

Chromosomal abnormalities in children with acute lymphoblastic leukemia

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Abstract. Acute lymphoblastic leukemia is the most conventional cancer in children and teenagers. In adults, this pathology is much less common. The paper presents the results of a retrospective analysis of chromosomal aberrations in clinically identified 1269 feeble children with acute lymphoblastic leukemia for the period from January 2013 to January 2023. The average age of the patients was 10.2 ± 1.69 years. The material for the study was bone marrow and blood cells obtained from a puncture biopsy of the sternum and peripheral vein. Cytogenetic studies were carried out using the generally accepted standard method using GTG banding. The results of the analysis showed the absence of genomic and chromosomal mutations in 215 (17%) children; translocation $t(1;19)(q23;p13)$ was detected in 75 (6%) children; in 221 (17.5%) children - $t(4;11)(q21;q23)$; in 234 (18.5%) children - $t(9;22)(q34;q11)$; 88 (7%) - $t(12;21)(p33;q22)$ and 139 (11%) patients had translocations between other chromosomes. Hyperdiploid translocations were detected in 139 (11%) children. No sick children with hypodiploid cells were found. No metaphase cells were obtained from 152 patients (12%). In sick children, a relatively low frequency of optimistic predicting chromosomal abnormalities, namely $t(12;21)(p13;q22)$ and hyperdiploid, has been established. The pervasiveness of chromosomal aberrations with a negative treatment prediction, such as $t(9;22)(q34;q11.2)$, is consistent with the accessible international scientific literature data. The results obtained indicate the importance of cytogenetic studies in the diagnosis and predictions of children with ALL.

1 Introduction

Acute lymphoblastic leukemia (ALL) is a form of cancer affecting the gore system, stemming from the malignant conversion of precursor cells of B- and T- lymphocytes [1]. Acute leukemia in children is a social problem since in terms of the number of deaths it is currently second only to injuries and poisonings. ALL is the most conventional form of youth cancer and accounts for about 75% of leukemias amid children under 15 years of age. It is the second leading cause of dying in children under 15 years of age. In the United States, approximately 75% of people under 20 years of age diagnosed with leukemia are diagnosed with ALL. Most cases occur between 2 and 5 years of age [2].

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Overall, about half of ALL cases occur in children and adolescents, and it is the most common acute leukemia until the early 20s, after which acute myeloid leukemia predominates [3]. The occurrence of cancer is usually caused by a restructuring of the genetic apparatus of the cell and is characterized by congenital genetic abnormalities for a number of tumors [4]. Characteristic genetic abnormalities are found in approximately 80% of cases of childhood B-cell lymphoblastic leukemia [5].

Cytogenetic and molecular cytogenetic methods show that most cancerous cell degeneration results from a combination of mutations. These genetic changes disturb the normal functioning and behavior of cells, resulting in different genetic abnormalities linked to distinct immunophenotypes of cancer cells. [6,7]. According to the National Research Oncology Center in Kazakhstan, more than 9,000 thousand patients are registered with oncological diseases of the hematopoietic and lymphatic tissue, and more than 1,500 new cases are registered annually [8]. The objective of the research was to conduct a retrospective examination to determine the prevalence and variety of chromosomal abnormalities in childhood acute lymphoblastic leukemia.

2 Materials and Methods

A retrospective cytogenetic examination was conducted on 1269 clinically diagnosed cases of childhood acute lymphoblastic leukemia admitted to the oncohematology department of JSC "Scientific Center of Pediatrics and Children's Surgery" in Almaty from January 2013 to January 2023. Cases of acute myeloid leukemia and other leukemia types were excluded from the analysis.

The diagnosis of acute lymphoblastic leukemia was made taking into account the 2016 WHO classification recommendations, which combine the characteristics of cell morphology, immunophenotypes, genetics and cytogenetics, as well as based on the French-American-British (FAB) classification [1,9]. The material for the study was bone marrow and blood cells obtained from a puncture biopsy of the sternum and peripheral veins. Cytogenetic studies were carried out in the laboratory of the center using the standard cytogenetic method, through differential G-staining of chromosomes [10]. 20 metaphase cells from one patient were analyzed on an Olympus BX63 microscope (Japan). In some cases, complete cytogenetic analysis was not performed due to the absence of mitoses.

In accordance with institutional protocol, parental written consent was acquired prior to collecting bone marrow and blood samples from all children. Parents of ill children were suitably advised about the predicted result of the identified disease. The karyotype is defined according to the ISCN2016 ("International System of Human Cytogenetic Nomenclature") [11]. Gender and various types of cytogenetic abnormalities were carefully considered during the analysis, with the findings presented as incidence rates.

3 Results and Discussion

Throughout this period, 1269 children diagnosed clinically with acute lymphoblastic leukemia were evaluated. Among them, 379 were girls, and 890 were boys, constituting 29.9% and 70.1% of the cases, respectively. Table 1 illustrates the occurrence and types of chromosomal abnormalities observed in children with ALL.

Table 1. Frequency of genomic and chromosomal mutations in children with acute lymphoblastic leukemia

	Types of genomic and chromosomal mutations		Number of patients	
			quantity	frequency, %
Acute lymphoblastic leukemia	Normal karyotype	46,XX	114	9
		46,XY	101	8
	Translocations	46,XX,t(1;19)(q23;p13)	25	2
		46,XY,t(1;19)(q23;p13)	50	4
		46,XX,t(4;11)(q21;q23)	95	7,5
		46,XY,t(4;11)(q21;q23)	126	10
		46,XX,t(9;22)(q34;q11)	95	7,5
		46,XY,t(9;22)(q34;q11)	139	11
		46,XX,t(12;21)(p33;q22)	38	3
	Other translocations	girls	63	5
		boys	76	6
	Hyperdiploidy	girls	63	5
		boys	76	6
	No mitosis		152	12
	Total		1269	100

As can be seen from the Table 1, a cytogenetic study did not reveal genomic and chromosomal mutations in 215 (17%) children. Translocation t(1;19)(q23;p13) was detected in 75 children, which amounted to 6%; in 221 children (17.5%) - t(4;11)(q21;q23); in 234 children (18.5%) - t(9;22)(q34;q11); 88 (7%) - t(12;21)(p33;q22) and 139 (11%) patients had translocations between other chromosomes. Hyperdiploid translocations were found in 139 (11%) children, in particular, a previously unobserved hyperdiploid karyotype in a girl with 72 chromosomes - 72, XX, +1, +del(1)(q32), +2, +3, +del(3), +5, +6, +7 +9,+10, +12, +13,+13, +14,+15, +15,+16, +20,+20, +21, +22,+22,+mar x3. No hypodiploid cells were found in sick children. In 152 patients, metaphase cells were not obtained, accounting for 12%. As an example, Figure 1 depicts the drawing of the karyotype of a 7-year-old boy with the Philadelphia chromosome (Ph+).

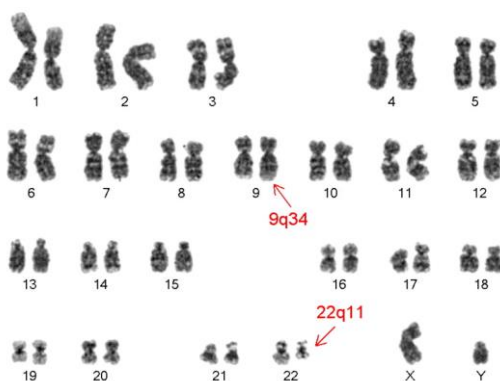


Figure 1. 46, XY,t(9;22)(q34;q11)

A retrospective analysis of cytogenetic results showed that the incidence of ALL between girls and boys is observed in a ratio of 1:2.3. The results obtained on the epidemiology of leukemia are consistent with literature data, which emphasize the significantly more frequent development of the disease in boys than in girls [12-14].

Abnormalities in the number and structure of chromosomes are often observed in ALL in children, and some of them have prognostic significance for the effective treatment of this pathology. It has been established that some chromosomal abnormalities are associated with both more favorable and poor prediction of treatment. Carriers of the t(12;21) translocation demonstrate more promising results in the therapy of this illness than other patients with other translocations [15]. Recurrent genetic abnormalities associated with poor prediction include t(9;22)(q34;q11.2), i.e., Philadelphia chromosome positive (Ph+) [16]. According to the outcome of our investigation, this translocation had the highest frequency of occurrence among other chromosomal abnormalities and was detected in 234 (18.5%) children.

Previously, it was believed that carriers of t(1;19)(q23;p13.3) had a negative prediction for treatment. Nevertheless, patients processed with intense contemporary treatment were found to have an advantageous consequence, and this genetic abnormality is no longer examined as a hazard factor in some treatment bands [17]. Translocation t(12;21)(p13;q22), which has a positive prediction [18], according to our data, is observed in 88 (7%) children.

Cytogenetic aberrations affect the general predictions of the illness, comprising reaction to chemotherapy and the probability of future lapse. For instance, some translocations, such as t(4;11) and t(9;22), are affiliated with unyielding illness and may demand concentrated chemotherapy. On the contrary, t(12;21), t(1;19) and aneuploid chromosomes have favorable treatment outcomes [19]. Lee (2017) also notes that patients with a hyperdiploid chromosome number (51–66) had a better prediction. Near triploidy (68–80 chromosomes) and near tetraploidy (>80 chromosomes) are much less common and have a favorable prediction [18].

The majority of patients diagnosed with ALL exhibiting hypodiploid cells containing 45 chromosomes, as well as those with low hypodiploidy (32–39 chromosomes) or near-haploidy (24–31 chromosomes), experience significantly diminished survival rates [20]. Thus, cytogenetic studies are a necessary stage in diagnostic procedures and prediction of ALL disease in children.

4 Conclusion

Acute lymphoblastic leukemia is an urgent medical and social problem due to the complexity of diagnosis and poor prediction for treatment outcome. The paper presents the results of a retrospective analysis of genetic abnormalities in clinically diagnosed 1269 sick children diagnosed with ALL over a 10-year period from January 2013 to January 2023. An analysis of the incidence of pathology depending on gender revealed a 2.3-fold increase in the disease in boys compared to girls. A different frequency of occurrence of numerical and structural chromosomal aberrations features of ALL was found. There is a comparatively low prevalence of optimistic predictions of chromosomal abnormalities, such as t(12;21)(p13;q22) and hyperdiploidy in ill children. The incidence of chromosomal aberrations with negative treatment predictions, such as t(9;22)(q34;q11.2), is consistent with the data of the accessible international scientific literature [16–18]. In our cohort of examined sick children, hypodiploid cells with an unfavorable prediction were not found. It should be noted that this study shows the results of a retrospective analysis of the distribution of frequency and spectrum of chromosomal abnormalities in many children suffering from ALL in Kazakhstan. The use of a standard cytogenetic research method made it possible to identify characteristic genomic and chromosomal mutations in the karyotype of sick children, which indicates the importance of cytogenetic studies in the diagnosis and prediction of therapeutic approaches in children with acute lymphoblastic leukemia.

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