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Original Article

Late-effects of Chemoradiotherapy on Growth and Puberty in Survivors of Childhood Acute Lymphoblastic Leukemia

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ABSTRACT

Objective: The survival rate of childhood leukemia has reached 80% with evolving treatment modalities over the last 30 years, which is followed by an increased incidence of treatment-related long-term side effects. This study, it was aimed to evaluate the endocrine late effects of chemoradiotherapy in childhood acute lymphoblastic leukemia (ALL).

Methods: Forty-eight patients with ALL treated at the University of Health Sciences Türkiye, İstanbul Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Pediatric Hematology and Oncology between 1997 and 2007 with at least 5-year follow-up after the chemotherapy, were included.

Results: Endocrine side effects were detected in 48% (n=23) of the cases. The most common endocrine side effect was short stature in the group treated with cranial radiotherapy (CRT), and obesity in the group that did not receive CRT. The median height standard deviation score (SDS) of the subjects who reached the final height (FH) was significantly lower [-1.44 (-2.1)-(-0.53)] compared with the median height SDS of the subjects who did not reach the FH [-0.24 (-1.23)-(0.6)]. There was a positive correlation between height SDS and IGF1 SDS, IGFBP3 SDS, body mass index SDS, and advanced bone age in subjects who did not reach FH (r=0.511, p=0.018, r=0.530, p=0.014, r=0.499, p=0.021, r=0.599, p=0.08, respectively). Precocious puberty was found in one patient who received CRT, and hypergonadotropic hypogonadism was found in one patient who did not receive CRT. Twenty-three percent of the group received CRT and 35% of the group who did not receive CRT had overweight/obesity. Central hypothyroidism was detected in one case and subclinical hypothyroidism was detected in two cases.

Conclusion: Long-term endocrine side effects were observed in approximately half of the cases with childhood ALL. Children treated with chemoradiotherapy should have regular endocrine system evaluation and growth monitoring starting from the diagnosis until the growth is completed.

Keywords: Acute lymphoblastic leukemia, growth, late effects, puberty, obesity

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. With the developments in the diagnosis and treatment over the last 50 years, the survival rate of children diagnosed with ALL has increased significantly. With the combined use of chemotherapy (CT), central nervous system prophylaxis, and supportive treatment, the 5-year disease-free survival rate has reached 85% and the overall survival rate has reached 90%.

Improvements in survival have increased the importance of treatment-related long-term morbidity and mortality. Treatment-related chronic complications were reported in 62.3% of survivors of childhood ALL and significant endocrine-related complications were reported in 40% of them.[1] The most common endocrine-related complications have been reported as short stature, deficiency of growth hormone (GH), obesity/overweight, and precocious puberty.[2] GH deficiency after CRT is dose-dependent and mostly seen at a dose of 24 Gray (Gy); however, it can also be seen at doses as low as 18 Gy, or a single dose of 10 Gy applied during total body irradiation.[3] A decline in height growth is frequent during ALL treatment, particularly during the first year of treatment, but it can persist over time compromising patients' final height (FH).[4] Therefore, early diagnosis of endocrine disorders is essential to improve the quality of life. Furthermore, comprehending the underlying mechanisms is critical for establishing safer treatment protocols and appropriate follow-up plans to ensure the long-term health of survivors.[5]

Several studies have evaluated the effect of CT and prophylactic cranial radiotherapy (CRT) on growth and puberty in childhood ALL, however, results are conflicting. The mechanisms underlying these long-term endocrine effects remain unclear.

In this study, we studied the effects of CT and CRT on growth and puberty by evaluating the long-term follow-up data of children treated with ALL.

MATERIALS AND METHODS

A total of 48 cases, consisting of 22 boys (46%) and 26 girls (54%), who were treated with ALL in Pediatric Hematology and Oncology Clinic at the Ministry of Health Kanuni Sultan Süleyman Training and Research Hospital, between 1997 and 2007 were evaluated retrospectively. Ethics Committee approval was obtained from University of Health Sciences Türkiye, İstanbul Kanuni Sultan Süleyman Training and Research Hospital (date: 05.10.2012, approval no: 315) in accordance with the Declaration of Helsinki. Families and patients were informed about the study, and all subjects or their legal guardians provided written consent.

Inclusion Criteria:

1. The patient's and family's consent for the tests and examination,

2. Patients who have completed at least 5 years after the completion of treatment.

Exclusion criteria:

1. Patients for whom parental consent is missing,

2. Central nervous system involvement,

3. Presence of secondary malignancy,

4. Past spinal irradiation.

The following CRT protocol was applied to the CRT group;

Prophylactic CRT:

SRG (standard risk group): Not applicable

MRG (medium risk group): <1 year old: Not applicable

>1 - <2 years old: 12 Gy in T ALL only, not applicable in others.

≥ 2 years old: 12 Gy

HRG (highrisk group): >1 - <2 years old: 12 Gy

≥ 2 years old: 18 Gy.

In the case of CNS (central nervous system) involvement:

<1 year old: Not applicable

>1 - <2 years old: 12 Gy

≥ 2 years old: 18 Gy.

Follow-up Protocol

Evaluation of growth

For all subjects, information including age, gender, height, weight, parents' heights, target height (TH), age at diagnosis, treatment protocols (CT, CT+radiotherapy), puberty stage, and bone age was obtained. Thyroid-stimulating hormone (TSH), free T4 (fT4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol or testosterone, insulin-like growth factor-1 (IGF-1), IGF-binding protein-3 (IGFBP-3) were measured using standard techniques.

The heights of the patients and their parents were measured by the same person at three-month intervals with the "Harpenden Stadiometer". The growth velocity was monitored for one year. Body weight was measured using scales sensitive to 100 g. Body mass index (BMI) was calculated as weight/height squared (kg/m^2). The standard deviation score (SDS) was calculated for the height and body weight of the patients according to the standards of Turkish children.[6] Values between +2 SDS and -2 SDS for height were considered normal. Cases with a BMI percentile greater than or equal to the 95th percentile for age and sex were considered obese and those with BMI percentile between >85th and 95th percentile for age and sex were considered overweight.[7] The annual growth rate of each case was evaluated. Those with a growth rate of <4.5 cm/year were considered as having insufficient growth. TH was calculated using the formula: [father's height + mother's height]/2±6.5 cm for males and females, respectively. Left hand and wrist radiographs were taken in the anteroposterior position and the bone age was assessed by a single observer using the Greulich and Pyle method.[8] Bone age difference (BAD)>+1-

year-old is defined as the advancement of bone age, and BAD<-1 year old is defined as a retardation of bone age. GH stimulation test was performed using clonidine in patients with insufficient growth rate and a retarded bone age. In patients with GH peak value <10 ng/mL in the first GH stimulation test, the second GH stimulation test was performed using L-dopa.

Serum IGF-1 and IGFBP-3 levels were measured with the chemiluminescence method (Immulyte 2000 R Siemens). SDS were calculated for IGF-1 and IGFBP-3. Values between +2 SDS and -2 SDS were accepted as normal.[9]

Evaluation of puberty

Pubertal development was performed according to the Tanner stage.[10] Delayed puberty was defined as the absence of breast development by the age of 13 in girls, and testicular weight <4 mL was measured by Prader orchiometry by the age of 14 in boys.

The thyroid functions of the patients were evaluated by measuring fT4 and TSH values. Increased serum TSH with low fT4 was defined as clinical hypothyroidism. Increased serum TSH with normal fT4 was defined as subclinical hypothyroidism.

Statistical Analysis

In this study, statistical analyzes were performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program.

In addition to descriptive statistical methods (mean, standard deviation), the Independent t-test was used in the comparison of the paired groups, and the chi-square and Fisher's exact test were used in the comparison of the qualitative data. Normally distributed continuous variables were given using the mean and standard deviation, and skewed continuous variables were given using the median and 25-75 percentiles. The Spearman's rank correlation test was used to analyze the association between the height SDS and the IGF1 SDS, IGFBP3 SDS, BMI SDS, and bone age progression in subjects who did not reach FH. The results were evaluated at a significance level of $p<0.05$.

RESULTS

The mean age at ALL diagnosis was 4.7±1.2 years and the mean age at the time of the study was 14.3±2.8 with an average follow-up duration of 9.7±1.9 years after CRT. All patients received the CT protocol, sixty-four percent (n=31) of the cases received CRT and thirty-six percent (n=17) of the patients did not receive CRT. The clinical and biochemical features of the cases are summarized in Table 1.

Endocrine system pathology was detected in 47.9% (n=23) of the cases at the time of the study. The most common endocrine pathology was short stature in the group of patients who received CRT, whereas obesity was the most common condition in the group who did not receive CRT.

Evaluation of growth

The median height SDS of the subjects at the final control was -0,48 [(-1.8)-(-0.1)] (Table 1), the TH SDS was -0.7 [(-1.38)-(0.01)], and the TH matches (TH SDS-height SDS) were -0.02 [(-0.9)-(0.6)]. Fifty-six percent (n=27) of the cases reached the FH. The median height SDS of the subjects who reached the FH was -1.44 [(-2.1)-(-0.53)], and among those subjects, 29.6% (n=8) had a FH below -2 SDS (Table 2). The median height SDS of the subjects who did not reach the FH was -0.24 [(-1.23)-(0.6)] and among those subjects, 14% (n=3) had a FH below -2 SDS. A significant difference in the height SDS was found between these two groups (p=0.022). There was no difference in the height SDS, TH SDS, and TH compliance between the groups who received CRT (n=31) and those who did not (n=17). The median IGF1 SDS value of all cases was 0.41 [(-0.37)-(1.3)], IGFBP3 SDS value was -0.4 [(-1.1)-(-0.18)]. IGF1 and IGFBP3 were lower in the group who received CRT compared with the group who did not (p=0.036, p=0.027) (Table 2). Eight of the nine patients with short stature (height SDS <-2) received CRT and two had GH deficiency.

The median FH SDS of 27 cases reaching FH is -1.44 [(-2.1)-(0.53)], FH/TH match (TH SDS-FH SDS) is 0.06 [(-0.17)- (1.1)] SDS. While the FH SDS of the patients who received CRT and those who did not receive CRT were similar (p>0.05), the difference between the TH SDS and the FH SDS values was higher in the CRT group (p=0.018). Thirty-three percent (n=7) of the patients who received CRT had a FH below -2 SDS, 28.6% (n=6) could not reach the TH, and all the patients who did not receive CRT were detected to have a FH consistent with the TH (Table 2).

There was a positive correlation between the height SDS and the IGF1 SDS, IGFBP3 SDS, BMI SDS, and bone age progression in subjects who did not reach FH (r=0.511, p=0.018, r=0.530, p=0.014, r=0.499, p=0.021, r=0.599, p=0.08) (Figure 1). A positive correlation (r=0.518, p=0.006) was observed between height SDS and TH SDS in subjects who reached the FH.

Evaluation of puberty

At the end of the study, 94% of the cases were pubertal. In the CRT group, a girl was diagnosed with precocious puberty, and Gonadotrophin releasing hormone (GnRH) analog therapy was given. In one patient in the group who did not receive CRT, despite the pubertal progress was initially appropriate for his age, hypergonadotropic hypogonadism developed during the follow-up. The pubertal findings and gonadotropin levels of all other cases were compatible with their age.

Obesity/Overweight

At the end of the study, the median body mass index (BMI) SDS of all cases was 0.88 [(0.15)-(1.66)]. Fourteen percent (n=7) of the cases had obesity and 13% (n=6) of the cases were overweight. The BMI SDS was similar between the group that received CRT and the group who did not receive CRT. Twenty-three percent of the group received CRT and 35% of the group who did not receive CRT were found to be obese or overweight. In the group who did not reach the FH, a positive correlation was found between BMI SDS and advanced bone age (r=0.555, p=0.009).

Table 1. Clinical and laboratory characteristics of the patients who received and did not receive CRT				
	Total (n=48)	**CRT (n=31)**	**CT (n=17)**	**p-value**
Age (years)	14.3±2.8	14.9±2.8	12.2±1.7	0.013
Gender (M/F)	22/26	16/15	6/11	0.037
Age of diagnosis (years)	4.67±1.23	4.38±1.1	4.72±1.4	
Height (SDS)	-0.48 [(-1.8)-(-0.1)]	-0.5 [(-2.02)-(0.1)]	-0.33 [(-1.05)-(0.13)]	0.306
BMI (SDS)	0.88 [(0.15)-(1.66)]	0,86 [(-0.2)-(1.32)]	1,05 [(0.3)-(1.9)]	0.291
Puberty % (n) Prepubertal Stage 2 Stage 3 Stage 4 Stage 5	 6.3 (n=3) 10.4 (n=7) 10.4 (n=7) 31.3 (n=15) 33.3 (n=16)	 3.2 (n=1) 12.9 (n=4) 9.7 (n=3) 29 (n=9) 45.2 (n=14)	 11.8 (n=2) 17.6 (n=3) 23.5 (n=4) 35.3 (n=11.8) 11.8 (n=2)	0.057
Endocrinologic pathology (%) Short stature GH deficiency Precocious puberty Obesity/Overweight Hypogonadism Hypothyroidism	47.9 (n=23) 18.7 (n=9) 4.1 (n=2) 2 (n=1) 27.1 (n=13) 2 (n=1) 6.2 (n=3)	48.4 (n=15) 25.8 (n=8) 6.4 (n=2) 3.2 (n=1) 22.6 (n=7) 0 6.4 (n=2)	47.1 (n=8) 5.9 (n=1) 0 0 35.3 (n=6) 5.8 (n=1) 5.8 (n=1)	
BMI: Body mass index, CRT: Cranial radiotherapy, CT: Chemotherapy, GH: Growth hormone, SDS: Standard deviation score				

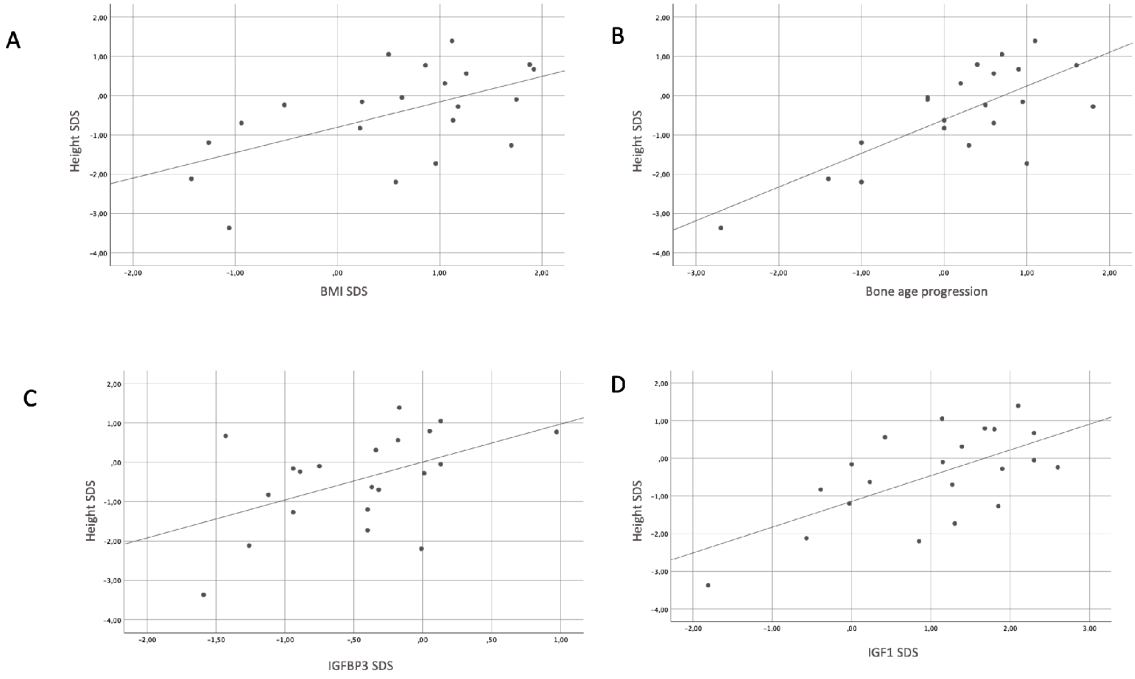

Figure 1. Correlation of factors influencing height SDS in cases who did not reach final height.

A) Correlation between height SDS and BMI SDS (r=0.499, p=0.021). B) Correlation between height SDS and bone age progression (r=0.599, p=0.08). C) Correlation between height SDS and IGFBP3 SDS (r=0.530, p=0.014). D) Correlation between height SDS and IGFBP3 SDS (r=0.511, p=0.018)

SDS: Standard deviation score, BMI: Body mass index, IGFBP3: insulin-like growth factor binding protein-3

Table 2. Laboratory characteristics of the patients who received and did not receive CRT

	Total (n=48)	CRT (n=31)	CT (n=17)	p-value
Bone age (years)	15 (12.5-17)	15.5 (13-18)	13 (12-14.5)	0.01
TH (SDS)	-0.7 [(-1.38)-(0.01)]	-0.71 [(-1.4)-(0.01)]	-0.61 [(-1.15)-(0.05)]	0.71
TH-height (SDS)	-0.02 [(-0.9)-(0.6)]	0.11 [(-0.94)-(0.75)]	-0.27 [(-1.07)-(0.6)]	0.438
Compatibility with the target % (n)	85.4 (n=41)	83.8 (n=26)	88.2 (n=15)	0.5
TSH (μIU/mL)	1.8 (1.4-4.2)	1.84 (1.5-2.2)	1.71 (1.26-2.31)	0.407
fT4 (ng/dL)	0.9 (0.8-1)	0.9 (0.8-1)	0.9 (0.77-1)	0.957
LH (mIU/mL)	3.55 (0.7-4.7)	3.1 (0.57-4.4)	3.79 (0.71-5.1)	0.539
FSH (mIU/mL)	4.3 (1.95-6.15)	4.2 (1.6-5.8)	5.4 (2.1-7.7)	0.414
IGF1	360.5 (260-413.7)	321 (249-412)	408 (312-415)	0.101
IGF1SDS	0.41 [(-0.37)-(1.3)]	0.03 [(-0.76)-(1.22)]	0.86 [(0.17)-(1.78)]	0.036
IGFBP3	4549 (3717-5097)	4370 (3500-5051)	4800 (4100-5160)	0.14
IGFBP3SDS	-0.4 [(-1.1)-(-0.18)]	-0.7 [(-1.23)-(-0.32)]	-0.3 [(-0.74)-(0.03)]	0.027
FH % (n)	56.3% (n=27)	67.7 (n=21)	35.3 (n=6)	0.03
FH SDS (%)	-1.44 [(-2.1)-(-0.53)]	-1.5 [(-2.15)-(-0.42)]	-0.98 [(-2.1)-(-0.3)]	0.04
FH SDS <-2 (%)	29.6% (n=8)	33.3% (n=7)	16.6% (n=1)	
TH -final height (SDS)	0.06 [(-0.17)-(1.1)]	0.55 [(-0.07)-(1.52)]	-0.19 [(-0.5)-(0.0)]	0.018
Case reaching the target in the final length % (n)	77.7 (21/27)	71.4 (15/21)	100 (n=6/6)	

CRT: Cranial radiotherapy, CT: Chemotherapy, FH: Final height, fT4: FreeT4, FSH: Follicle stimulating hormone, IGF-1: Insulin-like growth factor-1, IGFBP3: Insulin-like growth factor-binding protein 3, LH: Luteinizing hormone, SDS: Standard deviation score, TH: Targeted height, TSH: Thyroid stimulating hormone

Hypothyroidism

A subject who received CRT at an early age (2 years old) was diagnosed with central hypothyroidism with low fT4 and TSH and GH deficiency. In two cases diagnosed with subclinical hypothyroidism with mild TSH elevation (9.1 μIU/mL) and normal fT4 level, TSH elevation persisted during follow-up. LT4 replacement therapy was initiated in all three cases.

DISCUSSION

In our study, long-term follow-up data of 48 patients who were treated for childhood ALL and the long-term effects of chemoradiotherapy on growth and pubertal development were evaluated. It was shown that late effects related to the endocrine system were present in approximately half of the cases. The most common endocrine disturbances were growth retardation and obesity or overweight. CRT was associated with a loss in FH.

It has been reported that growth retardation/stagnation is frequently seen during childhood ALL treatment, but up to 70% of the cases would have a catch-up growth within the following 2 to 3 years after the end of treatment.[11] In contrast, others demonstrated that growth retardation persists with a loss in final adult height.[4,5,12,13] In our study, short stature was detected in 14% of the patients who did not reach the FH and in 30% of those who did reach FH.

The mechanism of action of CT and prophylactic CRT on the growth remains unclear. Regression in growth and loss of height is most evident in the first year of induction and continuation treatment. It has been reported that catabolic effects are observed during this acute period. Furthermore, CT agents and corticosteroids cause growth retardation due to the reduction of GH, IGF-1 levels, and IGF-1 tissue sensitivity.[14-17] However, the side effects of on growth are usually temporary. Although a significant decrease in height SDS was observed in these cases during the treatment, it has been shown that growth is often achieved after cessation of the treatment and patients reach a normal adult height with a minimal loss.[5,18] It has been reported that 31-48% of patients who received CRT have a FH loss of approximately 10 cm.[19] In another study, 71% of cases had a decrease in height of more than 1 SDS six years after the treatment. In our study, short stature was present in 22.8% (n=11) of the cases, and except for one case, all received CRT. Although the height SDSs were similar between the group of patients who received CRT and the group who did not, while their growth continued; we observed that the FH SDS of those who received CRT was lower and their Parental TH compatibility was worse. Similar to previous studies, it was concluded that the negative effects of CRT on growth continued until growth was completed.

The fundamental mechanism causing the negative effect of cranial RT on growth was proposed to be GH deficiency caused by damage to the hypothalamus.[20] This effect is dose-dependent and is usually seen at a dose of 24 Gy. However, recent data revealed that subjects who received 18 Gy CRT had a significant height loss in a 3-year follow-up compared with those who received 12 Gy CRT.[21] CRT exposure at an early age (<5 years old) has been reported as a risk factor for GH deficiency.[12,19] However, GH deficiency may not

always explain the short stature seen after CRT.[22,23] In our study, IGF1 SDS and IGFBP3 SDS were found to be significantly lower in patients who received CRT than those who did not receive CRT. Likewise, most of the patients with short stature received CRT at an early age, suggesting that GH deficiency developed secondary to CRT. However, in our cohort, only two of 11 patients with short stature were diagnosed with GH deficiency. This suggests that additional factors affecting growth should be considered in ALL.

CRT can also affect growth by changing the timing of puberty. It has been shown that CRT increases the risk of early puberty, particularly in girls diagnosed with ALL and in patients diagnosed at an early age.[13,18,23] In early puberty, growth and bone maturation are accelerated. Lack of adequate pubertal growth spurt and premature closure of epiphyseal plates result in decreased FH. Although early puberty was detected in only one of our cases, there was a high rate of short stature. It has been reported that although puberty starts at a normal time, CRT may cause height loss by disrupting the pubertal growth spurt without affecting the timing of the puberty.[24] According to a study in which the cases were followed from the time of diagnosis until the FH, it was found that the patients initially grew adequately after the completion of the treatment; however, by the age of 14 for boys and by the age of 11 for girls, a significant decrease in height SDS and a loss of -1.5 SDS in FH was observed.[4]

All of our cases were followed up for at least 5 years after the end of the treatment. The height SDS values of the cases who continued to grow were found to be significantly higher than those who were treated similarly and reached the FH. Additionally, in the growing group, advanced bone age was closely related to the height SDS. These results strongly suggest that although the pubertal timing is not effected, the course of the pubertal process is impaired in patients who received ALL treatment. Although the height SDS remains normal during the growth period, the final adult height may be compromised.

Conflicting results were obtained in the studies evaluating the effect of childhood ALL on obesity and overweight.[25,26] The prevalence of obesity in adults who received treatment for ALL has been reported to be 11-56%.[27,28] In our study, the rate of obese or overweight was high (27.2%) and there was no difference between the groups who received CRT and those who did not receive CRT. There was a positive correlation between BMI SDS and advanced bone age in cases that continued to growing. This suggests that obesity, which is common in patients who received ALL treatment, may be a factor that adversely affect the final length.

Study Limtations

The fundamental limitation of our study was that comparisons between small and heterogeneous subgroups were not statistically possible. Another limitation was that the cause-effect relationship could not be fully elucidated due to the inability to evaluate the growth patterns of the cases given the cross-sectional design of the study.

CONCLUSION

Especially in patients who received CRT, although the height SDS remained normal and parental TH compatibility was optimal during the growth period, there are loss in FH, higher rate of short stature, and parental TH incompatibility. Our findings suggest that advanced bone age causes loss of FH even in cases without precocious puberty. To elucidate the cause-and-effect relationship of these late negative effects of ALL treatment on growth, there is a need for prospective studies in which the pubertal course, growth pattern, and bone age are monitored from the time of diagnosis to the completion of growth.

Ethics

Ethics Committee Approval: Ethics Committee approval was obtained from University of Health Sciences Türkiye, İstanbul Kanuni Sultan Süleyman Training and Research Hospital (date: 05.10.2012, approval no: 315) in accordance with the Declaration of Helsinki.

Informed Consent: Families and patients were informed about the study, and all subjects or their legal guardians provided written consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.B.E., A.A., M.E., T.A., Z.Ş., G.A., Concept: S.B.E., A.A., M.E., Z.Ş., G.A., Design: S.B.E., A.A., E.B., T.A., G.A., Data Collection or Processing: S.B.E., E.B., M.E., G.A., Analysis or Interpretation: S.B.E., A.A., E.B., T.A., G.A., Literature Search: S.B.E., A.A., E.B., M.E., Writing: S.B.E., A.A., E.B., G.A.

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