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Original Research Article

Clinico-Hematological and Etiological Spectrum of Pancytopenia / Bicytopenia in Children Aged 1 To 15 Year in Southern Odisha (An Institute Based Study)

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Conflict of interest: Nil

Abstract:

Background: This study has been conducted to evaluate the underlying causes and the clinico-hematological profile of pancytopenia and bicytopenia in the pediatric age group.

Methods: This was a hospital-based prospective cross-sectional observational study conducted among 75 patients in the pediatric age group of 1-15 years in the Department of Pathology, MKCG Medical College and Hospital, Brahmapur, over a period of 2 years from August 2019 to September 2021 after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Results: Both bicytopenia and pancytopenia presented with fever (76%), followed by bleeding manifestations (18%). Clinical findings like pallor (97%) and hepatosplenomegaly (73%) were observed in the majority of the cases in both bicytopenia and pancytopenia. On CBC, anemia and thrombocytopenia in combination were the most common presentations of bicytopenia, followed by anemia plus leucocytopenia. Anemia and thrombocytopenia were seen in 97% and 94% of cases, respectively, while leucopenia was seen in only 8% of cases. On peripheral smear examination, normocytic normochromic RBCs were seen in 73% of cases, followed by microcytic hypochromic RBCs in 20% of cases. Bone marrow aspiration and biopsy revealed acute leukaemia to be the leading cause of bicytopenia and pancytopenia, with 40% of cases, followed by aplastic anemia, comprising 23.7% of cases.

Conclusion: Infectious causes like malaria and nutritional deficiencies (iron deficiency or vitamin B12 deficiency), though treatable, can lead to serious complications such as subacute combined degeneration of the spinal cord and growth and developmental delays if not diagnosed in a timely fashion and treated accordingly. The clinical findings and peripheral blood smear supplemented by bone marrow aspiration and biopsy can provide crucial information in the workup of patients with cytopenias and aid in early identification of the primary etiologies which will have profound impact on the morbidity and mortality in pediatric patients.

Keywords: Clinico-Hematological, Etiological Spectrum, Pancytopenia, Bicytopenia. Children.

Introduction

Cytopenia is defined as a depletion in any of the three lineages of blood cells, i.e., RBCs (Red Blood Cells), WBCs (White Blood Cells) and platelets. A diminution in any of the two cell lines is termed as bicytopenia, whereas a decrease in all three lineages is defined as pancytopenia. Pediatric patients frequently experience cytopenias, which are caused by neoplastic infiltration, immune-mediated bone marrow suppression, ineffective hematopoiesis, peripheral blood cell sequestration in hyperactive reticuloendothelial tissue, and failure of hematopoietic progenitor production in the bone marrow. [1,2,3] The etiological diagnosis is essential for clinical management and the prognosis of patients. The presenting symptoms of cytopenias are often ascribable to anemia or thrombocytopenia, while leucopenia is uncommon. They can manifest from mild symptoms such as fatigue, breathlessness, pallor, increased bruising, mucosal bleeding and purpuric spots to life-threatening symptoms such as cardiovascular symptoms, infections, septicemia and intracerebral hemorrhage. [4,5] A detailed

clinical history and physical examination provide important information for the workup of cytopenic patients. Peripheral smear studies and other complementary laboratory investigations aid in the diagnosis. A valuable and conclusive way of diagnosing and analyzing hematologic and metastatic neoplasms as well as non-hematological diseases causing cytopenia is bone marrow examination, which encompasses the study of marrow aspirates, imprint smears and trephine biopsy, which are harmonious with each other and the advantage of one procedure over the other depends on the specific disease process. [6,7] Studies related to pancytopenia and bicytopenia in the pediatric age group are scarce in the literature, especially in southern Odisha. Previous studies have emphasized the significance of megaloblastic anemia as a crucial cause of cytopenia. This study has been conducted for a comprehensive understanding of the underlying causes and the clinico-hematological profile of pancytopenia and bicytopenia in the pediatric age group.

Materials & Methods

This was a hospital-based prospective cross-sectional observational study conducted among 75 patients in the pediatric age group of 1 to 15 years to study the etiological and clinico-hematological profile of pancytopenia and bicytopenia in the Department of Pathology, MKCG Medical College and Hospital, Brahmapur, over a period of 2 years from August 2019 to September 2021 after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

- Children between 1 year and 15 years of age.
- Patients meeting the criteria of cytopenia.

-hemoglobin less than 10gm/dl,
-total leukocyte count (TLC) less than 4000/cu mm,
-total platelets count less than 1,50,000/cu mm.

Exclusion criteria

- Children aged less than 1 year or more than 15 years.
- Diagnosed cases of aplastic anemia and leukemia
- Patients having a history of recent blood transfusions and receiving chemotherapy and radiotherapy.

Statistical Methods

The data was processed and analyzed by Microsoft Excel software and qualitative (chi-square) statistical tests were applied. Gender, age and cause of pancytopenia were calculated as categorical variables and summarized using frequency and percentage.

Results

Both pancytopenia and bicytopenia presented with fever as the most common presenting symptom seen in 27 (75%) and 30 (76%) cases followed by bleeding manifestation in 7(19.44%) and 7(17.94%) cases respectively.

Table 1

Symptoms	Pancytopenia	Bicytopenia	Total Patients
Fever	30	27	57
Bleeding Manifestation	7	7	14
Progressive Paleness	6	7	13
Loss of Appetite	5	7	12
Generalized Weakness	5	6	11
Cough	6	3	9
Vomiting	4	5	9
Joint Pain	6	2	8
Malena	4	2	6
Shortness of Breath	4	2	6
Abdominal Pain	3	3	6
Abdominal Swelling	1	2	3
Discoloration of skin	2	0	2

In both pancytopenia and bicytopenia pallor was the most common presenting sign on clinical examination, with 39 (100%) and 34 (94%) cases, followed by hepatomegaly, comprising 15 (38.46%) and 20 (55.55%) cases respectively. Lymphadenopathy was seen in 12 (40%) cases out of 30 cases of acute leukemia.

Table 2

Signs	Pancytopenia	Bicytopenia	Total Patients
Pallor	39	34	73
Hepatomegaly	15	20	35
Splenomegaly	8	17	25
Lymphadenopathy	7	5	12
Pedal edema	2	1	3
Icterus	1	1	2

Table3 shows the hematological profile of bicytopenia with anemia and thrombocytopenia 33 (91.66%) in the majority of the children followed by anemia and leucopenia seen in 2 (5.55%) cases; while thrombocytopenia and leucopenia were the least common presentations seen in 1 case (2.77%).

Anemia, i.e., hemoglobin less than 10 g/dl was seen in 97% of cases of bicytopenia; thrombocytopenia was seen in 94% of cases; and leucocytopenia was seen in only 8% of cases, indicating that leucocyte count was seldom affected in bicytopenia.

Table 3

Presentation	Anemia+ Thrombocytopenia	Anemia+ Leukopenia	Thrombocytopenia+ Leukopenia
Count of Patient	33	2	1
%	92%	6%	3%
Haematological Profile in Cytopenia		**Pancytopenia**	**Bicytopenia**
Hemoglobin <10 g/dl		100%	97%
TLC <4.5*10^9/L		100%	8%
Platelet Count <150000/µL		100%	94%
Circulating Blast		31%	47%

On peripheral smear examination following findings were seen as presented in Table4 .

Table 4: Hematological Profile in cytopenia

Peripheral smear findings	Number of cases N=75	Frequency in percentage
Normocytic normochromic RBCs	53	73.33%
Microcytic hypochromic RBCs	15	20%
Macrocytic RBCs	5	6.66%
Dimorphic RBCs	2	2.66%
Hypersegmented neutrophils	5	6.66%
Circulating blasts	30	40%

Circulating blasts were seen in 31% of cases of pancytopenia and in 47% of cases of bicytopenia. Etiologically, acute leukemias were the predominant cause in both pancytopenia and bicytopenia, comprising 30 (40%) cases out of the 75 cases, followed by aplastic anemia in pancytopenia 9 (23.07%) cases, whereas in bicytopenia, the marrow of infection 3 (8.33%), megaloblastic anemia 3 (8.33%) and immune thrombocytopenic purpura 3 (8.33%) comprised the second most common cause.

As shown in Table5, in patients with acute leukemia, acute lymphoblastic leukemia consisted of the majority of cases, with 13 (33%) cases presenting with pancytopenia and 13 (36%) cases presenting with bicytopenia. Four (11%) patients had acute myeloid leukemia and presented with bicytopenia. On peripheral smear examination, circulating blasts were seen in all cases of leukemias, after which a bone marrow aspiration study was done along with special stains such as MPO and PAS stain to differentiate between ALL and AML. In inconclusive cases, a bone marrow biopsy was performed, and the patient was subjected to specific CD markers to delineate specific lineages.

Table 5

Etiological Profile	Pancytopenia	%	Bicytopenia	%
Acute Lymphoblastic Leukemia	13	33%	13	36%
Aplastic Anemia	9	23%	2	6%
hypoplastic marrow	7	18%	1	3%
Marrow of Infection	2	5%	3	8%
Megaloblastic Anemia	2	5%	3	8%
Iron Deficiency Anemia	2	5%	1	3%
Nutritional Deficiency Anemia	1	3%	2	6%
Erythroid Hyperplasia	1	3%	0	0%
Hemophagocytic lymphohistiocytosis	1	3%	1	3%
Amegakaryocytic Thrombocytopenia	1	3%	1	3%
Acute Myeloid Leukemia	0	0%	4	11%
Hypersplenism	0	0%	2	6%
Immune Thrombocytopenic Purpura	0	0%	3	8%

Aplastic anemia was the second most common cause in pancytopenia, with 23% of cases and the third most common cause in bicytopenia with 6% of cases.

Hypoplastic marrow was seen in 18% of cases of pancytopenia making it the third most common cause and in 3% of cases of bicytopenia.

Megaloblastic marrow was found in 5% of cases of pancytopenia and 8% of cases of bicytopenia and was the second most common cause of bicytopenia after acute leukemia. On peripheral smear examination macrocytes, basophilic stippling and hyper segmented neutrophils were seen, which was followed by bone marrow aspiration and biopsy, in which megaloblasts and giant metamyelocytes were found. Additional investigations such as the vitamin B12 assay were done to corroborate the findings.

2 cases (5%) in pancytopenia and 3 cases (8%) in bicytopenia were found to be of infectious etiology; on peripheral smear examination ring forms of malarial parasites were found.

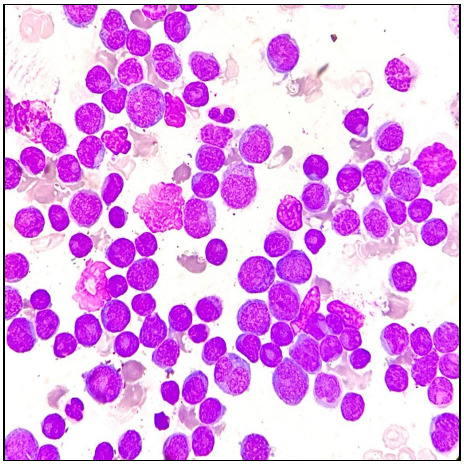

Figure 1: 40x- BMA showing myeloblasts with large size, scanty to moderate basophilic cytoplasm, round to oval nuclei, few with bilobed nuclei - Acute Myeloid Leukemia

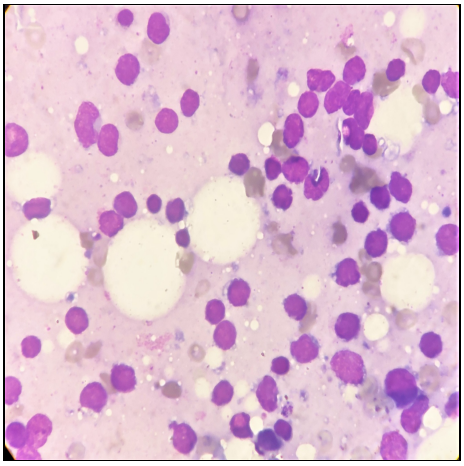

Figure 2- 40x – imprint smear shows monomorphic cells with scanty cytoplasm, high N/C ratio, no granules suggestive of Acute Lymphoblastic Leukemia

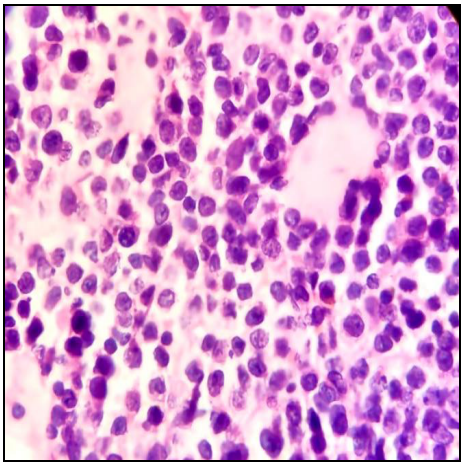

Figure 3- 40x- BMB showing blast cells replacing the marrow- Acute Lymphoblastic leukemia

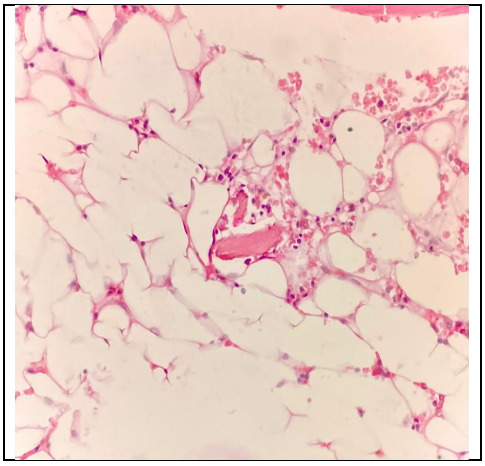

Figure 4: 40x- BMB shows severe aplasia of marrow with increase in fat spaces, there is marked reduction in cellularity- Aplastic Anemia

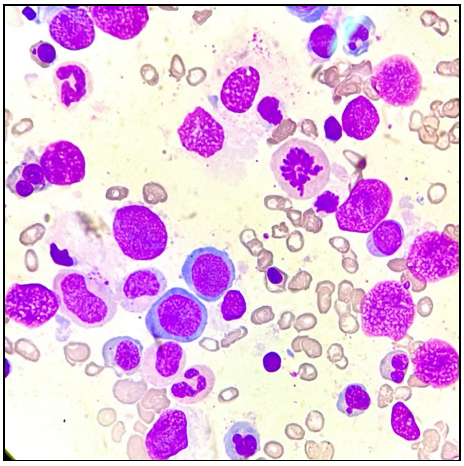

Figure 5: 40x-BMA shows megaloblasts with nuclear cytoplasmic asynchrony and dyserythropoiesis characteristic of Megaloblastic anemia

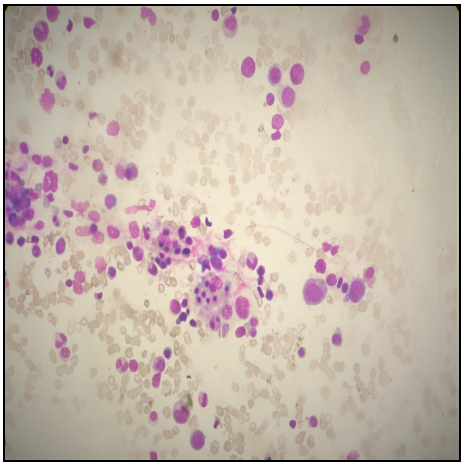

Figure 6: 40X- BMA- phagocytosis of marrow cells by marrow macrophages. Hemophagocytic lymphohistiocytosis

Discussion

Pancytopenia is described by the simultaneous presence of anemia, thrombocytopenia, and leucopenia, while biyctopenia can present with any two in combination. Cytopenia is a frequent hematological malady encountered in clinical practice and usually presents with unexplained pallor, prolonged fever, repeated infections, and a tendency to bleed. [8]

The underlying aetiology of pancytopenia and bicytopenia is the subject of conflicting reports from throughout the globe and varies in different

population groups based on their genetic pattern, prevalent infections in the geographical area, nutritional status and exposure to myelotoxic drugs among various other factors. Overlying phenotypes and pathophysiology pose a major diagnostic challenge. [9,10,11]

To provide an accurate diagnosis, bone marrow aspiration and biopsy work in tandem. Very little information has been published about the etiological and clinical range of cytopenias in children.

The present study included 75 patients, which were categorized into two groups, i.e., pancytopenia and bicytopenia.

In our study, the incidence of bicytopenia was 36 (48%) and pancytopenia was 39 (52%), respectively. In related research, bicytopenia was found in 45.5% of patients and pancytopenia in 54.5% of cases by SK Bhatnagar [2] et al. from Delhi, India. Almost similar findings were seen in studies by Shilpi Dosi et al. [3] and Bidisha De et al [4]. However, the incidence in the present study was different from the study of Naseem et al. [14] with bicytopenia seen in 40% and pancytopenia in 17% of cases. The variation in cytopenia can be attributed to variations in the study's methodology chosen diagnostic criteria, children's socioeconomic standing, and diet and nutritional status.

The present study showed a male (56%) predominance over females (44%) in both bicytopenia and pancytopenia. In bicytopenia 21 (58.33%) were males while 15 (41.66%) were females; with the male-to-female ratio being 1.4:1. Similar findings were seen in pancytopenia with males constituting 21 cases (53.8%) and females 18 (46.15%) with the male-to-female ratio being 1.16:1 The findings of the study were consistent with the findings of Naseem et al[5] which demonstrated a male predominance . However, Dubey et al [6] reported that females (53%) were more commonly affected than males (47%), with the male-to-female ratio being 0.88:1. This disparity may be attributed to a larger sample size than ours. In bicytopenia and pancytopenia, the distribution of males and females was statistically not significant (p-value 0.695). Socio-economic status, cultural beliefs and taboos, and preference for the health of the male child make health care facilities more readily available to males as compared to females, leading to the male predominance at hospitals seen in the present study and similar studies.

The most common age group to be affected in the present study was the 11–15-year age group, leading with 47% of cases, followed by 34% in the 1–5-year age group, and the least affected was the 6–10-year age group with 18.66% cases. Almost similar findings were seen in studies conducted by Wadhwa et al. [7] with 51.6% of patients above 11 years, followed by 38.7% in the 1–5-year age group; SK Dubey et al [6]. [11–15 years] (46.1%); and Pankaj Katoch et al. [8] 11–15-year age group with 42% cases, as there is a higher incidence of diseases in adolescents. Gunvanti et al. [9] found the < 5-year age group to be the most commonly affected, with 39% of patients, followed by the 6–10-year age group with 34% of children. Anwar Zeb Jan et al. [10] also showed the <5-year age group to be most commonly involved with 42.44% cases, followed by 6–10 years with 35.12% cases, as both of these studies included children from birth until 14 years, which was different from the age group included in our study, i.e., the 1–15-year age group. The age distribution during presentation was statistically significant (p = 0.006).

The frequency of the distribution of signs and symptoms was studied in children with cytopenia. Most of the cases presented with a combination of two to three symptoms. As per the frequency of symptoms, fever was seen in almost all the patients presenting with pancytopenia (76%) and bicytopenia (75%), followed by bleeding manifestations including gum bleeding, petechiae, and purpuric spots in 19.44% cases of bicytopenia and 17.94% cases of pancytopenia. Naseem et al [5], Zahide et al [11], Shilpi Dosi et al [3] , Pankaj Katoch et al [8], Fadil Abass Abid et al [12] also reported fever, bleeding manifestations and generalized weakness as the most common presenting symptoms, which can be attributed to the presence of anemia, thrombocytopenia, and leucopenia . The frequency of symptoms was statistically insignificant (p value = 0.869).

The majority of patients in the present study had pallor on clinical examination, with 100% and 94% having pancytopenia and bicytopenia, respectively. The second most common finding was hepatomegaly, comprising 38.46% and 55.55% of cases in pancytopenia and bicytopenia, respectively. Katoch et al [8], SK Dubey et al [6], Rasheed et al [13] and Wadhwa et al [7] also reported pallor and hepatomegaly as the most common presenting signs on physical examination. The frequency of symptoms (p = 0.869) and signs (p = 0.499) was not statistically significant.

The hematological profile of bicytopenia showed that thrombocytopenia and anemia were the most common combination in 91.66% of cases, followed by anemia and leucopenia in 5.55% of cases. A similar finding was that leucopenia with thrombocytopenia was the least common finding seen in only one case (2.77%). Similar findings were reported by N. Varma et al., Shilpi Dosi et al. [3], R. Thambi et al. [14], Shano Naseem et al. [5]. Leucopenia was seen in only 8% of cases of bicytopenia, indicating that red blood cells and platelets are the first to be affected and leucocyte counts are seldom and the last to be affected.

The most common etiology of pancytopenia in the present study was acute leukemia seen in 33% of cases. All of the cases were of ALL (Acute Lymphoblastic Leukemia) (100%). The second most common cause was aplastic anemia (23% cases), followed by hypoplastic marrow (18% cases). The findings were similar to those of Ahmad et al. [22] where acute lymphoblastic leukemia was seen in 26.65% cases; a study by Naseem et al. showed acute leukemia (26.6%) to be the most common malignant cause.

Mohammad Hussain Khan et al. reported acute lymphoblastic leukemia (51%) as the commonest cause of pancytopenia, followed by aplastic anemia (20%) and bone marrow hypoplasia (12%), similar to our study. Rehmana Waris et al. [23] also found acute leukemia (25%), aplastic anemia (20%), and enteric fever (19%) to be the leading causes of pancytopenia. Acute leukemias and aplastic anemias are common presentations in the pediatric age group, leading to their higher incidence in our study and similar other studies. [24]

Bhati et al [15], Neelima Bahal et al [16], Gunvanti B. Rathod et al [9], Chhabra et al [18] and SK Bhatnagar et al [2] found megaloblastic marrow as the predominant cause of pancytopenia , followed by hypoplastic/aplastic marrow which was significantly different from our study. Nutritional deficiency in growing children, socio-economic status, and gender differences can be attributable to megaloblastic anemia being the leading cause in studies by Bahal et al and Rathod et al. Infectious etiology such as malaria, pneumonia, acute gastroenteritis, urinary tract infection, malaria, scrub typhus and kala azar as the leading cause were seen in studies done by Zahide Yalaki et al [11], Katoch et al. [8] , and Fadil Abass Abid et al [12], Chaure Varsha [1] et al.

The differences in the etiology with infectious causes being the leading cause, can be due to these studies being conducted in the northern region of India and Pakistan, where kala azar, visceral leishmaniasis and scrub typhus are prevalent infections that are uncommon in Odisha.

Acute leukemia was also the predominant etiological factor in bicytopenia, seen in 47% of cases, followed by marrow infection, megaloblastic anemia, and immune thrombocytopenic purpura. Wadhwa et al [7], Waris et al [17], Dosi et al [3] , Naseem et al [5], also reported acute lymphoblastic leukemia as the predominant cause of bicytopenia, followed by hypocellular bone marrow similar to our study. ($p = 0.219$).

Conclusion

Bicytopenia and pancytopenia are common haematological problems encountered in clinical practice and frequently present with unexplained anemia, prolonged fever, and a tendency to bleed. Our study scrutinized the clinic-hematological and etiological profiles of bicytopenia and pancytopenia in children. The study concludes that:

- The majority of the children presented with pancytopenia and a male predominance was seen in both pancytopenia and bicytopenia.
- Adolescents were more commonly affected. Fever, bleeding manifestations, pallor and organomegaly were commonly seen at the time of presentation.
- Acute leukemia and aplastic anemia were the most important etiological factors seen in both pancytopenia and bicytopenia.
- Though the existence of pancytopenia is met with greater clinical concern than bicytopenia, we found that acute leukemia was seen in 47% of patients with bicytopenia as compared to 33% with pancytopenia.
- Acute leukemia, though life-threatening is treatable in many cases and an early and correct diagnosis can help formulate a better treatment plan for long-term quality of life.
- Infectious causes like malaria and nutritional deficiencies (iron deficiency or vitamin B12 deficiency), though treatable, can lead to serious complications such as complicated malaria, subacute combined degeneration of the spinal cord, and growth and developmental delays if not diagnosed in a timely fashion and treated accordingly.
- The clinical findings and peripheral blood smear supplemented by bone marrow examination can provide valuable information in the workup of patients with cytopenias and aid in early recognition of the underlying etiologies which will have a long-term impact on morbidity and mortality in pediatric patients.

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