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

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. 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.

According to a recent study in Iran, hematologic malignancies are the sixth most common malignancies in both sexes. Leukemia is responsible for 30% of childhood cancers and is the most common form of cancer in children under 15 years of age. 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. Genetic and epigenetic disorders play a role in the etiology of ALL.

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%. 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.

On the other hand, obesity has been shown to be a known risk factor for the development of hypertension, dyslipidemia, cancer, and cardiovascular disease 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. 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. Studies of pediatric cancer survivors have shown that high blood pressure (BP) rates range from 1.7% to 70.6%.

Today, even in the absence of radiotherapy, an increase in obesity has been reported in patients and it is not clear which of the elements of chemotherapy causes...
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 m²). 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). 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.

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. Hypertension is defined as average SBP and/or DBP that is >95th percentile for gender, age, and height.

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 χ² 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.
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%) was 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\[14] 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%.\[16,37\] 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. who 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.\[11\] 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.

References

1. Seiler A, Jenewein J. Resilience in cancer patients. Front Psychiatry 2019;10:208.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J
Cancer 2015;136:E359-86.

3. Dastgiri S, Fozounkah S, Shokrgozar S, Taghavinia M, Asvadi Kermani A. Incidence of leukemia in the Northwest of Iran. Health Promot Perspect 2011;1:50-3.

4. Belsom M, Kingsley B, Holmes A. Risk factors for acute leukemia in children: A review. Environ Health Perspect 2007;115:138-45.

5. Ghasemi A, Rostami S, Chahardouli B, Alizad Ghandforosh N, Ghotsalou A, Nadali F. Study of SFRP1 and SFRP2 methylation status in patients with de novo acute myeloblastic leukemia. Int J Hematol Oncol Stem Cell Res 2015;9:15-21.

6. Alizad Ghandforosh N, Chahardouli B, Rostami S, Ghadimi H, Ghasemi A, Alimoghaddam K, et al. Evaluation of minimal residual disease in acute myeloid leukemia with NPM1 marker. Int J Hematol Oncol Stem Cell Res 2016;10:147-52.

7. Ghasemi A, Nadali F, Chahardouli B, Ghandforosh NA, Zadeh AG, Rostami S. Study of correlation between SFRP-1 and SFRP-2 hypermethylation with relapse, complete remission, genetic mutations of FLT3-ITD and NPM1 and immunophenotypes of leukemic cells in patients with de novo acute myeloblastic leukemia. J Hematol 2014;3:34-42.

8. Ghasemi A, Ghotsalou A, Mohammadi M, Abbasian S, Ghaffari K. Methylation of the Wnt signaling antagonist, Wnt inhibitory factor 1 and dickkopf-1 genes in acute myeloid leukemia at the time of diagnosis. Zahedan J Res Med Sci 2016;18:1-6.

9. Ghasemi A, Ghotsalou A, Ghaffari K, Mohammadi M. Methylation status of SOX17 and RUNX3 genes in acute leukemia. Iran J Blood Cancer 2015;7:213-9.

10. Ghasemi A, Ghotsalou A, Mohammadi M, Ghaffari K, Abbasian S. Dysregulation of the WNT signaling pathway through methylation of Wnt inhibitory factor 1 and dickkopf-1 genes among AML patients at the time of diagnosis. Iran J Blood Cancer 2014;7:11-7.

11. Ofiran Y, Izraeli S. BCR-ABL (Ph)-like acute leukemia-pathogenesis, diagnosis and therapeutic options. Blood Rev 2017;31:11-6.

12. Ghaffari K, Ghasemi A, Mohammadi M, Abbasian S. Comparison of secreted frizzled-related protein-4 & -5 promoter methylation in patients with acute myeloblastic leukemia and healthy individuals. Iran J Blood Cancer 2021;13:1-5.

13. Vora A, Goulden N, Wade R, Mitchell C, Hancock J, Hough R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): A randomised controlled trial. Lancet Oncol 2013;14:199-209.

14. Veringa SJ, van Dulmen-den Broeder E, Kaspers GJ, Veening MA. Blood pressure and body composition in long-term survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2012;58:278-82.

15. Levy E, Samoilenko M, Morel S, England J, Amre D, Bertout L, et al. Cardiometabolic risk factors in childhood, adolescent and young adult survivors of acute lymphoblastic leukemia – A petale cohort. Sci Rep 2017;7:17684.

16. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham heart study: A cohort study. Lancet 2001;358:1682-6.

17. Gostynski M, Gutzwiller F, Kuulasmaa K, Döring A, Ferrario M, Grafnetter D, et al. Analysis of the relationship between total cholesterol, age, body mass index among males and females in the WHO MONICA Project. Int J Obes Relat Metab Disord 2004;28:1082-90.

18. Dossus L, Kaaks R. Nutrition, metabolic factors and cancer risk. Best Pract Res Clin Endocrinol Metab 2008;22:551-71.

19. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: Pathophysiology, evaluation, and effect of weight loss: An update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006;113:898-918.

20. Jafarí M, Lanning B, Bosaeus I, Johannsson G, Bjarnason R. Body composition in young adult survivors of childhood acute lymphoblastic leukemia. Eur J Endocrinol 2005;153:81-9.

21. Oeffinger KC, Mertens AC, Sklar CA, Yasui Y, Fears T, Stovall M, et al. Obesity in adult survivors of childhood acute lymphoblastic leukemia: A report from the childhood cancer survivor study. J Clin Oncol 2003;21:1359-65.

22. Gurney JG, Ness KK, Sibley SD, O'Leary M, Dengel DR, Lee JM, et al. Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia. Cancer 2006;107:1303-12.

23. Van Dongen-Melman JE, Hokken-Koelega AC, Hääkken L, De Groot A, Tromp CG, Egeler RM. Obesity after successful treatment of acute lymphoblastic leukemia in childhood. Pediatr Res 1995;38:86-90.

24. Garney EG, Liu Q, Sklar CA, Meacham LR, Mertens AC, Stovall MA, et al. Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: A report from the childhood cancer survivor study. J Clin Oncol 2008;26:4639-45.

25. Nottage KA, Ness KK, Li C, Srivastava D, Robison LL, Hudson MM. Metabolic syndrome and cardiovascular risk among long-term survivors of acute lymphoblastic leukaemia – From the St. Jude Lifetime Cohort. Br J Haematol 2014;165:364-74.

26. Koch VH, Colli A, Saito MI, Furusawa EA, Ignes E, Okay Y, et al. Comparison between casual blood pressure and ambulatory blood pressure monitoring parameters in healthy and hypertensive adolescents. Blood Press Monit 2000;5:281-9.

27. Baillargeon J, Langevin AM, Lewis M, Grady JJ, Thomas PJ, Mullins J, et al. Therapy-related changes in body size in Hispanic children with acute lymphoblastic leukemia. Cancer 2005;103:1725-9.

28. Dalton VK, Rue M, Silverman LB, Gelber RD, Asselin BL, Barr RD, et al. Height and weight in children treated for acute lymphoblastic leukaemia: Relationship to CNS treatment. J Clin Oncol 2003;21:2953-60.

29. Frese EM, Fick A, Sadowsky HS. Blood pressure measurement guidelines for physical therapists. Cardiopulm Phys Ther J 2011;22:5-12.

30. World Health Organization. 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension: Guidelines subcommittee. J Hypertens 1999;17:151-83.

31. Chow EJ, Piloker C, Hunt K, Wilkinson K, Friedman DL. Obesity and hypertension among children after treatment for acute lymphoblastic leukemia. Cancer 2007;110:2313-20.

32. Falkner B, Daniels SR. Summary of the fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Hypertension 2004;44:387-8.

33. Nuver J, Smit AJ, Postma A, Sleijfer DT, Gietema JA. The metabolic syndrome in long-term cancer survivors, an important target for secondary preventive measures. Cancer Treat Rev 2002;28:195-214.

34. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH.
Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med 1997;337:869-73.

35. Lauer RM, Clarke WR. Childhood risk factors for high adult blood pressure: The Muscatine Study. Pediatrics 1989;84:633-41.

36. Menghetti E, Striscuglio P, Spagnolo A, Carletti M, Paciotti G, Muzzi G, et al. Hypertension and obesity in Italian school children: The role of diet, lifestyle and family history. Nutr Metab Cardiovasc Dis 2015;25:602-7.

37. Xi B, Li H, Li S, Mi J. Recent prevalence of hypertension among Chinese children and adolescents based on 2010 China national blood pressure references. Int J Cardiol 2014;174:870-1.

38. Moradmand S, Ganji MR, Meysami AP, Akbari Z, Mirkhani SZ, Tabrizchi N, et al. Prevalence of hypertension and its impact on birth weight and current body weight in school children in Tehran. J Payavard Salamat 2012;5:16-23.

39. Kelishadi R, Razaghi EM, Gouya MM, Ardalan G, Gheiratmand R, Delavari A, et al. Association of physical activity and the metabolic syndrome in children and adolescents: CASPIAN study. Horm Res Paediatr 2007;67:46-52.

40. Ociepa T, Bartnik M, Zielezińska K, Urszynski T. Prevalence and risk factors for arterial hypertension development in childhood acute lymphoblastic leukemia survivors. J Pediatr Hematol Oncol 2019;41:175-80.

41. Esbenshade AJ, Simmons JH, Koyama T, Koehler E, Whitlock JA, Friedman DL. Body mass index and blood pressure changes over the course of treatment of pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer 2011;56:372-8.

42. Oeffinger KC. Are survivors of acute lymphoblastic leukemia (ALL) at increased risk of cardiovascular disease? Pediatr Blood Cancer 2008;50:462-7.

43. Meacham LR, Chow EJ, Ness KK, Kamdar KY, Chen Y, Yasui Y, et al. Cardiovascular risk factors in adult survivors of pediatric cancer – A report from the childhood cancer survivor study. Cancer Epidemiol Prev Biomarkers 2010;19:170-81.

44. Ness KK, Oakes JM, Punyko JA, Baker KS, Gurney JG. Prevalence of the metabolic syndrome in relation to self-reported cancer history. Ann Epidemiol 2005;15:202-6.