**Original article:**

# Clinicopathological and etiological spectrum of bicytopenia/pancytopenia in children : A five year experience in a tertiary health care centre

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**Abstract**

**Background –** Pancytopenia & bicytopenia are commonly seen in pediatric age group in India. The etiology varies from nutritional anemia, aplastic anemia to marrow infiltration by leukemias. Early detection of these conditions can prevent the associated complications with bicytopenia/pancytopenia in pediatric age group.

**Aims-** To evaluate the different etiological factors associated with bicytopenia/ pancytopenia in pediatric age group.

**Material & methods -** All patients age 2 months to 16 year having pancytopenia/ bicytopenia (2012-2016) were included in this study and detailed clinical data, hematological investigations including complete hemogram ,peripheral smear examination , bone marrow aspiration & biopsy were done.

Results-Among 107 cases evaluated, 59 cases had pancytopenia & 48 had bicytopenia. The most common clinical presentation was fever (45.8%) followed by generalized weakness & bleeding. On physical examination most common clinical finding was splenomegaly followed by hepatomegaly/ lymphadenopathy. Megaloblastic anaemia was the most common etiology in pancytopenia followed by acute lymphoblastic leukemia (27.1%) in bicytopenia.

**Conclusion -** This study emphasizes on identifying easily treatable cause such as megaloblastic anemia, other nutritional anemia & infections presenting with pancytopenia /bicytopenia. Careful evaluation of biocytopenia in pediatric patients for acute leukemia is important as they respond very well to therapy.

**Key words** –Pancytopenia ,Bictytopenia ,Splenomegaly ,Lymphadenopathy , Megaloblastic anaemia, Acute lymphoblastic leukemia

## Introduction:

Pancytopenia is defined as reduction of all the three formed elements of blood below the normal reference range, bicytopenia is decrease in any of the two cell line .[(1, 2)] Both bicytopenia and pancytopenia are commonly seen in pediatric age group. The etiological spectrum in children varies widely ranging from transient marrow viral suppression to marrow infiltration by hematological & non hematological malignancies. Pancytopenia/bicytopenia may also caused due to secondary to certain drugs, radiotherapy / chemotherapy used for different malignancies.

Bone marrow aspiration & biopsy studies are extremely useful in the evaluation of bicytopenia & pancytopenia. Depending upon the etiology, bone marrow finding may vary from hypocellular as in aplastic anemia to normocellular with non specific changes or hypercellular being replaced entirely by malignant cells.[(3)]

The aim of our study is to evaluate the different etiological factors associated with bicytopenia / pancytopenia in children.

**Material and methods:**

This retrospective study was conducted in a tertiary level hospital in Central India .Clinical data of children under 16 yrs of age with bicytopenia/ pancytopenia was retrieved & analysed over a period of 5 years (2012-2016). Pancytopenia was defined as hemoglobin ≤ 10 gm/dl , platelet count <1 lakh / $mm^3$and absolute neutrophil count ≤ 1.5 $x10^9$/L

Bicytopenia was defined as either two of these cytopenias.

Detailed history including symptoms & clinical signs like organomegaly, lymphadenopathy, hematological parameters including CBC, peripheral smear findings , bone marrow aspiration & biopsy findings were noted.

The exclusion criterias of the study were:

A Known cases of malignancies on chemotherapy/ radiotherapy .

B Hemodiluted bone marrow aspiration smears .

**Results:**

Out of 153 children presenting with pancytopenia/ bicytopenia, 46 cases were excluded because of hemodiluted smears and known cases of malignancies on chemotherapy / radiotherapy . Among 107 cases evaluated 59 cases had pancytopenia & 48 were of bicytopenia . Age of these patients ranged between 2 months -16 yrs of age with a male female ratio of 1.5:1.

Most common clinical presentation was fever accounting for (41.7%) in bicytopenia & 42.4% in pancytopenia. Other common symptoms were generalized weakness & bleeding.(Table -1)

On physical examination splenomegaly was most common accounting for 41.7 % in bicytopenia & 40% in pancytopenia . It was followed by hepatomegaly & lymph adenopathy.(Table -1)

Out of 48 cases of bicytopenia, hematologically, anemia & thrombocytopenia was the most common form of bicytopenia seen in 42 cases (87.5%) followed by anemia & neutropenia in 04 cases (8.3%) & thrombocytopenia & neutropenia in02 cases (4.2%).Circulating blasts were seen in 37.5% cases of bicytopenia & 18.6% cases of pancytopenia. (Table -2 )

Based on peripheral blood & bone marrow aspiration & biopsy findings, etiological spectrum was divided into 2 categories non malignant & malignant.(Table -3)

The MC non malignant cause for bicytopenia was megaloblastic anemia (18.8%) followed by iron deficiency (12.5% ) & mixed nutritional anemias (10.4%)

Out of 3 cases of infections 02 cases were of tuberculosis , 01 case of sepsis and 01 case of rare storage disorder – Niemann picks disease was also found.

The MC malignant cause for bicytopenia was acute lymphoid leukemia (27.1%) followed by acute myeloid leukemia (6.2%) and 01 case of spillover of neuroblastoma in bone marrow was also found.

**Pancytopenia :**

The MC non malignant cause for pancytopenia was megaloblastic anemia (45.8%) followed by aplastic anemia (11.9%) & mixed nutritional anemia (6.8%).



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Out of 3 cases of infections 01 case of leishmaniasis ,01 case of sepsis & 01 case of enteric fever was found.

The MC malignant cause for pancytopenia was acute lymphoid leukemia (18.6%) .

**Discussion:**

After exhaustive research in literature, we found, few studies published on pancytopenia/ bicytopenia in children.

Pancytopenia is common hematological entity noticed in day to day clinical practice &studied in patients presenting with fever, pallor & bleeding tendency.

Pancytopenia is a reduction of all the threeseries of formed elements of blood erythrocytes, leucocytes & platelets. It is not disease but triad of findings that may result from a number of disease processes.[5]

Pancytopenia can result from either a failure of production of hematopoietic progenitors as in aplastic anemia or destruction of cellular element due to infection, immune mediated damage or hypersplenism.[7]

The common clinical presentation in our study was fever ,generalised weakness, bleeding .On physical examination most common clinical finding was splenomegaly followed by hepatomegaly/ lymphadenopathy.Our results were comparable with previous studies.[3,4,6]In cases of bicytopenia, anemia & thrombocytopenia was the most common condition followed by anemia & neutropenia which is similar to study by Naseem et al. [3]

Megaloblastic anemia due to deficiency of Vitamin B12 or folic acid is a well recognized & established cause of cytopenias.[8]In our study, megaloblastic anemia documented for 45.8% cases of pancytopenia & 18.8% cases of bicytopenia. Various studies involving pediatric age group have documented pancytopenia in megaloblastic anemia ranging from 13% -28% (3,4,5,6). Ineffective erythropoiesis, leucopoiesis & thrombopoiesis due to increased programmed cell death in absence of vitamin B12 or folic acid & decreased survival of precursors in peripheral blood are most commonly implicated in causing pancytopenia in megaloblastic anemia .[9]Other than megaloblastic anemia, mixed nutritional deficiency anemia/ iron deficiency anaemia was found in 11.8% cases of pancytopenia. Memon et al [5] found 8.69% cases of mixed nutritional /iron deficiency anemia. This difference may be due to geographic variation ,sample size, nutritional status .

In our study, aplastic anemia was the II MC cause of pancytopenia, where other studies like Memon[5], Gupta[6]&Naseem etal[3]found aplastic anemia to be the most common cause of pancytopenia in children. Epidemiologically, aplastic anemia has a pattern of geographic variation with high frequency in the developing world than in the industrialized West.[10] Exact etiology of aplastic anemia in still unknown but on autoimmune mechanism has been suspected from positive responses to non transplant therapies & laboratory data. European studies have confirmed & quantified medical drugs as risk for thedevelopment of marrow failure .[11-12]

Out of 6 cases of infections we found 3 cases of enteric fever,1 case of TB, 01 of sepsis ,01 of leishmaniasis .In enteric fever pancytopenia is caused by varied mechanisms , bone marrow may undergo histiocytic hyperplasia along with hemophagocytosis or complete necrosis. Immune mediated hemolysis ,leucopenia, hypersplenism & transient disseminated intravascular hemolysis are other contributory mechanisms .[13,14 ]Varying degrees of cytopenias have been reported in many other series on enteric fever.[15-17]

In this study, most common malignant cause of pancytopenia/ bicytopenia was found to be acute lymphoblastic leukemia (ALL) accounting for 27.1% cases of bicytopenia & 18.6% cases of pancytopenia.This was comparable with study by Naseem et al who reported acute leukemia associated with bicytopenia in 66.8% cases & associated

with pancytopenia in 26.6 % cases. Acute lymphoblastic leukemia are diagnosed in the United state at a rate of approximately 2500 cases per annum accounting for about one third of all the cases of childhood cancers. [18]

Timely diagnosis of ALL is very important as response to treatment is excellent in children.

In our study, other than the common causes of pancytopenia like megaloblastic anemia ,acute leukemia, mixed nutritional anemia & aplastic anemia ,other causes including leishmaniasis , myelodysplastic syndrome & neuroblastoma was also found. Most common condition causing bicytopenia was acute leukemia followed by megaloblastic anemia & iron deficiency anemia . Other causes of bicytopenia like storage disorder, infections & neuroblastoma were also found.

Megaloblastic anemia was the most common cause of pancytopenia in our study .With availability of good automated cell counters, megaloblastic anemia can be easily diagnosed using various indices like mean corpuscular volume, mean corpuscular hemoglobin .These patients respond immediately with Vitamin B12/ folic acid therapy. Early detection of this condition will prevent the associated complications & have impact on their morbidity.

Cases of bicytopenia should be evaluated with equal importance as they had a strong association with malignancy i.e. acute lymphoblastic leukemia as compared to pancytopenia in this study. Therefore it is very important to know the exact etiology for treating physician as it affects the treatment, prognosis & further evaluation of the pediatric patients.

| | Bicytopenia | Pancytopenia |
|---|---|---|
| Total cases | 48 | 59 |
| Fever | 20( 41.7 %) | 25 (42.4%) |
| Petechial rash | 03 (06.2 %) | 05 (8.5%) |
| Bleeding | 06 (12.5%) | 06 (10.1%) |
| Generalized weakness | 13 (27.0%) | 12 (20.4%) |
| Hepatomegaly | 13 (27.0%) | 17 (28.8%) |
| Splenomegaly | 20 (41.7%) | 23 (40%) |
| Lymphadenopathy | 12 (25.0%) | 10 (16.7%) |

Table -1 :- Frequency of clinical feature in cases of bicytopenia and Pancytopenia .



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| | Bicytopenia | Pancytopenia |
|---|---|---|
| Total cases | N =48 | N=59 |
| Hb< 10 gm % | 46(95.8%) | 59 (100%) |
| ANC < $1.5x10^9$/ litre | 06(12.5%) | 59 (100%) |
| Platelet < 1 lakh/ $mm^3$ | 44 (91.6%) | 59 (100%) |
| Blasts | 18(37.5%) | 11 (8.6%) |

Table 2 – Peripheral blood findings with bicytopenia& pancytopenia in children

| | | Bicytopenia | Pancytopenia |
|---|---|---|---|
| **Total no of cases** | | **N= 48** | **N= 59** |
| Non Malignant | | | |
| 1 | Aplastic anaemia | | 07 (11.9%) |
| 2 | Megaloblasticanaemia | 09(18.8%) | 27 (45.8%) |
| 3 | Mixed nutritional | 05(10.4%) | 04 (6.8%) |
| 4 | Iron deficiency anaemia | 06(12.5%) | 03 (5.0%) |
| 5 | Infection | 03 (6.2%) | 03 (5.0%) |
| 6 | Storage disorder | 01 (2.1%) | |
| 7 | Immune Thrombocytopenia | 03(6.2%) | |
| 8 | Hypersplenism | 01 (2.1%) | |
| 9 | No cause identified | 01 (2.1%) | |
| **Malignant** | | | |
| 1 | Acute Lymphoblastic Leukemia (ALL) | 13(27.1%) | 11 (18.6%) |
| 2 | Acute Myeloblastic Leukemia (AML) | 03(6.2%) | 01 (1.7%) |
| 3 | Lymphoma Spill over | 02 (4.2%) | 01 (1.7%) |
| 4 | Neuroblastoma | 01 (2.1%) | 01(1.7%) |
| 5 | MDS | | 01 (1.7%) |

Table -3 Etiology of bicytopenia & Pancytopenia



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| Author | Year | Place | Study population | No of cases | Duration of study | M/C cause | II M/C cause | M/C Clinical findings |
|---|---|---|---|---|---|---|---|---|
| Bhatnagar etal [4] | 2005 | India | Children | 109 | 24 Month | Megaloblastic anaemia (28%) | Aplastic anaemia Infection (21% each) | Bleeding ,splenomegly, Hepatomegaly |
| Memon et al [5] | 2008 | Pakistan | Children | 230 | 17 months | Aplastic anaemia (23.9%) | Megaloasticanaemia leukemia (13% each) | Pallor,fever ,Petechial rash splenomegly |
| Gupta etal [6] | 2008 | India | Children | 105 | 30 Months | Aplastic anaemia (43%) | Acute leukemia (25%) | Fever,Pallor ,bleeding |
| Naseem etal [3] | 2010 | India | Children | 139 | 24 months | Aplastic anaemia (33.8%) | Acute leukemia (26.6%) | Fever, Pallor |
| Present study | 2017 | India | Children | 59 | 60 months | Megaloblastica naemia (45.8%) | Acute leukemia (18.6%) | Fever ,splenomegly, Hepatomegaly weakness |

Table -4 : Review of studies on Pancytopenia

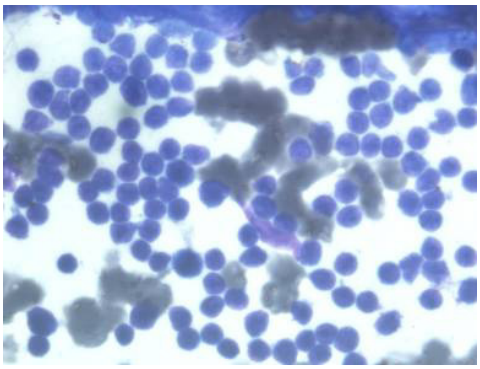

Figure-1: Bone marrow aspirate of Megaloblastic anaemia showing megaloblasts with sieve like chromatin (Giemsa, X1000).

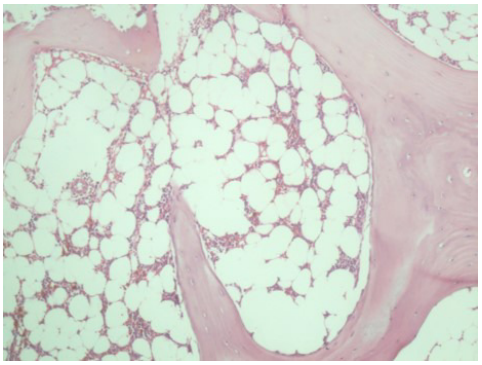

Figure-2: Bone marrow aspirate of Acute lymphoblastic leukemia showing lymphoblasts with coarse chromatin and scanty cytoplasm (Giemsa, X1000).

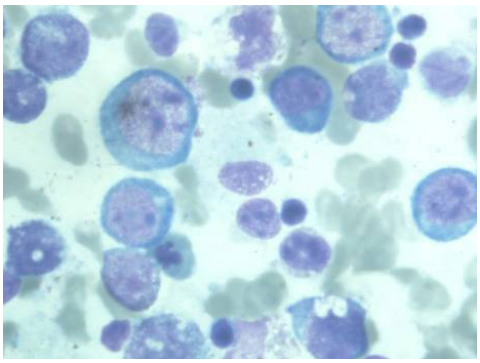

Figure-3: Bone marrow biopsy of Aplastic anaemia showing hypocellular marrow spaces , haematopoietic cells replaced by adipose tissue. (H&E, X 400).

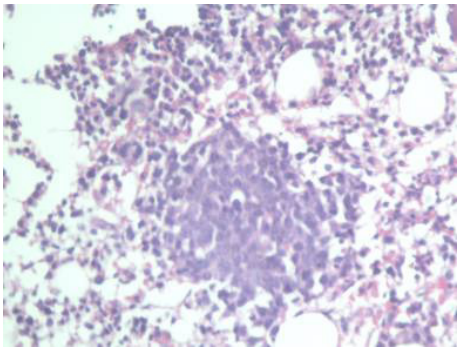

Figure-4: Bone marrow biopsy of Neuroblastoma showing atypical small round cells forming rosette (H&E, X100)



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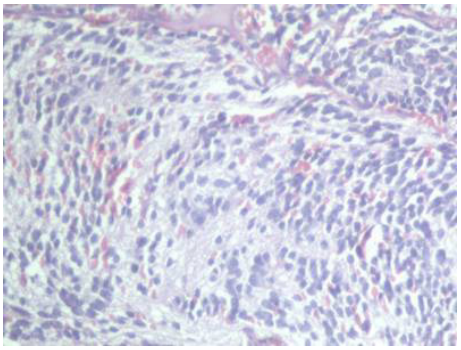

Figure-5: Bone marrow biopsy of Lymphoma spill over showing focal collection of atypical lymphoid cells (H&E, X400) .

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