

## Original Research Article

# Clinic-etiological profile of pancytopenia in children: a tertiary care center based study of Kumaun region, India

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### ABSTRACT

**Background:** Pancytopenia is not a disease entity but a triad of findings in which all blood cell lineages i.e leukocytes, erythrocytes and platelets are reduced in blood. It is consequence of various medical conditions. Present study was conducted to assess the etiology, clinical profile and bone marrow morphology of pancytopenia.

**Methods:** A cross sectional prospective study was carried out among 42 children of age between 1 to 15 year with pancytopenia. Blood samples of the patients were analyzed for complete blood count and peripheral smear along with presence and absence of immature cells and abnormal cells. In bone marrow examination, morphology of all cell's lineage, cellularity, parasite and abnormal cells were scrutinized. Trephine biopsy was done if indicated. Special investigations were done to confirm the diagnosis.

**Results:** Among the 42 cases studied, age of the patients ranged from 1 to 15 years with a slight male predominance. Most of the patients presented with generalized weakness and weight loss and fever. The commonest physical finding was pallor, followed by splenomegaly and hepatomegaly. The commonest cause for pancytopenia was megaloblastic anemia. Among the non-haematological causes kala azar 5 (11.9%) is the leading cause in this study.

**Conclusions:** The present study concludes that detailed primary haematological investigations along with bone marrow examination in pancytopenic patients are helpful for diagnosis and management. This study also suggests that megaloblastic anaemia, dimorphic anaemia and kala-azar should also be included in differential diagnosis of pancytopenia in this geographical area.

**Keywords:** Bone marrow, Megaloblastic anaemia, Pancytopenia, Pallor

### INTRODUCTION

Pancytopenia is an important clinico-hematological entity encountered in our day-to-day clinical practice. Pancytopenia is not a disease entity but a triad of findings in which all blood cell lineages i.e leukocytes, erythrocytes and platelets are reduced in blood.<sup>1</sup>

Pancytopenia was defined as haemoglobin <10 g%, total white cell count < 4.0 x 10<sup>9</sup>/L, absolute neutrophil count (ANC) < 1,500/ $\mu$ l, and platelet count < 100,000/ $\mu$ l.

Bicytopenia was a decrease in any of the two cell lines. Severe pancytopenia was defined as haemoglobin < 7 g%, ANC < 500/ $\mu$ l, platelet count < 200,00/ $\mu$ l, and reticulocyte count <1%.<sup>2</sup>

Presenting symptoms are usually attributable to anaemia, leucopenia or thrombocytopenia. Anaemia leads to fatigue, dyspnoea and cardiac symptoms. Thrombocytopenia leads to bruising, mucosal bleeding and neutropenia to sharply increased susceptibility to infection.<sup>3</sup> The common clinical manifestations of

pancytopenia are usually fever (86.7%), fatigue (76%), dizziness (64%), weight loss (45.3%), anorexia (37.3%), night sweats (28%), pallor (100%), bleeding (38.7%), splenomegaly (48%), hepatomegaly (21.3%), and lymphadenopathy (14.7%).<sup>4</sup>

The aetiology of pancytopenia varies widely in children, ranging from transient marrow suppression due to viral infection to marrow infiltration by life-threatening malignancy. These may also be caused iatrogenically, secondary to certain drugs, chemotherapy or radiotherapy for malignancies.<sup>5</sup>

The bone marrow picture may vary depending on the aetiology, from normocellular with non-specific changes to hypercellular being replaced completely by malignant cells. According to etiology, degree and duration of the impairment, clinically these cytopenia can lead to fever, pallor, infection, or serious illness and death. Knowing the exact aetiology is important for specific treatment and prognostication.

Marrow cellularity and composition in cases of pancytopenia differ in relationship to underlying pathological condition. The marrow is generally hypocellular in cases of pancytopenia caused by a primary production defect.

Cytopenia resulting from ineffective haematopoiesis, increased peripheral utilization or destruction of cells, and bone marrow invasive processes are usually associated with a normocellular or hypercellular marrow.<sup>6</sup>

It is recommended that bone marrow aspiration and biopsy be done simultaneously in cases of pancytopenia. Aspiration smears are superior for morphological details while biopsy provides a more reliable index of cellularity and often reveals bone marrow infiltration, fibrosis and granulomas.<sup>7</sup>

Although pancytopenia is a common clinical finding with extensive differential diagnosis, there is a paucity of data on children. There is a relatively little discussion of this abnormality in literature, although there have been several studies of the aetiopathogenesis of pancytopenia in adults but there is the lack of data on pancytopenia in paediatric age group, especially with regards to clinical and etiological findings, in kumaun region of north India.<sup>8,9</sup> This study has been undertaken to identify easily treatable and reversible causes of pancytopenia.

## METHODS

This was a Prospective cross-sectional study, conducted at the Department of Pediatrics, Government Medical College, Haldwani, Uttarakhand from February 2016 to November 2016. All the indoor children, admitted through OPD or emergency who meets the following criteria, were enrolled for the study.

### **Inclusion criteria**

- Children between 1 year to 15 year of age
- Having blood investigation report of hemoglobin (Hb) less than 10 gm/dL, total leukocyte count (TLC) less than 4000/cumm and platelet count less than 150000/cumm.
- Gave informed consent.

### **Exclusion criteria**

- Children of aged less than 1 year or more than 15 year
- Diagnosed cases of aplastic anemia and leukemia,
- History of recent blood transfusion
- Receiving chemotherapy and radiotherapy
- Not give consent

After taking informed written consent from parents/guardians, patients were enrolled into study. Detailed history and clinical examination were carried out.

Various clinical features like age at presentation, drug history, fever (>98.6°F), visceromegaly including hepatomegaly (if liver palpable >2cm below costal margin), splenomegaly (if spleen palpable below left costal margin) and lymphadenopathy (if cervical lymph nodes >1cm large, axillary lymph nodes >1 cm large and inguinal lymph nodes >1.5 cm large) on clinical examination, bleeding manifestations in the form of gum bleed, epistaxis, petechial rash, pallor, joint pains and bone pains was confirmed on history and clinical examination.

All relevant investigation was done including blood complete picture, peripheral film, Reticulocyte count, MP smear, Typhi dot, Widal Test, blood culture, lymph node biopsy and bone marrow aspiration and bone marrow biopsy. For the diagnosis of nutritional anaemia, serum iron, serum ferritin, vitamin B12 and folic acid levels were noted.

The investigative workup was directed by the suspected underlying pathology. In cases of kala azar, K39 antigen tests, splenic aspirates and cultures for *Leishmania donovani* bodies were carried out. Similarly, in other conditions such as typhoid, sepsis, dengue, typhus, HIV, Hepatitis B, Hepatitis C, Rheumatoid, SLE, malignancy and TB appropriate tests were done to confirm the diagnosis.

## RESULTS

During the study period of 9 months total number of admissions in the children hospital in the age group 1-15 year was 1352 and total numbers of pancytopenia cases were 42 making the incidence 3.10%.

**Table 1: Distribution of patient according to gender and age.**

Age	Male	Female	Total n=42
1 to 5 year	11	6	17
5 to 10 year	8	7	15
10 to 15 year	6	4	10
Total	25	17	42

Out of 42 patients, 25 (59.52%) were males and 17 (40.47%) females, with male to female ratio of 1.47:1 (Table 1), their ages ranged from one year to 14 years. Maximum number of patients 17 (40.47%) were in the age group of 1 year to 5 years, followed by 15 (35.71%) in the 6 to 10 years age group while minimum number 10 (23.80%) were those exceeding 10 years of age (Table 2), all age group had a male predominance.

**Table 2: Aetiology of pancytopenia (N = 42).**

Diagnosis	n	%
Megaloblastic anaemia	8	19.0
Megaloblastic anaemia with iron deficiency	6	14.2
Aplastic anaemia	4	9.52
Acute leukaemia	6	14.2
Kala Azar	5	11.9
Lymphoma	3	7.14
Septicaemia	2	4.76
Malaria	1	2.38
Typhus fever	2	4.76
HIV	1	2.38
Thalassemia major with hepatitis C	1	2.38
Miscellaneous	3	7.14
Total	42	

Table 2 shows the aetiology of cases with pancytopenia. Megaloblastic anaemia was seen in 8 (19%) cases – being the most common cause of pancytopenia. Dimorphic anaemia 6 (14.2%) is a second most common cause of anaemia.

**Table 3: Clinical profile of pancytopenia children.**

Clinical feature	n	%
Generalized weakness	38	90.4
Dyspnoea	7	16.67
Fever	29	69.04
Bleeding manifestation	14	33.34
Pallor	42	100
Weight loss	34	80.95
Hepatomegaly	30	71.42
Jaundic	6	14.28
Lymphadenopathy	21	50
Hepato-splenomegaly	23	54.76
Splenomegaly	34	80.95
Abdominal pain	11	26.19

Leukaemia (which included acute lymphoblastic leukaemia, acute myeloid leukaemia,) and Lymphoma (included Hodgkin and non-Hodgkin's lymphoma,) constituted 6 (14.2%) and 3 (7.14 %) respectively.

**Table 4: Bone marrow cellularity in pancytopenia cases.**

Etiology	n	%
<b>Hypercellular marrow</b>		
Megaloblastic anaemia	8	19.04
Dimorphic anaemia	6	14.28
Acute leukaemia	6	14.28
Kala azar	5	11.90
malaria	1	2.38
Total	26	
<b>Hypocellular marrow</b>		
Aplastic anaemia	4	9.52
sepsis	2	4.76
Typhus fever	1	2.38
Thalassemia major with hepatitis C	1	2.38
miscellaneous	1	2.38
Total	9	

Aplastic anaemia seen in 4 (9.52%) cases was another important cause of pancytopenia. Among the non-haematological causes Infections is most common entity. kala azar 5 (11.9%) is the leading cause in infection in this study. Rest infection are malaria 1 (2.38%), bacterial septicaemia 2(4.76%), typhus fever 2 (4.76%), HIV 1(2.38%) and miscellaneous caused pancytopenia in 3 (7.14%) of the patients.

The most common presenting complaint in current study was generalized weakness (90.4%) and weight loss (80.95%), followed by fever (69.04%). The most common physical finding was pallor (100%), followed by splenomegaly (80.95%) and hepatomegaly (71.42%). Hepato-splenomegaly and lymphadenopathy found in 54.76% and 50% cases respectively. Table-3. The presenting symptoms were usually attributed to anaemia or thrombocytopenia. Leukopenia was an uncommon cause of the initial presentation of the patient but can become the most serious threat to life during the disorder.

Marrow was hypercellular in 26 (61.90%) cases and megaloblastic anaemia 8(19.04%) was most cause showing hypercellular marrow. Bone marrow was hypocellular in 9(21.42%) cases and aplastic anaemia 4(9.52%) was most common cause. Table 4 shows the bone marrow cellularity and aetiology of pancytopenia.

## DISCUSSION

Peripheral pancytopenia is not a disease by itself; rather it describes simultaneous presence of anaemia, leucopenia and thrombocytopenia resulting from a number of disease processes. The variation in the pattern of disease has been attributed to differences in methodology and stringency

of diagnostic criteria and other demographic parameters. In present study the incidence of pancytopenia was 3.04%. Among all the admitted patients. Tilak et al, found the incidence to be 374 per million hospital attendance per year.<sup>10</sup>

In present study male dominated female in all the age group with male to female ratio of 1.47:1 which was comparable to other studies done by Amieleena C, et al and Goel RG, et al reported the male to female ratio of 1.64:1 and 1.76:1 respectively.<sup>11,12</sup> Similar results were found in the studies by Tilak V et al, Khunger et al, where the Male:Female ratio was 1.2:1; 1.3:1 respectively whereas a study carried out by Kumar R et al Male: Female was found 2.1:1 which was comparatively higher than current study.<sup>3,8,10</sup>

In current study, we came across 42 paediatric pancytopenia cases; again, megaloblastic anaemia 8 (19%) was the common cause for pancytopenia, followed by dimorphic anaemia and acute leukaemia 6 (14.2%) in both. Among the non-haematological causes Infections is most common entity. kala azar 5 (11.9%) is the leading cause in infection in this study.

However, in a study by Gupta et al 105 patients aged 1.5 to 18 years, with a mean age of 8.6 years, were included in the study.<sup>13,12</sup> Aplastic anaemia was the most common cause of pancytopenia (43%), followed by acute leukaemia (25%). Infections were the third most common cause of pancytopenia, of which Kala-azar was the most common. megaloblastic anaemia was seen in 6.7% of the patients by Khodke et al, Bhatnagar et al, in their retrospective study on paediatric patients presenting with pancytopenia, found megaloblastic anaemia (28.4%) as the single most common cause followed by acute leukaemia and infections in 21% patients each, and aplastic anaemia in 20% cases.<sup>14,15</sup> Bhatnagar et al, found enteric fever to be most common cause amongst all infectious aetiology.<sup>15</sup> Memon et al, found malaria in 8.69% and enteric fever in 10.8% of case, 4% cases remained undiagnosed.<sup>16</sup>

The most common presenting complaint in current study was generalized weakness (90.4%) and weight loss (80.95%), followed by fever (69.04%). The most common physical finding was pallor (100%), followed by splenomegaly (80.95%) and hepatomegaly (71.42%). Hepato-splenomegaly and lymphadenopathy found in 54.76% and 50% cases respectively. In the study conducted by Bhatnagar et al, the most common symptoms were weakness (97.8%), and breathlessness (75%), and signs were pallor (98.3%) and splenomegaly (25.5%).<sup>15</sup> Hepatomegaly (66%) and splenomegaly (21%) were seen in the study done by Gomber et al.<sup>17</sup> Pancytopenia either has hypocellular or cellular morphology in bone marrow. There are few studies in literature which explore the aetiological factors with hypocellular and cellular marrow.<sup>3,8,10,15</sup> The common causes vary in the different studies.<sup>3,8,10,15</sup> In the present

study, the marrow was cellular in 71.4% cases with megaloblastic anaemia being the most common cause while it was hypocellular in 28.5% cases where aplastic anaemia was the most common cause. Jha et al, from Nepal studied the causes of pancytopenia in 148 patients.<sup>7</sup> In children, hypoplastic bone marrow (38.1%) and in adults megaloblastic anaemia (30.2%) was the commonest aetiology reported by them. Study done by Santra et al, who had 60/111 cases of cellular marrow and 50 cases of hypocellular marrow.<sup>18</sup>

## CONCLUSION

Pancytopenia is not an uncommon haematological problem encountered in clinical practice and should be suspected on clinical grounds, when a patient presents with unexplained anaemia, weight loss, splenomegaly and prolonged fever. Bone marrow aspiration is an important diagnostic tool which helps to evaluate various cases of pancytopenia.

In this study, megaloblastic anaemia (19%) was the most common cause of pancytopenia, followed by dimorphic anaemia and leukaemia (14.2%). Among the non-haematological causes Infections are most common entity. Kala azar (11.9%) is the leading cause in infection from this geographical area. Other causes of pancytopenia such as typhus fever, lymphoma and HIV were also diagnosed in this study.

The present study concludes that detailed primary haematological investigations along with bone marrow examination in pancytopenia patients are helpful for understanding disease process, to diagnose the causes of pancytopenia. This study also suggests that megaloblastic anaemia, dimorphic anaemia and kala-azar should also be included in differential diagnosis of pancytopenia in this geographical area. It should also be concluded that amongst vegetarians, diet should be supplemented with regular intake of vitamin B12 and folic acid to avoid occurrence of megaloblastic anaemia, which is the most common disease, producing pancytopenia.

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