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Epidemiological Evaluation of Patients Diagnosed with Lymphoma and the Retrospective Evaluation of the Endocrinological Parameters as Late Side Effect of the Patients Without the Treatment

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ABSTRACT

In this study, it was aimed to retrospectively evaluate the epidemiological characteristics and long-term side effects related to hormon and bone metabolism in the follow-up of lymphoma patients between the ages of 0-18 years.
98 patients who were diagnosed with HL and NHL between 2007-2020 in the Van Yuzuncuyil University Pediatric Hematology Clinic were retrospectively scanned from the hospital database.
The mean age of children was 96 months. It was determined that 74 (75.5%) children were boys and 24 (24.5%) were girls. No statistically significant difference was found in terms of age at diagnosis, and gender distribution of children diagnosed with HL and NHL (p=0.347, p=0.095, respectively). 25 OH vit-D deficiency was found in 21 (84%) children with a diagnosis of HL and 10 (71.4%) children with a diagnosis of NHL (p=0.187). Growth and developmental delay was found in 2 (2%) children with a diagnosis of HL. Early puberty was observed in 4 (4.1%) children, and delayed puberty was detected in 3 (5.5%) children. The median TSH, 25 OH vit-D levels and puberty findings were similar in NHL and HL group (p=0.241, p=0.399, p=0.505, respectively). Hypothyroidism was 5.1% before ChT-RT, it increased to 11.1% after ChT-RT. However, this difference was not statistically significant (p=0.241).
We conclude that it is important to evaluate patients regularly in terms of endocrinological and metabolic side effects related to ChT and RT during the treatment process and long-term follow-up.

Keywords: Lymphoma, Puberty, Thyroid function, Bone metabolism

Introduction

Lymphoma is clonal tumoral formations originating from lymphoid precursor cells (T/B lymphocyte or natural killer cells) (1). Lymphoma is divided into two as Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL). Lymphoma is responsible for 10-15% of childhood cancers and Non Hogdkin Lymphoma (NHL) constitutes about 60%. Hodgkin lymphoma constitutes approximately 40% of childhood lymphomas and approximately 6% of all childhood cancers (2).

It is known that chemotherapy and radiotherapy used in the treatment process of these diseases have negative effects on many tissues and systems of the body. Some of these negative effects also occur on bone metabolism, growth development, hormone levels and puberty times of the patients by disrupting nutrition and metabolism (3-5).

In our study, we examined the epidemiological characteristics of lymphoma patients aged 0-18 years, who were followed up in Van Yuzuncuyil University Pediatric Hematology Clinic between January 2007 and December 2020. Also evaluated thyroid function tests and bone metabolism in lymphoma patients whose treatment were completed. In addition, we determined the parameters of FSH, LH and total testosterone in male patients and FSH, LH and estradiol parameters in female patients in terms of puberty disorders. We evaluated the parameters obtained in a retrospective study in terms of investigating the late side effects of the disease and the treatment of the disease.

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Materials and Methods

Our study was performed in children aged 0-18 years, who were followed up with the diagnosis of lymphoma (HL and NHL) in Van Yuzuncuyil University Pediatric Hematology Clinic between January 2007 and December 2020. Informed consent form was obtained from the families of the children. Ethics approval was obtained for the study from the Vanyuzuncuyil University Non-Pharmaceutical Clinical Practices Ethics Committee (Date:10/01/2021 Issue No: 021/01-22). A form was prepared for each patient included in the study, and the demographic and clinical characteristics and laboratory findings of the patients were recorded. Evaluation of clinical findings was done by Pediatric Hematology Specialists who were responsible for the clinic during hospitalization.

The data were recorded variables of the patients are as follows:

- Some sociodemographic characteristics (gender, age etc.),
- Lymphoma type
- Data of anthropometric measurements (Height, body mass index, etc.)
- Puberty stage
- Some laboratory findings (TSH, T4, Ca, P, ALP, 25 – OH D vit., PTH, FSH, LH, E2 for girls, total testosterone for boys)
- Treatment end date.

Anthropometric measurements are classified according to the following ranges:

Height standard deviation score (SDS):

- <-3: Stunted
- -3 to -1: Short
- -1 to 1: Normal
- 1 to 2: Long

Body mass index SDS:

- <-2: Very weak
- Between -2 and -1: Weak
- -1 to 1: Normal
- 1 to 2: Overweight

If the TSH is more than 10 mIU/mL in the patients, it was considered as hypothyroidism, and if it is between 5-10 mIU/mL, it was considered as subclinical hypothyroidism. Puberty stage was performed according to Tanner staging. If puberty did not start until the age of 13 in girls and before the age of 14 in boys, it was considered as pubertal tarda.

Statistical Analysis: The analyzes of the study were carried out in the SPSS 26.0 package program. Categorical variables are shown by number and percentage, continuous numerical variables by mean, standard deviation values, as well as center and prevalence measures. Pearson's Chi-square test was used to compare categorical variables between groups. Conformity of continuous numerical variables to normal distribution was evaluated statistically with the Shapiro Wilk test and visually with a histogram. Mann - Whitney U test was used in the comparison of independent non parametric samples. Independent t test was used for analysis of independent normal distrubition samples. As the statistical significance level, a p value below 0.05 was accepted as the limit.

Result

Demographic Characteristics of The Groups: A total of 98 children, 55 with HL and 43 with NHL were included in our study who were followed up and treated in Van Yüzüncü Yıl University Medical Faculty Pediatric Hematology Unit. 75.5% (n=74) of the cases were male and 24.5% (n=24) were female. The mean age at diagnosis was 106.7 ± 46.8 months in HL patients and 103 ± 50.3 months in NHL patients. This difference was statistically significant (p=0.032). The mean updated age was 6.3 ± 4.1 years in HL patients and 7.5 ± 5.0 years in NHL patients, and no statistically significant difference was found (p=0.701). Regarding gender distribution, 69.1% of HL cases and 83.7% of NHL cases were male, while 30.9% of HL and 16.3% of NHL were female, and this difference was not statistically significant (p=0.095) (Table 1).

When we looked for distrubition of HL types; mixed cellular HL was found in 27 (49.1%) patients with HL, while lymphocyte-rich HL was found in 15 (27.3%) and Nodular Sclerosing HL was found in 13 (23.6%) patients. When the ChT protocols received by the children were evaluated; 39 (70%) ABVD/COPP protocol, 14 (14%) BEA/COPP protocol, 2 (3.6%) OEPA protocol and one patient (1.8%) LCH.) and ICE (1.8%) protocol were applied. It was determined that a patient who was applied ICE protocol was applied because of relapse after 6 cycles of ABV/COPP treatment.

When the ChT protocols received by the patients with NHL were evaluated, LMB-89 protocol in 18 (70%) children, NHL-BFM 2012 protocol in 10 (18.2%) children, standard NHL ChT protocol in 4

Table 1: Demographic Values of Children With Lymphoma

	Total (n=98)	Hodgkin Lymphoma (n=55)	Non Hodgkin Lymphoma (n=43)	P
	Mean±Std.D	Mean±Std.D	Mean±Std.D	
Age of diagnosis (month)	104±48	106,7±46,8	103±50,3	0,032
Updated age (year)	7,1±4,5	6,3±4,1	15 (8)	0,701
	n (%)	n (%)	n (%)	
Sex				0,095*
Male	74 (75.5)	38 (69.1)	36 (83.7)	
Female	24 (24.5)	17 (30.9)	7 (16.3)	

(p:Independent Samples t Test, p*:Pearson Chi-Square Test)

Table 2: Laboratory Values of Children With Lymphoma

	Total (n=98)	Hodgkin Lymphoma (n=55)	Non Hodgkin Lymphoma (n=43)	P
	Median (Min.-Max.)	Median (Min.-Max.)	Median (Min.-Max.)	
25-OH Vit.D (ng/mL)	12 (5-32)	11 (5-32)	14,67 (6-30)	0,187
Calcium (mg/dL)	9,38 (8,8-10)	9,5 (8,8-10)	9,317 (8,8-9,9)	0,419
PTH (pg/mL)	59,3 (12,6-156)	56,3 (12,6-122)	60,4 (13,5-156)	0,740
Phosphate (mg/dL)	4,34 (2,70-6,54)	4,27 ((2,70-6,54)	4,55 (6,41-5,80)	0,679
ALP (IU/L)	232,5 (68-757)	217 (68-757)	274 (92-460)	0,490
TSH (mIU/L) (before ChT-RT)	1,9 (0,23-9,0)	2,1 (0,6-9,0)	1,35 (0.23-5,3)	0,241
fT4 (ng/dL) (before ChT-RT)	1,1 (0,7-1,4)	1,1 (0,85-1,4)	1,1 (0,7-1,2)	0,891
TSH (mIU/L) (after ChT-RT)	3,09 (0,60-9,08)	3,19 (0,60-9,08)	2,83 (0,90-6,10)	0,399
fT4 (ng/dL) (after ChT-RT)	1,01 (0,84-1,68)	1 (0,84-1,68)	1,08 (0,93-1,44)	0,322
FSH (mIU/mL)	3 (0,24-36,60)	8,05 (0,40-36,60)	2,19 (0,24-13,29)	0,037
LH (mIU/mL)	1,94 0,01-77,30)	2 (0,08-77,3)	0,86 (0,01-5,59)	0,226
Estradiol (pg/mL)	58 (0-216)	16 (80-111)	137 (58-216)	0,079
Testosterone (ng/dL)	4 (0-384)	6 (0-18)	2 (0-384)	0,198

There is a statistically significant difference between the groups for age at diagnosis.(p=0,032)
(p:Mann Whitney U Test)

(7.3%) children, 2 (3%) children. It was determined that NHL-BFM 95 was applied in 6% children, LMB-96 was applied in 2 (3.6%) children. NHL-BFM 89 protocol was applied in 3 (5.4%) children, and LMT-89 protocol was applied in 2 (3.6%) children. In the remaining three children, ICE (n=1, 1.8%), NHL IB-AL R4 (n=1, 1.8%) and ALL-BFM 2000 ChT (n=1, 1.8%) protocols were applied.

It was determined that only 23 of the patients with HL diagnosed in our study received RT in addition to ChT.

Relationship Between Lymphoma and Anthropometric Measurements and Laboratory Data: Growth retardation was detected in a total of 2 patients. All of these patients were diagnosed with HL. Pre-ChT height SDS values of the patients were -0.25 for HL, -0.32 for NHL and weight SDS values were -1.8 for HL, -0.95 for NHL. After ChT, height SDS values were -1 for HL, -0.7 for NHL and weight SDS values were -1.2 for HL, -1.7 for NHL, respectively. This results showed us that the patients' height and weight SDS values decreased after chemotherapy.

Early puberty was seen in 4 of the patients and delayed puberty was seen in 3 of patients. Of the patients with precocious puberty, 2 were diagnosed with HL and 2 were diagnosed with NHL. All patients with puberty tarda were diagnosed with HL. This difference was not statistically significant (p=0.694).

The median 25 – OH D vit. levels of the children included in our study were 12 (5-32) ng/mL, and

this value was 11 (5-32) ng/mL in the HL group and 14.67 (6-30) ng/mL in the NHL group. 25 – OH D vit. levels in the NHL group and the HL group were similar (p=0.187). Low 25 - OH vit. D was observed in 21 (38.2%) of the children with HL, while 10 (23.3%) of the children with NHL had low 25 - OH vit. D levels. This difference was not calculated as a statistically significant difference (p=0.206). And these values are smaller than average of Turkish people 25 – OH D vit. Values(Table 2).

The median PTH levels of the children included in our study were 59.3 (12.6-156) pg/mL, and this value was 56.3 (12.6-122) pg/mL in the HL group and 60.4 (13.5-156) pg/mL in the NHL group. The PTH levels in the NHL group and the HL group were similar (p=0.740)(Table 2).

The median Phosphate (mg/dL) levels of the children included in our study were 4.34 (2.70-6.54) mg/dL, and this value was 4.27 (2.70-6.54) mg/dL in the HL group and 4.55 mg/dl (6.41-5.80) in the NHL group. Phosphate (mg/dL) levels in NHL group and HL group were similar (p=0.679)(Table 2).

The median ALP levels of the children included in our study were 232.5 (68-757) IU/L, and this value was 217 (68-757) IU/L in the HL group and 274 (92-460) IU/L in the NHL group. ALP levels in the NHL group and the HL group were similar (p=0.490). According to our laboratory ranges; PTH, Phosphate (mg/dL) and ALP levels of children with lymphoma were within normal limits(Table 2).

The median TSH (pre-ChT) levels of the children included in our study were 1.9 (0.23-9.0) μU/mL, and this value was 2.1 (0.6-9.0) μU/mL in the HL group and 1.35 (0.23-5.3) μU/mL in the NHL group. TSH (pre-ChT) levels measured in the NHL group and the HL group were similar (p=0.241)(Table 2).

The median TSH (post-ChT) levels of the children included in our study were 3.09 (0.60-9.08) μU/mL, and this value was 3.19 (0.60-9.08) μU/m in the HL group and 2.83 (0.90-6.10) μU/mL in the NHL group. TSH (post-ChT) levels measured in the NHL group and the HH group were similar (p=0.399)(Table 2).

The median fT4 (pre-ChT) levels of the children included in our study were 1.1 (0.7-1.4) ng/dL, and this value was 1.1 (0.85-1.4) ng/dL in the HL group and 1.1 (0.7-1.2) ng/dL in the NHL group. The fT4 (pre-ChT) levels measured in the NHL group and the HL group were similar (p=0.891)(Table2).

The median fT4 (post-ChT) levels of the children included in our study were 1.01 (0.84-1.68) ng/dL, and this value was 1 (0.84-1.68) ng/dL in the HL group and 1.08 (0.93-1.44) ng/dL in NHL group. The fT4 (post-ChT) levels measured in the NHL group and the HL group were similar (p=0.322)(Table 2).

It was found that 5 (5.1%) of the children had hypothyroidism before ChT-RT. Hypothyroidism was found in 4 (4%) of the children diagnosed with HL and in 1 (2.3%) of the children with NHL. This difference was not statistically significant (p=0.269). It was observed that hypothyroidism developed in 6 children in addition to the TFT levels evaluated after the treatment. 4 patients diagnosed in HL and 3 patients diagnosed in NHL after ChT-RT. And also this difference was not statistically significant (p=0.241). No child with hyperthyroidism was detected (Table 2).

The median FSH levels of the children included in our study were 3 (0.24-36.60) IU/L, and this value was 8.05 (0.40-36.60) IU/L in the HL group and 2.19 (0.24-13.29) IU/L in the NHL group. FSH levels were statistically higher in the HL group than the NHL group (p<0.037) (Table 2).

The median LH levels of the children included in our study were 1.94 (0.01-77.30) IU/L, and this value was 2 (0.08-77.3) IU/L in the HL group and 0.86 (0.01-5) IU/L in the NHL group. LH levels in the NHL group and the HL group were similar (p=0.226) (Table 2).

The median Estradiol levels of the children included in our study were 58 (0-216) pg/mL, and this value was 16 (80-111) pg/mL in the HL group and 137 (58-216) pg/mL in the NHL group. Estrodiol levels measured in the NHL group and the HL group were similar (p=0.079) (Table 2).

The median Testosterone levels of the children included in our study were 4 (0-384) ng/mL, and this value was 6 (0-18) ng/mL in the HL group and 2 (0-384) ng/mL in the NHL group. Testosterone levels in the NHL group and the HL group were similar (p=0.198). And this results are within normal limits according to our laboratory ranges for children (Table 2).

Discussion

Although childhood HL is more common in boys, it has an incidence rate of 12 million cases / year in the 0-14 age group. Although NHL is rarely seen under the age of five, its frequency increases

after the age of five and constitutes 8-9% of all cancers over the age of 10 (6).

Different treatment protocols (chemotherapy, radiotherapy etc.) used in the treatment of lymphoma, while causing long-term complications such as a decrease in bone mineral density and puberty disorders etc. (7). The mean age of the patients diagnosed with HL and NHL included in our study was 96 months. Trehan A. et al. in the study he conducted with children diagnosed with HL in 2013, the mean age was found to be 7.9 years, similar to our study (8). In our study, the male/female ratio was found to be 2.24:1 in children with a diagnosis of HL, but this ratio was found to be 5.14:1 in children with a diagnosis of NHL. In the study of Zheng et al. in 2020, similar to our study, the male ratio was found to be 2.88 times higher in the gender distribution of children with lymphoma (9).

In our study, it was found that 25 – OH vit. D levels were <20 ng/ml, with a frequency of 79.5% in children with lymphoma diagnosis. While it was detected at a level of 80% in children with a diagnosis of HL, it was found at a rate of 71.4% in children with a diagnosis of NHL. In the study conducted by Graklanov V et al. in 2020, serum vitamin D levels were found to be between 20-30 ng/mL in 14 of 103 patients, while vitamin D deficiency (<20 ng/mL) was observed in all other patients and also according to study of Graklanov V. et al. vitamin D deficiency ratio was 86% (10). And this result is similar with our study. In addition, in the study of El-Ziny A. M. et al. on bone metabolism in children with lymphoma diagnosis, phosphate and parathormone levels did not show a statistically significant difference compared to the control group (11). These results were compatible with our study.

According to the study of van Beek D. R. et al. FSH and LH levels increased significantly after the MOPP treatment compared to the control group ($p<0.001$) (12). Since the FSH and LH values measured after chemotherapy in our study were found to be within the normal range, these results are not compatible with our study.

It was found that 5 (5.1%) of the children in our study had hypothyroidism before ChT-RT. Hypothyroidism was found in 4 (3%) of the children with HL and 1 (2.3%) of the children with NHL. It was observed that hypothyroidism developed in 6 (6%) more children after the treatment. Hypothyroidism was observed in 4 children who did not receive RT. It was found that hypothyroidism developed in two of the children who received RT. Inskip et al. In 2018, they presented a risk analysis study for hypothyroidism among childhood cancer survivors. A total of 1,193 cases of hypothyroidism were observed in this study, of which 777 (65%) occurred five or more years after cancer diagnosis. The cumulative rate affected by hypothyroidism is highest among Hodgkin lymphoma (32.3%; 95% CI: 29.5-34.9%) and cancers of the central nervous system (17.7%; 95% CI: 15.2-20.4) levels were detected. And these results were thought to be related to radiotherapy (13). In our results, while newly developed hypothyroidism cases were less common, new diagnoses were seen less frequently in patients who received radiotherapy.

With the advances in cancer treatment, the 5-year survival rate after childhood cancer has increased to 80%. Endocrine sequelae are seen in 40-60% of survivors. Among the endocrine problems, the most important sequelae are; growth retardation, gonadal and thyroid diseases (14, 15). Growth retardation was detected in 2 (2%) children who participated in our study. Early puberty was observed in 4 (4.1%) children, while delayed puberty was detected in 3 (5.5%) children. According to study of Dorp W. et al. in 2011, the effects of HL treatment on bone mineral density appear to be small effect but data on growth shows that radiotherapy in a dose of >30 Gy including the spine, especially in pre-pubertal children, results in reduced height (16). And also this results are similar with our study.

Our study has some limitations related to the retrospective file scanning method. First, there was missing data in the information obtained from the patient files. Second, the fact that the patients continued their treatment outside our center caused deficiencies in the follow-up of the patients. However, this problem was tried to be corrected by not including patients with missing data in the study.

The development of hypothyroidism after ChT-RT was lower than expected. 25 OH vit-D deficiency and pubertal disorders were found to be more than normal population of our nation. Based on these results, it is important to evaluate the pre-treatment TFT, rickets panel, puberty status of patients diagnosed with lymphoma. We conclude that it is important to evaluate patients regularly in terms of endocrinological and metabolic side effects related to ChT and RT during the treatment process and long-term follow-up. When all these results are evaluated; we think that our study has important findings regarding long-term survival, long-term

endocrinological side effects associated with ChT and RT in children with lymphoma.

Conflicts of Interest: There are no conflicts of interest.

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