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# A Cross-Sectional Study of Etiology and Clinico-Hematological Profile of Pancytopenia in Children at Tertiary Care Centre in Western India

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## ABSTRACT

**Objectives:** Pancytopenia is one of the most common blood disorders observed in routine clinical practice. There are few studies analyzing pancytopenia in Indian scenarios. This cross-sectional study is aimed to identify the cause of pancytopenia and analyze the clinico-hematological characteristics of children with pancytopenia in Western India. So this study was conducted to evaluate clinico-hematological profile of children presenting with pancytopenia and to determine the etiology of pancytopenia in Western India.

**Material and Methods:** This two-year descriptive cross-sectional study was conducted in a tertiary care referral hospital. All children with pancytopenia, ranging in age from 1 month to 18 years, were enrolled in the study. A thorough history was taken, as well as general and systemic examination findings, hematological parameters, and bone marrow examination findings were recorded.

**Results:** The age group of enrolled patients ranged from 1 month to 18 years in the 130 cases evaluated (63 males and 67 females), while the mean age was 9.8 years. Fever was the most prevalent symptom (n = 111, 85.40%), followed by generalized weakness and weight loss. Pallor was the most common physical manifestation, followed by knuckle pigmentation, hepatomegaly, and splenomegaly. Study results concluded that the most common cause of pancytopenia was megaloblastic anemia, followed by acute leukemia, aplastic anemia, and infections. Megaloblastic anemia can be distinguished from other causes of pancytopenia based on dietary habits, hematological parameters and serum B12 levels, potentially obviating the necessity for a bone marrow test in most pancytopenia patients.

**Conclusion:** In pancytopenia patients, detailed initial hematological investigations, including bone marrow examination, are beneficial for correct diagnosis. Although megaloblastic anemia is the most prevalent cause, other factors to examine include aplastic anemia, leukemia, Hemophagocytic Lymphohistiocytosis (HLH), hypersplenism, Systemic Lupus Erythematosus (SLE), and viral infections. When a complete history, clinical examination, and baseline hematological parameters are adequately assessed, bone marrow examination can be avoided in most pancytopenia patients.

**Keywords:** Bone marrow examination, Children, Megaloblastic anemia, Pancytopenia

## INTRODUCTION

Pancytopenia is defined by a drop in all three constituents of peripheral blood such as Hemoglobin (Hb) less than 9 g/dL, Total leukocyte count (TLC) below 4,000/L or Absolute Neutrophil Count (ANC) below 1,500/L, and Platelet counts less than 1,00,000/L.[1] Pancytopenia is a symptom of various diseases that affect the bone marrow, directly or indirectly. Failure of stem cell production in bone marrow, infiltration of bone marrow, immune-mediated bone marrow suppression,

increased destruction of blood cells, or sequestration of blood cells by the reticuloendothelial system are some of the mechanisms that cause cytopenia in these diseases.

The etiology of pancytopenia differs between groups, and these differences are due to differences in how you diagnose pancytopenia, the geographical area where the study is conducted, genetic variations, the nutritional condition of children enrolled, the prevalence of various infections and exposure to myelotoxic drugs, among other factors.[2] As a result, knowing the actual cause of pancytopenia is essential for determining prognosis and treatment options. Detailed medical history, thorough physical examination, and complete blood count with a peripheral smear review are still necessary and provide useful information. Anemia can manifest in various ways, including fatigue, breathing difficulties, and signs of cardiac failure. Leukopenia combined with neutropenia can make you more vulnerable to infections that cause fever or sepsis. Patients with thrombocytopenia may experience bleeding in various places, including the skin mucosa, epistaxis, etc.

Further pancytopenia evaluation might be planned based on clinical signals from the initial assessment, such as glossitis, diarrhea, and paraesthesia that are common in megaloblastic anemia; bleeding, on the other hand, typically indicates underlying marrow aplasia or leukemia. Severe neutropenia and thrombocytopenia are less common in megaloblastic anemia than in other hematological causes, such as aplastic anemia or leukemia, according to complete blood count and peripheral blood smear results. A peripheral blood smear study with blast cells is typical in acute leukemias, whereas myelodysplastic syndrome is associated with hypogranulated and segmented neutrophils. Furthermore, hypersegmentation of neutrophils indicates megaloblastic anemia. Other procedures, such as bone marrow aspiration and biopsy, can be planned based on these findings. A few studies have looked at pancytopenia in the Indian adult population and concluded that megaloblastic anemia remains the most prevalent cause of pancytopenia.[3–5] The number of studies examining the spectrum of pancytopenia in children still needs to be expanded.[6–8] As a result, this study aimed to evaluate the clinico-hematological profile of children with pancytopenia in Western India and determine the cause of pancytopenia.

## MATERIAL AND METHODS

This is a cross-sectional study that was conducted in a tertiary care hospital's Department of Pediatric Haematology and Oncology from October 2017 to October 2019.

Children under 18 with pancytopenia on a hemogram and a peripheral smear were enrolled only, if their parents gave informed and written agreement. This study excluded children with previously diagnosed diseases such as leukemia, aplastic anemia, and hypersplenism, patients receiving radiotherapy or chemotherapy, and those above 18. The primary outcome measure was to analyze the clinico-hematological profile of children with pancytopenia, and the secondary outcome measure was to find the etiology of pancytopenia. Pancytopenia is defined as a hemoglobin concentration of less than 9 g/dL, a TLC of less than 4,000 cells/cu.mm or an ANC of less than 1,500 cells/cu.mm, and a platelet count of less than 1,00,000/L.[1] Pancytopenia is defined as severe if having two or more of the following values: Hb 7 gm/dl, ANC 500 cells/cu.mm, and platelet count 20,000/L.[6] After enrolling in the study, a detailed history regarding blood transfusions, drug intakes like sulpha drugs, sodium valproate and family history was obtained.

A thorough general and systemic examination was performed to search for syndromic characteristics, knuckle pigmentation, lymphadenopathy, and organomegaly. All patients had a hematological profile that included a hemogram, red cell indices, total and differential leucocyte count, platelet count, and a peripheral smear test. Other tests, such as dengue serology, fast malaria test, blood culture, serum B 12, serum folic acid levels, bone marrow aspiration, and biopsy, were conducted in selected individuals where indicated based on clinical and basic hematological investigations. Bone marrow slides were stained with hematoxylin and eosin stain and examined by our institute's hematologist.

**Statistical Analysis:** Formula n = z2 p (1 – p)/d2 p = prevalence /Incidence (pancytopenia in children-1.86) 59 z = 1.96 (Constant for 5% of all error) d = 0.03 (Allowable error of 3%) This was calculated to 100 patients. However, we also considered 30 patients from a total sample size of 130 who presented at our institute during the study period.

The data were calculated using Statistical Package for the Social Sciences (SPSS) version 20.0 (USA) and standard statistical tests. To tabulate the data and prepare graphs for the sample, Microsoft Word and Excel version 2010 were utilized. When the frequencies of patients with a particular variable were considered, the Chi-square test was used to determine the significance of the data. When the mean age between the genders was compared, the p-value was calculated using an unpaired student's *t*-test. With a significant p-value of less than 0.05, the confidence intervals were set at 95%.

### Ethics

The study was conducted as per the ethical standards of the responsible committee on human experimentation

and with the Helsinki Declaration of 1964, revised in 2013. The Institutional Ethics Committee approved the study on October 25, 2017, with the following number: MGM/ECRHS/2017/45.

## RESULTS

A total of 130 patients having pancytopenia were studied during the study period, with 63 (48%) male patients and 67 (52%) female patients. Patients range from 1 month to 18 years [Table 1]. Fever (85.40%) was the most prevalent presenting symptom, followed by generalized weakness, weight loss, bone pain, bleeding, and so on [Table 2].

All patients had a pallor on physical examination and knuckle pigmentation, bleeding symptoms, hepatomegaly, and splenomegaly [Table 2].

In the study, megaloblastic anemia (n = 56, 43.08%) was detected to be the most prevalent cause of pancytopenia, followed by acute leukemia (n = 29, 22.30%) and aplastic anemia (n = 16, 12.30%) [Table 3].

Apart from common causes, we also noticed many patients had other disorders, such as hypersplenism with chronic liver disease (n = 10, 7.69%) and Systemic Lupus Erythematosus (SLE) (n = 4, 3.08%). Infectious causes such as viral fever and enteric fever are also noted. We diagnosed Hemophagocytic Lymphohistiocytosis (HLH) in 5 children who presented with pancytopenia and who had secondary HLH due to infectious etiology [Table 3]. Most of the 29 children diagnosed with malignancy had Acute Lymphoblastic Leukemia (ALL) (n = 25, 86.20%), followed by Acute Myeloid Leukemia (AML) and Acute Promyelocytic leukemia (APML). Bony pain is more common in leukemia than in other pancytopenia patients [Table 4].

Although there are several characteristics that all patients share with pancytopenia, compared to other kinds of anemia, megaloblastic anemia shows substantial knuckle pigmentation and a large Mean Corpuscular Volume (MCV) [Table 5]. Compared to other prevalent causes of severe pancytopenias, such as aplastic anemia and leukemia, megaloblastic anemia has a lower rate of severe pancytopenia [Table 6].

**Table 1**: Distribution of patients according to age.

| Age distribution | No of cases N (%) |
|---|---|
| Infants 1 month–1 year | 12 (9.23%) |
| Toddlers >1 to 3 years | 9 (6.92%) |
| Pre-school >3 to 6 years | 20 (15.38%) |
| School >6 to 12 years | 38 (29.23%) |
| Adolescent >12 to 18 years | 51 (39.23%) |
| Total 1 month–18 years | 130 (100%) |

N: number of cases

**Table 2**: Presenting signs and symptoms of pancytopenia.

| Presenting signs and symptom | No. of cases N (%) |
|---|---|
| Pallor | 130 (100%) |
| Fever | 111 (85.40%) |
| Generalized weakness | 109 (83.80%) |
| Hepatomegaly | 83 (64%) |
| Splenomegaly | 72 (55%) |
| Knuckle pigmentation | 67 (52%) |
| Weight loss | 56 (43.10%) |
| Angular stomatitis/cheilitis | 45 (35%) |
| Breathlessness | 44 (33.80%) |
| Bone pain | 24 (18.50%) |
| Bleeding | 22 (16.90%) |
| Bleeding manifestation | 26 (20%) |
| Icterus | 14 (11%) |

N: number of cases

**Table 3**: Etiological profile of pancytopenia.

| Etiology | No. of cases |
|---|---|
| Megaloblastic anemia | 56 (43.08%) |
| Acute leukemia | 29 (22.30%) |
| Aplastic anemia | 16 (12.30%) |
| Hypersplenism | 10 (7.69%) |
| Hemophagocytic Lymphohistiocytosis | 5 (3.85%) |
| Systemic lupus erythematosus | 4 (3.08%) |
| Enteric fever | 4 (3.08%) |
| Dengue fever | 2 (1.53%) |
| Sepsis induced myelosuppression | 1 (0.66%) |
| Hemolytic anemia | 1 (0.66%) |
| Cirrhotic liver disease | 1 (0.66%) |
| Viral fever | 1 (0.66%) |
| Total | 130 (100%) |

**Table 4**: Distribution of hematological malignancies.

| Hematological malignancies | No. of cases N (%) |
|---|---|
| Acute Lymphoblastic Leukemia (ALL) | 25 (86.20%) |
| Acute Myeloblastic Leukemia (AML) | 3 (10.34%) |
| Acute promyelocytic leukemia (APML) | 1 (3.45%) |

N: number of cases

**Table 5**: Comparison of presentation between megaloblastic anemia and other causes.

| Characteristic | Megaloblastic anemia | Other causes |
|---|---|---|
| Vegetarian diet | 33 | 18 |
| Knuckle pigmentation | 47 | 21 |
| MCV > 100fL | 12 | 3 |

MCV: Mean Corpuscular Volume

**Table 6**: Severe cytopenia in most common causes of pancytopenia.

| Parameters | Megaloblastic anemia (n = 56) | Aplastic anemia (n = 16) | Leukemia (n = 29) |
|---|---|---|---|
| Hemoglobin <7g/dL | 30 (53,57%) | 12 (75.00%) | 21 (72.41%) |
| ANC <500/µL. | 15 (26.78%) | 7 (43.75%) | 11 (37.90%) |
| Platelet count <20,000/µL. | 11 (19.64%) | 10 (62.50%) | 19 (65.50%) |

ANC: Absolute Neutrophil Count, n: number of cases

## DISCUSSION

The development of pancytopenia appears to be linked to a decrease in haematopoietic cell production due to toxins destroying the marrow tissue, replacement by aberrant or malignant tissue, or possibly suppression of normal growth and differentiation. As a result, determining the underlying cause of pancytopenia is critical for effective treatment.

In India, very few broad-spectrum studies include diverse etiologies and clinical correlations of pancytopenia. This study is aimed to evaluate the clinico-hematological profile of children having pancytopenia and determine the cause of pancytopenia.

A total of 130 patients with pancytopenia were investigated during the study period. In all instances, the gender-specific incidence, presenting complaints, peripheral blood picture and causes of pancytopenia were examined, and the results were compared to those found in previous studies.

Patients ranged in age from 1 month to 18 years. There were 63 (48%) male patients and 67 (52%) female patients [Table 1]. Statistically, there was a small female majority, but it was insignificant.

In the study, megaloblastic anemia (n = 56, 43.08%) was noted to be the most frequent cause of pancytopenia, followed by acute leukemia (n = 29, 22.30%) and aplastic anemia (n = 16, 12.30%) [Table 7]. Similar findings were discovered by Khunger *et al.*, with megaloblastic anemia being the most common cause.[3] Gayatri and Rao reported similar outcomes in the current investigation.[9] However, other studies have reported lesser proportions.[10,11]

Even though all patients with pancytopenia have similar symptoms to other causes as shown in Table 5, megaloblastic anemia exhibits substantial knuckle pigmentation and a high MCV.

Megaloblastic anemia is a common condition in developing countries due to nutritional deficiencies. Megaloblastic anemia was shown to be the most common in patients in the adolescent age group, which could be attributed to increased dietary needs and a lack of adequate food intake. It's a treatable condition that should be reported right away.

The prevalence of aplastic anemia in pancytopenia patients ranges from 10% to 52%. The prevalence of hypoplastic anemia in our sample was 16%, consistent with findings from

**Table 7**: Comparison of various studies on pancytopenia.

| S. No | Study | Years Place | Sample size | Megaloblastic anemia | Aplastic anemia | Acute leukemia | Hypersplenism | HLH | SLE |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Khunger *et al.*[3] | 2002 India | 200 ADULT PED | 144 (72%) | 28 (14%) | 10 (5%) | 6 (3%) | 0 | 0 |
| 2 | Bhatnagar SK[6] | 2001 India | 109 PED | 31 (28.40%) | 22 (20.00%) | 23 (21.00%) | 0 | 0 | 0 |
| 3 | Hamid *et al.*[13] | 2005 Yemen | 17 PED | 0 | 3 (17.6%) | 2 (11.7%) | 12 (70.5%) | 0 | 0 |
| 4 | Pine *et al.*[12] | 2010 U.S.A. | 64 PED | 0 | 7 (11%) | EXCLUDED | 1 (1.5%) | 0 | 2 (3%) |
| 5 | Gayatri and Rao[9] | 2011 India | 104 PED | 77 (74.0%) | 19 (18.3%) | 4 (3.9%) | 0 | 0 | 0 |
| 6 | AZ Jan[10] | 2013 Pakistan | 205 PED | 40 (19.5%) | 58 (28.3%) | 49 (23.9%) | 5 (2.4%) | 0 | 0 |
| 7 | Ghartimagar D[11] | 2017 Nepal | 138 ADULT PED | 26 (18.8%) | 38 (27.5%) | 19 (13.8%) | 0 | 1 (0.7) | 0 |
| 8 | Current study | 2019 India | 130 | 56 (43.08%) | 16 (12.30%) | 29 (22.30%) | 10 (7.69%) | 5 (3.85%) | 4 (3.08%) |

HLH: Hemophagocytic Lymphohistiocytosis, SLE: Systemic Lupus Erythematosus, PED: Pediatric

other studies.[3,5,12]. On the contrary, Kumar R *et al*. reported a higher incidence of aplastic anemia of 29.5%.[1]

Pancytopenia is seen in 30% of acute leukemia patients at diagnosis. In our analysis, 22% (n = 29) of patients with pancytopenia had a malignant etiology, the second most frequent cause of pancytopenia. Among all pancytopenia cases, Bhatnagar SK found nearly identical 21% of acute leukemia patients.[6] Most of the 29 youngsters diagnosed with cancer had ALL (n = 25, 86.20%), followed by AML and APML. In children, ALL is the most frequent hematological malignancy.

Aside from the typical reasons, we discovered that many patients had other conditions, such as hypersplenism with chronic liver disease (n = 10, 7.69%) and SLE (n = 4, 3.08%). Infectious reasons are also mentioned, such as viral fever and enteric fever. Hamid et al found that 70% cases of pancytopenia had hypersplenism, but sample size of the study was small.[13]

We diagnosed HLH in five children with pancytopenia, all suffering from secondary HLH due to an infectious etiology. In recent years, improved knowledge and understanding of HLH have resulted in a rise in the detection of cases. The most prevalent causes of secondary HLH include dengue fever, malaria, and enteric fever. Other diagnostic criteria should be met besides pancytopenia, but early suspicion and precise diagnosis are critical. If detected early, secondary HLH is treatable with the treatment of the original condition and just dexamethasone.

## LIMITATIONS

The current study does not examine the socioeconomic position and its impact on the causes of pancytopenia. The study's scope does not include the follow-up and result of pancytopenia.

### Future research directions

A community study might be conducted to determine the prevalence of megaloblastic anemia and the feasibility of providing regular vitamin supplements to all children who are at risk.

## CONCLUSION

Pancytopenia is a common entity in pediatric patients. Clinical findings, along with detailed primary hematological investigations, would be helpful in the early and exact diagnosis of patients with pancytopenia. A bone marrow examination is often optional when correctly examined by other basic parameters. Early detection of underlying problems will aid in the prompt commencement of decisive therapy, increasing the survival rate of children with pancytopenia.

### Data availability statement

The data used to draw conclusions from this study are available with the corresponding author and can be provided upon request.

### Acknowledgment

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### Ethical approval

The research/study approved by the Institutional Ethical Committee (MGM/ECRHS/2017/45).

### Declaration of patients consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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