Clinico-Etiological Spectrum of Pancytopenia in Children Presenting in Allied Hospital, Faisalabad

Amna Tufail, Muhammad Almas Hashmi, Imtiaz Ahmad, Muhammad Asghar Butt

ABSTRACT

Introduction: Pancytopenia is commonly encountered entity in paediatric patients characterized by reduction in the effective production of erythrocytes, leukocytes and platelets by bone marrow. Etiology includes infections, malignancies, bone marrow failure and nutrient deficiencies. **Objectives:** To determine the frequency of different clinical manifestations and etiological factors of childhood pancytopenia. **Study Design:** Descriptive study. **Setting:** Department of Paediatrics, Allied Hospital Faisalabad. **Duration:** Eight months from 01-08-2015 to 31-03-2016.**Sample Size:** total of 125 patients. **Sampling Technique:** Consecutive non-probability sampling. **Data Collection Procedure:** Patients with pancytopenia were enrolled and underwent detailed history and physical examination. Blood counts with peripheral smear, reticulocyte count, red cell indices, Vitamin B_{12} and folate levels, blood culture, bone marrow examination and any other investigation required were done. All data was analyzed using SPSS version 20. **Results:** The mean age was between 7.69 ± 2.36 years with 54 male and 71 female patients. Leukemia was in 28% cases followed by lymphoma in 24%, aplastic anemia in 20%, megaloblastic anemia in 8%, enteric fever in 8%, malaria in 6.4% and sepsis in 5.6%. The commonest clinical presentation was fever in 92% cases followed by pallor in 83.2%, visceromegaly 64.8%, petechiae/bruises 42.4%, joint pain 29.6% and bleeding tendency 20.8%. **Conclusions:** Common etiologies found were malignancy and aplastic anemia, while megaloblastic anemia and infectious etiologies were less frequent. Common presentation was fever, pallor, bleeding tendency and visceromegaly.

Keywords: Aplastic Anemia, Bone Marrow Biopsy, Leukemia, Megaloblastic Anemia, Pancytopenia.

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INTRODUCTION

Pancytopenia is a hematological entity in which all blood cell lineages i.e leukocytes, erythrocytes and platelets are reduced in blood.[1] There are multiple causes of pancytopenia but there are only few studies done on the frequency of its causes.[2] Pancytopenia per se is not a disease but a feature of various diseases causing impact on bone marrow and eventually resulting in this condition.[3] The causes of pancytopenia vary from viral infections that cause a self limiting bone marrow supression to hematological malignancies and storage disorders causing bone marrow replacement with malignant or storage cells.[4] There is variability in its clinical presentation, treatment options and prognosis.[5]

Among children other clinical manifestations of diseases leading to bone marrow suppression include fever, pallor, muco-cutaneous bleed, visceromegaly (hepato-splenomegaly) and lymphadenopathy.[6] The hematological investigations with bone marrow aspiration helps in understanding pathogenesis, making diagnosis, ruling out differentials diagnoses and guiding towards further investigations and management of pancytopenias.[7] Main stay of management is supportive care. Curative options depend upon the etiology such as bone marrow transplant for aplastic anemia and chemotherapy for hematological malignancies.[8] Timely diagnosis on the basis of suspected clinical features is required for early institution of treatment and avoidance of complications.[9] Most of the causes of pancytopenia in Paediatric age group, such as malaria, enteric fever, sepsis and even certain malignancies (ALL); are treatable.[10]

In one study leukemia (32.2%) was the most frequent etiology, other etiologies included aplastic anemia (30.8%), megaloblastic anemia (13.2%) and infections 21%. Pallor (81%) was the most common clinical presentation followed by fever (68%), petechial hemorrhages (51%), bleeding manifestations (21.5%), hepatomegaly (44.8%),

splenomegaly (37.2%) and lymphadenopathy (22.5%).[11]

Local data about the relative frequency of different causes of pancytopenia and their clinical manifestation is much lacking. This study is proposed to make the availability of data regarding the etiology and clinical presentations of pancytopenia which will help in early diagnosis and treatment. Early recognition of etiology of pancytopenia and institution of early treatment can improve the outcome and reduced mortality and morbidity.

Objective

The objective of the study was to determine the frequency of different clinical manifestations and etiological factors of pancytopenia in children.

METHODOLOGY

Study Design: Descriptive study

Setting: the Department of Paediatrics, Allied Hospital Faisalabad

Duration of Study: Eight months from 01-08-2015 to 31-03-2016.

Sample size was calculated by using WHO sample size calculator keeping absolute precision required 6%, confidence level 95% and least frequency etiology (megaloblastic anemia) 13.2%[11]. Sample size was 125 patients

Sampling Technique: Consecutive non-probability sampling.

Inclusion Criteria:

- Age 1 to 12 Years
- Both gender
- Pancytopenia defined as reduction in all three cell lines i.e. hemoglobin <10 g/dL, absolute neutrophil count < 1.5 x 10^9/L and platelet count <100 x 10^9/L
- Admission through noth outpatient department and emergency

Exclusion Criteria:

- Patients already diagnosed cases of Aplastic anemia and leukemia
- Patients having clinical suspicion of genetic or constitutional pancytopenia
- Patients unwilling for either admission or bone marrow examination

Data Collection Procedure:

After taking permission from ethical review committee of the hospital and informed written consent from parents/guardians, total 125 patients were enrolled into study. Detailed history and clinical examination was carried out. Various clinical features like age at presentation, drug history, fever (>98.6˚F), visceromegly including hepatomegly (if liver palpable >2cm below costal margin), splenomegly (if spleen palpable below left costal margin) and lymphadenopathy (if cervical lymph nodes >1cm large, axillary lymph nodes >1cm large and inguinal lymph nodes >1.5cm large) on clinical examination, bleeding manifestations in the form of gum bleed, epistaxsis, patechial rash, pallor, joint pains and bone pains was confirmed on history and clinical examination. All relevant investigation were done including blood complete picture, peripheral film, Reticulocyte count, MP smear, Typhidot, Widal Test, blood culture, lymph node biopsy and bone marrow biopsy from Allied Hospital, Faisalabad; all reports verified by consultant pathologist.

Spectrum of various etiologies like aplastic anemia megaloblastic anemia and hematological malignancies like ALL, AML and infectious causes including malaria, enteric fever and sepsis was studied. Aplastic anemia was defined as depression of 02 or more cell lines i.e hemoglobin <10g/dl, absolute neutrophil count <1.5×10^9/L, platelet count <100×10^9/L, reticulocyte count <1% and hypocellular (<30% hematopoietic cells) bone marrow biopsy. Megaloblastic anemia was defined as hemoglobin level <10g/dl, increased mean corpuscular volume (MCV >95fl) and mean corpuscular hemoglobin (MCH 27-33pg/cell), normal mean corpuscular hemoglobin concentration (MCHC 32-36g/dl), decreased reticulocyte count (normal= 0.5-2%), hypersegmented nuclei (>5 lobes) of neutrophils, anisocytosis, poikilocytosis, ovalocytes and Howell-Jolly bodies(chromosomal remnant) on peripheral smear. Hematological malignancies like ALL were diagnosed by presence of lymphoblasts on bone marrow biopsy, AML diagnosed by presence of myeloblast on bone marrow biopsy and Lymphomas diagnosed by presence of lymphoblasts &/or Reed-Sternberg cells on bone marrow biopsy (or lymphnode biopsy). Infectious causes such as Malaria was diagnosed by presence of malarial parasites on peripheral smear, Enteric fever by Widal test positive (salmonella O antigen titer is >1:160 and H antigen titer >1;160), Typhidot positive (IgM and IgG antibodies positive) and blood culture positive for salmonella and Sepsis was diagnosed on the basis of positive blood culture for colonies of causative organism.

Data Analysis:

Data was entered in predesigned proforma and analyzed by using SPSS version 20.0. Quantitative variables like age, duration of illness and laboratory parameters e.g Hb, TLC, platelet count, MCV, MCHC, reticulocyte count, vitamin B12 and folate levels were presented as mean ± SD. Categoric variables included gender, peripheral film, blood culture, bone marrow examination, clinical features

and etiological spectrum of pancytopenia; and were presented as frequencies and percentages. Effect modifiers like age, sex, recent viral infection, exposure to drug/chemicals/radiation, malabsorption syndrome and family history of pancytopenia were controlled by stratification. Post-stratification chi-square test was applied. p.value ≤ 0.05 was be taken as significant.

RESULTS

In our study 125 children were evaluated. Out of which 54 (43.2%) were male and 71 (56.8%) were female. Male to female ratio was 1:1.31 with a mean age of 7.69 ± 2.36 years. Mean duration of illness was 11 ± 2.46 days.

The most frequent etiology among these patients was leukemia 35 (28%), lymphoma 30 (24%), aplastic anemia 25 (20%), megaloblostic anemia 10 (8%), malaria 8 (6.4%), enteric fever 10 (8%), sepsis 7 (5.6%). The most frequent clinical presentation among these patients was fever 115 (92%) followed by pallor 104 (83.2%), visceromegaly 81 (64.8%), petechiae / brusis 53 (42.4%) and joint pain 37 (29.6%).

Mean hemoglobin was 6.87 ± 2.00 g/dL, TLC 0.85 ± 0.31 x 10^3/cmm, platelet count 68.75 ± 20.01, MCV 90.39 ± 5.85fL, MCHC 34.94 ± 4.68, reticulocyte count (mean 1.70 ± 0.71 %, vitamin B12 levels 241.94 ± 70.86, folate levels 397.13 ± 143.05. The peripheral film was positive in 98 (78.4%) and negative in 27 (21.6%), blood culture was positive in 7 (5.6%) and negative in 118 (94.4%), bone marrow examination was positive in 93 (74.4%) and negative in 32 (25.6%)

Cross tabulation between age stratification and etiological presentation was significant for aplastic anemia i.e. the frequency was much higher in age group of 9-12 yars (p-value < 0.0001) but insignificant for leukemia, lymphoma, megaloblastic anemia, enteric fever, malaria and sepsis (p-value > 0.05) with no significant difference of frequency among the age group. Cross tabulation between age stratification and clinical presentation was significant for visceromegaly which was much more frequent in the age group of 5-8 yeats (p-value < 0.05) but insignificant for fever, bleeding tendency, join pain, pallor and petechiae / bruises. There was no significance difference of etiology or clinical presentation across the both gender.

There was no statistical significant relationship between history of recent viral infection or exposure to drug/chemicals/radiation with etiological presentation. Effect modifiers like molabsoption syndrones and family history of pancytopenia was not found in any case.

Table 1: Frequency Distribution According To Etiology and Clinical Presentation (N =125)

Etiology	**Frequency**	**Percentage (%)**
Leukemia	35	28
Lymphoma	30	24
Aplastic Anemia	25	20
Megaloblastic Anemia	10	8
Malaria	8	6.4
Enteric fever	10	8
Sepsis	7	5.6
Total	125	100.0
Clinical Features		
Fever	115	92
Bleeding Tendency	26	20.8
Joint Pain	37	29.6
Pallor	104	83.2
Visceromegaly	81	64.8
Petechiae/Bruises	53	42.4

Table 2: Laboratory Parameters Of Study Population (n = 125)

Laboratory parameters	**Minimum**	**Maximum**	**Mean**	**SD**
Hemogloin (g/dL)	2.00	9.00	6.0720	2.00071
TLC (10^3/cmm)	0.20	1.40	0.8544	0.30992
Platelet count (10^6/cmm)	24.00	99.00	68.7520	20.01276
MCV (fL)	82.00	110.00	90.3920	5.84600
MCHC	31.00	56.00	34.9360	4.67792
Reticulocyte count (%)	0.10	2.50	1.6968	0.70539
Vitamin B12 levels (ng/L)	44.00	450.00	241.9360	70.86069
Folate levels (ng/mL)	50.00	600.00	397.1280	143.05576

Table 3: Distribution of Etiology and Clinical Features across Different Age Groups

Etiology	AGE			p-value
	1 – 4 (n=6)	5 – 8 (n=75)	9 – 12 (n=44)	
Leukemia	1 (16.7%)	26 (34.7%)	8 (18.2%)	0.126
Lymphoma	3 (50%)	22 (29.3%)	5 (11.4%)	0.027
Aplastic Anemia	0 (0%)	3 (4%)	22 (50%)	0.0001
Megaloblastic Anemia	2 (33.3%)	6 (8%)	2 (4.5%)	0.051
Enteric Fever	0 (0%)	6 (8%)	4 (9.1%)	0.743
Malaria	0 (0%)	7 (9.3%)	1 (2.3%)	0.254
Sepsis	0 (0%)	5 (6.7%)	2 (4.5%)	0.737
Clinical Features				
Fever	4 (66.7%)	70 (93.3%)	41 (93.2%)	0.064
Bleeding tendency	2 (33.3%)	15 (20%)	9 (20.5%)	0.739
Joint pain	3 (50%)	25 (33.3%)	9 (20.5%)	0.177
Pallor	6 (100%)	60 (80%)	38 (86.4%)	0.354
Visceromegaly	4 (66.7%)	59 (78.7%)	18 (40.9%)	0.000
Petechiae/Bruises	4 (66.7%)	34 (45.3%)	15 (34.1%)	0.228

Table 4: Correlation between Recent Viral Illness and Etiological Presentation

VARIABLE		Recent viral illness		p-value
		Yes n=4	No n=121	
Leukemia	Yes	0 (0%)	35 (28.9%)	0.205
	No	4 (100%)	86 (71.1%)	
Lymphoma	Yes	0 (0%)	30 (24.8%)	0.253
	No	4 (100%)	91 (75.2%)	
Aplastic Anemia	Yes	4 (100%)	21 (17.4%)	0.0001
	No	0 (0%)	100 (82.6%)	
Megaloblastic Anemia	Yes	0 (0%)	10 (8.3%)	0.549
	No	4 (100%)	111 (91.7%)	
Enteric Fever	Yes	0 (0%)	10 (8.3%)	0.549
	No	4 (100%)	111 (91.7%)	
Malaria	Yes	0 (0%)	8 (6.6%)	0.595
	No	4 (100%)	113 (93.4%)	
Sepsis	Yes	0 (0%)	7 (5.8%)	0.621
	No	4 (100%)	114 (94.2%)	

DISCUSSION

Reduction in all blood lineages is referred to as “Pancytopenia”. Bone marrow biopsy to assess overall bone marrow cellularity is the most important step in diagnostic refers to a reduction in all 3 peripheral blood cell lines: leukocytes, platelets, and erythrocyvaluation of patients with pancytopenia.[1]

According to a study conducted in Peshawar frequency of pancytopenia was 0.8%[12]. Other representative literature shows variation in the frequency ranging from 1.2% reported by Kanchanalak et al.[13] to12.6% in study done by Adil et al.[14] In present study, malignancies and aplastic anemia were commonest etiologies of pancytopenia, followed by megaloblastic anemia and infections.

Malignant etiology was recognized in nearly half of all patients in present study. Leukemia is among the commonest malignancies in United States with acute lymphoblastic leukemia alone accounts for about one third of all childhood malignancies. Acute and chronic myeloid leukemias constitute a major

portion of childhood malignancies.[15] Data from developing countries about the incidence of childhood malignancies is much deficient. Relative frequency of aplastic anemia in present study is in close concordance with the results of Bhatnagar et al.[16], however, the frequency of malignant etiology is much higher in our study (52% vs 21%) which is in slight contradiction.

Megaloblastic anemia was the third commonest etiology of pancytopenia in present study. Literature has ample evidence in favour of megaloblastic anemia presenting as pancytopenia. Gomber et al[17] reported a frequency of 11% while Dasgupta[18] reported 47% patients with megaloblastic anemia presented with pancytopenia.

Enteric fever is known to cause bone marrow suppression. Pathophysiology of such bone marrow suppression includes hemophagocytosis and bone marrow necrosis. Other mechanisms include immune hemolysis, disseminated intravascular coagulpathy and hypersplenism. Pancytopenia is a well documented complication of Enteric fever. [15-17]

Sepsis has been reported to cause pancytopenia, a finding that endorses the resulta of present study. Two cases of sepsis resulting in bone marrow necrosis were reported by Garewal et al.[18] Among rare etiologies one patient with dengue fever also presented with pancytopenia, in which case bone marrow biopsy showed a hypocellular marrow resulting from hemophagocytosis.

Infectious causes amounted to 20% in present study. Malaria was found to be an important infective cause of pancytopenia. Existing literature correlates well with this observation. Plasmodium vivax induced hemophagocytosis has been reported to cause pancytopenia.[19] Pathogenetic mechanisms include hemophagocytosis, immune mediated hemolysis, hypersplenism, direct invasion by the parasite and disseminated intravascular coagulapathy. [20-23] Isolated malarial parasite induced leucopenia, although reare has also been reported. [16]

Patients with lysosomal storage disorders have the tendency to develop cytopenias because of bone marrow replacement with storage cells. These patients can have pancytopenia at presentation although common ode of presentation is abdominal distension and viscermegaly.[24] Pancytopenia is usually not a consistent feature and suppression of one or two cell lines is more commonly encountered in patients with lysosomal storage disorders. None of the patient was diagnosed with lysosomal storage disorder in present study.

Pancytopenia is not a rare problem and is frequently encountered in Paediatric patients. Unexplained fever with pallor and bleeding tendency should be viewed with a very high index of suspicion for any of the etiologies of pancytopenia. Appropriate investigations should be initiated based on clinical features and a very low threshold should be kept for bone marrow examination.

CONCLUSION

Malignancy and bone marrow failure were common causes of pancytopenia, while infections and megaloblastic anemia are less frequent but easily treatable and reversible etiologies. Common presentation is with fever, pallor, bleeding tendency and visceromegaly.

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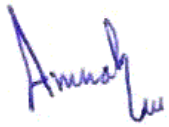
Dr. Amna Tufail Post Graduate Trainee Pediatrics Department, Allied Hospital, Faisalabad	Conceptualization, Data Collection	
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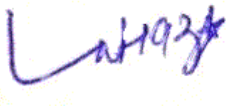
Dr. Imtiaz Ahmad Fellow Paediatric Cardiology The Children's Hospital & The Institute of Child Health, Lahore	Data Collection, Literaure review	
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