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ORIGINAL ARTICLE

Endocrinological disorders in childrens and adolescents survivors of Hodgkin lymphoma

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Abstract

Introduction: Hodgkins lymphoma (HL) is one of the main malignancies among adolescents and young adults, but with a high survival rate. Endocrinological disorders are frequent in post-treatment patients, affecting up to 44% of these individuals. **Objectives:** To evaluate the endocrinopathies existing in patients undergone HL treatment in childhood and adolescence, to correlate these changes with the treatment characteristics and to propose an evaluation and follow-up protocol. **Methods:** Retrospective longitudinal study, performed through medical records analysis, that evaluated children and adolescents aged 0-18 years, HL survivors, with initial treatment and minimum 3 years follow-up in a pediatric oncology service from 1990 and 2015. **Results:** The sample consisted of 75 individuals with a mean age at diagnosis of 9.2 years and follow-up time of 8.6 years. All had undergone chemotherapy and 85.3% radiotherapy, with an average dose of 25.7Gy. Twelve individuals were excluded due to treatment abandonment or death. At least one endocrinological disorder was present in 20.6% of the patients, and 100% of them had thyroid dysfunction, with hypothyroidism being the most frequent. It was not possible to assess gonadal function, bone mass, glucose metabolism or dyslipidemia in the sample due to lack of data and short follow-up. **Conclusion:** The elaboration of a protocol of evaluation and follow-up of these patients is necessary for standardization of management and early diagnosis of comorbidities. Knowledge of the repercussions of treatment is essential to provide better quality of life for the survivor.

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INTRODUCTION

Hodgkin's lymphoma (HL) is a lymphoproliferative neoplasm derived from B lymphocytes that affects the lymphatic system and is distinguished from other lymphoma subtypes by the presence of Hodgkin's cell, also called Reed-Sternberg cell[1]. It is responsible for 7% of childhood cancer cases, with approximately 12.1 new cases per million per year in the United States[1,2]. Its peak incidence occurs between 15 and 19 years of age, being rare in younger children, and its 5-year survival rate is currently greater than 90%[1,3].

Due to the progressive increase in the chance of survival of HL, there is also a growing recognition of the late adverse effects of treatment[2,3]. The *Childhood Cancer Survivor Study* (CCSS) states that 44% of patients after cancer treatment have at least one endocrine alteration, 16.7% two and 6.6% three or more[3]. Of these patients, those affected by HL have the highest prevalence, occurring in up to 60% of survivors[3,4].

The endocrinopathies found in these patients include thyroid diseases , obesity, diabetes mellitus, short stature or disproportionate growth, osteoporosis and hypogonadism[3-5]. Among them, thyroid alterations stand out for their higher incidence, being present in 18 to 43% of survivors[4-6]. The risk of developing hypothyroidism is 2.2 times higher when compared to siblings, 2.4 times higher for hyperthyroidism, 3.9 times higher for the appearance of nodules and 2.5 times higher for thyroid cancer[3].

The incidence of thyroid diseases , especially hypothyroidism, is closely related to high doses of radiotherapy (RT) in the cervical region and is more prevalent in women and white patients[5,6]. An American study reports that 30% of patients who received RT at doses lower than 21Gy (Gray) developed hypothyroidism, while 61% of those who received higher doses developed the disease[5]. RT is performed in practically all patients with HL, even those at low risk, but new studies suggest protocols with reduced use to limit side effects[1,3].

With regard to the emergence of obesity and diabetes, these are mainly associated with cases undergoing abdominal RT or TBI (*Total Body Irradiation*)[1,3]. Gonadal function and fertility impairment are related to high cumulative doses of alkylating agents used in chemotherapy (CT), age at diagnosis and especially pelvic RT[1,3,7]. A European study showed that only 30% of women treated with pelvic RT had children, while this percentage rose to 51% in those who received only RT above the diaphragm[7]. On the other hand, the risk of osteoporosis is 1.2 times greater in patients who used Methotrexate, glucocorticoids or underwent TBI, in relation to those who did not receive it[1].

Currently, it is estimated that there are more than 900,000 HL survivors in the United States, which corresponds to 6% of the total population of cancer survivors[8]. It is important to emphasize that many of these were submitted to older and more aggressive treatment protocols than those currently used[1,8]. This highlights the need to create a care plan for survivors, with monitoring of growth, puberty development and serial laboratory assessments[1,8].

The care of a large number of patients with HL in a reference service in pediatric oncology, together with the recognition of the importance of identifying comorbidities in the quality of life of these patients, motivated this study.

METHODS

is a retrospective, longitudinal study that included children and adolescents aged 0 to 18 years who survived HL, with initial treatment and a minimum follow-up of 3 years in a pediatric oncology service for 25 years (1990-2015). The project was approved by the Human Research Ethics Committee (CAAE 07696819.7.0000.0096).

By reviewing medical records, clinical and anthropometric data were analyzed, such as age at diagnosis, sex, height, Body Mass Index (BMI), subtype of disease, staging and treatment to which it was submitted , laboratory and radiological findings, at diagnosis and in oncology and pediatric endocrinology outpatient follow-up consultations. Height and BMI were converted into Z scores using the World Health Organization (WHO) software AnthroPlus® (2007). We chose to perform only descriptive statistics due to the sample size and scarcity of data.

RESULTS

The sample consisted of 75 individuals, 24% (18) were female and 76% (57) were male. The mean age at diagnosis was 9.2 years 2.8 SD , ranging from 3.7 years to 14.8 years. Most patients had no relevant comorbidities prior to HL, with only one patient with cystic fibrosis, one with neurofibromatosis , one HIV-positive patient, one with Down Syndrome, one patient after BMT due to Fanconi Anemia and one after liver transplantation due to atresia. of bile ducts.

The most affected site was the cervical region associated with the mediastinum in 25.3% (19) of the patients, in addition to 18.6% (14) with the cervical, mediastinum and other associated sites. Among the histological subtypes, the mixed cellularity variant was the most prevalent (49.3%; 37), followed by nodular sclerosis (30.6%; 23), lymphocyte predominance (13.3%; 10) and lymphocyte depletion (6.6%; 5). At the time of diagnosis, 40% (30) of the patients had stage II of the disease, 26.6% (20) stage IV, 24% (18) stage III and only 9.3% (7) stage I. – unexplained fever, weight loss greater than 10% in the last 6 months and night sweats – were observed in most of them (52%; 39), as well

as the presence of a mediastinal mass (56%; 42). On the other hand, bone marrow involvement was found in only 8% (6) of the patients.

Regarding treatment, all research subjects underwent chemotherapy (various protocols and number of cycles) (Graph 1). Among these, the ABVD chemotherapy regimen (adriamycin, bleomycin, vinblastine and dacarbazine) was the most performed (52%; 39). Except for this regimen, all the others contained high doses of corticosteroids (48%; 36). In addition, 89.3% (67) were exposed to alkylating agents, with an average dose of 5.09g/m2 2.4 SD, ranging from 1.8 at 13.6g/m 2 (median 4.65). The most frequently used alkylating agents were dacarbazine , not classical, and procarbazine , cyclophosphamide and mechlorethamine or nitrogen mustard, classical alkylating agents . Thirteen patients (17.3%) were exposed to at least two cycles of MOPP or COPP (mechlorethamine or cyclophosphamide and vincristine, prednisone, and procarbazine).

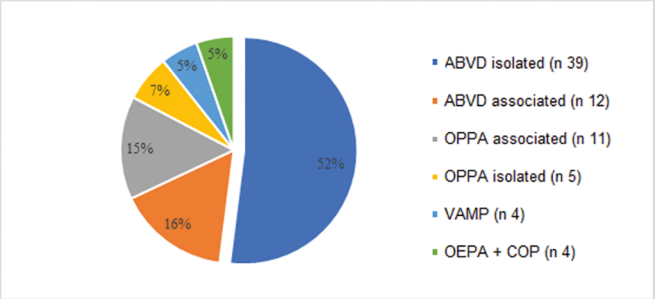
RT was performed in 85.3% (64) of the sample, the most prevalent regions being the supra and infradiaphragmatic associated (42.6%; 32), followed by the mantle (18.7%; 12) and the cervical region and fossa. supraclavicular (14%; 9). The mean radiation dose was 25.7Gy 7.62SD, ranging from 8.5Gy to 36Gy (median 24.5Gy). The duration of treatment was 7.16 months 4.5 SD (median 6.69) and 18.6% (14) of patients had relapse. Of these, 57.1% (8) a single episode, 35.7% (5) two episodes and 7.1% (1) three episodes. The most common site of recurrence was the abdomen, followed by the mediastinum, cervical, inguinal and other regions.

Twelve individuals were excluded from the follow-up research, 3 of them due to treatment abandonment and 9 deaths, leaving 63 patients. The mean follow-up time was 8.63 years 3.38SD, ranging from 3.0 to 16.7 years (median 7.9). The mean age at the last consultation was 17.9 years 3.7 SD, ranging from 10.2 to 26.2 years. The Z-score for height and BMI at the beginning of treatment were at -0.67 (1.27SD) and -0.24 (1.2SD), respectively. In the last consultation, they were at -0.74 (1.09SD) and -0.19 (1.21SD), respectively. There was no statistically significant difference between these measures.

At least one endocrinological alteration was present in 20.63% (13) of the patients, 100% of whom had thyroid dysfunction. Ten with hypothyroidism, 3 with thyroid nodules and 1 with papillary thyroid carcinoma (Table 1). In addition, one patient developed early ovarian failure requiring hormone replacement and osteopenia, one patient developed severe obesity, and one patient developed hypergonadotropic hypogonadism.

DISCUSSION

HL is most commonly diagnosed in adolescents and young adults aged between 15 and 24 years, however, our



Graphic 1. Chemotherapy performed in pediatric patients with HL (1990-2015). ABVD: adriamycin (doxorubicin), bleomycin , vinblastine and dacarbazine *; OPPA: vincristine, procarbazine *, prednisone and adriamycin ; VAMP: vinblastine, adriamycin , methotrexate and prednisone; OEPA: Vincristine, etoposide , prednisone and adriamycin ; COP: cyclophosphamide, vincristine, prednisone. * classical and non-classical alkylating agents. Source: The author (2019).

sample consisted of a younger group, with a mean age of 9.2 years[1,9]. A study carried out in Germany, Austria and Switzerland between 1978 and 2002 found 2548 cases of HL in children under 18 years old, with a mean age at diagnosis of 13.3 years, however, the follow-up time was 14.3 years, while the present study was only 8.6 years[10]. Another study at *St. Jude Children's Hospital,* in the United States, found 461 patients under 21 years of age, treated between 1980 and 2002, with a mean age of 15.3 years and follow-up time of 11.3 years[6].

As demonstrated in this study, most patients were in stage II of the disease at diagnosis, 38% in an American population-based study and 40% in our research[11]. The most prevalent histological subtype was mixed cellularity (49.3%), despite worldwide statistics indicating the nodular sclerosis subtype as the most prevalent in children and adolescents, representing approximately 80% of cases[1,11].

Combined chemotherapy in the treatment of HL started in the 1960s and was consolidated with the publication of studies in 1970 proving the effectiveness of the MOPP regimen[12]. Since then, new regimens have been proposed to reduce the side effects of chemotherapy, marked by the emergence of BADL in 1975[12,13]. Since our study consisted of individuals treated only after 1990, 52% were submitted to the ABVD regimen, which was used in 84% of patients from the year 2000 onwards in a study conducted in Southern California[9]. In this case, 95% of children and adolescents with HL received chemotherapy, as did our entire sample[9].

Gonadal function

The alkylating agents used and classically related to changes in gonadal function and fertility are cyclophosphamide and procarbazine, with mechlorethamine being disused[14-16]. Dacarbazine present in the ABVD regimen, a mild gonadotoxic agent , considered a non-classical alkylating agent, alone could be capable of leading to transient azoospermia in 1/3 of men and developing early ovarian

Table 1. LH survivors with endocrine disorders (1990-2015).

ID	SEX	AGE	QT	RT	Gy	AMENDMENT
1	F	9.0	OPPA + COPP*	SUPRA + INFRA	20	hypothyroidism; FOP; osteopenia
2	F	8.9	ABVD + MOP*	MANTLE	30	Thyroid Papillary CA
3	F	9.5	ABVD + MOP*	SUPRA + INFRA	21	hypothyroidism
4	M	14.6	BADL*	MANTLE	36	hypothyroidism
5	M	7.3	OPPA + COMP*	CERVICAL	25.5	hypothyroidism
6	M	9.6	BADL*	MINI MANTLE	36	thyroid nodule
7	M	7.0	BADL*	SUPRA + INFRA	24	thyroid nodule
8	M	8.9	BADL*	SUPRA + INFRA	30.6	hypothyroidism; HH
9	F	14.8	BADL*	MINI MANTLE	30.6	hypothyroidism
10	M	12.6	BADL*	SUPRA + INFRA	22.5	hypothyroidism
11	F	10.8	VAMPIRE	-	-	hypothyroidism
12	M	4.5	BADL*	MINI MANTLE	36	hypothyroidism
13	F	11.5	BADL*	MANTLE	36	Hypothyroidism / Thyroid Nodule / Obesity

*Alkylating agents. ID: identification; F: female; M: male; AGE at diagnosis; QT: chemotherapy; RT: radiotherapy; FOP: early ovarian failure; HH: hypergonadotropic hypogonadism . Source: The author (2019).

failure in women under 40 years of age, but its effect is potentiated if combined with other agents and RT[16]. A Greek study carried out in male patients, with a mean diagnosis of 10.8 years, who used classic alkylating agents, correlated doses of 6.3g/m^2 of cyclophosphamide and 4g/m^2 of procarbazine with FSH values greater than 10UI /L and reduced testicular size[14].

Almost 90% of our sample was submitted to an average dose of 5g/m^2 of alkylating agents and 17% were submitted to 2 or more cycles of MOPP or COPP, however, only 2 cases of alteration in the gonadal function were identified, suggesting a failure in the detection of these patients. A study showed that 6 cycles of MOPP could cause prolonged azoospermia in 90-100% of men and lead to ovarian failure in 5-25% of women under 30 years of age and in 50-80% of those over 30 years of age[16]. There is a reduction in ovarian volume and follicular reserve, with early menopause, reduced risk of breast cancer and increased risk of osteoporosis and cardiovascular disease[16,17].

The latest recommendations from *Children's oncology group* (COG), in 2008, highlighted the need for screening for patients undergoing 3 or more cycles of MOPP, cumulative dose of 7.5g/m^2 of cyclophosphamide or any dose of alkylating agent associated with abdominal, pelvic or TBI RT. It advises to perform the Tanner staging annually, with testicular volume measurement by the orchidometer , dosing LH, FSH and testosterone or estradiol in all men, from 14 years old, and women, from 13 years old, and repeat the exams according to signs pubertal delay or hormone deficiency[18].

There is no proven evidence that the use of GnRH analogues such as leuprorelin and triptorelin during the QT period is able to reduce follicular recruitment and estrogen levels, improving ovarian function and preserving fertility[16,19].

Bone metabolism

Patients who received chemotherapy protocols other than ABVD (48%; 36) were exposed to high doses of corticosteroids , ranging from 40 to 60mg/m2/day of prednisone for 15 days in each cycle, with an average of 4 to 6 cycles. This factor, associated with the risk of early ovarian failure that leads to estrogen deficiency and other toxic effects of chemotherapy, increases the risk of osteoporosis[15,18]. As recommended by the COG, patients exposed to cumulative prednisone doses of 9g/m ^{2} or more should undergo bone densitometry at the beginning of follow-up and repeat as needed, also remembering the importance of assessing daily calcium intake and serum vitamin levels. D[18].

Thyroid

thyroid function is considered the most common benign disorder after HL treatment, especially hypothyroidism[3,4,20,21]. The incidence can reach 60% of patients undergoing cervical RT[13,17,20]. It occurs mainly in the first 5 years free of disease, especially in the second and third years, but the risk remains for up to 25 years after RT[21,22]. It is more common in women, as well as in the general population, however, our sample was homogeneous between the sexes[21].

The risk of developing hypothyroidism after doses of 30Gy is 11.5% if the volume of the affected thyroid is less than or equal to 62.5% and increases to a 70.8% chance if

the volume is greater than 62.5%[22]. In our sample, 20.6% of the patients developed hypothyroidism, with a mean dose of 29Gy and only one patient did not receive RT. In comparison with other studies, the mean dose was higher, ranging from 32 to 38Gy[21,22].

The emergence of a second malignancy is one of the main causes of death in patients after HL treatment, with solid tumors responsible for most cases and RT the main risk factor[13,17]. The prognosis seems to be worse in younger patients undergoing treatment, especially before 15 years of age[11]. A study of 2548 post-HL patients, with a mean diagnosis of 13.3 years, found a 30-year cumulative incidence of 4.4% of thyroid carcinomas for men and women, with a mean age of 24.7 years; 13.2 years after LH. All of them had undergone cervical or mediastinal RT, with mean doses of 20Gy, and the most common subtype was papillary thyroid carcinoma[10]. This reinforces the importance of new treatment approaches, with reduced doses and RT prescription, in addition to improving the techniques used[13,22].

A US population analysis evaluated 174 cases of post-HL thyroid cancer diagnosed between 1973 and 2012 and compared their presentation and response to treatment with primary thyroid CA. There was no difference between the histological pattern, risk of metastasis or survival rate, however, the age at diagnosis was lower in patients with previous HL, probably due to the follow-up and greater surveillance of this subgroup[11]. Furthermore, it is recommended that the management of thyroid nodules in these patients is similar to the general population and, if removal of the nodule is indicated, total thyroidectomy should preferably be chosen[23].

COG guidelines recommend that annual thyroid palpation and thyroid function measurement be performed, with TSH and free T4, in all patients undergoing cervical, supraclavicular, mantle and mini mantle RT . Ultrasonography should only be performed in those with alterations in the physical examination[18].

Glucose metabolism and dyslipidemia

The CCSS showed that patients treated with RT were 1.8 times more likely to develop diabetes than their siblings and that this risk increased to 2.7 times in abdominal RT. No correlation was found with increased BMI or physical activity, but the chance was 2.4 times greater in patients undergoing treatment before the age of 5 when compared to adolescents aged 15 to 20 years[24]. A French and British study showed that RT doses greater than or equal to 10Gy in the pancreatic tail region, the site of the highest concentration of the Islets of Langerhans , are associated with an 11.5-fold greater risk of developing diabetes compared to patients who did not receive[25]. More recently, in another study, there was no increased risk of diabetes in patients treated with abdominal RT at doses lower than 35Gy, but those undergoing doses greater than or equal to 36Gy were 2.58 times more likely. Patients treated before the age of 25 years were particularly affected and the risk of diabetes remained for more than 30 years after treatment[26].

Regarding dyslipidemia, HL survivors, evaluated in the Czech Republic and compared with a control group, had 3 times more Metabolic Syndrome, with increases in insulin levels, fasting glucose, blood pressure and lipid profile. These changes were independent of RT doses[27]. In our research, probably due to the sample size and reduced follow-up time, it was not possible to identify patients with diabetes or dyslipidemia, however, according to the COG recommendations, it is important to maintain an anthropometric assessment of these patients, with an assessment of BMI and dosage. lipid profile every 2 years or earlier if necessary[18].

Growth

It is known that short stature and impaired linear growth may be related to malnutrition states, prolonged use of corticosteroids , tyrosine kinase inhibitors, retinoids and spinal RT. Bone structures undergoing RT have a high risk of low growth and disproportionate growth. Despite not being used in patients with HL, treatments that include cranial RT and TBI can lead to growth hormone deficiency and, at high doses (30Gy), multiple hypothalamic-pituitary deficiencies[28].

Evaluation and follow-up protocol

HL is an example of a curable neoplasm, with high survival rates, but with adverse pulmonary, cardiovascular, muscular and endocrinological effects resulting from the treatment. Among them, endocrinological alterations are the most commonly found and, with the correct screening, allow early identification and intervention. In addition, the importance of new therapeutic approaches, with the advancement of RT techniques, reduction of doses used and the emergence of less harmful chemotherapy protocols, reduce the impacts of therapy.

The development of an evaluation and follow-up protocol facilitates the understanding of the team, reduces failures, leads to the standardization of the service and anticipates the diagnosis (Table 2). In addition, long-term follow-up is necessary for a better evaluation of these patients. It is undeniable that the cure of the neoplasm is the priority, however, knowledge of the repercussions of the treatment are essential to enable an adequate quality of life for the survivor.

Table 2. Endocrinological follow-up protocol for surviving patients of Hodgkin's Lymphoma.

Gonadal function	- Anamnesis: sexual characters, menarche, cycles and sexuality; - Annual Tanner staging for all, with testicular volume measurement with the Prader orchidometer in boys; Patients undergoing alkylating agents (≥7.5g/m2 doses or any dose associated with abdominal, pelvic or TBI RT): - Measure LH, FSH and testosterone in men at age 14 and as needed if signs of pubertal delay or testosterone deficiency; - Measure LH, FSH and estradiol in women aged 13 years and as needed if there are signs of pubertal delay, amenorrhea or estrogen deficiency.
Bone metabolism	Patients receiving prednisone doses of 9g/m2 or more: - Bone densitometry after puberty or earlier as needed; - Evaluate calcium intake and serum levels of Vitamin D.
Thyroid	Patients undergoing cervical, supraclavicular, mantle and mini mantle RT: - Annual measurement of TSH and free T4; - Annual thyroid palpation; - Thyroid ultrasound as needed.
Glucose metabolism and dyslipidemia	- Avaliação do IMC anual para todos; Pacientes submetidos à RT abdominal: - Measurement of fasting glucose and lipid profile every 2 years.
Growth	- Annual weight and height assessment for all; Forward to the pediatric endocrinology service if short stature: - Height below the 3rd ^{percentile} or below -2SD for sex and age; - Growth velocity below the 25th ^{percentile}; - Growth below -2DP for the genetic target.

Source: Adapted from COG[18] (2008).

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