Pattern of childhood acute leukemia presentation at a tertiary hospital in Nigeria: a five-year review

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INTRODUCTION

More than 80 percent of global annual cancer diagnoses are in resource-poor countries.1 Globally leukemias are the most common childhood malignancies, accounting for about 30% of all paediatric malignancies with acute lymphoblastic leukemias constituting about 76% of all cases of acute leukemia.2,3 In developing countries like Nigeria, leukaemia accounted for about 10.2 to 12.9% of childhood malignancies.6 Several factors have been postulated to be associated with development of acute leukemia, but causal relationship remains to be substantiated.7

Many advances have been made in understanding the molecular biology, presentation and management of acute leukemia in the past few decades.8 Acute leukemias are heterogeneous group of haematological malignancies in which there are clonal expansion of immature precursors (blasts) in the bone marrow. The blast cells are either
myeloid or lymphoid and these are further classified as B cell or T cell. The blasts progressively replace the normal hematopoietic tissue and invade other organs of the body. Therefore, the pattern of presentation of acute leukemia is quite variable depending on the disease nature and its extent.

The observed variations in acute leukemia epidemiology and pattern of clinical presentation between resource-rich and resource-poor countries are postulated by William et al to be due to the differences in lifestyle/socioeconomic status. The common presentations of acute leukemia include fever, fatigue, pallor, bleeding, infection, lymphadenopathy and hepatosplenomegaly.\(^5\)\(^9\)\(^10\) Majority of the presenting clinical features are as a result of infiltration of organs, bone marrow and extramedullary sites. The initial presentation of leukemia is usually nonspecific which may include anorexia, fatigue and irritability with progressive bone marrow failure leading to pallor, bleeding, fever and infection. About 40% present with abnormal bleeding while 24% may present with significant bone and joint pains.\(^3\) A greater proportion of children with acute leukemia have clinical features for some weeks prior to presentation.

Remarkable progress has been made in diagnosis and treatment of childhood cancers especially in resource-rich countries, but most resource-poor countries still lag behind. With effective chemotherapy, most children with cancers can now be expected to have long term survival rate of about 80%, though more than 80% of African children still die without access to treatment.\(^11\) According to Hadley et al challenges like resource deficiencies and difficult healthcare access leading to loss to follow-up compromise management of childhood tumours. We aim to determine the pattern of presentation of acute leukemias in children at a tertiary hospital in Nigeria.\(^11\)

**METHODS**

This is a retrospective cross-sectional study of children managed for acute leukemia at the paediatric department of a tertiary hospital in a 5- year period from January 2012 to January 2017. The study was done at National Hospital Abuja which is located in the Central business district of the federal capital territory, the Capital of Nigeria. This is a fair representative of the country’s multicultural and ethnic background. The institution is a referral centre that provides tertiary healthcare to neighbouring cities and boundary states like Kaduna, Niger, Plateau, Nasarawa and Kogi at the North, West, East, South-East and South-West respectively.

The following information were retrieved from the case notes: patient’s demographics, clinical features and treatment outcome. Those with inadequate records were excluded from the study. Socioeconomic class was determined using the Olusanya’s classification.\(^12\) All the patients had bone marrow studies done which were prepared and read by the haematologist according to specified standards. Bone marrow aspiration was done using disposable bone marrow aspiration needles (Medax size 21G). About 0.5mls of aspirate was taken and smears were made (8-10 slides). The smears were air dried and fixed with methanol. Four marrow and two peripheral blood slides were stained with Romanosky stain. Cytochemical stains were done for 4 slides (Periodic acid Schiff, Non-Specific Esterase and Myeloperoxidase). The slides were reported and treatment options then suggested.

All data obtained for each patient were entered into database SPSS version 21 (SPSS, Inc., Chicago, IL, USA). A descriptive analysis was performed and associations between variables using Fisher’s exact test were done with statistical significance set at p-value <0.05. Ethical approval was obtained from the institutional review board. Data were analysed using SPSS version 21.

**RESULTS**

A total of 27 patients were studied giving an annual case per year to about 5.4 cases per year. Acute leukemia in this study accounted for 17.9% of all childhood tumours seen within the study period.
The demographics for the participants (Table 1) showed that there were 16 males and 11 females, M: F of 1.5: 1 and aged range 8 months to 16 years (mean 7.45±4.75 years).

| Variables | F | P-value§ |
|-----------|---|----------|
| Sex       |   |          |
| Male      | 16 (59.3) | 5 | 6 | 3 | 2 |
| Female    | 11 (40.7) | 4 | 3 | 3 | 1 |
| Total     | 27 (100)  | 9 | 9 | 6 | 3 |
| Source of referral | 7.55 | 0.24 |
| Primary/private healthcare | 3 (11.1) |  -  | 1 | 1 | 1 |
| Secondary healthcare | 11 (40.7) | 5 | 3 | 2 | 1 |
| Tertiary healthcare | 13 (48.1) | 4 | 5 | 3 | 1 |
| Total     | 27 (100)  | 9 | 9 | 6 | 3 |
| Socioeconomic status |   |          |
| Upper class | 7 (25.9) | 2 | 1 | 3 | 1 |
| Middle class | 14 (51.9) | 6 | 6 | 2 | - |
| Lower class | 6 (22.2) | 1 | 2 | 1 | 2 |
| Total     | 27 (100)  | 9 | 9 | 6 | 3 |

§ P-values for sex and socioeconomic status were not significantly associated with age group

Forty-eight percent of the patients were referred from other tertiary health centres while 40.7% were from secondary health centres.

Middle class was the predominant socio-economic status of caregivers (51.9%) then followed by upper class (25.9%).

| Clinical features | Number | Frequency (%) |
|-------------------|--------|---------------|
| Pallor            | 25     | 92.6          |
| Abnormal bleeding | 17     | 63            |
| Bone pain         | 14     | 51.9          |
| Fever             | 23     | 85.2          |
| Lymphadenopathy   | 19     | 70.4          |
| Hepatomegaly      | 20     | 74.1          |
| Splenomegaly      | 14     | 51.9          |

Table 2: Frequency (%) distribution of initial presenting clinical features.

The predominant pattern of presenting clinical features (Table 2) was pallor (92.6%), fever (85.2%), and splenomegaly (51.9%).

Pallor was the most common presenting clinical feature for both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) (Table 3). The specific leukemia type ratio for acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) was 1:2.9.

| Clinical features | Diagnosis | ALL | AML | Total |
|-------------------|-----------|-----|-----|-------|
| Pallor            | Yes       | 19  | 6   | 25    |
|                   | No        | 1   | 1   | 2     |
| Abnormal bleeding | Yes       | 11  | 6   | 17    |
|                   | No        | 9   | 1   | 10    |
| Bone pain         | Yes       | 12  | 2   | 14    |
|                   | No        | 8   | 5   | 13    |
| Fever             | Yes       | 18  | 5   | 23    |
|                   | No        | 2   | 2   | 4     |
| Lymphadenopathy   | Yes       | 14  | 5   | 19    |
|                   | No        | 6   | 2   | 8     |
| Hepatomegaly      | Yes       | 17  | 3   | 20    |
|                   | No        | 3   | 4   | 7     |
| Splenomegaly      | Yes       | 12  | 2   | 14    |
|                   | No        | 8   | 5   | 13    |

Table 3: Frequency (N) distribution of initial presenting clinical features with respect to Acute Leukemia type.

Figure 1 and Figure 2 show the distribution of ALL and AML subtypes respectively. Concerning the outcome variables (Table 4), the parents of three patients took their children away before commencement of treatment, one
patient completed treatment and 6 (22.2%) died before completing treatment.

**Table 4: Primary outcome variables.**

| Outcome variables               | No. | %   |
|---------------------------------|-----|-----|
| Discharged to follow-up         | 19  | 70.4|
| Lost to follow-up               | 14  | 51.9|
| Left against medical advice     | 3   | 11.1|
| Completed treatment             | 1   | 3.7 |
| Remission                       | 9   | 33.3|
| Mortality                       | 6   | 22.2|

**Table 5: Relationship between age, sex and socioeconomic status (SES) with lost to follow-up.**

| Variables      | Lost to follow-up | Total | P-value |
|----------------|-------------------|-------|---------|
|                | Yes   | No    |        |
| Age group      |       |       |        |
| 0-4            | 5     | 4     | 9      | 0.31   |
| 5-9            | 3     | 6     | 9      |        |
| 10-14          | 1     | 6     | 7      |        |
| 15-19          | 1     | 2     | 3      |        |
| Total          | 14    | 13    | 27     |        |
| Sex            |       |       |        |
| Male           | 8     | 8     | 16     | 0.81   |
| Female         | 6     | 5     | 11     |        |
| Total          | 14    | 13    | 27     |        |
| SES            |       |       |        |
| Upper class    | 3     | 4     | 7      | 0.78   |
| Middle class   | 7     | 7     | 14     |        |
| Lower class    | 4     | 2     | 6      |        |
| Total          | 14    | 13    | 27     |        |

**Table 6: Socioeconomic status and mortality based on diagnosis.**

| Diagnosis         | Total | P-value |
|-------------------|-------|---------|
| ALL               |       |         |
| AML               |       |         |
| Upper class       | 4     | 3       | 7      | 0.52   |
| Middle class      | 11    | 3       | 14     |        |
| Lower class       | 5     | 1       | 6      |        |
| Total             | 20    | 7       | 27     |        |
| Mortality         |       |         |
| Yes               | 5     | 1       | 6      | 0.08   |
| No                | 7     | -       | 7      |        |
| Lost to follow-up | 8     | 6       | 14     |        |
| Total             | 20    | 7       | 27     |        |

Nearly half of the patients were lost to follow-up to seek alternative care which was found not to be significantly associated with socioeconomic status, age and sex with p-values of 0.78, 0.31 and 0.81 respectively. However, 9 (33.3%) of the patients were in remission at the last follow up.

**DISCUSSION**

Annually, about 5.4 cases per year of acute leukemia were found in present study and constitute 17.9% of all childhood tumours. In Nigeria, reliable national figures are not readily available due to paucity of population-based childhood tumour registry.

However, Babatunde et al in Ibadan, Nigeria and Ali et al in Egypt reported that in their studies acute leukaemia accounted for 10.2% and 29.3% respectively of total childhood malignancies. Present study showed that ALL accounted for majority of leukemia with 74%, which is in keeping with other studies. However, Ochicha et al reported a higher prevalence of AML than ALL in their study in Northern Nigeria.

In the last decade, statistics show that in the developed nations, there has been an increase in the incidence of malignancies but due to under reporting in resource-poor countries this statistic are not available. There appears to be an increase in number of cases diagnosed per year but giving the short duration of the study such assertion had to be with caution.

The male to female ratio of 1.5:1 observed in this study is similar to other studies that reported male preponderance. Fleming in his review of leukemia in Africa attributed these observed disparities in leukemia epidemiology to inadequate record keeping, poor laboratory services, under-diagnosis by clinicians and poor access to healthcare service.

Most of the patients were in the middle or upper socioeconomic class and the association between demographic variables (sex, socioeconomic class) and age groups was not statistically significant.

We found no association between socioeconomic status and acute leukemia diagnosis although Williams et al reported an association between high socioeconomic class and prevalence of acute leukemia. Eden in his review reflected on the importance of genetic-environmental interaction in the aetiology of childhood leukemia. The common clinical features patients presented with were pallor, fever, hepatomegaly and lymphadenopathy which are similar to other reports. All of the observed symptoms were commoner in patients with ALL than AML, though our small sample size may have contributed to our findings. For patients with ALL, majority presented with pallor, fever and hepatomegaly while pallor and abnormal bleeding were the commonest amongst patients with AML. Nine of the patients went into remission (33%) and six deaths were recorded (22%). Mortality was not significantly associated with acute leukemia subtype in this study.
The death rate due to acute leukaemia is still unacceptably high in Nigeria. Most patients diagnosed did not however complete their treatment. They were either lost to follow up or refused treatment. In a similar study by Ahmad et al more than half of their patients with childhood malignancy did not complete their treatment. These high percentages in both studies could be due to the financial burden associated with the treatment of the disease, ignorance and poor supportive therapies in terms of blood and blood products.

Magrath et al in their study reiterated the significance of public enlightenment, health professional training and strengthening of health systems through international collaborations and health insurance in the care of childhood cancers in resource-poor countries. Our major finding was that demographic variables; age, sex and socioeconomic status were not significantly associated with major outcome variables; loss to follow-up and mortality from acute leukaemia.

However, Hossain et al found significant variations in survival by age of presentation. The disparity in our finding may be explained by our relatively small sample size in relation to the study of Hossain et al.

Flow cytometry and cytogenetic studies are not readily available in our country hence limits adequate subclassification of leukemias. The retrospective nature of the study and small sample size limits its findings and analysis as many factors that could have influenced acute leukemia presentation, management and outcome were not determined. Our results could also have been limited by the effects of unmeasured confounders.

CONCLUSION

Acute lymphoblastic leukaemia remains the predominant type of childhood leukaemia in our setting. Majority of the patients presented with fever and pallor; moreover, loss to follow-up plagues treatment completion. There is need for massive enlightenment, training and retraining of personnel at the lower health facilities to ensure early referral.

Funding issues also need to be addressed as the commonest cause of loss to follow up or refusal to accept treatment is the cost implication of the treatments. Further studies will need to be done to substantiate the above assertion and other possible causes of loss to follow-up that may negatively influence treatment completion.

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