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Original Research Article

Peripheral cytopenia in children: a hospital-based study

Aditi Gupta, Ruchika Bhatnagar*, P. L. Prasad

Department of Paediatrics, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India

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***Correspondence:**
Dr. Ruchika Bhatnagar,
E-mail: ruchu.bhatnagar@gmail.com

ABSTRACT

Background: Peripheral cytopenia with its ramifications as pancytopenia and bicytopenia is a common hematological phenomenon in children. Its etiology ranging from benign self-limiting illness to severe life-threatening conditions decide the management and prognosis in these children. This study aims to describe the clinical, haematological and etiological profile of peripheral blood cytopenia in children of Rohilkhand region.
Methods: A hospital based prospective observational study conducted in the Pediatric ward of a teaching hospital over a period of 30 months. All children between age 6 months to 14 years with bicytopenia and pancytopenia on hemogram were included. Detailed history, clinical examination, haematological tests followed by bone marrow aspiration wherever indicated was performed. Additional tests like parasitological and sepsis work up was undertaken on case to case basis, to ascertain the cause of cytopenia.
Results: Bicytopenia was more common than pancytopenia (61.2% vs. 38.8%) The most common age group observed was 10-14 years. Normocytic normochromic blood picture was seen in all cases of cytopenia while macrocytic normochromic blood picture had statistically significant association with pancytopenia. Fever was the commonest symptom, while pallor was the commonest sign followed by hepatosplenomegaly. Most common etiology in bicytopenia was infective (68%) while pancytopenia reported equal incidence of infective (50%) and non-infective causes. Malaria was the commonest infective cause of bicytopenia (46.3%) and pancytopenia (27%). Children with bicytopenia had higher incidence of malignancy (22% vs. 7.7%) and lesser incidence of nutritional causes (7.3% vs. 27%), and aplastic anemia (2.4% vs. 15.4%) as compared to pancytopenia.
Conclusions: Clinical assessment coupled with haematological tests plays a pivotal role in ascertaining the cause of cytopenia in children. As the etiologies are varied, their knowledge and distribution unique to a particular region may help in better management and outcome.

Keywords: Bicytopenia, Children, Infections, Malaria, Megaloblastic anaemia, Pancytopenia

INTRODUCTION

Peripheral cytopenia is defined as reduction in either of the cellular elements of blood, i.e. red cells, white cells or platelets. Bicytopenia is reduction in any of the two cell lines and pancytopenia is reduction in all the three.[1] Pancytopenia and bicytopenia is not an uncommon hematological entity, the underlying causes of which differ according to the geographical distribution and genetic alterations.

The wide array of etiological spectrum ranges from transient, self-limiting viral illnesses, preventable and treatable conditions like megaloblastic anemia, tropical infectious diseases to severe and life-threatening illnesses like aplastic anemia, leukemia and other malignancies. The underlying mechanism for cytopenia include decreased hematopoietic cell production, trapping of normal cells in overactive and hypertrophied reticuloendothelial system as in hypersplenism,

ineffective hematopoiesis or replacement by abnormal or malignant tissue in the marrow.[2,3]

Though the etiologies of bicytopenia and pancytopenia are different, yet the clinical presentations are very similar. Symptoms are attributable to anemia, thrombocytopenia and/or leucopenia. The most common presenting features are fever and pallor and signs being hepatomegaly and/or splenomegaly.[4,5] The understanding of etiology is important for specific management and further prognostication. Pancytopenia in children has been extensively explored through various studies, but there is paucity of such data on pediatric bicytopenia. The present study intends to describe the clinical, etiological and hematological profile of pancytopenia and bicytopenia in children of Rohilkhand region. It also aims to emphasize on preventable and treatable causes of cytopenia like megaloblastic anemia, viral illness and infectious diseases which account for majority of the clinical conditions resulting in peripheral cytopenia in developing world.

METHODS

A prospective observational study was conducted in the Pediatric ward of a teaching hospital from November 2015 for 30 months. After seeking Institutional Ethics Committee (IEC) approval and written informed consent, all patients of age 6 months to 14 years who fulfilled the inclusion criteria i.e. bicytopenia or pancytopenia on hemogram were enrolled into the study. Previously diagnosed cases of aplastic anemia and leukemia, and children with history of receiving blood transfusion in past six weeks were excluded from the study. Hemogram was done using 2ml blood collected in EDTA vial and processed using automated analyzer based on the Coulter principle, 3-part differential counter. Pancytopenia was defined as decrease in all three cell lineages that is hemoglobin based on age: 6 months to 4 years- <11 gm %, 5 to 7 years- <11.5 gm%, 8 to 14 years- 12 gm%, platelet count- <1,50,000, total leukocyte count 6 to 23 months- <6,000/cu.mm, more than 2 years- <4,000/cu.mm.[1,6,7] Bicytopenia was defined as decrease in any of the two peripheral cell lines.[1] Based on further clinical assessment and hemogram results, patients were subjected to bone marrow aspiration wherever indicated, after taking written informed consent from the parents. It was done as per the standard norms.[8] On the basis of clinical assessment, provisional diagnosis and also to ascertain the etiology of bicytopenia/pancytopenia, additional investigations performed included peripheral smear for malarial parasite, malaria antigen test, dengue antigen test (NS1 and 2), typhoid test (Widal), blood culture and sensitivity, serum Vitamin B12 and folic acid levels. Deficiency of vitamin B12 was considered when serum B12 levels were less than 100 pg/ml while deficiency of folic acid was considered when serum folate level was less than 3 ng/ml.[9]

After calculating the sample size using the standard formula and assuming working error of 10%, 153 children were enrolled into this study over a period of 30 months. Statistical tests applied for qualitative and quantitative data were chi square test and student-t test respectively using SPSS Software version 17, p value of <0.05 was considered to be statistically significant.[10]

RESULTS

In this study 153 admitted children fulfilled inclusion criteria, 13 were excluded as parents did not give consent, 2 children left against medical advice, and thus 138 children were enrolled, of which 85(61.2%) had bicytopenia and 53(38.8%) had pancytopenia with male : female ratio being 1.6:1. Both bicytopenia and pancytopenia were seen more commonly in age group 10-14 years with 46.3% and 61.5% of their total cases respectively.

Normocytic normochromic blood picture constituted 65.7% of all cases of cytopenia, out of which 55 cases belonged to the bicytopenia group and 36 cases of pancytopenia. The next most common blood picture seen was macrocytic normochromic. As compared to bicytopenia, pancytopenia was found to have statistically significant association with macrocytic normochromic blood picture (Table 1).

Bone marrow study was done in 21 cases and hypercellular marrow was the commonest (65%) finding followed by hypocellular marrow. Amongst all the cases of bicytopenia, red blood cells and platelets were the most commonly affected cell lineages as observed in 92.7% of the cases (Table 2). Most common infective cause of cytopenia evident from this study was malaria followed by dengue, sepsis and typhoid.

Based on clinical assessment and investigative workup, all cytopenia cases were classified into two groups: infective and non-infective. Infective etiology comprised of 61.2% of all the cases.

Table 1: General blood picture in children with pancytopenia and bicytopenia.

General blood picture	Total no. of cases(n=138)	%	Pancytopenia (n=53)	Bicytopenia (n=85)	p value
Macrocytic normochromic	29	20.9%	18	11	0.028
Microcytic hypochromic	18	13.4%	02	16	0.138
Normocytic normochromic	91	65.7%	33	58	0.570

Table 2: Distribution of cell lines affected in bicytopenia.

	Total no. of cases (n=138)	%
Anemia and thrombocytopenia	127	92.7%
Anemia and leucopenia	08	4.9%
Leucopenia and thrombocytopenia	03	2.4%

Of the total 83 cases of infective etiology, 57 cases presented with bicytopenia while non infective etiology presented equally with pancytopenia and bicytopenia.

The most common infective cause of pancytopenia and bicytopenia was malaria and its association with bicytopenia was found to be statistically significant (Table 3). Amongst the noninfective etiology, malignancy was observed to be the commonest one followed by the nutritional causes like vitamin B 12 and folate deficiency. Although pancytopenia is considered to be the common hematological finding in malignancy but in this study, bicytopenia was found to have statistically significant association with all malignant cases (Table 3).

Table 3: Etiological profile of children with bicytopenia and pancytopenia.

Etiology	Bicytopenia (n=85)	Pancytopenia (n=53)	p value
Infective	57(68%)	26(50%)	
Malaria	39(46.3%)	14(27%)	0.035
Dengue	06(7.3)	4(7.7%)	1.000
Sepsis	04(4.9%)	4(7.7%)	0.638
Typhoid	02(2.4%)	4(7.7%)	0.555
Tuberculosis	02(2.4%)	0	1.000
Others	04(4.9%)	0	0.518
Non infective	28(31.7%)	27(50%)	
Malignancy	19(22%)	4(7.7%)	0.006
Nutritional	07(7.3%)	15(27)	0.107
Aplastic anemia	02(2.4%)	8(15.4)	0.136

Table 4: Clinical profile of children with bicytopenia and pancytopenia.

Symptoms	Bicytopenia (n=85)	%	Pancytopenia(n=53)	%
Fever	85	100%	47	88.5%
Jaundice	12	14.6%	4	7.7%
Malena	10	12.2%	4	7.7%
Epistaxis	6	7.3%	4	7.7%
Lethargy	6	7.3%	12	23.1%
Weight loss	2	2.4%	4	7.7%
Gum bleed	0		2	3.8%
Joint pain	0		2	3.8%
Signs				
Pallor	76	90.2%	49	92.3%
Hepatomegaly	60	70.7%	20	38.5%
Splenomegaly	39	46.3%	18	34.6%
Lymphadenopathy	19	22%	8	15.4%
Petechiae	12	14.6%	8	15.4%
Mucosal bleed	2	2.4%	2	3.8%
Bony tenderness	2	2.4%	0	

The most common clinical symptom observed in all cytopenic children was fever. Jaundice was seen more frequently in bicytopenia while lethargy was found to be more commonly associated with pancytopenia (Table 4).

DISCUSSION

Peripheral blood cytopenia is a common hematological entity manifesting as pancytopenia or bicytopenia on the basis of number of cell lines affected. It may be due to decreased bone marrow production or, increased splenic sequestration or an immune mediated destruction of blood cells. Initially there is mild impairment in the marrow function which may go undetected and becomes apparent in times of stress or increased demand. The frequency of bicytopenia and pancytopenia was observed to be 61.2% and 38.8% respectively. This predominant occurrence of bicytopenia over pancytopenia is also reported by various authors.[11,12] Contrary to this, Dosi et al, found pancytopenia more common than bicytopenia with frequency of 55.2% and 44.8% respectively.[13]

Most common age group involved in both bicytopenia and pancytopenia was 10 years and above and was found uncommon amongst infants and toddlers. Similar

findings were shown by other workers, while few authors reported it maximally among children of under 5 years of age.[12,14] This difference could be attributed to difference in methodology and period of observation.

Male preponderance has been reported by other authors in both bicytopenia and pancytopenia and this study also had similar findings.

Peripheral blood smear examination should be the first basic investigation in all cases of anemia. Normocytic normochromic blood picture constituted 65.7% of all cases of cytopenia followed by macrocytic normochromic picture, of which later had statistically significant association with pancytopenia, thereby reflecting the underlying etiology. There is scarcity of data on such correlation in pediatric patients and to the best of knowledge, no study has analyzed the general blood picture findings in cytopenic children.

Pancytopenia in children is thoroughly evaluated in literature as witnessed by numerous studies, but there is paucity of data on comparative evaluation of pancytopenia and bicytopenia.[15] As the etiological spectrum of cytopenia in children is wide and diverse depending upon the genetic background, nutritional milieu, socioeconomic status and topographical conditions, it is prudent to delineate the self-limiting and benign conditions from the life-threatening illnesses. Considering this fact, the present study is undertaken to apprise the pediatricians and general physicians of the various clinical conditions resulting in bicytopenia and pancytopenia in children, prevalent in the Rohilkhand region.

Infections are the predominant cause accounting for 68% of the total bicytopenic cases while pancytopenia had equal distribution amongst infective and non-infective cases. Similar results were reported by Chand et al, and Ameileena et al, in Uttarakhand region with megaloblastic anemia as the commonest cause of pancytopenia with frequency of 19% and 31.8% respectively.[16,17] Contrary to this, a study from Madhya Pradesh, classified etiologies into malignant and non-malignant, of which the most common non-malignant cause for pan/bicytopenia was megaloblastic anemia (18.8% and 45.8% respectively) while acute lymphoblastic leukemia dominated the malignant causes (27.1% and 18.6%).[13] A comparative analysis of pan/bicytopenia in adults and children by Shams et al, in Agra region revealed aplastic anemia to be the commonest cause among pediatric subjects (32.5%) while megaloblastic anemia seen more frequently among adult cases (37.5%).[18]

No study has grouped etiology as infective and non-infective for the researchers to compare. This separation was done to highlight the high incidence of infective etiology of cytopenia and consequently its prevention which would reduce morbidity and improve overall health status of the community. Higher prevalence of infections in this study could be explained by the fact that this hospital being a tertiary care center caters to the rural population of Rohilkhand region where the overall health awareness is suboptimal. As a result of which patients arrive after considerable delay and overwhelming infections.

Malaria was found to be the commonest infective cause amongst all the cytopenic cases while nutritional causes like vitamin B12 and folate deficiency dominated the non-infective etiologies of pancytopenia in this study. Pancytopenia in malaria is attributable to direct bone marrow invasion by the parasite, immune hemolysis, hypersplenism, bone marrow necrosis or hemophagocytosis. These findings were consistent with the study done in southern Maharashtra.[19] It is contrary to the results obtained in Uttarakhand study, where kala azar was the leading infectious cause of pancytopenia.[16] The frequency of megaloblastic anemia in the present study was 80%, of which cobalamin deficiency contributed to 60%, which is similar to the findings of Chandra et al, which reported low folate and cobalamin levels in 50% and 62% cases respectively.[20]

This change in trend may be related to the introduction of National Nutritional Anemia Prophylaxis Program introduced by the government of India in 1970 and revised to National Nutritional Anemia Control Program in 1991. Under this programme, 5mg of folic acid and iron to all pregnant women, as a result of which children born to these mothers have adequate folate and iron stores at birth.[21] Malignancy was observed to be the commonest non-infective etiology amongst the bicytopenia cases. Of the total 11 cases of malignancy, 9 presented with bicytopenia, making the correlation between bicytopenia and malignancy statistically significant. Similar findings were reported by other authors reflecting the fact that malignancies should also be suspected as the underlying cause of bicytopenia after ruling out other common causes.[11,15] Tufail et al, reported malignancy to be more commonly associated with pancytopenia in more than half of the cases.[22]

Peripheral blood cytopenia usually presents with the clinical signs and symptoms such as pallor, lethargy, and bleeding, bruising and increased tendency of acquiring infection. As platelets have the shortest half-life, platelet count is first to be affected while anemia develops slowly because red blood cells have the longest half-life.

This study demonstrated fever to be the commonest symptom in all cases of bicytopenia and in 88.5% cases of pancytopenia, while pallor was a frequently reported symptom in other studies.[14,19] This variation could be explained because of grouping signs and symptoms together as clinical features in above mentioned studies.

The most common clinical sign observed in all children of cytopenia was pallor, which is in accordance with the

studies done by Dubey et al, and Rathod et al, while bleeding manifestations were commonly seen in other study.[17,14,23] It was followed by hepatosplenomegaly, as also observed by other authors.[15]

Comparative studies on pancytopenia and bicytopenia among pediatric population are lacking in literature. Understanding and knowledge of varied etiologies prevalent in this geographical area along with differential presentation in both these groups may help in better evaluation and prompt management of patients.

CONCLUSION

Pancytopenia and bicytopenia are commonly encountered haematological entities. The present study analysed and compared the clinical, haematological and etiological profile of pancytopenia and bicytopenia in children. The former condition is looked upon with great concern while bicytopenia is considered to be a trivial phenomenon. This study emerged out with varied etiologies giving rise to pancytopenia and bicytopenia in children, of which potentially treatable and reversible causes like infections and nutritional deficiencies account for majority of the pancytopenia cases. On the contrary, malignancies were found to be have significant association with bicytopenia. Clinical examination and general blood picture further help in planning the investigations and management of patients thereby influencing the quality health care.

Pancytopenia and bicytopenia presents with wide array of diagnostic possibilities was already known.

This study adds,

- Bicytopenia as a more common haematological finding in malignancies with statistically significant association.
- Emerging use of estimation of serum vitamin B12, folate levels and parasitological tests obviate the use of invasive procedures like bone marrow aspiration in evaluating cytopenia.
- Malaria emerged as the commonest infective cause of bicytopenia.

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