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CLINICAL AND HEMATOLOGICAL PROFILE OF HOSPITALIZED CHILDREN OF 3 MONTHS TO 12 YEARS OF AGE WITH BICYTOPENIA OR PANCYTOPENIA

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ABSTRACT

Introduction: Hematological malignancies present as a wide spectrum of clinical manifestations, with overlapping features of infectious and nutritional diseases. Although bicytopenia and pancytopenia are common entities, very few studies have looked into the clinical and hematological profile in children, especially in infective and nutritional causes which are prevalent in tropical countries like India. **Objectives:** To study the clinical and hematological profile (including blood cell indices) of hospitalized children of 3 months to 12 years of age with bicytopenia and pancytopenia. **Methods:** 193 children aged 3 months to 12 years with bicytopenia and pancytopenia were enrolled in the study. Those with previous blood transfusion or already on treatment were excluded. Details were collected as per the proforma regarding complete history and clinical findings. A complete hemogram and peripheral smear was done. Further investigations done as indicated. Data was collated and analyzed. **Results:** 193 children who were studied were treated according to etiology and followed till discharge or death. Analysis showed that the most common hematological finding in bicytopenia is thrombocytopenia with leucopenia and a new hematological parameter immature reticulocyte fraction can play a role in diagnosing aplastic anemia.

KEYWORDS: Details were collected as per the proforma regarding complete history and clinical findings.

INTRODUCTION

Cytopenias are a very common presentation in the paediatric age group. They are very common and encountered in day-to-day practice. Cytopenia is defined as a decrease in one cell line, bicytopenia in two, and pancytopenia as decrease in all three cell lines.[7] There is appreciable overlap between the etiologies and hence, the approach to bicytopenia and pancytopenia and investigations done in such cases are almost the same. The pathogenic mechanisms of bicytopenia or pancytopenia are variable and include a decrease in hematopoietic stem cell production, replacement of marrow by abnormal cells, suppression of growth and differentiation of hematopoietic cells, ineffective hematopoiesis, defective cell formation which is removed by the system, antibody- mediated trapping of cells or destruction of cells by the overactive reticuloendothelial system. The symptoms and signs of bicytopenia and pancytopenia depend upon the duration and severity of suppression of cell lines. Accordingly, they can present with mild pallor to severe anemia requiring transfusion. They can present with fever due to etiology per se or due to infections as a result of low white cell count. They can have petechiae, bruises, mucosal bleeds to life-threatening intracranial bleeds. Children with bicytopenia or pancytopenia can have hepatomegaly, splenomegaly, lymphadenopathy, or bony tenderness at the time of presentation. Bone marrow picture also varies. It can be normocellular with non specific changes to hypercellular as in malignancies. It is usually hypocellular in etiologies causing primary production defects as in aplastic anemia. and can be hypercellular as in leukemias. The etiological factors can be nutritional like Vitamin B12 deficiency or folate

deficiency, infections such as transient suppression of bone marrow with non specific viral infections, dengue fever syndromes, malaria, enteric, scrub typhus, and other causes. Hematological malignancies like leukemias can present as bicytopenia or pancytopenia and marrow failure syndromes like aplastic anemia often present as pancytopenia. Primary or genetic causes include Fanconi's anemia, dyskeratosis congenital, shwachman's syndrome but they are not very common. The cellular and morphological analysis is an integral part of determining the etiology of pancytopenia/bicytopenia.

OBJECTIVE

To study the clinical and hematological profile (including blood cell indices) of hospitalized children of 3 months to 12 years of age with bicytopenia and pancytopenia.

MATERIALS AND METHODS: A prospective observational study was conducted over 18 months in inpatient ward department of Paediatrics, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi in collaboration with hematology department.

Children admitted with bicytopenia or pancytopenia were included in the study. A total of 193 children with bicytopenia and children with pancytopenia were enrolled in the study.

Pancytopenia-[8] was defined as all the three major formed elements of blood (red blood cells, white blood cells, and platelets) are decreased in number, pancytopenia is defined as hemoglobin ≤10gm %, WBC<4000/cu mm, platelets (PC)≤100×10^9/L. Bicytopenia was defined as a decrease in the number of only two of the three cell lines in the blood namely red blood cells, white blood cells, and platelets. Severe Pancytopenia-[8] was defined as hemoglobin ≤7gm %, ANC < $0.5 \times \times10^9$/l, and Platelet Count (PC)≤20×10^9/l.

For all the children who were included in the study, a detailed clinical history was taken for fever, pallor, skin rash, mucosal bleeds like epistaxis, gum bleeding, melena, hematochezia, and hematemesis. A clinical examination was done to detection of pallor, jaundice, rash, hepatosplenomegaly, lymphadenopathy, sternal tenderness, skin bleeds, and joint swelling. A complete hemogram along with a peripheral smear was done in all children. Following investigations were done depending on clinical presentations and hemogram findings. Blood culture, malaria antigen ,peripheral smear for malaria parasite, serum widal, serum folate level, serum B12 level, dengue serology/NS1 antigen, ANA profile kidney function test, liver function test and bone marrow examination MCV, MPV, PDW, PLC-R, and IRF were recorded using 6 part autoanalyzer (if child had to be transfused urgently, a sample for hematological analysis was collected before transfusion). The children were treated according to the etiology using standard protocols. The children were followed till discharge or death and all the clinical findings, laboratory investigations, final diagnosis, major events, and outcomes were recorded in the preset case record proforma.

RESULTS

One hundred fifteen children with bicytopenia and seventy eight with pancytopenia were enrolled in the study.

Demographic profile in study population (n=193)

The mean age of the bicytopenic children was (7.25±3.64) whereas the mean age of children with pancytopenia was (6.33±5.40).

The age group-wise distribution of children with bicytopenia and pancytopenia is shown in table 1. Children in the age group (>5 years)most commonly presented with bicytopenia and in the age group (1 to 5 yr)pancytopenia respectively.

In children with bicytopenia male to female ratio was (1.3:1) and in children with pancytopenia it was (1.22:1).

Fever was the most common presenting feature present in 87.82 % of children with bicytopenia and 88.46 % of children with pancytopenia. The bleeding manifestation was the symptom in 40.86% of bicytopenic and 74.35% of pancytopenic children. Abdominal pain was seen in 33% of bicytopenic patients. Tiredness/Weakness was present in 56.41% of children with pancytopenia.

The most common physical finding was hepatomegaly, present in54.78 % of children with bicytopenia followed by petechiae in 36.52%. The other finding on physical examination were Pallor, Splenomegaly, and Lymphadenopathy present in 22.6%, 19.13% & 6.95% respectively.

In children with pancytopenia, the most common physical finding was Pallor present in 85.89% of children followed by petechiae present in 71.7% of children. Other findings were Hepatomegaly, Splenomegaly & Lymphadenopathy present in 28.2%, 20.51%, and 7.69% respectively.

A total of 56 of children had anemia, 99 children had thrombocytopenia and 75 children had leucopenia in bicytopenic children.

All children in pancytopenia group had anemia, thrombocytopenia, and leucopenia. Blasts were present in 11 children with bicytopenia and 3 children with pancytopenia.

There were 34.78% of children with anemia and thrombocytopenia, 13.91% with anemia with leucopenia, and 51.3 % with thrombocytopenia with leucopenia in children with bicytopenia.

DISCUSSION

Our prospective study enrolled 193 out of 279 screened children with bicytopenia or pancytopenia and documented their etiology, clinical feature, and outcome.

In our study there were 65 male and 50 female children with bicytopenia, with a male to female ratio of 1.3:1. There was a slight male preponderance in children with bicytopenia in our study. This result is similar to the m:f ratio of 1.6:1reported by Gupta A et al.[9]

Sixty-four percent of our children with bicytopenia were greater than 5 years and 29%were in age group1-5 years. Small percentage (7%) of children were in the age group 3 months to 1 year. Bicytopenia was more common between 1 to 12 years. It was rare in infancy. On the contrary, Gupta A et al.[9] in their study reported bicytopenia to be more common in age group 10-14 years of age. This difference may be explained by referral bias and local epidemiology as malaria was reported as the most common cause of bicytopenia by the authors.

In our study, the common presenting symptoms in children with bicytopenia were fever, followed by bleeding manifestations, abdominal pain, and tiredness. Other less common symptoms were joint and bone pains and jaundice. Fever was also reported as most common presenting symptom by Gupta A et al.[9] and Shano Naseem et al.[11] Gupta A et al found fever as presenting symptom in 100 % of the patient whereas in Naseem et al. found fever in 69.2% In our study, common clinical signs in children with bicytopenia were hepatomegaly, present in 55% of cases followed by petechiae in 36%, pallor in 22.6%, and splenomegaly in 19.13% of cases. In comparison to Naseem S et al study, the incidence of pallor was 40.9%, hepatomegaly 69.2%, and splenomegaly in 60.5% of the cases . In the study by Gupta et al.[9] pallor was present in 90% of cases of bicytopenia. The incidence of pallor is lower in our study. This may be due to different etiology prevalent in different areas. In their study anemia with thrombocytopenia was a commonest hematological presentation in children with bicytopenia.

In our study, out of the all children admitted with bicytopenia, 52% had leucopenia and thrombocytopenia, almost 35% has anemia and thrombocytopenia and 14% of children had anemia and leucopenia. So, the most common bicytopenia in our study was leucopenia and thrombocytopenia. This is contrary to the study done by Shano Naseem et al.[11] in which, the most common bicytopenia were anemia and thrombocytopenia. The reason for this disparity is probably Naseem S et al.[11] conducted the study in the pediatric hematoncology unit and the children referred for bone marrow examination having bicytopenia or pancytopenia were included. The etiological profile in children with bicytopenia differs in both the studies. Most common cause of bicytopenia in our study is dengue fever which seldom requires bone marrow examination. The second most common cause of bicytopenia in our study is enteric fever. Acute lymphoblastic leukemia is the most common malignant cause of bicytopenia.

In our study, the most common cause in children with leucopenia and thrombocytopenia was dengue fever present in 33% of cases followed by enteric feverin 24% and septicemia in 13%. Infections were the cause of leucopenia with thrombocytopenia in almost all children. So, if child presents with leucopenia and thrombocytopenia, infective etiology should be investigated first. in our study, the most common causes in children with anemia and thrombocytopenia were enteric fever and acute lymphoblastic leukemia. In the study done by Gupta A et al.[9] the mostcommon finding was anemia with thrombocytopenia present in almost 93% of children with bicytopenia. It could be due to differences in etiologies prevalent in the area of the study.

In our study, almost 75% of cases of bicytopenia are due to infectious etiology, of the remaining majority are due to malignant etiology, and very few are due to non-malignant non-infectious etiology. Most common infections causing bicytopenia were dengue fever followed by enteric fever and septicemia.

In our study, the common malignancies presented with bicytopenia are ALL followed by NHL. Almost 60% of the acute leukemias presented as bicytopenia (anemia with thrombocytopenia) rather than pancytopenia.

In our study, the non malignant non-infective etiology causing bicytopenia were megaloblastic anemia, hemolytic anemia, SLE, HLH, and ITP.

Our study results were similar to the study done by Gupta A et al.[9] in which 2/3rd of cases of bicytopenia were due to infective etiology followed by malignancies, though the commonest infection in our study was dengue fever followed by enteric fever whereas in the study by Gupta A et al commonest infective etiology was malaria. In a study done by Naseem S et al.[11] in which the commonest cause of bicytopenia was malignancy and the commonest malignant condition causing bicytopenia was acute lymphoblastic leukemia. Idiopathic Thrombocytopenic Purpura is the second most common cause. This may be because in the study by Naseem S et al only those cases who were referred for bone marrow examination were included.

In our study, almost 80% children with bicytopenia recovered. Of the remaining 10% majority of children are on regular treatment and follow-up as they have malignancy. Around 10% children with bicytopenia died.

A total of 78 children with pancytopenia were enrolled in this study out of which 43 were male children and the rest were female children, with a male to female ratio of

1.28:1. There was male preponderance in children with pancytopenia in this study. This result was similar to the study done by Menon S et al.[13] and Bhatnagar S K etal.[12] in pediatric pancytopenic patients.

In children with pancytopenia 50% of children were in the age group 1-5 years. Of the remaining, 42% are in the age group of greater than 5 years and the rest are in age group 3 months to 1 year. In this study, pancytopenia was common between 1 to 5 years of age. This result is similar to the study done by Chand R et al.[14] in children with pancytopenia in which 40.47% of children were between 1 year to 5 years.

In this study, the most common presenting symptoms in children with pancytopenia were fever 89% followed by bleeding manifestations 74.35% (petechial rashes, gum bleeding, epistaxis, and Malena) and tiredness. Joint pains/ bone pains, abdominal pain, and jaundice were less common, which is similar to studies done by Gupta A et al. and Naseem S et al. Gupta A et al. found fever in 100% of children with pancytopenia wheras Naseem S at al. found fever in 65.5% of children with pancytopenia

In this study bleeding manifestations were the second most common presenting symptom. Bleeding manifestations were more common in pancytopenia than bicytopenia in our study.

In this study, 90 % of children with pancytopenia had pallor, 71 % of children had petechiae, 28% had hepatomegaly and 20 % had splenomegaly. This result is similar to the study done by Chand R et al in children with pancytopenia in which all children with pancytopenia had pallor. Pallor was the most common physical finding in children admitted with pancytopenia.

In our study, 50% of cases of Pancytopenia are due to infectious etiology, 20% due to megaloblastic anemia, 17% due to aplastic anemia, and the remaining are either dueto malignant etiology or undiagnosed.

In our study, the common infections causing pancytopenia are septicemia 22%, enteric fever 13%, malaria 7%followed by dengue fever, Kala Azar, and scrub typhus. Thus, the most common cause of pancytopenia in our study is septicemia.

In our study, the common non-malignant non-infectious etiologies causing pancytopenia were megaloblastic anemia (20.5%)followed by aplastic anemia(18%). Non-malignant non-infectious etiology was the second common cause of pancytopenia in our study. In our study, common malignancy causing pancytopenia is acute lymphoblastic leukemia.

Many studies have been done in various parts of the world on pancytopenia and each study has given different underlying etiology for pancytopenia. Naseem S et al.[11] from India in their study on pancytopenia children found that aplastic anemia was the most common etiology causing pancytopenia, followed by acute leukemia. In this study, aplastic anemia is present in 17% of pancytopenic children, also acute leukemia is the most commonest malignant etiology for pancytopenia.

Bhatnagar S K et al.[12] from India in their study on pancytopenia children found that Megaloblastic anemia was the most common etiology causing pancytopenia, followed by infections and acute leukemia. They found enteric fever as the commonest infectious cause. Most common cause of pancytopenia in our study is septicemia. Megaloblastic anemia is the most common non-infective, non-malignant cause of pancytopenia in our study closely followed by aplastic anemia. Most common malignancy presenting with pancytopenia in our study is acute lymphoblastic leukemia. Gupta A et al.[9] from India in their study in pancytopenia children found that aplastic anemia was the most common etiology causing pancytopenia, followed by acute leukemia. They found Infections as the third common etiology of pancytopenia, of which Kala-azar is common.

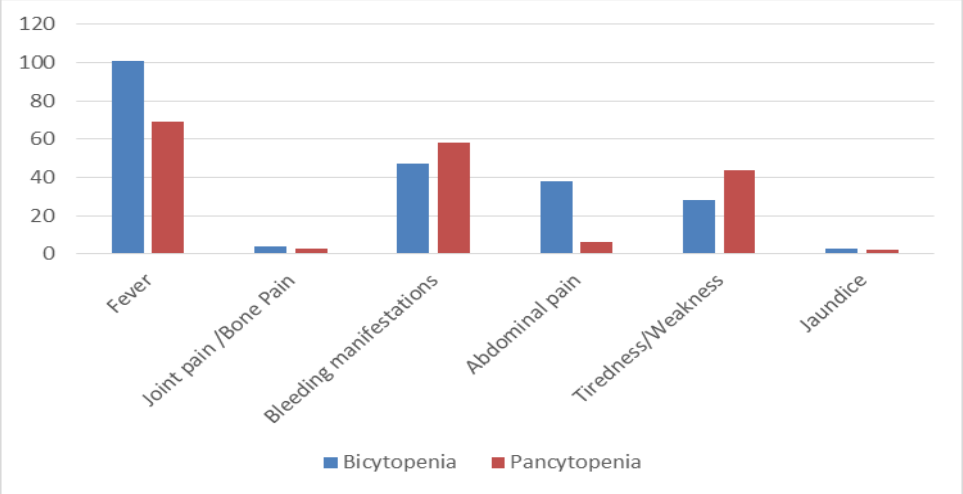
In our study, the common causes of pancytopenia were septicemia in 20% of cases followed by megaloblastic anemia present in 20.5% of cases, aplastic anemia in 17%. In our study, severe pancytopenia is present in 18 % of children. The most common cause of severe pancytopenia is aplastic anemia contributing almost half of cases of severe pancytopenia. Similar findings were observed by Bhatnagar S K et al.[12] In their study aplastic anemia was present in 52% of cases with severe pancytopenia.

In our study, almost 75% of patients who presented with pancytopenia recovered completely, 15% of patients died, and the remaining are on regular treatment and follow-up or lost to follow-up.

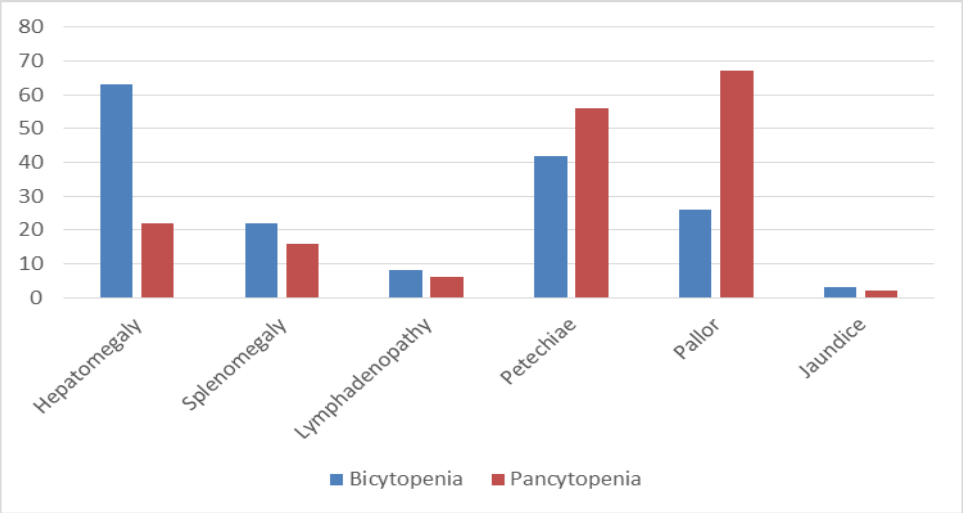
In cases of septicemia, almost half of the children who presented with pancytopenia died due to septic shock and DIC, and the remaining half recovered. In cases of septicemia if a child presents with pancytopenia the mortality is high. Of the total deaths in pancytopenia, 75% of deaths are due to septicemia, remaining 25% are death due to aplastic anemia and acute leukemia. The death rate is more in children with pancytopenia than in children with bicytopenia.

Table 1.

Age group	Bicytopenia(115)	Pancytopenia(78)	Total(193)
3 months to 1 year	8(6.95%)	11(14.10%)	19(9.84%)
1 year to 5 years	33(28.69%)	34(51.28%)	67(34.71%)
>5years	74(64.34%)	33(42.39%)	107(55.44%)



Symptoms	Bicytopenia (n =115)	Pancytopenia(n=78)
Fever	101(87.82%)	69(88.46%)
Joint pain /Bone Pain	4(3.47%)	3(2.63%)
Bleeding manifestations	47(40.86%)	58(74.35%)
Abdominal pain	38 (33.0%)	6(7.6%)
Tiredness/Weakness	28(24.34%)	44(56.41%)
Jaundice	3(2.60%)	2(2.56%)



Physical Examination findings	Bicytopenia (n =115)	Pancytopenia (n=78)
Hepatomegaly	63(55.78%)	22(28.20%)
Splenomegaly	22(19.13%)	16(20.51%)
Lymphadenopathy	8(6.95%)	6(7.69%)
Petechiae	42(36.52%)	56(71.7%)
Pallor	26(22.60%)	67(85.89%)
Jaundice	3(2.60%)	2(2.56%)

CONCLUSION

Our study confirms that infective etiology is the most common cause of bicytopenia or pancytopenia. In children with bicytopenia most common infection is dengue fever, followed by enteric fever and septicemia. In children with pancytopenia most common infective etiology is septicemia.

The most common hematological finding in children with bicytopenia is thrombocytopenia with leucopenia, and dengue fever is the most common cause in this group.

A new hematological parameter, Immature Reticulocyte Fraction, can play a role in diagnosing aplastic anemia.

As mortality is relatively high in children with pancytopenia, irrespective of the cause, early referral, rapid diagnosis, and prompt treatment are required to reduce the adverse outcome.

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