*International Journal of Pathology; 2011; 9(2): 67-70*

**Original Article**

# Acute Myeloblastic Leukemia in Children

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**Background:** Children constitute 15-20% of Acute Myeloid leukemia cases. Children may have different presentations and may have different subtypes.
**Objective:** To study the frequency of acute myeloblastic leukemia, its subtypes and clinical manifestations in children in a tertiary care hospital
**Material & Methods:** A Cross-sectional descriptive study was conducted at Department of Pathology Pakistan Institute of Medical Sciences from July 2007- July 2009. All patients below 15 years (n 26) with diagnosis of Acute Myeloid leukemia were included in the study. The detailed clinical history with physical findings was entered on specially designed performa. Subtyping of AML was done on the basis of morphology and cytochemical stains. Results were statistically analyzed through SPSS version 14.
**Results**: Children constituted 32% of all diagnosed cases of Most common subtype was M1 (35%) followed by M3 (31%). None of the children were diagnosed as AML-M5, M7 or M0
**Conclusion:** Total number of children among AML cases was 32%. Most patients presented with pallor, fever and bleeding. Hepatosplenomegaly was more common than lymphadenopathy. The most common subtype was AML-M1 followed by M3
**Key words:** acute leukemia, acute myeloblastic leukemia, childhood malignancies, clinical manifestations.

## Introduction

Acute myeloid leukemia (AML) is characterized by arrest in maturation of myeloid cells leading to increase in number of myeloblasts in the bone marrow, hemopoietic insufficiency (with or without leukocytosis) and infiltration of bone marrow and other tissues by blast cells.[1] Acute leukemia is the commonest childhood cancer; however, acute myeloid leukemia (AML) constitutes only 15 to 20% of such cases with an overall incidence of 4.3 per 100,000 persons in the U.S.[2] Diagnosis of AML is established when more than 30% [20% according to Word Health Organization criteria] of nucleated marrow cells are blast cells. However, in this age group acute lymphocytic leukemia (ALL) is approximately 4-5 times more common than AML, accounting for approximately 80% of all childhood leukemia diagnoses. Conversely, AML comprises only 15% to 20% of cases in patients less than 15 years. [3, 4] Though the ratio of AML and ALL in children is 1:4, it is still the 7th most common pediatric malignancy. Its incidence peaks at 2 years and again at 16 years of age.

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Gender distribution shows that the incidence of AML in first years of life incidence rate is equal for both boys and girls. Later on there is a slight male predominance. Whereas, ALL is curable in vast majority of cases, the long-term survival of AML in children (even with current chemotherapy protocols and intensive supportive care) is only 30- 40%.
Childhood AML has also been found associated with certain genetic disorders, for example children with Down syndrome have a 10-20-fold increased likelihood of developing acute leukemia. [5] Other inherited diseases associated with AML include Klinfelter's syndrome, Fanconi anemia, and neurofibromatosis.[6] Risk factors for developing AML in children include race/ ethnicity, parent's age at time of conception. [7]
AML is further classified into 8 subtypes. The common subtypes in children include, AML-M1, M2, M3 and M6, however in children with Down Syndrome M5 and M7 are frequently seen. Clinical features of various subtypes are generally similar and are the result of marrow replacement and infiltration of other tissues by blast cells. Symptoms related to AML are caused by replacement of bone marrow and failure of normal

hemopoiesis, resulting in anemia, bleeding and increased risk of infections. These may be general or related to specific organ system. Bone pains, CNS infiltration and testicular involvement are less frequent in children with AML as compared to ALL. However the symptoms also depend upon the subtype. Bleeding is a common feature of AML-M3. Extramedullary involvement is most common in monocytic and myelomonocytic leukemia.This study was aimed to look for the frequency of AML, its various subtypes and clinical manifestation in children (< 15 years). The objective of this study was to study the frequency of acute myeloblastic leukemia, its subtypes and clnical manifestations in children

## Materials & Methods

A Cross-sectional descriptive study was conducted at the Department of Pathology,
Pakistan Institute of Medical Sciences (PIMS), Islamabad, from July 2007 to July 2009 on children with freshly diagnosed acute myeloid leukemia. Patients already diagnosed as AML, and receiving cytotoxic therapy, chronic myeloid leukemia (CML), myeloproliferative disorders (MPDs), myelodysplastic syndrome (MDS) were excluded. The detailed clinical history of patients especially regarding age, sex, symptoms, signs Indication for which bone marrow biopsy, findings of bone marrow biopsy with final diagnosis were noted.
In every patient, about 2.5 ml blood sample was collected in EDTA containing tube by a clean venepucture using a 5 ml disposable syringe. From this blood complete blood picture was done on Sysmex KX 21. Peripheral blood smears were freshly made and stained by Wright stain. Two slides were made for Reticulocyte count by Brilliant cresyle blue. All the patients were subjected to bone marrow aspirations using disposable lumbar puncture needle size 16g, from posterior superior iliac spine and from tibia in children < 2 years age. Bone marrow smears were also stained by Wright stain. On the blood smear, differential leukocyte count (DLC) was done and myelogram in 500 cells was done in bone marrow smears. Cytochemical stains (Sudan Black B, Non-specific esterase and PAS) were performed and findings were entered on specially designed proforma.
Different variables of the study were entered on SPSS version 14 for final analysis. Mean and $\pm$ SD were calculated for numerical values wherever required.

## Results

Among a total of 82 cases of acute myeloid leukemia belonging to both sexes and all age groups, total number of children which were included in the study was 26 (32%). Adult to children ratio was 2.2:1. Among these 26 children, 12 (46%) were males and 14 (54%) were females with male to female ratio to1:1.2.
Age range among children was from 2 months to 13 years with the mean age of 7$\pm$ 4.09 SD years. Number of patients below 2 years was 5 (19%), 10 patients (38.5%) were below 5 years. Majority (77%) of the children was below 10 years and only 6 (23%) patients in this pediatric age group were above 10 years. (Table 1)

**Table 1: Age Range in Children**

| Age Range (in years) | n = 26 (%) |
|---|---|
| < 2 | 05 (19) |
| < 5 | 10 (38.5) |
| < 10 | 10 (38.5) |
| > 10 | 06 (23) |

The most common subtype of AML in children was AML-M1 (35%) followed by AML-M3 (31%); an equal number (15% each) of AML-M2 and M4 was observed. None of children were diagnosed as AML-M5, AML-M7 or AML-M0 during the study duration. (Table 2)
Pallor and fever were the most common presenting features seen in 100% and 88.5% cases respectively. 69% children presented with bleeding and 21% patients complained of bone pains. Weight loss and weakness were seen in 3.8% and 15% cases respectively. Hepatomegaly was observed in 73% children, splenomegaly in 69% and lymphadenopathy was observed in 35% cases. Gum hyperplasia was noted in only 2 cases. (Table 3)

**Table 2: AML Subtypes in Children**

| AML FAB Type | n = 26 (%) |
|---|---|
| AML-M1 | 09 (35) |
| AML-M2 | 04 (15) |
| AML-M3 | 08 (31) |
| AML-M4 | 04 (15) |
| AML-M5 | 00 (00) |
| AML-M6 | 01 (4) |
| AML-M7 | 00 (00) |

| | |
|---|---|
| AML-M0 | 00 (00) |

**Table 3: Clinical Features of AML in Children**

| Clinical Feature | n = 26 (%) |
|---|---|
| Fever | 23 (88.5) |
| Pallor | 26 (100) |
| Bleeding | 18 (69.2) |
| Weight loss | 01 (3.8) |
| Weakness | 04 (15.4) |
| Bone pains | 07(20.9) |
| Lymphadenopathy | 09 (34.6) |
| Hepatomegaly | 19 (73.1) |
| Splenomegaly | 18 (69.2) |
| Gum Hyperplasia | 02 (7.7) |

## Discussion

Acute leukemia is the commonest childhood malignancy. They have a large effect on cancer survival statistics.[8] In children the ratio of AML to ALL is around 1:4 [9, 10] and AML accounts for 15-20% of such cases. Zahid et al has reported AML in 16% of all leukemias in children. [11] In our study in total of 82 cases, AML was diagnosed in 32% of children. A higher number of patients at our institute is probably due to rapid turnover of patients at children hospital PIMS. In present study among the total of 26 patients, 46% were males and 54% were females with male to female ratio of 1:1.2. Almost similar observation was made by Lyngsie L et al, with male to female ratio of 1:1.6. However these findings were not comparable with other studies. [12] A higher male to female ratio was reported in other studies. [13, 14, 15, 16] Thus in majority of studies, sex distribution in children has shown a male predominance. These findings are however not comparable with our results.

Among children the peak incidence of AML occurs in the first year of life and then decreases steadily. It then remains relatively constant throughout the years of childhood and early adulthood. [4] Among children majority (77%) of our patients were less than 10 years age and 38.6% are less than 5 years. Similar observations were made by Frascella E et al as majority of their children were less than 10 years of age. [16]

The FAB classification has been the major system used by hematologists for more than 20 years. This classification is best suited for the places where sophisticated investigations like immunophenotyping, cytogenetic studies and molecular studies are not available. We observed that the most common subtype among was AML-M1 followed by AML-M3. None of the cases of AML-M5, M7 or M0 was seen in this age group. In one of the local studies done by Ikram N. and Hassan K. et al in 2003 on "Leukemias in children" the most frequent subtype was AML-M2 followed by AML-M3. Ghosh et al noted a similar trend in subtypes of AML in both children and adults. [17] Zaki S et al observed M3 as most common subtype followed by M4. [18] However various studies have shown that the incidence of FAB type varied with age and FAB types M5 and M7 were more common in very young children, whereas FAB types M0, M1, M2, and M3 were more frequent in older children. [14] The similar observations were made by Horibe K et al, in a study done on Japanese children and young adults. They noticed that among patients aged 1 to 4 years, M7 was the most frequent FAB subtype. The relative frequency of M3 gradually increases during adolescence. [19] Variable observations have been made in different studies regarding frequency of AML subtypes. According to Frascella E. et al the most frequent FAB subtype was AML-M2 followed by M5 and M3. [16] These results are however somewhat different from our study as we found no case of AML M5 in our study population.

In our study majority of patients presented with pallor (100%), fever (88.6%) and bleeding (69%). However in a study done by Zaki S. et al the most common symptom was fever (82.6%) followed by bleeding (44%) and pallor (22%). [18] In Acute myeloid leukemia malignant cells accumulate not only in the bone marrow but any organ system may become involved. Once leukemic cells enter the peripheral blood, the lymph nodes, liver, spleen, central nervous system (CNS), and skin are the most common sites detected clinically. In the present study hepatomegaly, splenomegaly and lymphadenopathy were observed in 73%, 69% 35% cases respectively. Only 2 patients had gum hyperplasia and they belonged to AML-M4 subtype. Lymphadenopathy in AML is not as common as seen in ALL. Ghosh S. et al, noticed hepatosplenomegaly in 26.2% and lymphadenopathy in 36% patients. Frascel-

la E et al noted Hepatomegaly in 41%, Splenomegaly in 37%, lymphadenopathy in 15% and CNS involvement in 8% cases with extramedullary involvement predominantly seen in M4 and M5 and least in M3. Cervical lymph nodes were most often involved followed by the axillary nodes. The same pattern of lymph node enlargement was also observed in our study. Two patients with acute myelomonocytic leukemia presented with orbital masses. Geographic variations have been reported in the distribution of extramedullary leukemia and are more frequently reported from the African countries such as Uganda, Egypt and Turkey. Shome et al have reported an incidence of 17.9% for orbital granulosarcoma occurring in patients with AML. It is commonly associated with the AML-M4 subtype. [20]

A higher number of children with AML were found in our study slight female predominance was observed. AML-M1 and M5 were most frequent subtypes in children. No case AML-M0, M5 and M7 were found in 2 years study duration.

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