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RESEARCH

Association between fetal growth restriction and late complications in long-term survivors of pediatric acute lymphoblastic leukemia

Pediatrik akut lenfoblastik lösemi hastalarının uzun dönem sağ kalanlarında fetal büyüme geriliğinin geç komplikasyonlarla ilişkisi

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Abstract

Purpose: This study aimed to investigate the association between fetal growth restriction (FGR) and the development of late complications in long-term survivors of pediatric acute lymphoblastic leukemia (ALL).

Materials and Methods: This study enrolled 108 long-term survivors of pediatric ALL, who were subsequently divided into two groups. Group 1 consisted of 48 patients with a history of FGR, while Group 2 included 60 patients with normal fetal growth. The groups were compared based on demographic characteristics, treatment status, duration of remission, maternal and paternal age at conception, maternal weight gain during pregnancy, parental smoking and alcohol use, and the incidence of late complications.

Results: No significant association was found between the groups regarding treatment status, demographic factors, remission duration, or familial risk factors. However, the number of late complications was statistically significantly higher in Group 1 (37/48, 77.1%) compared to Group 2 (18/60, 30.0%). The most frequently observed late complications were endocrine (47/108), cardiac (21/108), osseous (18/108), metabolic (8/108), and neurological (3/108).

Conclusion: ALL treatment may induce late complications by affecting various systems and tissues through oxidative mechanisms, particularly in patients with a history of FGR. Our findings may aid clinicians in predicting the risk of late complications and developing early prevention strategies for ALL survivors with a history of FGR.

Keywords: Fetal growth restriction, acute lymphoblastic leukemia, late complications, childhood, long-term survivors.

Öz

Amaç: Pediatrik akut lenfoblastik lösemi'nin (ALL) 'uzun dönem sağ kalanlarında fetal büyüme geriliği (FBG) ile geç komplikasyonlar arasındaki ilişkiyi araştırdık.

Gereç ve Yöntem: Çalışmada, pediatrik ALL hastalarından uzun dönem sağ kalan 108 hasta; FBG'ye (grup 1, n=48) ve normal büyümeye (grup 2, n=60) göre iki gruba ayrıldı. Gruplar tedavi durumu, demografik özellikler, remisyon süresi, maternal gebelik yaşı, paternal gebe kalma yaşı, gebelik sırasında maternal kilo alımı, ebeveynlerin sigara ve alkol tüketimi ve geç komplikasyonlar açısından değerlendirildi.

Bulgular: Çalışmada hastaların tedavi durumu, demografik faktörler, remisyon süresi ve ailevi risk faktörleri arasında bir ilişki bulunmadı. Geç komplikasyon sayısı grup 1'de (37/48, %77,1) grup 2'ye (18/60, %30,0) göre istatistiksel olarak daha yüksekti (p<0,001). En sık görülen geç komplikasyonlar endokrin (47/108), kardiyak (21/108), osseöz (18/108), metabolik (8/108) ve nörolojik (3/108) komplikasyonlardı.

Sonuç: ALL tedavisi, özellikle FBG öyküsü olan hastalarda, oksidatif mekanizmalarla, çeşitli sistem ve dokuları etkileyerek geç komplikasyonlara neden olabilir. Çalışmamız, FBG öyküsü olan sağ kalanlarda geç komplikasyon riskini ve erken önlemeyi tahmin etmede klinisyenlere fayda sağlayacaktır.

Anahtar kelimeler: Fetal büyüme geriliği, akut lenfoblastik lösemi, geç komplikasyonlar, çocukluk çağı, uzun dönem sağ kalanlar

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INTRODUCTION

Acute lymphoblastic leukemia (ALL), the most common childhood cancer, occurs in children younger than 15 years at a rate of approximately 1 in 2000[1]. It is an essential cause of cancer-related deaths in children and adolescents[2]. However, the five-year survival rate of patients has increased to as high as 90% due to improved treatment modalities, resulting in an overall life expectancy equivalent to that of the general population[3,4]. Therefore, it is very important to evaluate survivors of pediatric ALL patients for late complications related to treatment effects in young adults. In particular, secondary malignancies, cardiac toxicity, obesity, neurological and endocrine abnormalities, and bone morbidity may be observed in survivors[5].

Intrauterine growth retardation (IUGR), a fetal growth retardation (FGR), is a fetal developmental disorder in which the expected fetal weight for gestational age is below the 10th percentile (< 2500 gr)[6]. Placental insufficiency, chromosomal abnormalities, perinatal infections, and exposure to teratogenic agents can lead to IUGR[7]. In IUGRs, morbidity and mortality are increased in the short and long term due to FGR[8]. Therefore, adequate fetal growth is critical for later health. Due to decreased blood flow to the placenta during FGR, oxidative stress occurs during placental ischemia. Increased free oxygen radicals lead to the oxidation of lipids and nucleic acids and the disruption of transcription factors and activities of signaling pathways[9].

Mitochondria produce cellular energy via the electron transport chain, and oxidative phosphorylation has an important antioxidant function and maintains placental development, ensuring proper fetal growth and development. Mitochondrial damage due to oxidative stress-induced mitochondrial mutations in mitochondrial DNA (mtDNA) may be higher in IUGRs than in individuals with normal birth weight and birth time[10]. In our previous studies, we hypothesized that chemotherapeutic agents such as anthracyclines inhibit mitochondrial biogenesis and cause cell death, resulting in increased cardiac toxicity in cancer survivors with IUGR due to structurally low-content mtDNA[11,12]. In their study, Jones et al. stated that IUGR is characterized by placental oxidative stress and increased mtDNA abundance, which alters placental metabolism[10].

It has been hypothesized that late complications related to leukemia treatment may be more common in patients with FGR due to oxidative mechanisms. Therefore, determining this relationship will be useful for clinicians in assessing the risk of late complications after treatment in children with a history of FGR and will guide early prevention. Our study aimed to investigate the association between late complications in survivors of pediatric ALL and FGR and other risk factors.

MATERIALS AND METHODS

Sample

The study was conducted on ALL survivors between January 2002 and December 2020 at Dr. Sami Ulus Maternity Child Health and Diseases Training and Research Hospital, Department of Pediatric Hematology and Oncology, Ankara, Turkey. The study included 108 pediatric long-term survivors ALL.

As a result of the power analysis performed using the G*Power 3.1 program based on the Type I error level (α) = 0.05, statistical power ($1 - \beta$) = 0.80 and medium effect size (Cohen's d = 0.50), the minimum sample size required for a two-group comparison with a sample distribution ratio of 5:4 was calculated as 57 for the large group and 45 for the small group. In order to prevent possible data loss, three participants were added to each group and the final sample size was determined as 60 and 48, respectively.

Procedure

The study protocol was approved by the Ethics Committee of Dr. Sami Ulus Maternity Child Health and Diseases Training and Research Hospital (No: E-20/10-014) and informed consent was obtained from all participants and their parents.

The study enrolled patients who had completed their treatment at least three years ago. Patient data were obtained retrospectively from the medical record archives. All incomplete records were excluded from the study. Hematopoietic stem cell transplant recipients and patients who had relapsed were excluded from the study. In addition, patients had no other genetic or chronic diseases that would increase morbidity before the diagnosis of ALL.

Sex, age, diagnosis, disease risk group, age at diagnosis, treatment protocol, history of radiotherapy, remission time, birth weight, time of birth, final height and weight, body mass index (BMI), secondary malignancies, endocrine, osseous, metabolic, cardiac, and neurological complications that occurred during the follow-up period were recorded in the medical records. Maternal gestational age, paternal age at conception, maternal weight gain during pregnancy, and parental smoking and alcohol consumption before conception and during pregnancy were also recorded.

Patients were stratified into two groups based on birth weight: Group 1 (FGR group, n=48), defined as a birth weight ≤2500 grams, and Group 2 (non-FGR group, n=60), with a birth weight >2500 grams. The groups were compared to evaluate the association between these recorded factors and the incidence of late complications.

The treatment was performed by pediatric hematology and oncology doctors at Dr. Sami Ulus Maternity Child Health and Diseases Training and Research Hospital in accordance with current international treatment protocols. Depending on the risk group, patients received the St. Jude Total Therapy Study XIII or the St. Jude Total Therapy Study XV chemotherapy treatment protocol and cranial prophylactic radiotherapy. Patients at high risk of central nervous system (CNS) relapse received prophylactic cranial radiation of 2400 rad (24 Gy).

Statistical Analysis

Statistical data analysis was performed using the SPSS 20.0 Statistical Package program. For categorical variables, frequency and percentage values were calculated with the Kolmogorov-Smirnov test, and for continuous variables, mean ± standard deviation (SD), median, minimum, and maximum values were calculated. The significance of differences between groups was assessed with the Student t-test or the Mann-Whitney U test. Logistic regression analysis was used in multivariate analysis. Nominal variables were compared with Pearson's chi-square or Fisher's exact probability tests. $p < 0.05$ values were considered statistically significant.

RESULTS

The demographic and clinical characteristics of 108 long-term survivors of ALL patients enrolled in the study are shown in Table 1 and Table 2. Patients were divided into two groups: Group 1 (FGR group) and Group 2 (non-FGR group). There was no statistically significant difference between the groups in age, age at diagnosis, remission duration, weight, height, BMI, maternal gestational age, paternal conception age, and maternal weight gain during pregnancy. No statistically significant difference was found in either group with regard to sex, risk group, treatment protocol, radiotherapy, secondary malignancy, maternal/paternal smoking, and alcohol consumption before conception and during pregnancy. One patient in group 1 who received prophylactic cranial radiotherapy was found to have a meningioma as a secondary malignancy. There was no statistically significant difference between the duration of remission and late complications in either group.

Patients were evaluated for endocrine, metabolic, cardiac, and osseous complications that developed during follow-up. It was found that late complications were statistically significantly more frequent in group 1 (37/48, 77.1%) than in group 2 (18/60, 30.0%) ($p < 0.001$). The most common late complications were endocrine complications (47/108). This was followed by cardiac (21/108), osseous (18/108), metabolic (8/108), and neurological (3/108) complications (Table 3).

The most common endocrine complications in patients were obesity (32/108), short stature (16/108), hypothyroidism (6/108), insulin resistance (3/108), type 2 diabetes mellitus (2/108), early puberty (2/108), and hypogonadism (1/108). Cardiac complications were minimal tricuspid regurgitation (14/108), minimal mitral regurgitation (3/108), arrhythmias (2/108), left ventricular failure (1/108), and hypertension (1/108). Osteoporosis was noted as a osseous complication in 18 of 108 patients. Hepatosteatosis (7/108) and hyperlipidemia (4/108) were indicated as metabolic complications in patients. Epilepsy was pointed out as a neurological complication in 3 of 108 patients.

Table 1. Mean values and distribution of variable numerical datas in Group 1 and Group 2.

	Group 1 n:48 (44.4%) mean±SD	**Group 2 n:60 (55.6%) mean±SD**	**p**
Age (years)	18.2±5.1	18.8±5.9	0.546
Age at diagnosis	6.5±3.8	7.1±4.5	0.492
Remission duration (years)	11.0±5.1	10.8±5.8	0.883
Weight (kg)	61.0±18.0	60.4±18.1	0.864
Height (cm)	157.6±14.9	159.2±16.0	0.591
Body mass index (BMI)	24.1±4.8	23.5±4.2	0.503
Maternal pregnancy age (years)	24.9±5.4	24.3±6.3	0.625
Paternal conception age (years)	29.5±5.0	30.7±6.0	0.269
Maternal weight gain during pregnancy (kg)	11.2±9.0	11.1±3.6	0.948

n, number; SD, standard deviation

Table 2. Distribution of variable categorical datas in Group 1 and Group 2.

		Group 1 n:48 (44.4%)		**Group 2 n:60 (55.6%)**		**p**
		n	**%**	**n**	**%**	
Gender	Female	19	39.6	18	30.0	0.294
	Male	29	60.4	42	70.0	
Risk group	Low risk	32	66.7	38	63.3	0.719
	High risk	16	33.3	22	36.7	
Treatment protocol	St. Jude XIII	18	37.5	31	51.7	0.142
	St. Jude XV	30	62.5	29	48.3	
Radiotherapy	Positive	10	20.8	9	15.0	0.429
	Negative	38	79.2	51	85.0	
Secondary malignancy	Positive	1	2.1	0	0.0	0.261
	Negative	47	97.9	60	100.0	
Maternal smoking	Positive	8	16.7	15	25.0	0.293
	Negative	40	83.3	45	75.0	
Maternal alcohol consumption	Positive	0	0.0	1	1.7	0.369
	Negative	48	100.0	59	98.3	
Paternal smoking	Positive	31	64.6	42	70.0	0.550
	Negative	17	35.4	18	30.0	
Paternal alcohol consumption	Positive	3	6.3	7	11.7	0.335
	Negative	45	93.8	53	88.3	
Late complications	Positive	37	77.1	18	30.0	**<0.001**
	Negative	11	22.9	42	70.0	

p<0.05*; n, number

Table 3. Late complications seen in Group 1 and Group 2.

		Group 1 n:48 (44.4%)		Group 2 n:60 (55.6%)		p
		Number	%	Number	%	
Endocrine complications	Positive	34	70.8	13	21.7	**<0.001**
	Negative	14	29.2	47	78.3	
Osseous complications	Positive	16	33.3	2	3.3	**<0.001**
	Negative	32	66.7	58	96.7	
Metabolic complications	Positive	6	12.5	2	3.3	0.071
	Negative	42	87.5	58	96.7	
Cardiac complications	Positive	18	37.5	3	5.0	**<0.001**
	Negative	30	62.5	57	95.0	
Neurological complications	Positive	1	2.1	2	3.3	0.694
	Negative	47	97.9	58	96.7	

p<0.05*; n, number

DISCUSSION

Advances in therapeutic regimens for ALL, the most prevalent childhood cancer, have markedly improved survival rates. This success has, in turn, heightened clinicians' awareness of the late effects of therapy. Common late complications include secondary malignancies, neurological/neurocognitive disorders, cardiotoxicity, endocrine dysfunction (e.g., thyroid issues, gonadal dysfunction, short stature, obesity), bone disorders (osteopenia, osteoporosis), and metabolic disorders (e.g., hyperlipidemia, hepatosteatosis)[13].

Perinatal characteristics such as birth weight, gestational age, and gender have been associated with the risk of childhood leukemia[14]. In addition, studies have shown an increased risk of leukemia associated with advanced parental age, maternal and paternal alcohol consumption, and smoking before conception and during pregnancy[15,16]. Studies show that prematurity and low birth weight are risk factors for the development of childhood cancers[17-20]. However, the association between these factors and late complications in pediatric ALL survivors is unknown. Because of placental insufficiency in babies born with FGR, hypoxia causes oxidative stress. This results in impaired apoptosis, detoxification, cellular signal transduction, and enzymatic activity[9]. This situation can lead to problems that affect the entire life as organelle functions are disrupted. These patients may suffer from long-term health problems in adulthood, such as metabolic, neurological, cardiac, endocrinological, or bone diseases[7,21]. We hypothesized that the incidence of adverse effects may be higher in the fetal restriction patient group because of the increased oxidative stress associated with pediatric ALL therapy. Late effects may develop due to the toxicities of the treatments. However, it has been hypothesized that the decrease in antioxidant capacity because of mitochondrial insufficiency may also exacerbate these effects.

In this study, the association between late complications in pediatric ALL survivors and FGR was investigated. Endocrine disorders are particularly common in cancer survivors. Recent data suggest that 40-50% of survivors develop endocrinopathy at least once in their lifetime[22,23]. In our study, it was found that endocrine complications in particular were most common in group 1 survivors. Among the endocrinological disorders, obesity, short stature, hypothyroidism, insulin resistance, type 2 diabetes mellitus, puberty precocious, and hypogonadism were more common in group 1 than in group 2. Hypothalamo-pituitary dysfunction due to cranial radiotherapy may occur in patients with leukemia[24]. However, we did not find a significant association between prophylactic cranial radiotherapy and late endocrine complications among the patients in our study.

Obesity is a substantial morbidity that affects the lives of survivors in the long term. In a meta-analysis, adolescents and adults who survived childhood ALL had a BMI 12-28% higher than the general population, and these individuals were classified as overweight or obese[25]. Similarly, in our study, 29.6% (32/108) of patients were found to be obese during follow-up.

Decreased physical activity, obesity, and chemotherapeutic agents such as methotrexate and high-dose corticosteroids in treating ALL lead to a decrease in bone mineral density by disrupting bone structure[26]. As a result, the prevalence of low BMD and osteoporosis in ALL survivors ranges from 20% to 50%[27,28]. In our study, 18 of 108 (16.6%) patients, more commonly in group 1, were found to have osteoporosis during follow-up.

Many metabolic abnormalities can be observed in ALL survivors due to the effects of chemotherapy and radiotherapy. Morel et al compared the plasma lipid and lipoprotein profiles of 80 childhood survivors of ALL with 22 healthy controls[29]. They showed that 50% of survivors from ALL had dyslipidemia characterized by low HDL cholesterol and elevated plasma triglycerides (TG) and LDL cholesterol. In addition, the incidence of fatty liver increased in the long term in patients associated with obesity[30]. We found hepatosteatosis (7/108) and hyperlipidemia (4/108) in follow-up patients.

The most serious complications associated with treatment in ALL survivors are cardiotoxicities such as heart failure, arrhythmias, and coronary artery disease. This risk increases especially as the cumulative anthracycline dose is higher[31]. Subclinical changes in cardiac function are more common than serious clinical toxicities[32]. Our patients also had subclinical changes rather than advanced cardiac toxicities affecting cardiac function. Pediatric ALL survivors are at risk for late neurologic sequelae such as headache, seizures, and focal neurologic deficits. The Childhood Cancer Survivor Study (CCSS) studied 4151 ALL survivors and reported that they are at high risk for headaches, seizures, focal neurologic deficits, and auditory-vestibular-visual sensory deficits in adulthood[33]. Three of our patients were found to have epilepsy as a neurologic complication.

Secondary malignancies are among the serious late sequelae of acute leukemia therapy[34]. Chemotherapy treatments such as alkylating agents, anthracyclines, etoposide, and irradiation (especially cranial) have increased the risk of secondary malignancies[35]. Acute myeloid leukemia, myelodysplastic syndrome, thyroid cancer, breast cancer, central nervous system tumors, meningiomas, and melanomas are among the secondary cancers that occur in survivors of ALL patients[36]. Studies have reported that the cumulative risk of developing a secondary malignancy after ALL therapy is 1-11% at 10-15 years of follow-up[36-38]. In our study, fibrous meningioma was diagnosed at the 11th year of follow-up in a group 1 female patient who had received a low-risk St. Jude Total Therapy Study XIII treatment protocol and prophylactic cranial radiotherapy.

In conclusion, chemotherapeutic agents and radiotherapy used in treatment can affect various systems and tissues, causing secondary malignancy, neurological/neurocognitive disorders, cardiotoxicity, endocrine disorders, bone disorders, and metabolic disorders in the long term. In our study, it was hypothesized that these complications may be more common in patients with FGR because of oxidative mechanisms. Therefore, patients receiving ALL treatment and born with FGR should be evaluated more closely in terms of long-term complications. There are very few studies examining the association between these factors and late complications after treatment in survivors. To our knowledge, this is the first study to examine the association between FGR and late complications in survivors of pediatric ALL. It will therefore be useful to clinicians in assessing the risk for late complications after treatment in children with a history of FGR and will lead to considerations for early prevention. Our study has a number of limitations that need to be considered. These include the limited number of patients, shorter follow-up time, inability to assess mitochondrial dysfunction and oxidative/antioxidant capacity. Therefore, further studies with larger populations are needed.

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