

Frequency of Hematological Disorders in Children Diagnosed on Bone Marrow Examination

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ABSTRACT

Aim: To determine the frequency of hematological disorders in children diagnosed on bone marrow examination.

Methods: A total of three hundred patients suspected of different haematological disorders were included in the study based on their history and clinical examinations. It was a descriptive case series study conducted at Department of Haematology and transfusion Medicine of the Children Hospital and the Institute of Child Health, Lahore during August 9, 2007 to May 28, 2009. Haematological disorders were diagnosed on bone marrow aspiration morphology and trephine biopsies.

Results: Of the 300 patients, 45.6% were found to have Acute lymphocytic leukemia, 10% were found to have acute myeloid leukemia, 13.3% patients had aplastic anemia, 10% had idiopathic thrombocytopenic purpura, 9% had storage diseases and 3.3% patients had infiltration of bone marrow by round blue cell tumors. Almost 9% of patients had other haematological disorders which included megaloblastic anemia, pure red cell aplasia, juvenile myelomonocytic leukemia, chronic myeloid leukemia, hemophagocytic syndrome and congenital dyserythropoietic anemia. 1% of patients were diagnosed to have histiocytic sarcoma and myelofibrosis.

Conclusion: Acute leukemia is quite frequent in Pakistani children. ALL/L1 being the predominate type affecting children under 5 years old. Amongst AML, M4 is seen more frequently in children. This disorder is followed by Aplastic anemia and Idiopathic thrombocytopenic purpura. Storage diseases are also common in children, and it mainly includes Gauchers disease and Neiman Pick disease. Other haematological disorders are less common and they include infiltration of bone marrow by round blue cell tumor, megaloblastic anemia, CML, JMML, CDA and so on.

Keywords: Bone marrow aspirate, Hematological disorders, acute leukemia, aplastic anemia

INTRODUCTION

Bone marrow aspirations and biopsies are becoming increasingly common practice in routine pathological procedures¹. The familiarity with the normal marrow histology plays an important role in understanding of the pathology of marrow². The traditional role of bone marrow biopsy remains certain, however it should be reviewed with knowledge of history, clinical examination, peripheral smear and bone marrow aspiration³. The disorders which are diagnosed on bone marrow aspirates are acute leukemia, aplastic anemia, disorders which primarily originate in extra medullary organs and then involve the bone marrow as secondary process e.g., lymphoma. Bone marrow examination usually involves two procedures i.e., cytological and histological specimens. Cytological examination is obtained by aspiration, and allows morphological assessments of cells. Histological specimens usually obtained with Jamshidi needle, allows evaluation of fibrosis, cellularity and infiltrative disease⁴.

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Bone marrow aspirates and biopsies allow the complete assessment of marrow architecture and pattern of involvement of any abnormal infiltrate and for the detection of isolated bone lesion^{5,6}.

Bone marrow biopsies has wide applications in clinical medicine having greatest utility in the evaluation of patients with malignant lymphoma, leukaemia, metastatic tumours, granulomatous disorders, myelofibrosis, aplastic anemia and plasma cell dyscrasias.

Bone marrow biopsy also serves as an important tool for the diagnosis of fever of unknown origin. In some cases due to bone marrow fibrosis bone trephine biopsy is the only available specimen for examination. Bone marrow aspiration and biopsy is an invasive procedure with moderate discomfort and rare complications. It is a simple and safe procedure which can be performed in all sexes and in all ages. This procedure is sometimes helpful in detecting the micro metastasis when primary is not known in correlation with other diagnostic modalities.

Commonly, bone marrow is done for the evaluation of unexplained cytopenias and malignant conditions like leukemia. Bone marrow examination is

also at times done for the diagnosis or staging of a neoplasm and storage disorder.

In most of the international studies the commonest hematological disorders diagnosed by bone marrow examination are acute leukemias, aplastic anemia, immune thrombocytopenic purpura, nutritional anemias and visceral leishmaniasis^{7,8}. A few studies estimating the relative frequencies of various hematological disorders diagnosed on bone marrow examination have been conducted in Pakistan as well. In one study conducted at the District Headquarters Hospital Rawalpindi and Pakistan Institute of Medical Sciences, Islamabad, iron deficiency concomitant with megaloblastic anemia was the commonest hematological finding. Other hematological lesions diagnosed were leukemias, idiopathic thrombocytopenic purpura, anemia due to underlying disorder, severe aplastic anemia, myeloid hyperplasia, visceral Leishmaniasis, isolated megakaryocytic depression, pure red cell aplasia, lipid storage diseases, sideroblastic anemia and congenital dyserythropoietic anemia⁹.

Another study which was carried out in PAF hospital, Islamabad and Army Medical College, Rawalpindi showed acute leukemia was the commonest one, followed by erythroid hyperplasia, lymphoma, aplastic anemia and granulomatous infections¹⁰. Another local study was carried out in Department of Paediatrics, Liaquat University of Medical and Health Sciences, Hyderabad also showed that children who were presenting with pancytopenia showed acute leukemia the most common one followed by megaloblastic anemia, iron/mixed deficiency anemia, acute myeloid leukemia, some cases of lymphoma, neuroblastoma, nephroblastoma and chronic myeloid leukemia¹¹. There was another study which was conducted in New Delhi, showed that patients which were presenting with pancytopenia had megaloblastic anemia the commonest one followed by acute leukemia, aplastic anemia and kala-azar¹².

A few studies estimating the relative frequencies of various hematological disorders diagnosed on bone marrow examination have been conducted in Pakistan as well. In one study conducted at the District Headquarters Hospital Rawalpindi and Pakistan Institute of Medical Sciences, Islamabad, iron deficiency concomitant with megaloblastic anemia was the commonest hematological finding. Other hematological lesions diagnosed were leukemias, idiopathic thrombocytopenic purpura, anemia due to underlying disorder, severe aplastic anemia, myeloid hyperplasia, visceral Leishmaniasis, isolated megakaryocytic depression, pure red cell aplasia, lipid storage diseases, sideroblastic anemia and congenital dyserythropoietic anemia⁹. Another

study conducted at the Khyber Teaching Hospital and Khyber Medical College, Peshawar has reported similar frequencies of the above mentioned disorders¹³. No such study has been carried out in paediatric group in Pakistan.

We planned this study to determine which hematological disorders are most frequent in our setup and also to have an insight into their patterns of presentations. This study is to be carried out at the Haematology and Transfusion Medicine Division of the Children Hospital and the Institute of Child Health, Lahore. Each year variable number of these haematological disorders are identified at this institute. Finding out the frequency of these haematological disorders will help us identify which disorders are more common, the burden of the disease in our region, the age bracket most affected in children, the mode of presentation etc. By utilizing this information we can eventually facilitate not only etiological research but also appropriate direction of health care resources in Pakistan.

MATERIALS AND METHODS

A total of 300 children male /female age 0-15 yrs, all new children presenting for bone marrow aspiration for diagnosis were included in the study while diagnosed patients undergoing bone marrow aspiration and trephine biopsy to look for response of treatment were excluded. This descriptive case series study was carried out in the Haematology and Transfusion Medicine Division of the Children Hospital and the Institute of Child Health, Lahore between August 2007 to May 2009. Every selected subject was given a case number. After introduction with the subject and the attendants, an informed consent was taken from them. Demographic details including age and gender and a brief, relevant clinical history was recorded. Haematological disorders were diagnosed on bone marrow aspiration morphology and trephine biopsies.

The collected data was transferred to SPSS 10.0 for analysis. Frequency and percentages were used for qualitative data such as gender, presenting complaints (pallor, bleeding, lymphadenopathy, hepatosplenomegaly), blood counts, cytochemical staining, diagnosis of haematological disorders. Mean and standard deviation were calculated for numerical variables such as age. As this was a descriptive study no test of significance was applied.

RESULTS

Out of 300 patients 167 were diagnosed with acute leukemia according to FAB classification, 40 patients were suffering from aplastic anemia, 30 patients had

idiopathic thrombocytopenic purpura, 27 patients were diagnosed with storage diseases (including both Gauchers and Neiman pick disease) and 10 patients had bone marrow infiltration by round blue cell tumor. The remaining 26 patients had other haematological disorders which included megaloblastic anemia, pure red cell aplasia, juvenile myelomonocytic leukemia, chronic myeloid leukemia, hemophagocytic syndrome and congenital dyserythropoietic anemia. Of the leukemia 45.6% were found to have Acute lymphocytic leukemia, 10% were found to have acute myeloid leukemia, 13.3% patients had aplastic anemia, 10% had idiopathic thrombocytopenic purpura, 9% had storage diseases and 3.3% patients had infiltration of bone marrow by round blue cell tumors. Almost 9% of patients had other haematological disorders which are mentioned earlier. 1% of patients were diagnosed to have histiocytic sarcoma and myelofibrosis.

The age range of the entire population was 0-15 years with a mean of 2.9 and standard deviation of 1.0 for ALL, mean of 2.6 and standard deviation of 1.0 for AML, mean of 2.6 and standard deviation of 1.09 for aplastic anemia, mean of 3.0 and standard deviation of 1.04 for ITP cases, mean of 1.33 and standard deviation of .48 for Gauchers disease and mean of 1.00 and standard deviation of 0.00 for Neiman Pick disease.

As for sex in leukemia patients 41% were males and 15% were females, in aplastic anemia 13% were males and 3% were females, in ITP patients 5.3% were males and 4.6% were females, in gauchers disease 4.33% were males and 2% were females and in Neiman pick disease males were 1.33% and females were also 1.33%.

Regarding the presenting complaints pallor was present in 92% of the patients and fever in 89%. These were followed by blood transfusion and bleeding history. Similarly hepatomegaly and splenomegaly were the most common signs found in 89% and 87% of patients respectively, followed by lymphadenopathy and jaundice.

On peripheral smear 50% of the patients had microcytic hypochromic picture, 45% had normochromic normocytic and 4.4% had macrocytic picture. Blasts were present in all leukemic patients.

In bone marrow aspirates the cellularity was adequate except in the cases of aplastic anemia where it was reduced. Few cases of hypocellular leukemias were also seen.

The normal erythropoiesis, leucopoiesis and megakaryopoiesis in bone marrow aspirates of acute leukemias, aplastic anemia and infiltrative diseases were depressed, whereas in other cases they were found to be essentially normal. In 4% of the cases of AML patients, the aspirate also showed dysplasia in more than 50% of cells in one or more of the cell lineages. In myeloproliferative disorders comprising of CML and JMML, the aspirates were hypercellular and leucopoiesis was invariably increased. The trephines of the corresponding aspirates showed similar findings.

In 3% of the cases, bone marrow aspirates showed infiltration by round blue tumour cells. Iron stores were decreased in leukemias, ITP, aplastic anemia, and were increased in CDA whereas in rest of the cases they were normal. Iron stores were also reduced in iron deficiency anemia.

Table 1: Distribution of cases on the basis of diagnosis (n=300)

	Frequency	Percent
ALL1	97	32.3
ALL2	33	11
ALL3	7	2.3
AML1	4	1.3
AML2	1	0.2
AML3	7	2.3
AML4	11	3.6
AML5	2	0.7
AML6	3	1.0
AML7	2	0.6
Aplastic anemia	40	13.3
ITP	30	10
Gauchers disease	19	6.3
Neiman Pick Disease	8	2.7
Infiltration by round blue cell tumors	10	3.3
Megaloblastic anemia	9	3
PRCA	7	2.3
JMML	3	1.0
Hemophagocytic syndrome	3	1.0
CML	2	0.7
CDA	2	0.7

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Table 2: Distribution of Cases on The Basis of Age (n=300)

Diseases	0-5yrs	%age	5-10yrs	%age	10-15yrs	%age	>15yrs	%age	total	Mean(+/-)SD
ALL	58	19.3	42	14	30	10	7	2.33	137	2.82(+/-)0.88
AML	8	2.66	7	2.33	5	1.66	10	3.33	30	2.61(+/-)0.94
Aplastic anemia	8	2.66	14	4.6	10	3.33	8	2.66	40	2.58(+/-)1.09
ITP	11	3.66	10	3.33	7	2.33	2	0.66	30	2.93(+/-)1.04
Gauchers disease	17	5.66	2	0.66	--	--	--	--	19	1.33(+/-)0.48
Neiman Pick Disease	8	2.66	--	--	--	--	--	--	8	1.00(+/-)0.00
Infiltration round blue cell tumors	--	--	5	1.66	3	1.0	2	0.66	10	2.3(+/-)1.1
Megaloblastic anemia	7	2.33	2	0.66	--	--	--	--	9	1.8(+/-)0.9
PRCA	7	2.33	--	--	--	--	--	--	7	1.2(+/-)0.4
JMML	3	1.0	--	--	--	--	--	--	3	1.3(+/-)0.5
Hemophagocytic syndrome	2	0.66	1	0.33	--	--	--	--	3	1.0(+/-)0.0
CML	--	--	2	0.66	--	--	--	--	2	2.0(+/-)0.7
CDA	2	0.66	--	--	--	--	--	--	2	1.0(+/-)0.0

Table 3: Distribution of Cases on The Basis of Gender

Diseases	Males	Percent	Females	Percent	Total
ALL	100	33.33	37	12.33	137
AML	21	7.0	9	3.0	30
Aplastic anemia	31	13.33	9	3.0	40
ITP	16	5.33	14	4.66	30
Gauchers disease	13	4.33	6	2.0	19
Neiman Pick Disease	4	1.33	4	1.33	8
Infiltration round blue cell tumors	7	2.33	3	1.0	10
Megaloblastic anemia	5	1.6	4	1.33	9
PRCA	5	1.6	2	0.66	7
JMML	1	0.3	2	0.66	3
Hemophagocytic syndrome	3	1.0	--	--	31
CML	2	0.66	--	--	2
CDA	1	50	1	50	2

Table 4: Distribution of cases on the basis of presenting complaints

Presenting complaints	Present	Percentage	Absent	Percentage	Total
Pallor	275	91.6	25	8.4	300
Fever	266	88.7	34	11.3	300
Bleeding	158	52.7	142	47.3	300
Blood Transfusion	162	54	138	46	300

Table 5: Distribution of cases on the basis of symptoms

Symptoms	Present	Percent	Absent	Percent	Total
Jaundice	62	20.6	238	79.4	300
Lymphadenopathy	137	45.6	163	54.4	300
Hepatomegaly	206	68.7	94	31.3	300
Splenomegaly	202	67.3	98	32.7	300

Table 6: Distribution of Cases on The Basis of Peripheral Smear (n=300)

Peripheral Picture	Present	Percent
Microcytic Hypochromic	152	50.6
Normochromic Normocytic	135	45
Macrocytic	13	4.4

Table 7: Distribution of cases on the basis of Hb and RBC count

Disease	Mean Hb	Standard deviation	Mean RBC Count	Standard deviation
ALL	2.22	0.6	2.1	0.57
AML	1.88	0.72	1.84	0.74
Aplastic Anemia	2.15	0.70	1.85	0.70
ITP	2.73	0.78	2.46	0.73
Gauchers Disease	1.83	0.61	1.11	0.32
Neiman Pick Disease	2.0	0.0	2.12	0.35
Infiltration By Round Blue Cell Tumors	1.90	0.31	2.0	0.47
Megaloblastic Anemia	1.88	0.33	1.00	0.0
PRCA	1.20	0.42	1.00	0.0
JMML	1.33	0.57	2.0	0.0
Hemophagocytic Syndrome	2.33	0.57	2.0	0.0
CML	2.00	0.0	2.0	0.0
CDA	1.50	0.70	1.50	0.70

Normal range in children(100) : Hb(gm/dl) : 8.0—18.0

RBC Counts :Red Blood Cell Counts (100): normal range in children RBC Count(x10¹²/L) 3.7—6.0

Table 8: Distribution of Cases on The Basis of WBC Count and Platelet Count

Diseases	Mean WBC	Standard deviation	Mean PLT. Count	Standard deviation
ALL	2.05	1.07	3.12	1.07
AML	1.84	0.94	2.76	1.33
Aplastic Anemia	1.00	0.0	2.12	0.94
ITP	1.00	0.0	2.86	1.00
Gauchers Disease	2.16	0.70	4.16	0.92
Neiman Pick Disease	1.0	0.0	4.6	0.51
Infiltration By Round Blue Cell Tumors	1.60	1.2	4.40	0.84
Megaloblastic Anemia	2.0	0.70	3.77	1.39
PRCA	1.0	0.0	4.6	0.51
JMML	2.66	0.57	2.33	0.57
Hemophagocytic Syndrome	1.0	0.0	2.33	0.57
CML	2.0	0.0	5.0	0.0
CDA	1.0	0.0	5.0	0.0

Table 9: Distribution of case on the basis of prescence of blasts in peripheral smear

		ALL (n=137)	Present	AML (n=30)	Present	JMML (n=3)	PRESENT	CML (n=2)	Present
Blasts	0-50%	35	25.54	12	40	3	100	2	100
Present	50-100%	77	56.20	10	33.33	--	--	--	--
Blasts absent		25	18.24	08	26.66	--	--	--	--

Table 10: Distribution of cases on the basis of iron in bone marrow stores and iron in developing red cells

Diseases	Adequate	%age	Reduced	%age	Increased	%age	Total
ALL	50	36.5	87	63.5	----	----	137
AML	9	30	21	70	----	----	30
Aplastic Anemia	25	62.5	15	37.5	----	----	40
ITP	6	20	24	80	----	----	30
Gauchers Disease	19	100	----	----	----	----	19
Nieman Pick Disease	8	100	----	----	----	----	8
Infiltration By Round Blue Cell Tumors	10	100	----	----	----	----	10
Megaloblastic Anemia	9	100	----	----	----	----	9
PRCA	7	100	----	----	----	----	7
JMML	3	100	----	----	----	----	3
Hemophagocytic Syndrome	3	100	----	----	----	----	3
CML	2	100	----	----	----	----	2
CDA	----	----	----	----	2	100	2

DISCUSSION

In our study done on 300 patients suspected of different haematological disorders, 167(55.6%) were diagnosed with Acute leukemia (ALL 45.6%, AML 10%) 40(13.3%) were diagnosed with aplastic anemia, 30(10%) were found with Idiopathic thrombocytopenic purpura, 27(9%) had storage disorders and 10(3.33%) cases were of bone marrow infiltration by round blue cell tumors. While the rest of 26(7%) cases included other haematological disorders comprising of megaloblastic anemia, JMML, PRCA, CML, CDA, and haemophagocytic syndrome. These results coincide with other studies done in various parts of Pakistan. Nadeem et al did a similar study in District Head Quarter Hospital, Rawalpindi and Pakistan Institute of Medical Sciences, Islamabad and found acute leukemias to be the most common haematological malignancy followed by aplastic anemia and idiopathic thrombocytopenic purpura. In the non malignant causes he found nutritional anemias to be the most common one⁹. Rahim et al did another study in

Khyber Teaching Hospital and Khyber Medical College, Peshawar, he also had similar with acute leukemias being the most common haematological malignancy followed by the rest¹³. Ghazaly et al also had acute leukemias as the commonest haematological disorder, who carried out his study in Department of Medicine & Haematology at Jomhori Hospital in Yemen⁴.

Age as a prognostic factor bears much importance as emphasized by Trueworthy et al¹⁴. It carries importance in relation to therapy, its outcome and after therapy event free survival. Malik et al and Zaki et al found in their studies that the age group for males and females were between the range of 5 to 10 years of age which is slightly higher than what we concluded from our studies^{15,16}.

In our study in Leukemias i.e., ALL, males comprised 33.33% and females comprised 12.33% of the total diagnosed haematological disorders, with a male to female ratio of 2.70:1. Amongst AML, male to female ratio was 2.33:1. Asif et al in his study at Lahore worked out a male to female ratio of 2.21:1¹⁷

in ALL. Harani et al did a study on AML in Karachi and he derived a male to female ratio of 1.5:1¹⁸.

The presenting complaints and clinical signs were recorded for all the haematological disorders. It was seen that pallor and fever were the main complaints in all the haematological disorders. These results were comparable to results seen by Idris et al⁸.

Bleeding was more common in leukemic patients and ITP patients, in which history of blood transfusion was also present. Likewise jaundice, hepatomegaly and splenomegaly was more commonly seen in patients of acute leukemia and storage disorders whereas it was absent in patients of aplastic anemia and of ITP. Lymphadenopathy was another sign present in acute leukemic patients while it was absent in other disorders.

WBC is an important prognostic factor in hematological malignancies. It has its significance in relation to prognosis of the disease, response to initial therapy, event free survival rate etc.

Trueworthy et al at University of Kansas identified WBC count as a prognostic value in cases of acute leukemias. A WBC count less than or more than 50×10^6 /L was considered to be the cutoff point and similarly it was also associated with 80.5% and 50.4% EFS rates (coupled with age and DNA index). Miller et al also reported age and initial WBC count to have a significant effect on outcome of therapy¹⁹. In case of CML WBC count is always elevated, it is usually in the range of 25,000/microl to 100,000/microl¹⁹. WBC count is always increased in untreated patients. WBC changes, including Pelger-Huet abnormalities, hypersegmentation, and hypogranularity, may be subtle in JMML and WBC count is elevated ($<100,000/\text{mm}^3$) with persistent monocytosis in such cases²⁰.

Similarly RBC count has its diagnostic importance in cases of PRCA and CDA patients. Pure red cell aplasia is a syndrome characterized by normochromic, normocytic anemia, reticulocytopenia (reticulocyte count $<1\%$), and almost complete absence of erythroblasts ($<0.5\%$) from the bone marrow²¹. In cases of PRCA the degree of anemia is highly variable at diagnosis. Erythrocytes may be macrocytic or normocytic²².

In most of the cases of CDA the anemia is mild to moderate, with hemoglobin concentrations between 8 and 11 g/dl²³.

Peripheral blast count in acute leukemias, CML and JMML is also emerging as a significant prognostic factor. Griffin et al studied the rate of disappearance of peripheral blood blasts in childhood ALL, and its association with treatment outcome (24). Rapidity of response may therefore be a clinically

useful prognostic factor for patients with ALL. In CML patients blasts count has considerable value in establishing the different phases of the disease.

Platelet count is another important parameter for the evaluation of acute leukemias and ITP. In leukemic patients platelet count is an important consideration since leukemic patients frequently develop thrombocytopenia during induction and consolidation phases of therapy. It is important in regard to when to begin prophylactic platelet transfusion in these patients to prevent bleeding episodes from different diagnostic procedure like lumbar puncture etc. There has been an ongoing debate over whether the traditional threshold for platelet transfusion of 20,000/microl is really sufficient to prevent hemorrhagic complications in these patients. A study done by Wandth et al in Germany established the safety of platelet transfusion trigger of 10,000/microl or even lower when leukemic patients are clinically stable without active bleeding²⁵. In his study, it was observed that prophylactic platelet transfusion is not necessary in children with platelet count higher than 10×10^9 /l. Similarly a study was done by Kalim et al, who concluded that in ITP patients, platelet count less than 20,000/microl bleed profusely when subjected to any procedure²⁶. It is therefore important to observe the platelet count in these patients to avoid unnecessary complications.

Determining the frequencies of different haematological disorders, identifying the age groups most affected, and also identifying the prognostic factors will facilitate the development of strategies that will help us deliver proper health care to these patients. We can devise health plans to assure that patients with a good prognosis to receive maximum benefits and longer event free survival from our limited health resources. Studies should be carried out to identify the risk factors present in our society that predisposes children to developing haematological disorders so that proper endeavours can be made to remove them.

CONCLUSION

Acute leukemia is quite frequent in Pakistani children. ALL/L1 being the predominate type affecting children under 5 years old. Amongst AML, M4 is seen more frequently in children. This disorder is followed by aplastic anemia and Idiopathic thrombocytopenic purpura. Storage diseases are also common in children, and it mainly includes Gauchers disease and Neiman Pick disease. Other haematological disorders are less common and they include infiltration of bone marrow by round blue cell tumor, megaloblastic anemia, CML, JMML, CDA and so on.

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