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Research Article

Frequency and types of chromosomal abnormalities in acute lymphoblastic leukemia patients in Turkey

Abstract

Objectives: Acute lymphoblastic leukemia (ALL) is the most common malignancy in children and is usually associated with numerical and structural chromosomal changes. The correlations of specific cytogenetic findings with presenting clinical features indicate the prognostic significance of chromosomal abnormalities (CAs) in patients with ALL.

Design and methods: The aim of this study was to describe the types and frequencies of CAs in the childhood and adult ALL patients. To date, this was the largest study to date in children with ALL in Turkey, and presented the general cytogenetic characteristics of 260 patients diagnosed as having with ALL in a 17-year period. The cytogenetic analyses were performed in the diagnosis of ALL patients.

Results: The karyotype results were normal in 76,9% of 260 patients. However, CAs were detected in 23.1% of all patients. The male-female ratio was 1,5 and median age at diagnosis was 8.58 years in children. The incidence of abnormal karyotype was higher in males than that of females (the male-female ratio=2,62). The 18.1% of these CAs was structural aberrations, and also numerical aberrations were 5.0%. The Ph chromosome t(9;22) translocation was present in 1,2% of children. CAs in addition to Ph+ was observed in one case. Specifically, deletions are the most common karyotype (5,8%) among the patients, Duplications was present in 6 (2,3%) patients. Inversions were detected in two patients (0,8%). The ratio of fragilities and other CAs was 1,9% and 2,3% of all patients, respectively. Among numerical chromosome abnormalities, 7 patients (2,7%) had aneuploidies and polyploidies. One patient also had microchimeric cells.

Conclusion: This study showed that anomalies detected in ALL patients have shown correlations between specific abnormalities and clinical characteristics of the patients. This information could contribute to an understanding of the role of chromosomal changes in ALL malignancy, and confirms the previously reported association between level of CAs and cancer risk.

Introduction

ALL is a malignant disorder of the bone marrow in which a lymphoid progenitor cell becomes genetically altered. It is the most common malignancy of childhood with an annual incidence rate of 3–4 cases per 100,000 children. The disease is most common in children but can occur at any age. Although, there are few identified factors associated with an increased risk of developing ALL such as genetic, parental and environmental factors, the etiology of the disease remains largely unknown [1,2]. Prognostic impact of CAs in ALL patients is complex. The disease has a bimodal distribution: a sharp peak in incidence among children aged 2–5 years [3]. ALL results from somatic mutation in a single lymphoid progenitor cell at one of several discrete stages of development.

The lymphoblasts have acquired genetic changes included both the number and structure of chromosomes. The translocations, inversions, deletions and duplications affect gene expression in ways that subvert normal programs of cell differentiation, proliferation, and survival, and these factors likely act in concert with each other in multistep pathways leading to leukemic transformation. Specific genetic abnormalities have been useful in diagnosis and defining prognostically important patient subgroups [4]. Several numerical and structural CAs are associated with childhood leukemia. The clonal origin of ALL has been established by cytogenetic analysis. Numerous genetic alterations have been and continue to be discovered in ALL, and it has been repeatedly shown that specific genetic abnormalities are present in the majority of successfully karyotyped patients with ALL [5–7]. Aneuploidy is seen in 30–40% of all cases of

childhood ALL. Numeric chromosomal changes are usually encountered in chromosomes 4, 6, 8, 10, 14, 17, 18, 20 and 21 [8-11]. Recurrent chromosome translocations play a critical role in the pathogenesis of ALL, and many translocations have important prognostic significance. Moreover, the molecular characterization of breakpoints from such rearrangements has led to the identification of oncogenes and to the design of novel therapeutic approaches. The most common structural change is the t(12;21) translocation, which accounts for 25% of cases of ALL [12].

This study was presented the cytogenetic characteristics of pediatric patients diagnosed as having ALL within a 17-year period.

Materials and Methods

The childhood and adult ALL patients -referred to our genetics laboratory from 1 May 1992 to 28 April 2009 were recruited. The diagnosis of ALL was made on the basis of a chromosomal analysis. In this study, karyotypes of patients referred with AAL were retrospectively analysed. ALL was initially, diagnosed by the referring clinical hematologist, based on the available clinical details. The cytogenetic analyses were performed in the Cytogenetics Laboratory, at the Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University. Metaphase chromosome preparations from peripheral blood were made according to the standard cytogenetic protocols. Fifty metaphases were analyzed in all the patients, but in cases of abnormalities and mosaicism the study was extended up to 100 metaphases. All CAs were reported according to the current international standard nomenclature (ISCN, 2009).

Results

Cytogenetics was performed in 260 patients diagnosed with ALL. The male-female ratio was 1,5 and median age at diagnosis was 8,58 years. The incidence of abnormal karyotype was higher in males (n=43, 72,4%) than that of females (n=17, 27,6%). The male-female ratio with abnormal karyotype was 2,62. Out of 260 patients, 60 (23,1%) were found to have abnormal karyotype and rest of 200 (76,9%) were normal. The results of abnormal karyotype were divided into three categories: Philadelphia chromosome-positive (Ph+), CAs in addition to Ph+ and the others CAs wereshown in Table 1.

The structural aberrations (translocations, deletions, inversions, duplications and fragilities) and numerical aberrations were 18,1% and 5,0%, respectively. The Ph chromosome t(9;22) translocation was present in approximately 1,2% of children. CAs in addition to Ph+ was observed in one case [46,XY,Ph+(90%),dup(1)(q12;q23)]. Specifically, deletions are the most common karyotype (5,8% and 15 cases) among the patients, followed by 46,XY,del(1p-); 46,XY,del(4p13); 46,XX,del(6q16); 46,XY,del(6q-); 46,XY,del(7q32); 46,XY,del(7q11)(50%); 46,XY,del(8q24); 46,XY,del(11q11),t(9;11); 46,XY,del(11); 46,XY,del(11q-); 46,XY,del(12p13); 46,XX,del(12q11); 46,XY,del(12p13); 46,XY,del(14q22) and 46,XY,del(17p11). The ratio of translocations in all CAs was 3,9% (10 cases),

Table 1: Characteristics of the patients and results of karyotypes.

Sex/Age	Karyotypes	No. of cases	Frequency in all cases (%)
	Normal	200	76.9
	Abnormal	60	23.1
	General Total	260	
	Abnormalities		
F/54 M/29	Philadelphia chromosome positive (Ph+)	1	
	=	1	
	Chromosomal aberrations in addition to Ph+		
M/2	46,XY, Ph+ (90%), dup(1)(q12;q23)	1	
	Total	3	1.2
	Ph-, the others chromosomal aberrations		
	Structural chromosome abnormalities		
	Deletions		
M/2	46,XY,del(1p22)		
M/2	46,XY,del(4p13)x2		
M/7	46,XX,del(6q16)		
M/6	46,XY,del(6q-)		
M/3	46,XY,del(7q32)		
M/5	46,XY,del(7q11) (50%)		
M/6	46,XY,del(8q24)		
M/2	46,XY,del(11q11),t(9;11)		
M/1	46,XY,del(11q)		
M/51	46,XY,del(11q)		
M/3	46,XY,del(12p13)		
F/13	46,XX,del(12q11)		
M/3	46,XY,del(12p13)x1		
M/5	46,XY,del(14q22)x1		
M/6	46,XY,del(17p11), fra(8%)		
	Total	15	5.8
	Translocations		
F/8	46,XX,t(1;2)(q12;q37)		
M/2	46,XY,t(1;11)(q21;q23)		
M/4	46,XY,t(2;6)(p25;p21.3)		
M/5	46,XY,t(4;11)(q25;p13)		
F/11	46,XX,t(4;11)		
M/5	46,XY,t(4;11)		
F/4	46,XX,t(4;9),del(11q-)		
M/7	46,XY,t(8q;?)		
F/6	46,XX,t(11;14)		
F/3	46,XX,t(15;17)		
	Total	10	3.8
	Duplications		
M/2	46,XY,dup(1)(q12;q23)		
M/4	46,XY,1q+		
M/6	46,XY,1qh+		
M/10	46,XX,14q+		
M/7	46,XY,4q+,CA (16%)		
F/2	46,XY,Yqh+		
	Total	6	2.3
	Inversions		
M/1	46,XY,inv(2)x1, CA (10%)		
F/4	46,XX,inv(9)(p11;q12)		
	Total	2	0.8
	Fragilities		

M/3	46,XY, fra (32%), CA (22%)		
F/15	46,XX, fra (25%)		
F/6	46,XX, fra (20%)		
M/6	46,XY, del(17p11-ter), fra (8%)		
M/1	46,XY, fra (3p21)		
	Total	5	1.9
	The others chromosome abnormalities		
M/4	46,XY, CA (20%)		
M/2	46,XY, CA (15%)		
F/9	46,XX, CA (10%)		
F/6	46,XY, CA (15%)		
M/8	46,XY, CA (15%)		
M/6	46,XY/46,XX (20%) microchimerism		
	Total	6	2.3
	General total	47	18.1
	Numerical chromosome abnormalities		
F/3	47,XX,+21		
M/4	47,XY,+21		
F/7	47,XX,+21		
M/5	47,XY,+21, t(15;17)(p12;q23)		
M/13	47,XXY		
M/10	46,XY/45,X (23%)		
	Total	6	2.3
	Aneuploidies and poliploidies		
M/48	46,XY, anoploidy		
M/35	46,XY, poliploidy		
M/9	46,XY, anoploidy		
M/4	46,XY, anoploidy		
M/6	46,XY, anoploidy		
F/8	46,XX, anoploidy		
F/7	46,XX, anoploidy (12%)		
	Total	7	2.7
	General total	13	5.0

followed by 46,XX,t(1;2)(q12;q37); 46,XY,t(1;11)(q21;q23); 46,XY,t(2;6)(p25;p21.3); 46,XY,t(4;11)(q25;p13); 46,XX,t(4;11); 46,XY,t(4;11); 46,XX,t(4;9),11q-; 46,XY,t(8q;?); 46,XX,t(11;14) and 46,XX,t(15;17). Duplications was present in 6 (2,3%) patients [46,XY,dup(1)(q12;q23); 46,XY,1q+; 46,XY,1qh+; 46,XX,14q+; 46,XY,4q+ and 46,XY,Yqh+]. Inversions were detected in two patients (0.8%) [46,XY, inv(2); 46,XX,inv(9)(p11;q12)]. The ratio of fragilities and other CAs were 1,9% and 2,3% of all patients, respectively. Among numerical CAs, 7 patients (2,7%) had aneuploidies and poliploidies. The other numerical changes were chromosomes +21 (n=3), +X (n=1) and -Y (n=1). One patient also had microchimeric cells [46,XY/46,XX (20%)].

Discussion

In present study diagnostically and prognostically important CAs were detected in 23,1% of patients by Cytogenetics. But, data from Turkey using this system which was applied to specimens from 34 ALL patients showed that CAs were detected in 74% of the patients [14]. It was reported that he frequency and spectrum of CAs were not similar between the current study and previous reports in patients with ALL [10,11]. The frequency of genetic abnormalities observed in our study was lower than that of previous reports [14-18]. The difference

between the findings of our study and previous reports was our some patients show different clinical presentations which, sometime, are mixing with clinical features of CML, AML and AAL.

In our study, deletions was found to be most frequent structural abnormalities (5,8%), and 15 chromosomal deletions. Losses of these regions were identified at 1p22, 4p13, 6q16, 6q-, 7q32, 7q11, 8q24, 11q11, 11q-, 12p13, 12q11, 14q22, 17p11, suggesting the presence of multiple tumor suppressor genes (Table 1). We were detected one del(1p22), two t(1;2)(q12;q37), t(1;11)(q21;q23), one dup(1)(q12; q23) and 1q+ in 5 patients. The numerical and structural aberrations of chromosome 1 have been observed in chronic and acute leukemias and solid tumors as well. Previous reports on a CML-BC patient found the involvement of the long arm of chromosome 1 [19]. It was marked that consistent breaks and deletions involving specific oncogenes/tumor suppressor genes were present in 1p36 and other regions of chromosome 1, such as 1p22-q21 [20,21]. It is remarkable to have found the ABL2 gene in 1q25, which is a proto-oncogene whose protein is a non-receptor tyrosine kinase, and the TPR gene in the same region; its extreme 5' end fuses with several different kinase genes in some neoplasias and could be involved in leukemogenesis mechanisms [22]. Gene deletions and translocations are responsible for initiating of cancer progression. The loss or inactivation of one or more tumor suppressor genes are associated with many types of cancer, as chromosomal regions associated with tumor suppressors are commonly deleted or mutated.

Aberrations involving chromosome 6q are common in childhood ALL occurring in 7-18% of patients [23,24]. Frequently, the breakpoints are 6q15, 6q21-23 regions and interstitial deletion are also common in both B lineage and T lineage. Overall the breakpoints occur predominantly in 6q21 [25]. The deleted region is mostly large, involving a number of genes and genes affected by the deletion are presumably essential for normal cellular homeostasis. FOXO3A, a transcription factor involved in the control of proliferation and apoptosis, is one of the candidate genes located in the deleted 6q21 region. In the present study, 3 patients also had del(6q) and t(2;6)(p25;p21.3), and this break point was in the region of 6p21.3. Sinclair et al. [26] also suggested that the incidence of balanced rearrangements involving 6q in ALL may be much higher than previously thought. These findings show that the (6q) abnormality is a good prognostic indicator. In present study, we also found del(7q) in two patients, and there was a correlation between an isolated deletions of the long arm of chromosome 7 (q31, q32 and q-) and patients with ALL. The partial deletions of 7q might represent a secondary event in the context of preexisting genomic instability. Complete loss of chromosome 7 or partial deletion involving its long arm are highly recurrent CAs in myeloid disorders [27,28]. Also, we found deletion at bands 8q24 in a patient. These results were consistent with the hypothesis that the 8q24 region affected the susceptibility of cancer.

Recurrent balanced translocations are observed in specific types of leukaemia and lymphomas, and are known to drive tumorigenicity [29,30]. About 50% of hematopoietic neoplasms

somatically acquire translocations, which activate proto-oncogenes in most cases. The major translocations in ALL affect proteins that have critical functions in cell proliferation, differentiation, or survival [31]. The translocations in all metaphases were found in 10 patients with ALL (3,8%). These translocations was found in specific regions of chromosomes 1q12, 1q21, 2q37, 2p25, 4q25, t(4;11)x[2], t(4;9), 6p21.3, t(8q;?), 11p13, 11q23, 11q, t(11;14) and t(15;17) (Table 1). First, rearrangements affecting the same chromosomal region may involve different genes and represent clinically and biologically diverse entities. For example, the t(11q23) translocation is a poor prognostic factor, accounting for 2–4% of childhood ALL, and it is expressed in 80% of all infants with ALL [32]. In the present study, chromosomes 11 translocation was found to be most frequently involved in structural abnormalities (in six cases). In particular, translocations between 11 and 4 chromosomes in three patients are noteworthy. Similarly, in other Turkish study, the t(11q23) translocation was found in one patient of thirty four patients with childhood ALL [14]. The chromosomal translocation t(4;11)(q21;q23) is associated with high-risk ALL of infants. These findings show that 11 chromosomes are very important in the prognosis of ALL. Because, chromosomal translocations that activate specific genes are a defining characteristic of human leukaemias and of acute lymphoblastic leukaemia in particular. Translocation t(4;11)(q21;q23)/KMT2A-AFF1 was the most frequent rearrangement found. In a recent study, five most common fusion genes i.e. BCR-ABL (t 9;22), TCF3-PBX1 (t 1;19), ETV6-RUNX1 (t 12;21), MLL-AF4 (t 4;11) and SIL-TAL1 (del 1p32) were found in 79% of the patients, and MLL-AF4 t(4;11) positivity characterized a subset of adult ALL patients with aggressive clinical behaviour and a poor outcome [33]. This study also supports our findings. 12p13 and 12q11 deletions were detected in two patients. The prognostic importance of simultaneously occurring 12p13 deletions is currently unknown. Thus, we suggested that more information should be obtained from patients with different variants of deletions. The role of the 12p-q deletions in prognosis, incidence of relapse and follow-up should also be evaluated. In addition, we observed rare structural chromosomal rearrangements on 17 chromosome [del(17p11), t(15;17)]. The p53 mutation occurs rarely in ALL. Kim et al., [34], have also shown a case with acute promyelocytic leukemia of t(15;17)(q22;q21) rearrangement associated with other abnormalities. Our results, in addition to other previously reported findings, suggested that losses and structural rearrangements of chromosome 17 could play a role in the pathogenesis of ALL. These deletions might have an overall unfavorable prognosis in our patients.

In the present study, the Ph chromosome t(9;22) translocation was present in approximately 1,2% of children. CAs in addition to Ph+ was observed in one case [Ph+(90%), dup(1)(q12;q23)]. Ph chromosome was the most frequent recurrent abnormality (29%). Its incidence increased with age, as already reported [35], but peaked in the 40- to 50-year-old age range. Thus, two of our three Ph-positive patients were older (29 and 54 years). Gene duplications and increases in gene copy numbers can also contribute to cancer. We describe six patients (2,3%) of a rare type of duplications, such as dup(1)(q21;q23), 1q+, 1qh+, 14q+, 4q+ and Yqh+ (Table 1).

These chromosomal gains may be relevant to the pathogenesis of ALL transformation in some cases. Balanced rearrangements are infrequent and can occur as a single additional abnormality or as a part of complex cytogenetic changes. In our study, The inversions were evaluated in 2 patients (0,8%) such as inv(9) (p11;q12) and inv(2) (Table 1). Some genes on chromosomes 2 that are known to play a role for tumor development. Therefore, 2p-q could play a role in the pathogenesis of ALL. However, there have been very few reports on the inv(9) variation as an acquired CAs in hematologic malignancies [36]. It has reported pericentric inversion in chromosome 9 at a frequency of 0,8–2% in normal population and at a similar frequency in ALL patients. This inversion is usually considered as a polymorphism, and its clinical consequences remain unclear [37].

Autosomal recessive genetic diseases associated with increased chromosomal fragility (FSS) and a predisposition to ALL include ataxia-telangiectasia, Nijmegen breakage syndrome, and Bloom syndrome [38]. FSS are known to be associated with genes that relate to tumorigenesis. They have been found the FSS in 8–32% of our patients-cells (1,9%) (Table 1), and ALL children have the others CAs in 10–20% of cells (2,3%). These CAs may affect the susceptibility to tumors. These aberrations are also the most common ones in ALL cases with variant translocations and additional abnormalities. The most interesting finding in this study was the involvement of microchimeric cells [46,XY/46,XX(20%)] was seen in one patient (Table 1). Microchimerism is the existence of small amounts of DNA in the body coming from a genetically different person. It recently found male microchimerism presence to be associated with a 70% reduced odds of developing breast cancer, and a 4-fold increased odds of developing colon cancer [39]. In one other study, FMc were identified in 50% of papillary thyroid tumors [40]. Unfortunately, we were not able to determine the nature of these cells. This suggests to us that the can microchimerism take place in the etiology of cancer?

Numerous genetic alterations have been and continue to be discovered in ALL, and it has been repeatedly shown that specific genetic abnormalities are present in the majority of successfully karyotyped patients with ALL [3,41]. In the present study, 5% of the patients revealed numerical CAs (Table 1). The rate of chromosomal gains and losses can lead to aneuploidy was termed chromosomal instability. Aneuploidy is also features of cancers that are usually associated with poor prognosis. Aneuploidy is a remarkably common feature of human cancer, present in ~90% of solid human tumours and >50% of haematopoietic cancers [42]. The common aneuploidy observed in our patients (2,3%), occurring in 10–15% of metaphases (Table 1). Several studies have shown that aneusomies of different chromosomes were associated with aggressive tumor behavior [11,12]. For example, gain of chromosome 8 is found in ~10–20% of cases of acute myeloid leukaemia [43,44]. Autosomal monosomies are observed to be the most frequent in our patients, and the most frequently observed numerical changes involve the chromosomes +8, -7, -17, -21, +21, -22 and -Y. Trisomy of chromosome 8 is frequently reported in myeloid lineage disorders and also detected in lymphoid neoplasms as well as solid tumors

suggesting its role in neoplastic progression in general. These chromosomes may affect the susceptibility to tumors.

One of the main results in our patients, the 1,7% of them revealed the trisomy 21 chromosome (Down syndrome=DS), and one patient has one translocation of 15p12 and 17q23 in addition to the presence of trisomy 21 chromosome. Just as, children with DS have a 10- to 30-fold increased risk of leukemia. DS cases are more likely to have B-cell precursor ALL, and their leukemic cells lack adverse genetic abnormalities [45]. Leukemia cells with either i(21q10) or trisomy 21 have the potential for basophil formation [46]. It has reported a transient leukemic condition in a phenotypically normal newborn bearing i(21q10) clones, suggesting that the q arm of chromosome 21 contains sufficient genetic information for the development of transient leukemia [47]. Consistent with the literature, in our study hyperdiploidy was detected in 26% of ALL patients, with the most common copy gains seen in chromosomes 4, 6, 10, 21 and X. Previous studies have suggested that gaining a copy of chromosomes 4, 10 or 17 is associated with favorable prognosis; however, trisomy of chromosome 5 confers poorer outcome among highhyperdiploid patients [48,49]. In the present study, we observed the complete or partial loss of chromosome 7 in several metaphases (Table 1). Monosomy 7 was also observed in several clones analyzed. An association between the complete or partial loss of chromosome 7 and ALL has been recognized from the early days of tumor cytogenetic analysis. Detection of such abnormalities usually heralds a poor prognosis [50]. Amare [51], reported monosomy of chromosomes 7 and 17 as secondary CAs that occur when disease progresses from CML to a more aggressive blastic phase or transforms into lymphoid leukemialike acute myeloid, lymphoid leukemia, or lymphoid blast crisis of CML. Sabine [52], have shown that monosomy 7/del(7q) causes loss an important tumor suppressor, and upregulation of oncogene in AML.

We detected two patients with 47,XXY (Klinefelter's syndrome) and 46,XY/45,X -Y (23%) (Table 1). Sex chromosome aneuploidies may be affect susceptibility to the tumors. The 47,XXY karyotype in hematological disorders has not been clearly established yet. Gain of an X chromosome is relatively common in leukemias, lymphomas and prostate cancer, and generally occurs in association with other karyotypic changes [53,54]. Risk of acquiring breast carcinoma in 47,XXY is relatively increased, with relative risk exceeding 200 times. It is generally not known whether this gain involves the active or the inactive X chromosome. Although, there are numerous X-linked genes that may be involved in neoplasia, including the MAGE tumor-specific antigen loci [55], the pseudoautosomal GM-CSFR gene that likely escapes X chromosome inactivation [56], and the ARAF1 [57], ELK1 [58], and MCF2 [59], oncogenes. With regard to Y chromosome, deletions have been shown to be involved in prostate cancer [60,61], male breast carcinomas [62,63], and pancreatic adenocarcinomas [64]. Loss of Y chromosomes is a common secondary change in cancer cells and in a few leukemias [65]. Possible significance of loss of Y chromosome in neoplasia have been postulated as; Y chromosome harbors a tumor suppresser gene, which when lost or modified, gene(s) presumably located on the X chromosome

may be affected leading to abnormal proliferation. Polyploidy and endoreduplication of chromosomes occur more often in patients with disseminated cancer and vary with the extent of disease.

Conclusion

The patients showed a high frequency of loss and gains of chromosome increased incidence of deletions, translocations, duplications, inversions, chromatid breaks and aneuploidies, along with other chromosomal alterations, could contribute to the progression of the disease. This study could detect a wide variety of common, rare and novel chromosomal abnormalities in patients with hematological disorders, providing valuable diagnostic and prognostic information. In addition, aneuploidies of X can play a role in the pathogenesis of ALL. Further understanding of the CAs may help in anticipating its implications in hematological cancers.

Ethics

Ethics Committee Approval: The study was a retrospective, the results analyzed in our laboratory were used.

Authorship Contributions

Concept: Osman Demirhana, Nilgün Tanrıverdia, Dilara Süleymanovaa; cytogenetic analysis. Osman Demirhana; date collection and writing of the article.

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