantia et al. (15) detected 5 of 45 (11.1%) patients developed subclinical hypothyroidism following RT in their study. In the study of Demirkaya et al. (10), 78.6% of the patients with abnormal thyroid functions were diagnosed as subclinical and 11.4% as overt hypothyroidism. In our study, the subclinical hypothyroidism rate was higher than in the studies in the literature. All 7 patients with thyroid dysfunction were diagnosed as subclinical hypothyroidism. None of our patients had overt hypothyroidism.

In our study, there was no statistically significant difference between the subclinical hypothyroid patients in terms of gender. Many of studies on cases with RT applied to the thyroid gland as a part of head and neck tumors and HL treatment, the majority of the patients showed that there was no gender effect on thyroid hormone impairment (10,16). Our study was compatible with the literature.

In our study, a statistically significant relationship was found between the development of subclinical hypothyroidism and the diagnosis under the age of 10 years. Paulino et al. (16) found that the risk of hypothyroidism was increased with the reduction of treatment age. Jin et al. (17) conducted a study about thyroid dysfunction in medulloblastoma and primitive neuroectodermal tumor patients and younger age at radiation exposure was found to be significantly associated with an increased risk for permanent thyroid dysfunction. In contrast to these studies, Louis et al. (18) showed that the thyroid dysfunction risk was increased with increased age. However,

Table V: Evaluation of the patients in terms of possible risk factors for thyroid functions and USG abnormalities

	Subclinical Hypothyroidism	Normal TSH	p*	USG Abnormal	USG Normal	p*
Age at diagnosis (yrs)†						
<10	6 (40.0)	9 (60.0)	0.006	4 (26.7)	11 (73.3)	0.32
≥10	1 (4.5)	21 (95.5)		3 (13.6)	19 (86.4)	
Follow-up time (yrs)†						
<3	0	9 (100.0)	0.010	1 (11.1)	8 (88.9)	0.491
≥3	7 (25.0)	21 (75.0)		6 (21.4)	22 (78.6)	
RT dosage (Gy)†						
<25	2 (8.0)	23 (92.0)	0.014	2 (8.0)	23 (92.0)	0.014
≥25	5 (41.7)	7 (58.3)		5 (41.7)	7 (58.3)	

***:** *Chi-square test,* **†:** *n(%),*

in the mentioned study, younger patients had low doses of RT, whereas older patients had higher doses.

The dose of RT and the development of thyroid disorders were correlated in many studies in the literature. In the study comparing the frequency of hypothyroidism in 32 children diagnosed with medulloblastoma and who were treated with 23.4 Gy or 36 Gy craniospinal RT, it was found that the incidence of hypothyroidism did not decrease with the reduction of craniospinal RT dose, and risk was increased in the younger patients and in the patients who had CT (16). In another study that compared thyroid doses of 10, 20, and 30 Gy, the predicted average risk of subclinical hypothyroidism was 12%, 25%, and 44% respectively (19). Laughton et al. (20) found that primary hypothyroidism was found in 54% of those who had a 23.4 Gy dose and 89% of those treated with a 36 Gy or more dose in 88 embryonal tumor patients. In our study, we found that the RT dose of 25 Gy or more was correlated with the development of subclinical hypothyroidism. In contrast, Jin et al. (17) showed that the proportion of patients developing thyroid dysfunction was not significantly different depending on whether patients received less than 23.4 Gy of or more in their study.

In a review evaluating radiation exposure and thyroid lesions; it was estimated that 88% of the thyroid cancers in children are attributable to radiation exposure (21). Crom et al. (22) reported that a nonhomogenous thyroid gland was found in 44% of patients when they investigated thyroid abnormalities with USG in 96 childhood cancer survivor patients who had RT to the head and neck region. In the same study, thyroid nodules were detected in 22 (23%) of 96 patients, 6 patients with cold nodules had FNAB and only one had papillary carcinoma (22).

Somerville et al. (23) conducted a study with 142 patients who survived childhood cancers and found cancer in only 6 of 78 patients who received direct thyroid gland RT but found thyroid cancer in 12 of 65 patients who did not directly have RT to the thyroid gland but received radiation therapy such as cranial RT. Krawczuk-Rybak et al. (24) found an ultrasonographic abnormality (hypoechoic appearance, heterogeneous appearance, solid nodule) in 9.7% of 31 patients who underwent RT to the neck, upper mediastinum, and cranial region. Baran et.al. (25) performed thyroid USG screening in childhood cancer survivors following RT, 150 of 306 (49%) patients had thyroid nodules. In their cohort, the number of CNS tumor and HL diagnoses was 94. In our study, 18.9% of the patients had thyroid USG abnormalities that were consistent with the literature. The risk of developing benign or malignant thyroid disease after RT is controversial.

As a result, today, successful results are obtained in the treatment of childhood cancers, however late side effects become a serious problem. Side effects of cancer treatment can be seen immediately, as well as, can be seen after 20 years. Early intervention to side effects will positively affect the social and physical life of the patients and will reduce morbidity.

Serum thyroid hormone and thyroid antibodies should be routinely examined in any patient who has been treated for cancer to evaluate thyroid dysfunction regardless of clinical findings. Regular thyroid imaging is required from patients especially those who had RT to the head and neck region or directly to the thyroid gland and the follow-up of these patients should be lifelong.

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