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Children with bicytopenia and pancytopenia – clinical picture, etiological spectrum, and outcome

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ABSTRACT

Background: Children who develop cytopenias present with several etiological causes, posing diagnosis, and management difficulties for both physicians and pathologists. With these in mind, we assessed the clinical profile and etiology of children who attended a healthcare facility in South India with bicytopenia or pancytopenia. **Aims and Objectives:** (1) The primary objective of this study was to find out the clinical and etiological spectrum in children with bicytopenia and pancytopenia who were admitted to the Institute of Child Health and Research Center, Government Rajaji Hospital, Madurai. (2) The secondary objective of this study is to follow-up children with bicytopenia and pancytopenia to find out the outcome and prognosis. **Materials and Methods:** This study was in the Department of Pediatrics at the Government Rajaji Hospital in Madurai, Madurai Medical College's Institute of Child Health and Research Center, which is where we carried out the study. Two hundred and sixty-four patients with bicytopenia and 36 patients with pancytopenia were included in this study. Once in 2 weeks, all children with bicytopenia and pancytopenia were assessed in our Saturday hematology outpatient clinics. **Results:** Fever was the most prevalent sign of both pancytopenia and bicytopenia in this investigation. Etiological variables among cases of pancytopenia, cancer, infections, non-infections, and idiopathic causes were recorded in 11%, 58%, 17%, and 14% of cases, respectively. Similarly, bicytopenia, malignancy, infections, non-infections, and idiopathic causes were found in 23%, 70%, 4%, and 3% of cases, respectively. According to the prognosis, 28%, 33%, 6%, and 33% of cases with pancytopenia recovered, passed away, were lost to follow-up, or were undergoing treatment, respectively. Similar to those individuals, 67%, 11%, 4%, and 18% of bicytopenia cases were treated, recovered, or lost to follow-up, respectively. **Conclusion:** In children, there is a wide etiological range of cytopenias. Infections and dangerous diseases like acute leukemia are among the reasons. The geographical location of the hospital, the frequency of malnutrition, and the regional presence of certain diseases such as malaria and enteric fever determine the causes reported in a hospital environment.

Key words: Pancytopenia; Bicytopenia; Acute lymphoid leukemia; Outcome

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INTRODUCTION

The majority of pediatric cytopenic patients requiring hospitalization had pancytopenia and bicytopenia. Pancytopenia is characterized by a decline in the quantity of platelets, leukocytes, and erythrocytes. Bicytopenia is the word used when blood cell lines are reduced, although the method for diagnosis is the same as for pancytopenia.[1] Low hemoglobin and platelet levels are responsible for signs and symptoms. Leukopenia is rarely a prevalent cause of initial presentation, but when it does occur, it can be fatal to the patient. Pallor, headache, palpitations, shortness of breath, tiredness, bodily swelling, bleeding gums, petechial rashes, recurrent infections, and oral ulcers are among the clinical signs. Fanconi anemia, the Shwachman-Diamond disease, and congenital dyskeratosis are examples of

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congenital causes of pancytopenia.[2] While acquired causes include non-inherited aplastic anemia, malignant marrow infiltrative disorders, non-malignant infiltrative disorders, infections, poisons, immunological disorders, peripheral blood cell destruction, and megaloblastic anemia brought on by nutritional inadequacy are among the conditions that can cause the condition.

In a study, Bhatnagar et al.,[3] presented an analysis of 109 children admitted with pancytopenia. Megaloblastic anemia, acute leukemia, and aplastic anemia were discovered with underlying causes in 28%, 21%, and 20% of cases, respectively. Of all infectious causes, 30% of patients had enteric fever. Fever was the most common clinical characteristic (92%) in a research by Tufail et al.,[4] followed by pallor (83.2%) and enlarged viscera (64.8). The most frequent causes of pancytopenia were malignancy and aplastic anemia.

Nevertheless, these patients' clinical pictures vary based on underlying cause. Acute leukemia, idiopathic thrombocytopenic purpura, megaloblastic anemia, and aplastic anemia are common causes of bicytopenia, while acute leukemia, megaloblastic anemia, and aplastic anemia are common causes of pancytopenia.[5] Bicytopenia and pancytopenia in children coming to tertiary level hospitals from India are only briefly described. Most are infrequent case reports that focus on a single ailment. Notably, data on pediatric patients are few[6-8] until date, in south India.

The main factor in determining the underlying etiology of pancytopenia is bone marrow examination.[9] The underlying etiology of bi/pancytopenia differs from region to region and has evolved over time as a result of different genetic backgrounds, changing lifestyles, dietary habits, rising levels of daily radiation exposure, rising levels of drug exposure, and improved knowledge and diagnosis of metabolic genetic disorders. A sizable percentage of kids are treated every day with prognosis of cytopenia. Children who appear with cytopenias deal with evaluation and management challenges for clinicians and pathologists alike. Considering these we evaluated the clinical profile and etiology of children admitted with bicytopenia or pancytopenia to a tertiary care facility in South India.

Aims and objectives

1. The primary objective of this study was to find out the clinical and etiological spectrum in children with bicytopenia and pancytopenia who were admitted to the Institute of Child Health and Research Center, Government Rajaji Hospital, Madurai.
2. The secondary objective of this study is to follow-up children with bicytopenia and pancytopenia to find out the outcome and prognosis.

MATERIALS AND METHODS

This study was in the Department of Pediatrics at the Government Rajaji Hospital in Madurai, Madurai Medical College's Institute of Child Health and Research Center, which is where we carried out the study. This trial was take place from April 2021 to July 2022, with approval by the Madurai Medical College's Ethical Committee. Before the study, the parents' informed agreement was obtained. Two hundred and sixty-four patients with bicytopenia and 36 patients with pancytopenia out of 9675 patients aged 2 months–12 years who were admitted to our facility during the study period were included in the study. Findings of the bone marrow aspiration/biopsy, the complete hemogram, the peripheral smear, the erythrocyte sedimentation rate, the C-reactive protein, the culture reports, the viral tests, the liver function tests, the results of the liver function tests, and any other pertinent investigation reports were all recorded in the pro forma.

The automated hematology analyzer from SYSMEX evaluated the entire hemogram. Blood counts from an automated analyzer were compared to a peripheral smear report from a pathologist. Hemoglobin 10%, total leukocyte count 4000/mm^3, and platelet count 1 lac/mm^3 were used to define cytopenia. Reduction in either two of the aforementioned indicators was referred to as bicytopenia. Pancytopenia was characterized as a decrease in each of the three variables. Exclusion criteria included a child with known acute leukemia and lymphoma, aplastic anemia, and chronic immune thrombocytopenic purpura, diagnosed before the study period and receiving regular therapy in our institute.

According to the clinical indication, a bone marrow aspiration and biopsy were performed. It was carried out in all cases of pancytopenia, as well as cases of bicytopenia with anemia, thrombocytopenia, leukocytosis, and in kids whose peripheral smear report showed atypical cells or blast cells. When necessary, immunohistochemistry and cytogenetic analysis were performed along with morphological evaluation of bone marrow smears or biopsy samples to establish the diagnosis.

Once in 2 weeks, all children with bicytopenia and pancytopenia were assessed in our Saturday hematology outpatient clinics. We evaluated the short-term prognosis for bicytopenia and pancytopenia, including recovery, relapse, and treatment failure or death. SPSS version 19 was used for analysis.

RESULTS

Most of the study participants with pancytopenia and bicytopenia were in the age group of 1–6 years and

7–12 years, respectively, with notable male predominance in both conditions. Leucopenia along with thrombocytopenia, anemia along with thrombocytopenia, and anemia along with leucopenia were noted among 66%, 32%, and 2% of the participants, respectively. Hematological picture of participants with pancytopenia and bicytopenia is given in Table 1.

Fever was the most common presentation among both pancytopenia and bicytopenia followed by among cases with pancytopenia, bleeding manifestations, lethargy, loss of weight, abdominal distension, abdominal pain, convulsion, joint pain, loose stools, and jaundice were reported. Similarly, among the cases with bicytopenia, the common symptom includes abdominal pain, bleeding manifestations, loss of weight, lethargy, abdominal distension, convulsion, joint pain, loose stools, and jaundice were reported. Presenting symptoms and clinical signs is given in Table 2.

Notably, on assessing, the etiological factors among the cases with pancytopenia, malignancy, infections, non-infections, and idiopathic causes were reported in 11%, 58%, 17%, and 14% of cases, respectively. Similarly, the cases with bicytopenia, malignancy, infections, non-infections, and idiopathic causes were reported in 23%, 70%, 4%, and 3% of cases, respectively (Table 3).

On assessing the prognosis, among cases with pancytopenia 28%, 33%, 6%, and 33% of cases were recovered, died, lost to follow-up, and on treatment, respectively. Similarly, among cases with bicytopenia 67%, 11%, 4%, and 18% of cases were recovered, died, lost to follow-up, and on treatment, respectively (Table 4).

Table 1: Profile of study participants

Variables	Pancytopenia (%)	Bicytopenia (%)
Age group		
2–12 months	8 (22)	14 (5)
1–6 years	22 (61)	108 (41)
7–12 years	6 (16)	142 (54)
Gender		
Male	20 (56)	155 (59)
Female	16 (44)	109 (41)
Hematological parameters		
Hemoglobin <10 g/dL	36 (100)	89 (34)
Total leukocyte <4000/μL	36 (100)	179 (68)
Platelet count <1 lakh/μL	36 (100)	259 (98)
Circulating blasts	4 (11)	53 (20)

Table 2: Clinical presentation of study participants

Clinical presentation	Pancytopenia (%)	Bicytopenia (%)
Presenting symptoms		
Fever	31 (86)	247 (94)
Abdominal pain	4 (11)	116 (44)
Bleeding manifestations	10 (28)	24 (9.7)
- Petechial rashes	3 (8)	8 (3)
- Hematemesis	-	4 (2)
- Malena	2 (6)	2 (0.7)
- Bleeding from gums	2 (6)	5 (2)
- Epistaxis	3 (8)	5 (2)
Joint pain/leg pain	3 (8)	9 (3)
Jaundice	1 (3)	2 (0.7)
Loss of weight/appetite	7 (19)	23 (9)
Abdominal distension	7 (19)	17 (6)
Lethargy	8 (22)	18 (7)
Convulsion	4 (11)	3 (1)
Loose stools	2 (6)	7 (3)
Clinical signs		
Pallor	36 (100)	99 (38)
Lymphadenopathy	4 (11)	32 (12)
Icterus	2 (6)	2 (0.7)
Hepatomegaly	13 (36)	97 (37)
Splenomegaly	8 (22)	58 (22)

DISCUSSION

In the present study, the most frequent symptom of both bicytopenia and pancytopenia was fever. On assessing the etiology, cancer, infections, non-infections, and idiopathic

Table 3: Etiology of pancytopenia and bicytopenia

Etiology	Pancytopenia (%)	Bicytopenia (%)
Malignant	4 (11)	60 (23)
- ALL	4 (11)	50 (19)
- AML	-	10 (4)
Infectious	21 (58)	184 (70)
- Dengue fever	4 (11)	162 (61)
- Septicemia	13 (36)	18 (6)
- Enteric fever	-	4 (2)
- Tuberculosis	3 (8)	-
- Falciparum malaria	1 (3)	-
Non-infectious	6 (17)	12 (4)
- Aplastic anemia	3 (8)	-
- Chronic liver disease with portal hypertension	1 (3)	3 (1)
- Neonatal hepatitis	1 (3)	1 (0.3)
- SLE	1 (3)	-
- Chemotherapy-induced		3 (1)
- Bernard-Soulier syndrome	-	1 (0.3)
- Hereditary spherocytosis	-	1 (0.3)
- Wiskott-Aldrich syndrome	-	1 (0.3)
- Gauchers disease	-	1 (0.3)
- Megaloblastic anemia	-	1 (0.3)
Undiagnosed	5 (14)	8 (3)

Table 4: Prognosis of study participants

Prognosis	Pancytopenia (%)	Bicytopenia (%)
Recovered	10 (28)	176 (67)
Death	12 (33)	30 (11)
Lost to follow-up	2 (6)	10 (4)
On treatment	12 (33)	48 (18)

causes were reported in 11%, 58%, 17%, and 14% of cases, respectively, when analyzing the etiological factors among cases with pancytopenia. Similarly, 23%, 70%, 4%, and 3% of cases, respectively, were observed to have bicytopenia, malignancy, infections, non-infections, and idiopathic causes. Among instances with pancytopenia, the prognosis showed that 28%, 33%, 6%, and 33% of cases recovered, died, were lost to follow-up, and were receiving therapy, respectively. Similar to those patients, 67%, 11%, 4%, and 18% of cases with bicytopenia were recovered, died, lost to follow-up, and were receiving therapy, respectively.

The clinicoetiological characteristic of pancytopenia and bicytopenia in children was examined by Sharma et al.[10] According to their findings, 46 of the 50 cases under investigation had non-malignant origins, 92.3% of them involved bicytopenia, and 91.7% involved pancytopenia. Twenty of the 46 cases had infectious origins. The most frequent factor, accounting for 35% of cases, was sepsis. Malaria, enteric fever, and dengue fever were some of the additional reasons. In 53% of instances, nutritional anemia was shown due to bicytopenia. Megaloblastic anemia and aplastic anemia were the most frequent causes of pancytopenia. The bicytopenic and pancytopenic groups have significantly varied hematological characteristics. There were no appreciable differences in mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) between the groups. Aplastic anemia was characterized by hemoglobin and a low white blood cell (WBC), whereas megaloblastic anemia individuals had more severe thrombocytopenia. In four out of 50 instances, leukemia was determined to be the cause; in these two, pancytopenia and bicytopenia were present at the time of presentation. They came to the conclusion that nutritional deficiencies and infections were the main causes of pancytopenia and bicytopenia. The majority of the time, a history, examination, and simple diagnostic tests were successful in providing the diagnosis.

To ascertain the prevalence of various clinical manifestations, hematological findings, etiological profiles, and outcomes of cytopenias in children, Rasheed et al.,[11] conducted a study. They stated that 64.2% of the 53 total patients were men. At the time of presentation, the average age was 6 years. Malnutrition affected patients in a 52% rate. Fever (90.6%) and pallor (98.1%) were the most prevalent first symptoms. Of the patients, 62.3% had pancytopenia. The main contributing factors were megaloblastic anemia (22.6%), infections (24.5%), and hematological malignancy (26.4%). Compared to pancytopenic children, bicytopenic individuals had more infections and megaloblastic anemia. They asserted that the most typical but non-specific symptoms of bi/pancytopenia in children are fever and pallor. The most frequent cause of bi/pancytopenia was hematological malignancies, but infections and megaloblastic anemia can also manifest similarly.

A study was conducted by Patil[12] to identify the clinical characteristics, etiology, and hematological spectrum of pancytopenia in children from Kalaburagi, Karnataka, India, ranging in age from 1 month to 18 years. With mean age of 69.47 months, they noticed that of the 60 patients, 43.3% were male and 56.7% were women. Fever, arthralgias, weight loss, and failure to thrive were all present in 71.7%, 55.5%, and 18.3% of patients, respectively. Aplastic abnormalities were found in 37.5%, hyperplastic changes in 21.9%, and normal cellularity in 40.6% of patients, based on bone marrow analysis. Common dietary cause of pancytopenia, observed in 21.7% of patients, was pancytopenicanemia. Common neoplastic etiology, found in 8.3% of patients, was acute lymphoblastic Leukemia (ALL). Other significant etiologies included aplastic anemia, miliary tuberculosis (TB), parvovirus B19, systemic lupus erythematous, and hemolytic anemia. They asserted that the majority of causes of pancytopenia in children in our area can be avoided.

The etiohematological profile, clinical correlations, and prognosis of pancytopenia in Indian children were examined by Alim et al.[13] Mean age at diagnosis was 70 months out of 84 cases. About 37% of patients' bone marrows exhibited aplastic alterations, and 14% of individuals had hyperplasia. In their investigation, aplastic anemia, acute leukemia, and nutritional anemia were common causes. In the 1st year of follow-up, 67% of pancytopenic patients survived, whereas 12% passed away, and 26% of children with aplastic anemia and 9% of children with ALL did not. Patients' anthropometric status and severity of aplastic anemia were substantially related to the result. Since both benign nutritional deficits and malignant hematological neoplasms were prevalent in their research population, their data indicate a complicated picture of pancytopenia in that community.

To find the prevalence of different types of pancytopenia in the pediatric population, Zubair et al.,[14] mean age of 96 patients was 69.47 months, with 43.8% of them being male. Fever, arthralgias, weight loss, and failure to thrive were all present in 71.9%, 56.3%, 35.4%, and 18.8% of patients, respectively. Aplastic abnormalities were found in 37.5%, hyperplastic changes in 21.9%, and normal cellularity in 40.6% of patients, based on bone marrow analysis. Common dietary cause of pancytopenia, which was present in 21.85% of patients, was megaloblastic anemia. A common neoplastic cause, found in 19.8% of patients, was ALL. Other significant etiologies included hemolytic anemia, parvovirus B19, aplastic anemia, and miliary TB. They concluded that prevalent curable

etiologies of pancytopenia in the pediatric age group were megaloblastic anemia and infections like TB. Common neoplastic etiology was ALL.

Sarbay[15] analyzed the grades of hematological abnormalities according to etiology among children. About 56.2% of the 130 patients who participated were men, and 43.8% were women. The patients were 4.9 years old on average. Patients had bicytopenia in 65.3% of cases and pancytopenia in 34.6%. One hundred and thirty patients totaled, and three of them had hyperleukocytosis (WBC >50.000/mm^3). Thirty-five patients had Vitamin B12 insufficiency that was found. Leukocyte count, hemoglobin level, mean corpuscular volume (MCV) elevation, and low platelets were more among patients with secondary causes of cytopenias. They asserted that differentiating between primary hematological disorders and secondary causes of pancytopenia and bicytopenia may be aided by determining the severity of cytopenias in the differential diagnosis.

Bahal et al.,[16] included 126 cases in total, 126 of which had bone marrow aspiration, and 78 of which underwent trephine biopsy. Bicytopenia and pancytopenia were noted in 57.9% and 42.1% of cases in our study, respectively. Most cases were noted during the second decade. Clinical signs of pallor and fever were often noted in both cytopenias. Bicytopenia was linked with splenomegaly, lymphadenopathy, and hepatomegaly. In pancytopenia, bleeding and petechial rash were more frequent. Common bicytopenia combinations were anemia and thrombocytopenia (67.1%), followed by anemia and leucopenia (26.0%) and thrombocytopenia and leucopenia (6.8%). They asserted that trephine biopsy and aspiration of bone marrow are crucial diagnostic methods for assessing cytopenia instances. The two techniques work best when used together.

De et al.,[17] assessed the clinicohaematological and etiological characteristics in kids with cytopenias. Common benign causing bicytopenia was megaloblastic anemia and aplastic anemia in pancytopenia, and the common malignant cause being ALL. Primary hematological examinations and aspiration of bone marrow in cytopenic patients are important for understanding the illness process, diagnosing cytopenia or excluding other possible causes, and planning follow-up tests and patient care.

Rawat et al.,[18] reported average age of cases as 10.58 years. MCV was 90.9 fl, MCH was 30.1 pg, MCHC was 33.1%, and retic count was 1.21%. The mean Hb was 5.31 g/dL and TLC was 2492.68/mm^3. Aplastic anemia (24%), followed by nutritional insufficiency (28%), was the two most frequent etiology of pancytopenia. The most frequent kind of nutritional anemia with pancytopenia (71.4%) was megaloblastic anemia. According to their claims, aplastic anemia and nutritional anemia are a common causative factor of pancytopenia, which is a significant presentation in the pediatric population. The most frequent cause of nutritional anemia with pancytopenia is megaloblastic anemia.

Thappa et al.,[19] assessed the prevalence of the etiological spectrum of pancytopenia in children between the ages of 2 months and 12 years. They included 91 children with pancytopenia among them majority (43.9%) of the children were aged 1–6 years. Unaccounted-for fever (82.9%), pallor (10.8%), and bleeding (9.8%) have been recognized as the most frequent clinical presentations for admission. Megaloblastic anemia (25.2%), ALL (18.6%), and aplastic anemia (13.1%) were the most prevalent major etiologies. Infected children with HIV, TB, and EBV can also have pancytopenia. They came to the conclusion that frequent causes of pancytopenia in children were ALL and bone marrow failure. When diagnosing pancytopenia in children from underdeveloped countries, it is highly recommended to note both the symptoms of specific viral and bacterial illnesses in addition to symptoms of iron deficiency anemia.

Limitations of the study

1. Investigations like viral antigen and antibody testing for CMV, EBV, Parvo virus, genetic analysis for storage disorders were not available in our hospital setup, so in few cases etiological diagnosis could not be made.
2. The study period was one and half years, which is not sufficient to predict the outcome in children with acute leukemia and other chronic disorders.

CONCLUSION

In children, there are wide etiological ranges of cytopenias. Infections and dangerous diseases like acute leukemia are among the reasons. The geographical location of the hospital, the frequency of malnutrition, and the regional presence of certain diseases such as malaria and enteric fever determine the causes reported in a hospital environment. To make a general diagnosis and to prepare for more tests, a comprehensive history and clinical examination are essential. Extensive thorough studies should only be carried out after excluding common cytopenia-causing factors. This study demonstrated that most illnesses that cause bicytopenia and pancytopenia are curable and have a favorable prognosis.

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VAM- Definition of intellectual content, literature survey, prepared the first draft of the manuscript, implementation of the study protocol, data collection, data analysis, manuscript preparation, and submission of the article; **LK-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **SA-** Design of study, statistical analysis and interpretation, and review manuscript; **SSR-** Literature survey and preparation of figures, coordination, and manuscript revision.

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