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Cytogenetic profile of pediatric acute lymphoblastic leukemia (ALL): analysis of 31 cases with review of literature

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Abstract — Pre treatment diagnostic cytogenetics is one of the most important prognostic indicators of pediatric acute lymphoblastic leukemia (ALL).Bone marrow aspirate samples of 31 cases of pediatric ALL were analyzed by routine G- Banding technique. Karyotype analysis was done as per International System for Cytogenetic Nomenclature (ISCN), 2005 criteria. Sixteen out of 31 (51.2%) cases were hypodiploid (2n<46), 10/31(32.0%) hyperdiploid (2n>46) and 5/31(16.0%) aneuploid. Among hypodiploid groups, nine (29.0%) had modal chromosome number as 31-39, five (16.0%) as 40-45 and two (6.5%) as 25-30. Among hyperdiploid group, 07(22.5%) had modal chromosome number as 51-60 followed by 2n=47-50 (three cases, 6.5%). The chromosomes (Chr.) 2, 10, 12, 15, 17, 19 were commonly deleted in hypodiploid cell lines whereas gain of Chr. 4, 8, 10, 14and 20 were observed in hyperdiploid group. Translocations t(10;14),t(9;22),t(2;22),t(8;22) andt(4;11)were seen in 04(12.8%),03(9.6%),and02(6.4%each) and one case respectively. To conclude a high proportion of cases in this study showed adverse cytogenetic parameters such as hypodiplody and translocations such as t(10;14),t(9;22),t(2;22),t(8;22)andt(4;11).

Key Words: cytogenetics, ploidy, prognosis, translocation.

INTRODUCTION

Molecular genetic analysis of acute leukemia has been at the forefront of research in the pathogenesis of cancer because the presence of recurring chromosomal abnormalities provides immediate clues to the genetic events leading to leukemia and the means to clone and identify the dysregulated oncogenes. In the majority of acute leukemia and 54 to 78% of adult acute myeloid leukemia (AML), cytogenetic abnormalities are detected on karyotype analysis of peripheral blood or bone marrow. Large clinical studies of both acute myeloid and lymphoblastic leukemia (ALL) have demonstrated that the pretreatment diagnostic cytogenetic is one of the most valuable prognostic indicators for acute leukemia. Results from these studies are routinely used to classify leukemia as favorable or unfavourable (Thompson 2009). The present study was aimed to evaluate the various chromosomal abnormalities in pediatric ALL patients with a brief review of literature.

MATERIAL AND METHODS

This was a prospective study done over a period of one year (December 2007 to November 2008). The Institutional Ethics Committee had approved the study and written consent was obtained from the parents of the patients. Forty-four (44) patients (30 males, 14 females, M: F=2:1) of

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newly diagnosed pediatric (1 to 14 years) acute lymphoblastic leukemia (ALL) were included for cytogenetic analysis. Infants, those in induction and maintenance chemotherapy and relapse were excluded from the study. The French-American-British (FAB) criteria (BENNETT *et al.* 1976) were used to categorize ALL from Leishmann stained bone marrow aspirate smears. Clinical parameters were obtained from patient records and routine hematological data were obtained from Beckman Coulter counter LH500. Bone marrow aspirate samples were subjected to routine cytogenetic analysis as per Direct Flame Drying Giemsa staining technique (SANDBERG 1990; BARCH *et al.* 1997). Well spread metaphase plates were obtained in 31/44 cases for analysis. A minimum of 15 to 20 well spread metaphase plates were analyzed in all cases and the modal number of chromosome (defined as the highest number of chromosome present among 15-20 metaphase plates studied for individual patient and hence the indicator of ploidy) was calculated for each patient. The karyotype analysis was performed as per International System for Cytogenetic Nomenclature (ISCN) (MITELMAN 2005). The results of cytogenetic analysis were correlated with patients' clinical and hematological parameters for risk stratification.

RESULTS

As depicted in Figure 1, 15/31(48%) were in the age group of 5 to 9 years with male predominance. Eighteen of 31 cases (57.6%) belonged to ALL-L2 category. Seventeen of 31(54.5%) cases revealed abnormal and normal metaphase plates, 10/31 (32%) showed only abnormal plates whereas normal/near normal metaphase plates were seen in only 4 cases (13%) (Fig. 2). A high proportion of patients (16/31, 51.2%) had hypodiploid karyotype (modal number of chromosomes <46), whereas hyperdiploidy (2n>46) and aneuploidy were seen in 10 (32.0%) and 05(16.0%) cases respectively (Table-1). Nine of sixteen hypodiploid cases had modal chromosome number as 40-45 followed by 31-39 cell line (five cases). Numerical chromosomal abnormalities alongwith FAB phenotype is presented in Table 2 and Fig. 3.

A majority of cases (18/31, 57.6%) had no detectable structural abnormalities on G-banding technique whereas 13/31cases (41.6%) showed chromosomal translocations. Translocation t(10;14) was the commonest structural abnormality seen in four cases (12.8%) followed by t(9;22) (three cases, 9.6%), t(8;22) (two cases, 6.4%), t(2;22) (two cases, 6.4%) and t(4;11) (one case, 3.2%) (Figs. 4a-d). Stickiness, fragmentation, pulverization, and endomitosis, as

TABLE 1 — Type of metaphase plates obtained in 31 cases of Acute Lymphoblastic Leukemia.

Type of metaphase plates	No. of cases	%age
Abnormal & normal	17	54.5
Abnormal only	10	32.0
Normal/near normal	04	13.0

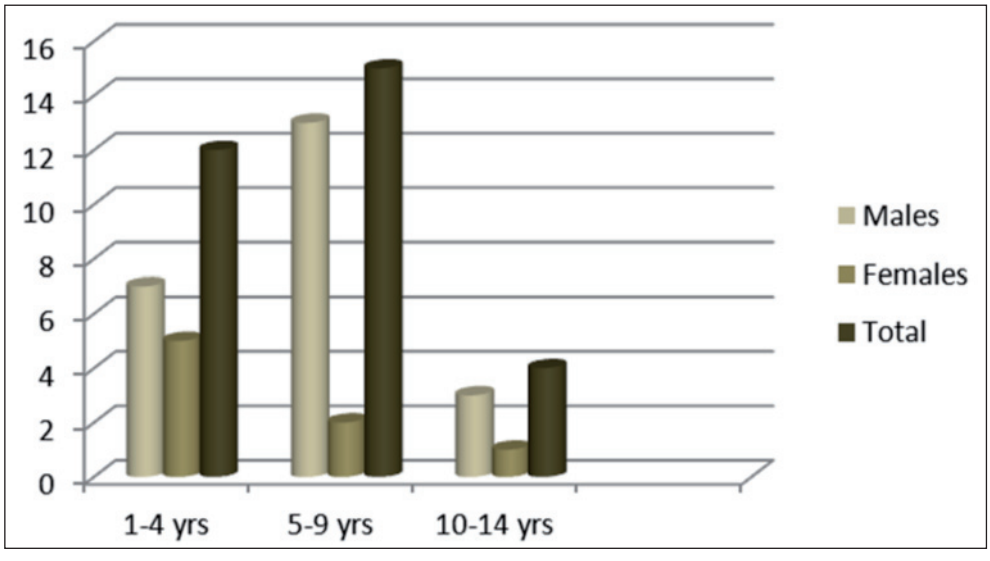

Fig. 1 — Age and sex distribution in 31 cases of pediatric acute lymphoblastic leukemia.

secondary chromosomal aberrations, were observed in high proportion of the cases (Table 3) (Figs. 5f-h). None of the patients were subjected to advanced molecular analyses because of lack of these facilities in our institute as well as patients' financial constraints.

DISCUSSION

Acute leukemia is characterized by the unrestrained clonal proliferation of hematopoietic precursor cells coupled with aberrant or arrested differentiation. With the advent of newer diagnostic modalities, the association between morphology and specific cytogenetic abnormalities related to it, are increasingly recognized. This has led to the development of newer treatment modalities based upon specific genetic defects (THOMPSON 2009).

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosed in children and represents 23% of cancer diagnoses among children younger than 15 years. A sharp peak in ALL incidence is observed among children aged 2 to 3 years (>80 per million per year), with rates decreasing to 20 per million for ages 8 to 10 years (SMITH *et al.* 1999).The majority of patients (15/31, 48%), in the present study, were in the age group of 5 to 9 years with a male predominance, and ALL-L2 was the most common blast phenotype. Fever, lymphadenopathy (cervical, axillary with or without mediastinal) and hepatomegaly were the predominant clinical signs observed at the time of diagnosis. Laboratory evaluation revealed hemoglobin ranging from 18 to 130 gram per liter (g/L) (mean=75g/L), total leukocyte count (TLC) 25 to 120x10^9/L (mean=75 x10^9/L) and total platelet count (TPC) varying from 10 to 360x10^9/L (mean=170 x10^9/L).

It has been well known that both chromosome (Chr) number (ploidy) and structural alterations have independent prognostic significance in childhood ALL (WHITLOCK & GAYNON 2009). Patients with 'normal cytogenetics' can have clonal abnormalities detected by molecular analyses (PUI *et al.* 2008). Among all the chromosomal abnormalities identified in childhood ALL, hyperdiploidy (2n>50) has been associated with the most favorable prognosis compared to other cytogenetic groups (PUI *et al.* 2008; WHITLOCK & GAYNON 2009). High hyperdiploidy (2n=51 to 65) generally occurs in cases with

TABLE 2 — Distribution of FAB* morphology according to numerical abnormalities in ALL†.

Numerical changes	L1‡	L2§	L3‖	Total cases	%
Hypodiploid(2n<46)	07	09	00	16	51.2
Hyperdiploid(2n>46)	05	05	-	10	32.0
Aneuploid	-	04	01	05	16.0

*; French American British, †; Acute Lymphoblastic Leukemia, ‡; ALL-L1, §; ALL-L2, ‖; ALL-L3

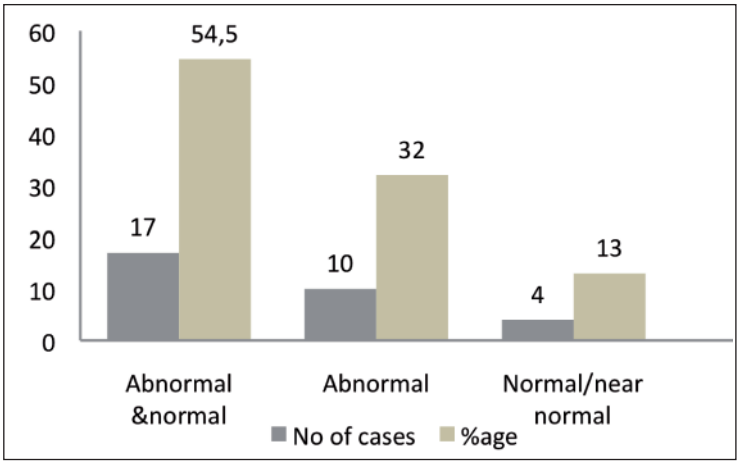

Fig. 2 — Type of metaphase plates in seen in 31 patients of pediatric acute lymphoblastic leukemia.

clinically favorable prognostic factors (patients aged 1-9 years with a low WBC count) and is itself an independent favorable prognostic factor (ARICO *et al*. 2008; PAULSSON & JOHANSSON 2009). In contrast, progressively worse outcome is associated with a decreasing chromosome number (hypodiploidy). Cases with 24 to 28 chromosomes (near haploidy) have the worst outcome and those with fewer than 44 chromosomes have a worse outcome than patients with 44 or 45 chromosomes in their leukemic cells (NACHMAN *et al*. 2007; PUI *et al*. 2008).

On conventional cytogenetic analyses, all the 31 cases in the present cohort demonstrated chromosomal abnormalities, either numerical or structural or both. A significantly higher proportion of patients (16/31, 51.2%) were hypodiploid which was in sharp contrast to the reported incidence from the Western studies (2-6%) (BLOOMFIELD *et al*. 1981; BOWMAN *et al*. 1982; PUI *et al*. 1990; HEEREMA *et al*. 1999), but comparable to the data(35-65%) from India (SUSHEELA *et al*. 1997; AMRE *et al*. 1999; JENA *et al*. 2002) and Pakistan (KHAN *et al*. 1999).

Hypodiploid ALLs, in the present series (Figs. 5a-e), were grouped into three categories based upon the modal number of chromosomes. Of 31 cases, nine (29%) had modal chromosome number as 41-45 followed by 31-40 (5/31, 16%) and 25-30 (two cases). The chromosomes most frequently deleted in hypodiploid cell lines were Chr. 15, 17, 18 and 20 whereas Chr.6, 9 & 13; 2

TABLE 3 — Age, FAB*subtypes and numerical changes in all cases of ALL†.

Type of numerical changes	No of pts	%	Age range (yrs)	ALL-L1	ALL-L2	ALL-L3	Chromosome gain(+)/loss(-)
Hypodiploid (2n=25-30)	02	6.4	4-5	-	02	-	-6,-9,-13,-15,-17,-18,-20
Hypodiploid (2n=31-39)	05	16.0	1-14	03	02	-	-2,-10,-15,-17,-19,-20
Hypodiploid (2n=40-45)	09	29.0	1-10	02	07	-	-3,-10,-11,-18,-20
Hyperdiploid (2n=47-50)	03	9.6	2-5	02	01	-	+14,+17
Hyperdiploid (2n=51-60)	07	22.5	3-8	04	03	-	+4,+8,+10,+14,+20
Aneuploid	05	16.0	2-10	03	01	01	-9,-10,-14,-17, +12,+19

*; French American British, †; Acute Lymphoblastic Leukemia.

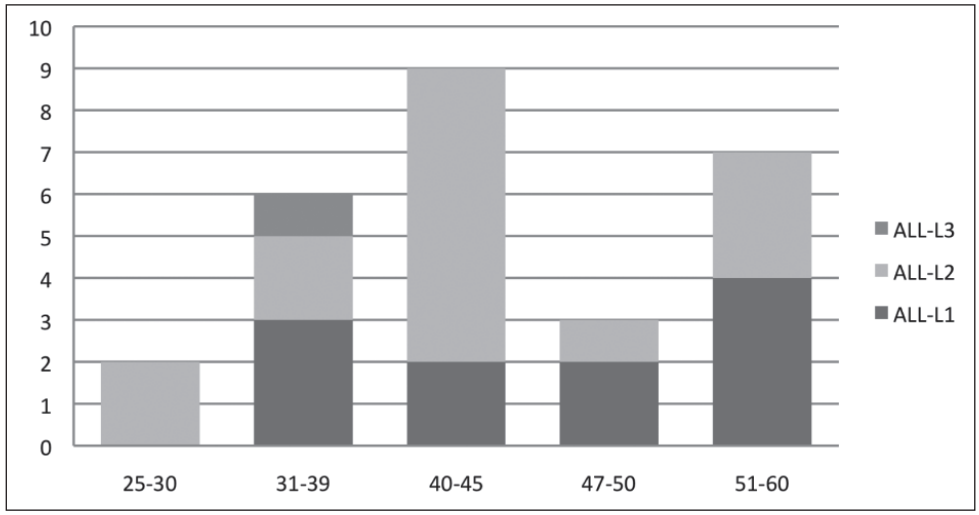

Fig. 3 — Distribution of modal chromosome number (X-axis) and the FAB* phenotype.
*; French American British.

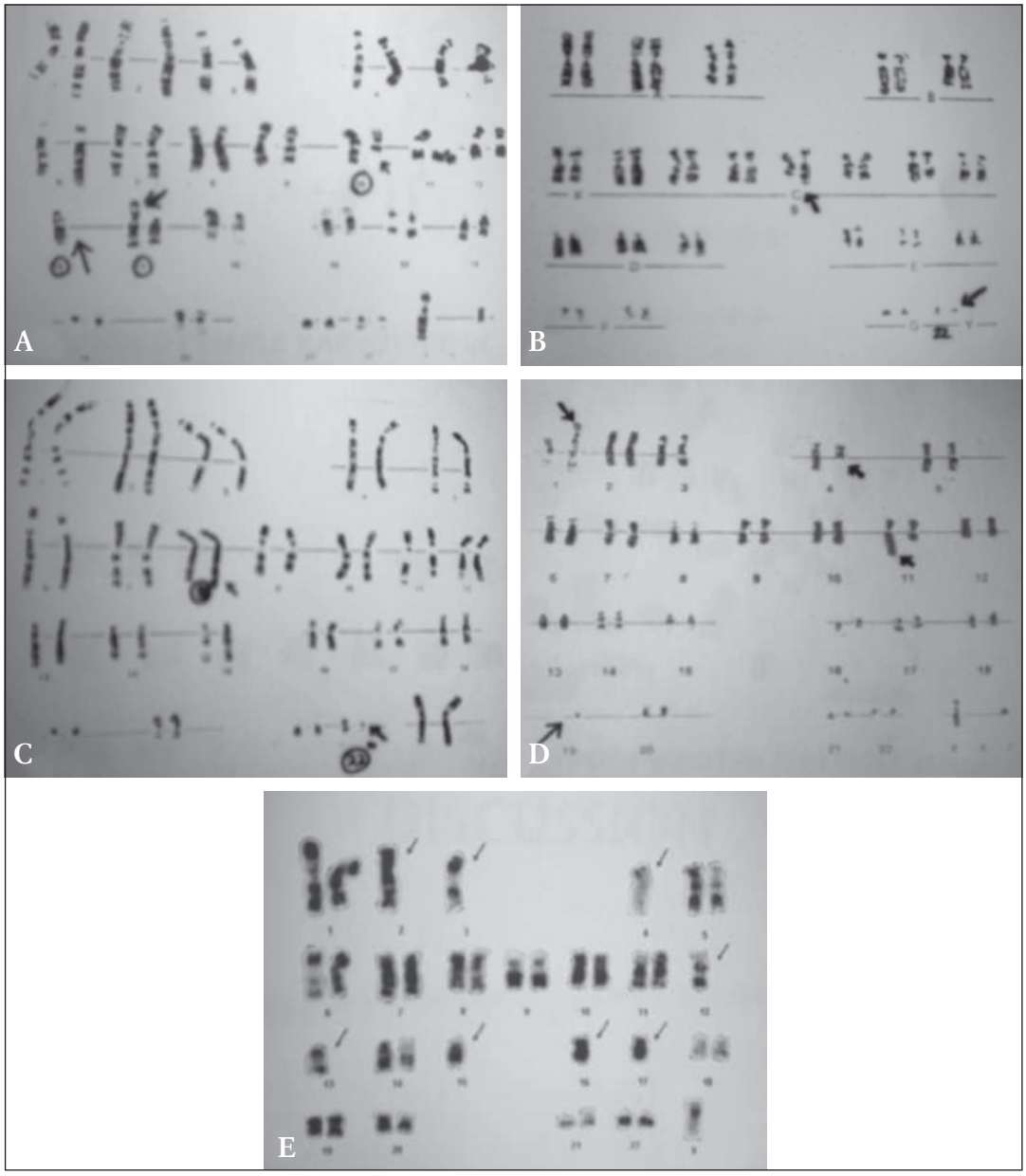

Fig. 4 — (A) G-Banded Male karyotype in a patient of acute lymphoblastic leukemia showing translocation t (10; 14) and deletion of chromosome 13 (arrow) (40X). (B) G-Banded karyotype in a female child of acute lymphoblastic leukemia showing translocation t (9; 22) (arrow) (40X). (C) G-Banded karyotype in a female child of acute lymphoblastic leukemia showing translocation t (8; 22) (arrow) (40X). (D) G-Banded karyotype in a male child of acute lymphoblastic leukemia showing translocation t (4; 11), deletion of chromosome 19(-19), gain of short arm of chromosome 1 (arrow) (40X). (E) G-Banded male karyotype in a patient of acute lymphoblastic leukemia showing deletion of chromosomes 2, 3, 4, 12, 13, 15, 16, 17&Y (arrow) (40X).

& 10; and 3, 10&11 were monosomic in 25-30, 31-39, and 40-45 cell lines respectively (Table 2, Fig.4e). Similar cytogenetic profile was observed in majority of patients in hypodiploid (30-39) cell lines in another study by CHARRIN et *al*. 2004.

High hyperdiploidy (51-67 chromosomes) is the most common cytogenetic abnormality reported in childhood B-cell precursor acute lymphoblastic leukemia (ALL), occurring in 25-30% of such cases. High hyperdiploid ALL is characterized cytogenetically by a nonrandom gain of chromosomes X, 4, 6, 10, 14, 17, 18,

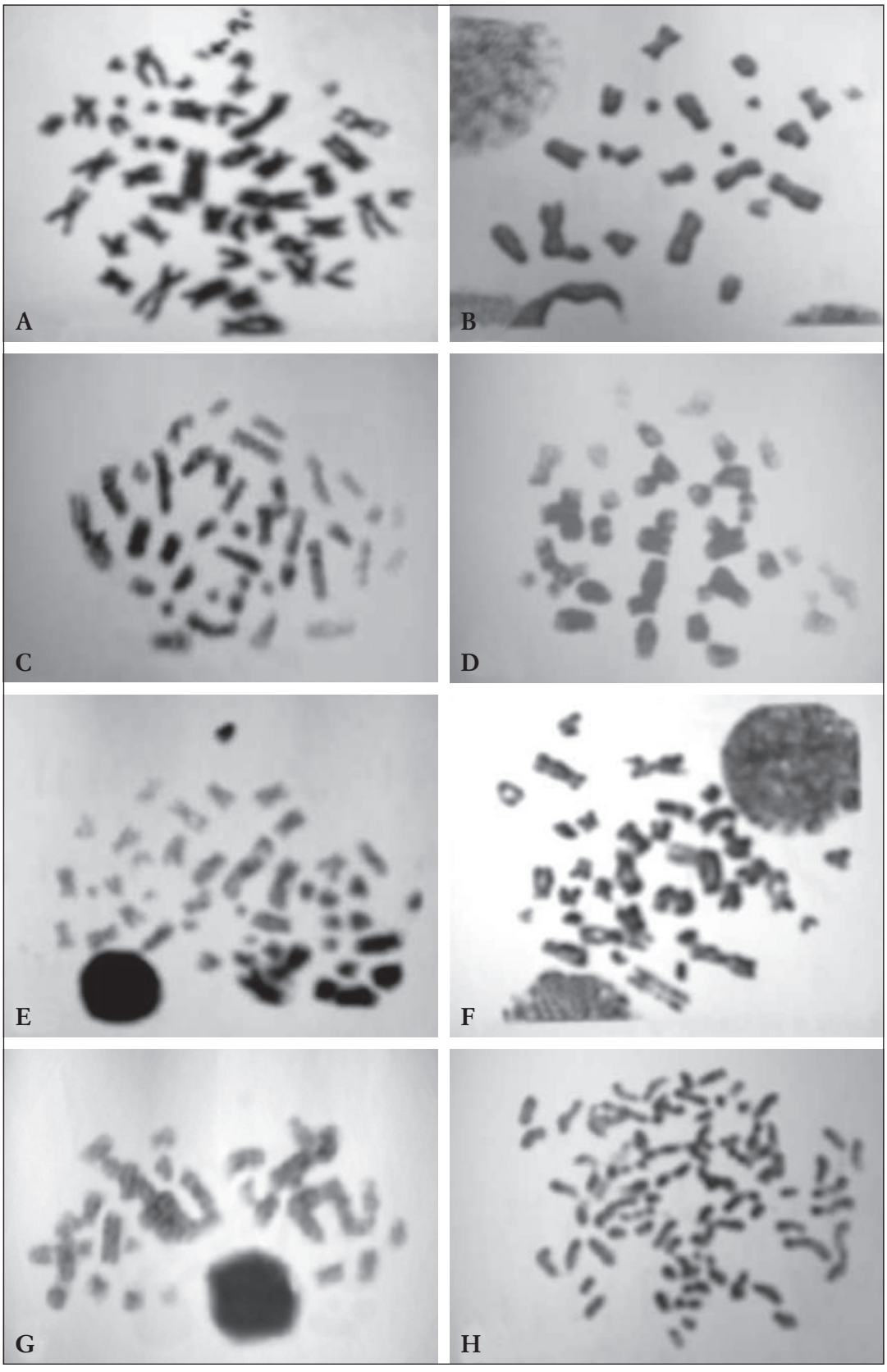

Fig. 5 — (A) Metaphase spread in a male child with acute lymphoblastic leukemia showing Philadelphia chromosome (arrow) (Giemsa, 40X). (B) Metaphase spreads in patients of acute lymphoblastic leukemia showing hypodiploidy (2n=27) (Giemsa, 40X). (C) Metaphase spreads in patients of acute lymphoblastic leukemia showing hypodiploidy (2n=38) (Giemsa, 40X). (D) Metaphase spreads in patients of acute lymphoblastic leukemia showing hypodiploidy (2n<46) (Giemsa, 40X). (E) Metaphase spreads in patients of acute lymphoblastic leukemia showing hypodiploidy (2n=43) (Giemsa, 40X). (F-G) Metaphase spreads in acute lymphoblastic leukemia showing stickiness (Giemsa, 40X). (H) Metaphase spreads in acute lymphoblastic leukemia showing endomitosis (Giemsa, 40X).

and 21 and clinically by a favorable prognosis (SUTCHLIFFE *et al.* 2005; PAULSSON & JOHANSSON 2009; WHITLOCK & GAYNON 2009). Hyperdiploid leukemia cells harboring trisomy 14 and 17 are particularly susceptible to undergoing apoptosis and accumulate higher levels of methotrexate and its active polyglutamates metabolites, which may explain the favorable outcome commonly observed for these cases (SYNOLD *et al.* 1994; ITO *et al.* 1999).

In the present study, trisomy 14 and 17 were observed more commonly in the hyperdiploid cell lines (47-50) whereas trisomy 4, 8 and 10 were more common among 51-60 cell lines. These findings were in accordance with the observations made by various authors (PUI *et al.* 1992; HARRIS *et al.*1992; RAIMONDI *et al.* 1993). In constrast to our findings, trisomy 8, 12, and 19 were common in another study by KHALID *et al.* (2007).

The possible mechanism of hypo and hyperdiploidy is an area of research. The most plausible cause of gain or loss of a whole chromosome is "nondisjunction at mitosis" (PEDERSON-BIERGAARD & ROWLEY 1994). Hyperploid karyotype usually arises by simultaneous gain of chromosomes from a diploid karyotype during a single abnormal cell division, and occasionally by doubling of chromosomes from a near-haploid karyotype (ONODERA *et al.* 1992; PAULSSON *et al.* 2003). It is postulated that extensive chromosome loss in the hypodiploids may occur due to the development of a haploid karyotype with gain of certain chromosomes or multiple losses by nondisjunction. In addition to nondisjunction, formation of micronuclei, chromosome lagging, deletion of parts of chromosomes or telomeric loss may also result in chromosome loss or aneuploidy (PEDERSON-BIERGAARD & ROWLEY 1994). Moreover, the haplodiploid cell lines (2n<30) in a younger patients of ALL was postulated to be an example of "age restricted leukemia" (CALLEN *et al.* 1989).

Nearly half of childhood ALL have chromosomal abnormalities in the form of translocations, which are nearly equally divided between random and nonrandom rearrangements (PUI *et al.* 1990). In the present study, 13/31(41.6%) cases demonstrated Chr. translocation; whereas no abnormalities could be demonstrated in 18 cases (58.6%) by conventional G-banding technique. Among all translocations, t (10; 14) was the most common abnormality seen in 13% cases followed by t(9;22) (9.6%), t(8;22) (6.4%) ,t(2;22) (6.4%) and t(4;11) (3.2%) (Figs.4a-d). Translocation t(10;14) had been reported in adult ALL in various studies (GROUPE FRANCAIS DE CYTOGETIQUE HEMATOLOGIQUE 1996; SUSHEELA *et al.* 1997; SCHNEIDER *et al.* 2000) and was associated with favorable prognosis. The incidence of t(9;22) in childhood ALL varies from 3-5% but various authors (KHAN *et al.*1999; KHALID *et al.* 2007; CHRIST *et al.* 1990; FLETCHER *et al.* 1991; CHAN *et al.* 1992) have reported its incidence ranging from 2-50%. SUSHEELA *et al.* (1997) had demonstrated t (4; 11) in their study of childhood ALL from Chennai, India whereas overall incidence worldwide was estimated to be 8% (BLOOMFIELD *et al.* 1981; KHALID *et al.* 2007). In the present study, t (4; 11) cases were observed in 1-4 year age group of patients. Translocation t (12; 21), the most common cryptic chromosomal abnormality in pediatric ALL (WHITLOCK & GAYNON 2009), was not observed

TABLE 4 — Structural abnormalities in all cases of ALL†.

Structural abnormalities	No of cases	%
A) No identifiable abnormalities	18	57.6
B) With structural abnormalities	13	41.6
I) Primary chromosomal translocation		
1) t‡(10;14)	04	12.8
2) t(9;22)	03	9.6
3) t(4;11)	01	3.2
4) t(2;22)	02	6.4
5) t(8;22)	02	6.4
II) Secondary/additional aberration		
1) Stickiness	21	67.0
2) Chromatid fragmentation	19	60.8
3) Pulverization	17	54.5

†; Acute Lymphoblastic Leukemia, ‡; translocation.

in any of the patients evaluated. Majority of the translocations were observed with hypodiploid karyotype (31-45 cell lines).

The majority of ALL cases in our study exhibited poor cytogenetic abnormalities such as hypodiploidy, translocation t (9; 22), t (4; 11) and t (8; 22) similar to the world literature. All the three patients with t (9; 22) in this study were males who presented with hepatosplenomegaly with high TLC at the time of diagnosis. One had complete remission following intensive chemotherapy whereas rest two patients succumbed to the complications of sepsis during their hospital stay, thus highlighting the adverse prognosis associated with this cytogenetic group. This finding reinforces the concept that intensive treatment approaches including bone marrow transplantation at first remission must be considered for this group of patients (FLETCHER *et al*. 1991; CHAN *et al*. 1992).

The study also demonstrated secondary chromosomal abnormalities (Figs.5f-h) in ALL. Stickiness, chromatid fragmentation, chromatid gap, pulverization, and endomitosis were observed in our patients. The exact mechanism leading to these abnormalities in the leukemic cells are still not known. These aberrations are mostly unstable ones causing loss of genetic material and their frequency seems to increase with the progression of the disease. Both numerical and structural abnormalities are the result of accumulated genetic errors during repeated mitotic perpetuation of leukemic cells or the effects of the products of the transformed cells (JENA *et al*. 2002).

To conclude, adverse clinical, hematological and cytogenetic parameters in childhood ALL were more prevalent in the present study. However, this study had few drawbacks such as 1) non performance of these tests at the time of remission and relapse, 2) non availabity of advanced molecular methods to detect subtle abnormalities and to substantiate our observations, 3) patients' financial constraints and 4) lack of proper patient follow up system in our institute. We, therefore, strongly believe that a large number of patients should be subjected to routine cytogenetic analysis in order to reach at a rational conclusion, for prognostic stratification, planning appropriate management and better understanding of the neoplastic process.

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