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RESEARCH ARTICLE

Late endocrine side effects in children with acute leukemia

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ABSTRACT

This study was carried out in 28 patients (10 female, 18 male) diagnosed with acute leukemia, and aimed to investigate the abnormalities of endocrine system. Twenty-five of 28 patients were acute lymphoblastic leukemia and 3 were acute non-lymphocytic leukemia. Sixteen children were treated using BFM-90 chemotherapy protocol, and the rest with various regimens. Two patients were exposed to 12-13 Gy of total body irradiation followed by bone marrow transplantation. All patients were in remission at least five years. One (3%) of 28 patients had short stature and 4 (14%) had obesity. Pubertal status was retarded in 2 (7%) patients. Glucose intolerance, secondary hypothyroidism and hypergonadotropic hypogonadism were detected in 2, 1 and 2 patients, respectively. TSH response to TRH test was exaggerated in 1 and blunted in 3 patients.

Key Words: Children, acute leukemia, endocrine, late side effects

ÖZET

Akut lösemili çocuklarda geç endokrin yan etkiler

Bu çalışmaya akut lösemi tanısı almış ve en az 5 yıldır remisyonda olan 28 hasta (10 kız, 18 erkek) dahil edildi ve bu olgularda endokrin yan etkiler araştırıldı. Yirmibeş hasta akut lenfoblastik lösemi, 3 hasta akut non-lenfositik lösemi tanısı almıştı. Onaltı çocuğun tedavisinde BFM-90 tadavi protokolü kullanılırken diğerleri farklı tedavi rejimleri aldılar. İki hastaya 12-13 Gy total vücut ışınlaması sonrası kemik iliği transplantasyonu uygulandı. Yirmisekiz hastadan birinde (%3) boy kısalığı, dördünde (%14) obezite mevcuttu. Hastaların ikisinde (%7) gecikmiş puberte, ikisinde glukoz intoleransı, birinde sekonder hipotroidizm ve ikisinde de hipergonadotropik hipogonadizm saptandı. Bir olguda TRH testine abartılı TSH yanıtı, 3 olguda baskılanmış yanıt gözlendi.

Anahtar Sözcükler: Çocuklar, akut lösemi, endokrin, geç yan etki

INTRODUCTION

The prognosis in children with acute leukemia has dramatically improved with the use of intensive treatment regimens. Meanwhile, some adverse effects resulting from chemotherapeutic drugs and prophylactic central nervous system (CNS) irradiation have increased in long-term survivors. Cranial irradiation (CI) and chemotherapy for CNS prophylaxis may result in intellectual, psychomotor and neuroendocrine disabilities [1,2]. Cardiomyopathy due to anthracyclines [3], gonadal dysfunctions especially in patients treated with cyclophosphamide [4], the abnormalities in thyroid functions [5] and secondary malignancies [6] are the main adverse effects seen in long-term survivors of childhood cancers. As a result of these undesired effects, the quality of life of the young adults has been impaired.

There are a number of comprehensive studies assessing the frequency and variety of late effects in survivors of acute lymphoblastic (ALL) or myeloid (AML) leukemia, and the majority of those adverse effects are associated with the endocrine system [7-16]. However, the different results reported in those studies are probably due to the different treatment regimens and the variety of diagnostic criteria for endocrine abnormalities. In this study, we evaluated the long-term endocrine side effects of treatment in children with acute leukemia.

MATERIALS and METHODS

Twenty-eight survivors (18 male, 10 female) of childhood acute leukemia (25 ALL, 3 AML) who were in remission for at least 5 years were included in this study. All patients were diagnosed and followed up in the Ege University Pediatric Oncology Department. The patients were 1.6-15 (median 5.6 years) and 6.8-26.4 (median 15.07 years) years old at the time of diagnosis and evaluation, respectively. Four patients had been treated because of the relapse. Two patients had CNS relapse, one had bone marrow and one had testicular relapse.

Sixteen of 28 patients had been treated according to ALL BFM-90 chemotherapy protocol and the rest by different regimens. All patients were given CI (12 Gy in 12 patients, 18 Gy in 14 patients, and 24 Gy in one patient), except for one patient who had 1230 cGy of total body irradiation (TBI). Another patient who was given 24 Gy CI also had 14 Gy of spinal radiotherapy and TBI (1320 cGy). Two patients having TBI underwent bone marrow transplantation (BMT). One of them diagnosed with AML (allogeneic BMT) and the other with mature-B ALL (autologous BMT).

Table 1. Endocrine abnormalities of the patients

		n (%)
Growth	7/28 (25)	
	Growth failure	1/28 (3)
	Obesity	4/28 (14)
	Delayed bone age	3/25 (12)
Thyroid functions	5/28 (17)	
	Secondary hypothyroidism	1/28 (3)
	Blunted TSH response	3/28 (10)
	Exaggerated TSH response	1/28 (3)
Gonadal functions	3/28 (10)	
	Hypergonadotropic hypogonadism	2/27 (7)
	Delayed puberty	2/28 (7)
Glucose intolerance	2/25 (8)	
Total	**14/28 (50)**	

Growth status was investigated by measurement of body mass index (BMI) and height standard deviation score (SDS) for Neyzi's Turkish standards [17]. BMI percentages >95 and between 85-95 were accepted as obesity and overweight, respectively [18]. The patients having height SDS <-3 were accepted as short stature. Bone age was evaluated by radiographic atlas of Greulich and Pyle [19].

Thyroid function tests (total T_3, total T_4, free T_3, free T_4 and thyroid stimulating hormone-TSH) and thyrotropin releasing hormone (TRH) testing were used for evaluation of hypothalamic-pituitary-thyroid axis. Autoimmune thyroiditis was investigated by measurement of anti-T and anti-M thyroid auto-antibodies. The volume and structure of the thyroid gland were assessed by thyroid ultrasonography.

Sexual maturation was investigated in all patients by Tanner criteria [20]. Hypothalamic-pituitary-gonadal axis was evaluated by assessing follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone levels. The serum levels of hormones were measured by chemiluminescent enzyme immunoassay methods. Spermiogram was performed in patients whose sexual maturation was P5. The patients having sperm count greater than 20,000/ml, of which

Table 2. Characteristics of the patients with thyroid dysfunction

Patients	*Age D* (year)*	*Age A** (year)*	*Cranial RT (Gy)*	*TT3 (ng/dl)*	*TT4 (μg/dl)*	*FT3 (ng/dl)*	*FT4 (ng/dl)*	*bTSH (micU/ml)*	*pTSH*	*Comment*
1	5.09	13	18	111	7.8	2.2	0.6	0.2	2.7	SH
2	2.91	15.15	18	105	5.7	3	1.1	1.4	3.3	BRTSH
3	5	17.09	18	130	9.9	4.1	1.4	0.02	0.04	BRTSH
4	6.91	21.33	18	95	8.08	3.2	1.6	1.3	4	BRTSH
5	15	21.65	18	114	6	3	1	1.5	63	ERTSH

(*) Age at diagnosis. **(**)** Age at assessment. **SH:** Secondary hypothyroidism. **BRTSH:** Blunted response to **TSH. ERTSH:** Exaggerated response to **TSH. bTSH:** Basal TSH level. **pTSH:** Peak TSH level in TRH stimulation test.

>50% was motile and >30% was morphologically normal, were accepted as normal [21].

Oral glucose tolerance testing (OGTT) was performed in 25 patients.

RESULTS

Fourteen of 28 patients had at least one endocrine adverse effect (Table 1). Only one patient who was in normal range at the time of diagnosis had short stature. His puberty and bone age were also delayed. He had undergone BMT following TBI because of the diagnosis of AML, and had been given cranio-spinal irradiation (24-14 Gy) due to the CNS relapse. Sitting height of this patient was less than the -3SDS. Growth hormone stimulation tests by insulin and L-dopa revealed sufficient responses.

Four patients (3 girls, 1 boy) were obese and three boys were overweight. The BMI of all those patients were less than 85% at diagnosis. One patient had a BMI <5%. Delayed bone age was detected in three patients: two had undergone BMT after TBI, and the third had hypergonadotropic hypogonadism.

Thyroid function tests were normal in all patients except in one who had low free T_4 level and decreased TSH response to TRH test and was diagnosed as secondary hypothyroidism. He had CNS involvement at diagnosis, and leukoencephalopathy appeared during the therapy. Other results of the TRH stimulation tests revealed that three patients had blunted and one had exaggerated response (Table 2). Thyroid auto-antibodies were found in normal range in all patients. Ultrasonography showed a cystic lesion of 4 mm diameter in one patient and multiple hypo-echoic nodules in another. However, thyroid function tests of those patients were not abnormal.

All female patients had normal pubertal development and gonadal functions. Hypergonadotropic hypogonadism was diagnosed in two male patients and sexual maturation was delayed in one of them (Table 3). One boy had been given bilateral testicular irradiation and the other received intensive chemotherapy including cyclophosphamide for testicular and bone marrow relapse, respectively. Delayed puberty was also detected in the patient with short stature. Spermiogram in four patients, whose pubertal stage was 5, was normal.

Glucose intolerance was revealed in two of 25 patients. Family history of those patients was unremarkable in terms of diabetes, and their BMIs were between 5 and 50 percentiles.

DISCUSSION

Growth failure, which is mostly attributed to CI and cytotoxic drug treatment, is a common problem in survivors of childhood cancers. Eighteen Gy of prophylactic irradiation does not result in growth failure; however, the risk of hypopituitarism increases in patients receiving CI in doses of greater than 20 Gy [22-24]. Gözdaşoğlu *et al.* [8] detected short stature in 2 of 16 long-term survivors of ALL. Schell *et al.* [9] found that 45% of patients treated with 24 Gy of cranial or cranio-spinal irradiation had height below fifth percentile. Von der Weid [16] reported that 5% of 140 children with ALL had growth failure after follow-up for at least five years. All those patients had received 24-30 Gy cranial or cranio-spinal irradiation, and had growth hormone deficiency.

Table 3. Characteristics of the patients with hypergonadotropic hypogonadism

Patients	*Age D* (year)*	*Age A** (year)*	*Relapse*	*RT (Gy)*	*Pubertal stage*	*FSH (IU/L)*	*LH (IU/L)*	*TTes (ng/ml)*
1	4.83	22.09	Bone marrow	18 cranial	3	51.70	22.20	0.50
2	3.83	14.83	Testis	18 cranial 24 testicular	3	34.10	10.50	0.20

(*) Age at diagnosis. **(**)** Age at assessment. **TTes:** Total testosterone.

One of 28 patients in our group had short stature and low sitting height. He was diagnosed with isolated CNS relapse and given radiotherapy (24 Gy cranial and 14 Gy spinal) two years after TBI (1320 cGy) and BMT. His pubertal stage delayed at assessment; however, growth hormone response to stimulation tests was normal. Growth failure may be caused by spinal irradiation and delayed puberty in this patient. TBI also has an important role in the development of growth failure [5,25,26].

Thirty- eight to 57% of patients had BMI in the range of obesity at the time of final height [9,11,27]. In our study, 25% of patients had BMI over 85th percentile but 14% were obese (BMI>95 percentile).

Thyroid dysfunction in children with acute leukemia is mostly associated with prophylactic CI, 3-7% of which is absorbed by the thyroid gland. Thyroid function studies revealed no disabilities in many studies including in long-term survivors also treated with CI [12,24,28]. However, Von der Weid [16] found that one (0.7%) patient, who was treated with cranio-spinal irradiation, suffered from primary hypothyroidism. Gözdaşoğlu *et al.* [8] reported that 12.5 and 18.7% of survivors had subclinical primary and subclinical central hypothyroidism, respectively. All those patients had undergone 18-30 Gy CI. Mohn *et al.* [10] showed that one third of the children treated with CI (18-24 Gy), has low resting TSH level or blunted response to TRH test. Ten percent of our patients had blunted and 3% had exaggerated TSH response to TRH test. One of 28 patients was diagnosed with central (secondary) hypothyroidism. He had suffered from encephalopathy and subsequent leukoencephalopathy during high dose (5 g/m^2) methotrexate therapy due to CNS relapse. All our patients with thyroid dysfunction had been given 18 Gy of CI.

Von der Weid [16] reported cases with primary hypogonadism associated with bilateral testicular irradiation or cyclophosphamide administration. Gözdaşoğlu *et al.* [8] showed that 41% of the boys had hypergonadotropic hypogonadism. Fifty percent of those patients received testicular irradiation. One of our two patients with hypergonadotropic hypogonadism had undergone testicular irradiation. He had been diagnosed two years before, and treated with testosterone. Hence, his sexual maturity was in agreement with age. The other one had relapsed two years after diagnosis, and was treated with a new chemotherapeutic regimen including cyclophosphamide. Although chemotherapy was administered at an early age, his bone age and pubertal stage were retarded.

Pubertal development may be associated with CI in children with ALL. Early puberty can occur especially in girls having CI [22,24]. We did not observe precocious puberty in our patients. However, delayed puberty was detected in two boys. One had hypogonadism and the other had a history of TBI and BMT, which are the risk factors for gonadal dysfunction [29].

Gözdaşoğlu *et al.* [8] reported that all patients in whom spermiogram was performed had oligospermia or azoospermia. Two of five patients had received testicular irradiation, and all suffered from some disabilities including isolated Sertoli dysfunction and hypergonadotropic hypogonadism. We performed spermiogram only in patients whose sexual maturation was P5, and found normal results.They had neither undergone testicular irradiation nor had gonadal dysfunction.

Reversible hyperglycemia resulting from pancreatic dysfunction can be observed during the induction therapy including asparaginase and steroids in patients with leukemia [30]. However, the long-term effects of those drugs on glucose metabolism are undetermined. Talvensaari *et al.* [31] evaluated the late effects in 50 children with cancer (28 of them ALL) about 12 years after diagnosis and observed

that the fasting levels of plasma glucose and insulin were higher than in healthy controls. In this study, the results of OGTT showed glucose intolerance in two (8%) non-obese patients whose fasting glucose and insulin values were in normal range. There was no history of hyperglycemia following any medication in the course of therapy. Also, the family history of those children was negative for diabetes. These findings suggest that the endocrine functions of the pancreas may be affected by chemotherapeutic regimens in long-term survivors of childhood leukemia.

In conclusion, leukemia survivors must be followed for long-term side effects of treatment on the endocrine system. The probable endocrine disabilities can be prevented with early diagnosis and treatment. Our results show that assessment of pancreatic endocrine functions must be performed in addition to the usual laboratory and clinical investigations.

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