Original Article

Evaluation of Blood Pressure in Pediatric Survivors of Acute Lymphoblastic Leukemia and Healthy Children; A Case-control Study

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Abstract

Background: The exact prevalence of hypertension in children surviving acute lymphoblastic leukemia (ALL) has not been fully estimated. The aim of this study was to investigate the prevalence of arterial hypertension (AH) and to determine the risk factors for the development of AH in children surviving ALL with current treatments. **Materials and Methods:** A total of 150 patients (84 males, 66 females, with an age range of 1–16 years) were included in the study. Demographic and clinical information of patients were initially recorded. Hypertension is defined as average systolic blood pressure (BP) and/or diastolic BP that is greater than the 95th percentile for gender, age, and height. **Results:** The mean age at the assessment of BP was 11.3 and 9.8 years in the ALL and control group, respectively. A total of 20.6% of survivors of ALL and 10% of controls had high BP. Most patients in both groups had normal BP (65.3% patients in ALL group and 75.4% subjects in the control group). The number of patients with hypertension was significantly higher in ALL patients as compared with the control group (P = 0.026). **Conclusion:** The prevalence of AH in children surviving ALL is higher than in children in the general population, which emphasizes the need for regular monitoring of BP in children surviving ALL and intervention in the lifestyle of this population. Careful follow-up of BP status is warranted for long-term survivors of childhood cancer.

Keywords: *Acute lymphoblastic leukemia, Children, Hypertension, Survivors*

Introduction

Cancer usually has a sudden onset and is considered a life-threatening and potentially traumatic disease.[1] Cancer is also a major cause of death in developed and developing countries. Cancer in childhood and adolescence usually occurs between the ages of 0 and 19 years.[2]

According to a recent study in Iran, hematologic malignancies are the sixth most common malignancies in both sexes.[3] Leukemia is responsible for 30% of childhood cancers and is the most common form of cancer in children under 15 years of age.[4] Within these ages, the frequency of acute lymphoblastic leukemia (ALL) is about five times that of acute myelogenous leukemia, accounting for approximately 70% of all pediatric leukemia diagnoses.[4] Genetic and epigenetic disorders play a role in the etiology of ALL.[5-12]

Intensive chemotherapy combined with supportive care has improved the survival of children with ALL so that the cure rate of patients has reached more than 90%.[13] Compared to the general population, the prevalence of cardiovascular diseases such as obesity, atherosclerosis, heart failure, and hypertension may be higher in survivors of pediatric ALL.[14,15]

On the other hand, obesity has been shown to be a known risk factor for the development of hypertension,[16] dyslipidemia,[17] cancer,[18] and cardiovascular disease[19] in the general population. The most important risk factors associated with weight gain and hypertension among all patients with ALL are cranial radiotherapy and long-term treatment with corticosteroids.[20-23] It has also been reported that the incidence of cardiovascular disease in children with ALL leads to an increased risk of obesity and hypertension in adulthood.[24,25] Studies of pediatric cancer survivors have shown that high blood pressure (BP) rates range from 1.7% to 70.6%.[14,26]

Today, even in the absence of radiotherapy, an increase in obesity has been reported in patients,[27,28] and it is not clear which of the elements of chemotherapy causes

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obesity. By determining the prevalence of hypertension in survivors of AL, it can be prevented in adulthood. The exact prevalence of hypertension in children surviving ALL has not been fully estimated. The aim of this study was to investigate the prevalence of arterial hypertension (AH) and to determine the risk factors for the development of AH in children surviving ALL with current treatments.

Materials and Methods

Patient population

In a descriptive cross-sectional study from May 2013 to April 2020, a total of 185 newly diagnosed patients with ALL between the ages of 1 and 17 years were selected at the Amir Kabir Hospital, Arak, Iran. Intensive chemotherapy was performed for all patients based on risk factors at our center according to ALL BFM protocols.

Inclusion criteria included the following: definitive diagnosis of ALL using cytochemistry, morphology, cytogenetic analysis, and flow cytometric analysis, and patients who survived in the first remission included in the study with informed consent. It was obtained from all parents with children under 7 years old and all children over 7 years old. Study exclusion criteria included patients with renal disorders, congenital heart disease, thyroid disease, Cushing's syndrome, Down syndrome, hyperthyroidism, patients who experienced a relapse during their initial treatment, conscious dissatisfaction, patients who died, other cancers, and unwillingness to continue to participate in the study. A total of 150 patients (84 males, 66 females, with an age range of 1–16 years) were included in the study according to the inclusion and exclusion criteria.

The control group consisted of 150 children without any disorders that lead to possible hypertension (81 males, 69 females, with an age range of 4–15 years).

All ethical principles were observed according to the ethical protocol approved by the Research Ethics Committee of Arak University of Medical Sciences (IR.ARAKMU.REC.1397.369).

Anthropometric data

Demographic and clinical information of patients were initially recorded. Body mass index (BMI) was measured using Quetelet's equation (weight in kg/height in m^2). BMI *Z*-score was calculated.

BP was also measured three times at 1-min intervals after the subjects had rested for 10 min in a sitting position using a standard mercury sphygmomanometer (Model 1002/Presameter, Riester, Germany).[29] BP was measured every 20 min during the day until 8 pm and every 30 min during the night until 8 am. A suitable cuff was used based on the size of the subject's arm to prevent false results. The mean values of the first two readings for systolic BP (SBP) and diastolic BP (DBP) were calculated separately. If the difference in the first two readings was more than 10, the average of the two close readings was calculated. SBP and DBP were measured by a researcher on the right arm using a standard sphygmomanometer according to the World Health Organization recommendations.[30] In this study, BP results were categorized as normal, prehypertension, and hypertension. Prehypertension is defined as average SBP and/or DBP that is 90%–94% or >120/80 mmHg.[31] Hypertension is defined as average SBP and/or DBP that is >95th percentile for gender, age, and height.[32]

Statistical analysis

Data were expressed as mean ± standard deviation. The analysis was performed applying SPSS version 21 (Inc., Chicago, IL, USA). The two-tailed Mann–Whitney test was used to identify the correlations for continuous variables between groups. Pearson's χ^2 test (or Fisher's exact test) was utilized for qualitative variables. The significance level of the *P* value was considered >0.05.

Results

The mean age at the assessment of BP was 11.3 and 9.8 years in the ALL and control group, respectively. The median duration of ALL diagnoses until the diagnosis of hypertension was 60 (mean, 58.1 ± 2.33) months. When groups were compared in terms of age and gender, no significant difference was observed between the groups ($P > 0.05$) [Table 1]. There was a significant difference in the prevalence of hypertension between female and male individuals in the ALL patients ($P = 0.022$) so that females suffer from high BP more than males. No significant difference was observed between female and male individuals in the control group ($P = 0.474$).

Demographic and therapeutic findings of subjects including age, sex, BMI Z-score at diagnosis, BMI Z-score at last follow-up, SBP, DBP, duration of treatment, and duration of recovery are listed in 1. A total of 20.6% of survivors of ALL and 10% of controls had high BP. Most patients in both the groups had normal BP (65.3% patients in ALL group and 75.4% subjects in the control group). The number of patients with hypertension was significantly higher in ALL patients as compared with the control group ($P = 0.026$).

Both BMI Z-score at diagnosis and BMI Z-score at last follow-up increased significantly between diagnosis and last follow-up [Table 1]. The BMI Z-score at diagnosis and BMI Z-score at last follow-up were significantly different between the two groups so that the control group showed lower values ($P < 0.05$) [Table 1].

No significant difference was observed between ALL patients and the control group with respect to the occurrence of SBP and DBP ($P > 0.05$). Clinical characteristics in relation to blood pressure are shown in Table 2.

Table 1: Demographic and treatment characteristics of the subjects

Variable	Patients (*n*=150)	Control (*n*=150)	*P*
Age (years)	11.52±2.14	12.51±2.26	0.925
Gender (female/male)	71/79	69/81	0.999
BMI *Z*-score at diagnosis (mean±SD)	0.31±1.34	−0.12±1.02	0.038
BMI *Z*-score at last follow-up (mean±SD)	0.67±0.97	0.21±1.56	0.041
SBP (mmHg)	102±15.48	96.6±7.85	0.254
DBP (mmHg)	62.6±13.67	57.3±8.7	0.067
Duration of treatment) months)	36.72±12.51	NA	
Duration of recovery) months)	32.10±17.89	NA	

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, NA: Not applicable, SD: Standard deviation

Table 2: Clinical characteristics in relation to blood pressure

Blood pressure	Hypertention	Prehypertention	Normal BP	*P*
Gender (%)				
ALL patients				
Male	11	8	65	0.022
Female	20	8	38	
Control group				
Male	2	4	75	0.474
Female	4	5	60	
*P**	0.026	0.135	0.367	
Radiation, *n* (%)				
Yes	6 (19.4)	3 (18.8)	6 (5.8)	0.041
No	25 (80.6)	13 (81.2)	97 (94.2)	
Subtype leukemia				
Pre-B ALL	23 (74.2)	2 (12.5)	53 (51.4)	0.001
Common B-ALL	8 (25.8)	2 (12.5)	16 (15.5)	
T-ALL	0	12 (75)	15 (14.6)	
Early B ALL	0	0	11 (10.7)	
Pro-B ALL	0	0	8 (7.8)	
BMI				
ALL	23.5±2.1	23±2.8	21.1±2.4	0.202
Control	24.1±1.9	22.3±2.5	22.2±2.8	0.187
Age				
ALL	13.5±0.7	13±1.4	11.3±2.2	0.257
Control	12.5±1.6	13±1.7	11.2±2.17	0.190
Duration of treatment (months)				
ALL	35±2.4	36±0.1	37.2±13.8	0.579
Duration of treatment discontinuation (months)				
Case	31±20.9	32±6.9	31.6±17.1	0.897

**P* value: Comparison of values in ALL patients and control group. BMI: Body mass index, ALL: Acute lymphoblastic leukemia, BP: Blood pressure

Most patients with ALL received dexamethasone treatment with prednisolone (or anthracycline). Only a limited number of patients (n = 16, 10.7%) received cranial radiotherapy at doses of 18 or 24 grays, which were classified as yes or no. Of these, six patients (5%) had hypertension, three patients (2%) had prehypertension, and six patients (4%) had normal BP.

Most patients with hypertension and prehypertension did not receive radiotherapy, so radiotherapy alone could not increase BP. The prevalence of hypertension in the pre-B-ALL patients (74.2%) and patients with common B-ALL (25.8%) ws significantly higher ($P < 0.05$). Furthermore, the prevalence of prehypertension in T-ALL patients (75%) was significantly higher ($P < 0.05$).

Discussion

Several groups of children are at risk for high BP, such as ALL survivors. The exact prevalence of AH in the general pediatric population has not been fully estimated. The rate of improvement in pediatric lymphoblastic leukemia is now more than 80%, leading to a growing group of recovered people who are exposed to long-term risks of anticancer

drugs. Pediatric ALL survivors are at higher risk for obesity and hypertension than the general population.[33] The development of obesity and hypertension in childhood and adolescence increases the risk of obesity and adult hypertension[34] and is often associated with insulin resistance and dyslipidemia.[35] Available data show that the prevalence of hypertension in this population varies from 6.8% to even 20%.[36,37] One of the reasons for the discrepancy in the results of the studies may be the difference in the method of measuring BP and also the difference in the inclusion and exclusion criteria of patients.

In the present study, the prevalence of hypertension in the control group was 4%, which is in line with the study of Moradmand *et al*. who estimated the prevalence of hypertension in the age group of 6–19 years to be 3.4%.[38] Studies of pediatric cancer survivors have shown that high BP rates range from 1.7% to 70.6%.[14,26] The results of this study showed that in ALL survivors, the prevalence of hypertension (20%) and prehypertension (10.7%) is consistent with the study of Kelishadi *et al*. which showed that 14.1% of patients had metabolic syndrome.[39] Ociepa *et al*. reported a high prevalence of hypertension in ALL survivors (37%) and also showed that ALL survivors had significantly higher BP than the control group,[40] but the results of our study showed that hypertension in ALL survivors and the control group did not have a statistically significant difference with each other. High sample size, longer follow-up time, and measurement of BP by ambulatory BP monitoring method in the mentioned study can be the possible reasons for the difference between the results of this study and our study.

Furthermore, in the study of Ociepa *et al*., the mean SBP, DBP, and daily BP were significantly higher in the survivors of ALL than in the control group,[40] but in our study, the results showed that there is no statistically significant difference in the mean systolic and diastolic in two groups.

In the study of Veringa *et al*., the prevalence of hypertension was reported to be 22%,[14] which was higher than the results of our study, but the subjects had a higher mean age than our study (25 years vs. 11.52 years) and a longer follow-up period (16 years vs. 3 years). In the study of Levy *et al*., the prevalence of hypertension and prehypertension was 19%[15] which was in line with the results of our study. In addition, in the study of Chow *et al*., 15.3% of patients had high BP,[31] which is in line with our study.

There are several suggested risk factors for AH progression in ALL survivors, including medication (glucocorticoids, methotrexate, and anthracyclines), cranial radiotherapy, metabolic syndrome, and obesity.[41-43]

In the Ociepa *et al*.'s study, no association was found between AH risk and leukemia subgroup, leukemia risk group (severity of treatment), patient gender, and obesity, as well as the history of cranial radiation.[40] In the study by Chow *et al*., intensities of cranial therapy and radiotherapy were not associated with changes in BMI or BP.[31] In our study, the frequency of hypertension was not significantly associated with age, sex, duration of treatment, duration of treatment discontinuation, and BMI. These results are similar to the above study, except that according to the results of our study, the prevalence of hypertension in the pre-B-ALL group was higher than in other subgroups of leukemia. Veringa *et al*. reported that women who received cranial radiotherapy had significantly higher BMIs than women who did not.[14] The results of our study in these cases do not agree with the results of other studies that the small number of samples receiving radiotherapy and the effect of other factors affecting BP can be the reason for this difference. A study of treated children with Scottish ALL showed that the prevalence of obesity increased more than fivefold after 3 years. Similar results (threefold increase) after treatment were reported in children with ALL of England.[44]

In summary, we believe that our results support the need for regular BP monitoring in all survivors of pediatric ALL early in follow-up. Further studies are needed to confirm the very high prevalence of AH in all survivors of ALL. Longer follow-up is probably associated with even higher frequencies of AH. Careful follow-up of their BP status is warranted for long-term survivors of childhood cancer.

Conclusion

The prevalence of AH in children surviving ALL is higher than in children in the general population, which emphasizes the need for regular monitoring of BP in children surviving ALL and intervention in the lifestyle of this population. Careful follow-up of BP status is warranted for long-term survivors of childhood cancer.

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Conflicts of interest

There are no conflicts of interest.

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