Original Article

SPECTRUM OF CYTOGENETIC ABNORMALITIES IN PEDIATRIC PATIENTS WITH ACUTE MYELOID LEUKEMIA

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ABSTRACT

Objective: To determine the frequency and types of cytogenetic abnormalities in pediatric Acute Myeloid Leukemia.

Material and Methods: This cross-sectional study was conducted from January 2021 to October 2021 in Hematology department of the CHUGHTAI Institute of Pathology in Lahore Pakistan. Total 60 patients who were newly diagnosed with Acute myeloid leukemia in CHUGHTAI Institute of Pathology and were also referred from Children Hospital Lahore were included. Patients under the age of 16 years and from both gender were included. Informed consent was taken from patient's guardian/parents. Patients had their bone marrow aspirates processed for standard G-banding and their karyotypes were examined using a cyto-vision system, where the number of chromosomes was counted and examined for any changes, such as damaged, missing, rearranged, or additional copies of chromosomes. Morphology, immunophenotyping of aspirate, and trephine biopsy are used to make the diagnosis of AML. Data was entered in SPSS version 23.0.

Result: There were total 60 patients included in the study. The mean age was 10.2+ 3.2 years. There were n=32(53.3%) males and n=28(46.6%) female. Normal karyotype was observed in n=36(60%) patients, abnormal were seen in n=14(23.3%) and unsuccessful was shown in n=10(16.6%) patients. Favorable cytogenetic results were seen in n=6 (10%), intermediate in n=41 (68.3%), and unfavorable in n=4 (6.6%) cases. t(8;21) (q22:q22) and t(15;17)(q24;q21) were found in 8.3% and 1.6% of our study population respectively which have favorable prognosis . One of our patients had complex cytogenetic abnormalities, including [del5p, del7q, del11q-17+] which shows poor prognosis.

Conclusion: The study discovered that 14 (23.3%) of the total pediatric patients with acute myeloid leukemia showed aberrant cytogenetic abnormalities. Chromosomal abnormalities should be identified as early as possible since they can be used for AML risk stratification and prediction of prognosis**.**

Key Words: Acute myeloid leukemia, Complex cytogenetic, Cyto-vision, Karyotype, Morphology, Pediatric.

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INTRODUCTION

Acute myeloid leukemia (AML) is a clinically and genetically heterogeneous disease. It accounts for 15-20% of all pediatric leukemias, which may develop either spontaneously or as a consequence of prior chemotherapy or myelodysplasia [1]. In the United States, the age-adjusted incidence of AML is 4.3 per 100,000 people per year (US) [2]. Incidence increases with age, with the average age at diagnosis in the US being 68 years [2]. The spectrum of chromosomal aberrations associated with leukemogenesis in acute myeloid leukemia (AML) is large and diverse compared with chronic myeloid leukemia and other myeloid neoplasms [3]. The importance of cytogenetic findings in acute myeloid leukemia is increasingly recognized, as evidenced by the World Health Organization's 2016 classification of acute myeloid leukemia, which now relies heavily on cytogenetics [3]. Chromosomal abnormalities are recognized as an important factor in diagnosis and as an independent prognostic indicator [4]. The most important prognostic variables in AML are age and cytogenetic abnormalities [5]. The importance of karyotype abnormalities in juvenile AML has only recently been discovered due to the rarity of the disease [6].

As patients get older, the proportion of those with unfavorable risk cytogenetic increases. Cytogenetic analysis shows that 70-85% of children with AML have clonal chromosomal abnormalities [5-6]. Myeloid progenitor cells exhibit clonal proliferation and differentiation arrest in acute myeloid leukemia (AML), a malignant disease of the bone marrow[7]. Clonal chromosomal abnormalities can be structural (including deletions, inversions, and translocations) or quantitative (including changes in chromosome number) or both [7]. Numerous morphologic groups

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have been associated with specific chromosomal translocations, which are now recognized as critical diagnostic, prognostic, and advancing features [7].

The most effective prognostic factor for predicting survival and response to induction therapy in AML patients is the diagnostic karyotype [6,7]. Patients with AML can be divided into favorable, moderate, and unfavorable risk categories based on cytogenetic results [5,6,7]. The overall 5-year survival rate for children with AML has increased from around 30% to more than 65% over the period of last 20 years [7]. The incidence of cytogenetic abnormalities was comparable to that documented in the literature, which described the existence of chromosomal alternations in 70–80% on average of juvenile AML cases.[8] Numerous chromosomal abnormalities from AML exist like such t(8;21), t(15;17), and inv 16, in addition to recurrent chromosomal translocation [9]. With conventional treatment, complete remission rates for AML patients under 65 years with a good karyotype range from 85-90%, patients with unfavorable-risk cytogenetic range between 45-55%, 5-year overall survival is between 50-60% for favorable cytogenetic [5], and approximately 10-20% for unfavorable cytogenetic abnormalities [10].

Karyotyping for cytogenetic abnormalities can be of immense value in diagnosing clonal neoplasms like myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) [11]. Cytogenetic findings like Karyotype sequences are common in pediatric patients [11]. In elderly individuals, however, monosomal karyotype (MK) & complex karyotype (CK) are more prevalent [12,13]. Recent studies have shown a relationship between the frequency of chromosomal abnormalities and death rates in both pediatric and adult AML patients [14]. Due to limited availability of cytogenetic testing and its cost, it is neither a routine clinical practice nor such studies have been conducted in Pakistan, but there is a strong impact of karyotyping on the plan of treatment. The current study set out to determine the most common, cytogenetic abnormalities in acute myeloid leukemia in children.

MATERIAL AND METHODS

This cross-sectional study was carried out in the cytogenetic and hematology departments of the Chughtai Institute of Pathology in Lahore, Pakistan; from January 2021 to October 2021 (CIP/IRB/1054) Selection of subjects was performed using a non-probability sampling technique. A total of 60 children with newly diagnosed acute myeloid leukemia were taken from the Hematology Department of CHUGHTAI Lab and referred from Children Hospital, Lahore. Both male and female patients under the age of 16 were included. Leukemia other than AML, patients older than 16 years, and those currently undergoing chemotherapy were excluded from the study.

Before sampling, the patient's legal guardian or parents provided their informed consent. Bone marrow aspirates from patients were processed for standard G-banding, and their karyotype were analyzed using a cyto-vision system, where the number of chromosomes was enumerated and analyzed for any changes, such as damaged, missing, rearranged, or extra copies of chromosomes. The International System for Human Cytogenetic Nomenclature was used to describe and report the cytogenetic results. Regardless of the number of metaphases studied, an aberrant karyotype was defined as having at least two metaphases with structural abnormalities, monosomy, or three metaphases with polysomy [15]. The presence of 20 evaluable metaphases did not exclude individuals from study inclusion in order to be compatible with technique employed in recent research, provided that 10 metaphases were evaluated in those patients with 'normal' reports. SPSS version 23:00, was used to enter and evaluate the data. Age was shown as mean and SD. The frequency and proportion of gender and cytogenetic anomalies were shown. To examine the relationship between cytogenetic abnormalities and age groups, the Chi-square test was used. P values under 0.05 were deemed significant.

RESULTS

This study was conducted on 60 patients with mean age 10.2+3.2 years. There were n = 28 females (46.6%) and n=32 (53.3% males) (Table-I). n=36 patients (60%) had normal karyotype, n=14 (23.3%) had abnormal cytogenetics and n=10 (16.6%) had unsuccessful ones (Table-II). 8 of the 14 individuals (57.1%) with abnormal karyotype, had more than one chromosomal abnormality, such as additions, deletions, inversions, and other translocations (Table-III).

Out of these 14 aberrant cytogenetic alterations, six (42.85%) were favorable, eleven (78.5%) were intermediate, and three (21.4%) were unfavorable. One patient had a complex cytogenetic abnormality that was comprised solely of chromosomal deletions. Age groups significantly differed in the recurrence of both favorable and unfavorable cytogenetic abnormalities (P = 0.001).

The favorable and unfavorable cytogenetic aberrations in either gender did not differ significantly (p>0.05) (Table-IV).

Table-I: Descriptive of Age, Gender

	Frequency (%)
Age (years)	10.2 ± 3.2
Gender	
Male	32 (53.3%)
Female	28 (46.6%)

Table-II: Distribution of Cytogenetic Abnormalities

Cytogenetic Abnormality	Frequency (%) in abnormal cases (n=14)	Frequency (%) in total study (n-60) population
t(8;21)	5 (35.7%)	8.3%
t(15;17)	1 (7.1%)	1.6%
Hyperdiploidy	2 (14.2%)	3.3%
Trisomy 21	3 (21.4%)	5.0%
Trisomy 8	1 (7.1%)	1.6%
-5/Del(5p)	1 (7.1%)	1.6%
-7/Del(7q)	1 (7.1%)	1.6%
-12(loss of chromosome)	1 (7.1%)	1.6%
-10	1 (7.1%)	1.6%
-17	1 (7.1%)	1.6%
Del (11q)	1 (7.1%)	1.6%
Del(9q)	1 (7.1%)	1.6%
+18	1 (7.1%)	1.6%
+20	1 (7.1%)	1.6%
Del(19p)	1 (7.1%)	1.6%

Table-III: Results of cytogenetic abnormalities detected in individual patient (n=14)

S. No	Results
1.	46, XX, t(8;21) (q22:q22), del(19p) [20]
2.	46, XY, t(15;17) (q24;q21), del (17q)(q22;q24) [20]
3.	45, XX, -(7), t(8:21) (q22;q22) [20]
4.	46/45, t(8:21) (q22;q22), -(10) [20]
5.	46, XX, 18p+ [20]
6.	47, XY, +21 [20]
7.	47, XY, del(5p), del(7q), del(11q), -(17)[20]
8.	Hyper diploidy (>50) [20]
9.	Hyper diploidy (>50) [20]
10.	48, XX, +(8), +(21) [20]
11.	48, XY, +(20), +(21) [20]
12.	46, XX, del(9q) (q13) [20]
13.	46, XY/45, XY, t (8;21) (q22; q22), -(12) [20]
14.	46, XX, t (8;21) (q22; q22) [20]

Table-IV: Distribution of Karyotype in age and gender strata.

Age1 (yrs)	Favorable	Inter-mediate	Un-favorable	P value
0-5	2 (3.3%)	32(53.3%)	0	0.001
5-10	3 (5.0%)	9(15.0%)	1(1.6%)	
>10	1 (1.6%)	6(10%)	2(3.3%)	
Gender				
Male	4 (6.6%)	17 (28.3%)	2(3.3%)	0.498
Female	2 (3.3%)	30(50%)	1 (1.6%)	

DISCUSSION

In 23.3% of the individuals in our investigatio n, cytogenetic abnormalities were found. The most co mmon chromosomal aberration we found was t(8;21) (q22:q22), which was present in 8.3% of patients,1.6 % of cases had the t(15;17) (q24;q21), 5.0% had trisomy 21, 1.6% had trisomy 8, and 3.3% had hyper diploidy.

One of the biggest risk factors for the development of AML is age. Age played a key effect on cytogenetic changes, with most changes occurring in children aged 5 to 10 years old. However, cytogenetic modifications were mostly favourable (5%) in children aged 10 or older. Nevertheless, both gender had comparable alterations [6]. Best prognostic indicator for determining a leukaemia patient's chance of survival and how well they will respond to induction therapy is their diagnostic karyotype[3].

Most leukemia therapeutic protocols base initial risk stratifications for treatment on chromosomal and molecular abnormalities of the leukemic cells [17]. Patients with AML are classified into three prognostic groups based on cytogenetic abnormalities: good (favorable), intermediate, and adverse (poor) [7]. Age and cytogenetic abnormalities are the most important prognostic factors in AML. As patients age, the proportion of those with favorable risk cytogenetic falls [5].

Children have better outcomes than adults because they have more prognostic genetic features and are more tolerant of intensive treatment [5,6]. Complete remission is now achieved in 90% of cases, whereas event-free survival and overall survival rates are typically in the 50-70% range[3]. Cytogenetic analysis is also advised for AML patients to monitor minimal residual disease (MRD) [19-21].

AML with complex cytogenetics & monosomies of chromosomes 5 and 7 are less frequent in children, but they are associated with a poor outcome [16,17,18]. The complete remission rates for AML patients with unfavorable-risk cytogenetic range between 45-55%, and their 5-year survival rates are approximately 10-20% [10]. Although males are approximately two times more likely than females to develop acute myeloid leukemia, there was no recognizable gender difference in the distribution of favorable and unfavorable chromosomal aberrations in one study [22]. The aforementioned study is supported by our study's 32 (53.3%) male and 28 (46.6%) female participants with ratio 1:14. There were 2(3.3%) favorable, 32(53.3%) intermediate and no patient with unfavorable cytogenetic abnormality under the age of 5 years, 3(5.0%) favorable and 1

(1.6%) unfavorable, and 9(15.0%) intermediates between the ages of 5 and 10 years. There were 1(1.6%) favorable, 6(10%) intermediate, and 2(3.3%) unfavorable among those over the age of ten. There was a significant difference in the frequency of favorable and unfavorable cytogenetic abnormalities across age groups.

60% of the children in our study had normal karyotype. It is believed that a significant number of AML diagnostic1bone marrow karyotype that would be classified as normal by traditional cytogenetic analysis contain diagnostically significant molecular translocations [1]. Risk stratification remains difficult for 50% of AML patients with normal karyotypes [23]. Normal karyotype AML (NK-AML) has traditionally been associated with favorable or intermediate-risk disease. However, despite the fact that most patients respond to induction chemotherapy, relapse is common, and clinical response within this subgroup has been extremely variable, making this patient group one of the most difficult to risk-stratify and treat[23]. The prognosis of patients with a typical karyotype is variable and they are categorized as having a moderate risk [3]. In children, the typical cytogenetic group is smaller (15- 30%) than in adults (40-47%). Rearrangement t(8;21) (q22;q22), which leads to the merger of the AML1 (RUNX1) gene on 21q22.2, is one of the most common structural abnormality in pediatric Acute myeloid leukemia[24]. According to one study, the frequency is 18-19%, and it manifests morphologically as AML-M2 [23]. Previous research found that translocation (8;21) (q22;q22) and t(15;17) (q22:q12) were the only recurring abnormalities with an increased frequency of 3.0%[1]. These two abnormalities account for 15-8% of AML [22, 24]. Translocation t(15;17) (q24;q21) occurred in 1 (1.6%) of our AML patients.

More people die as a result of 5q, 7q, and/or 17p deletions than as a result of Monosomal karyotype loss. Acute myeloid leukemia in children with 5q [del(5q)], Monosomy 7 (-7), and 7q del(7q)] is rare. In our study, we discovered that children had del 5p and -7/del7q in 1.6% each, which are poor prognostic markers [14,24,25]. One of the most common numerical abnormalities in acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and chronic myeloproliferative diseases (MPD) is trisomy 8[2]. Although we only detected +8 in one case, it was a bad prognostic indicator regardless of whether it represented the underlying abnormality [7,28,29]. The incidence of the chromosomal aberration del(9q) long arm [del(9q)] in acute myeloid leukemia ranges from zero to 4.7% [27].

Unsuccessful cytogenetic karyotype is the absence of analytic metaphasis (UC). There is no doubt that some cases of UC are brought on by a lack of cells in the bone marrow aspirates, but human factors like taking too few samples or diluting the bone marrow cells with peripheral circulation cannot be fully ruled out [7,8,30].

CONCLUSION

The goal of the current research was to identify the most prevalent cytogenetic abnormalities in pediatric acute myeloid leukemia. There is a significant impact of karyotyping on the treatment plan of denovo AML that's why early identification of chromosomal abnormalities will aid in AML risk stratification and prognosis prediction. There will be an expansion of the current trial to include more patients and follow their treatment plan according to their cytogenetic abnormalities.

AUTHOR CONTRIBUTION

Shereen Umer: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work

Shazia Riaz: Drafting of the study

Mohammad Jamil Awan: Data interpretation and result analysis

Hassan Raza & Tayyab Noor: Literature search

Ayisha Imran: Drafting the work, final approval, critical analysis and overall supervision of the research

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