Aetiology of Cytopenia's in Children - A Five Year Study in a Tertiary Health Care Centre in Kerala

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ABSTRACT

BACKGROUND

Cytopenia is the most common condition in paediatric population which requires detailed haematological evaluation. The objective of this study was to understand the, aetiological factors of the three types of cytopenia (single cytopenia, bicytopenia, pancytopenia) in children.

METHODS

This study is a descriptive & retrospective 5 year study conducted in the Haematology wing of a paediatric tertiary health care centre in South India. Data of all cases who underwent detailed haematological evaluation like Complete blood count, peripheral smear and bone marrow examination for cytopenias during the study period were included in the study.

RESULTS

The study sample was 365. The total number of patients with single cytopenia (isolated anaemia / leukopenia / thrombocytopenia) was 240 (65.7 %), bicytopenia were 90 (24.6 %) and pancytopenia was 35 (9.58 %). There was slight female predominance (M: F = 1: 1.05). Bicytopenia and pancytopenia were commonly observed between 1 - 5 years of age, while single cytopenias were more common in 5 - 10-year age group. The analysis of symptoms and signs in all cytopenia groups showed petechiae / purpura as the most common presentation in single cytopenia. The analysis of clinical symptoms showed significant correlation (P value < 0.05). Single cytopenia was the most common observed type of cytopenia with Immune thrombocytopenic purpura as the commonest aetiologic factor. In the present study most common causes of bicytopenia were reactive conditions like ITP with and without anaemia, infections etc. Acute Lymphoblastic Leukaemia (ALL) was the most common aetiologic factor for pancytopenia (ANOVA test and Bonferroni test P value < 0.05). Isolated thrombocytopenia was the most common peripheral smear picture observed, followed by hypochromic microcytic picture and combination of hypochromic microcytic anaemia (HMA) with thrombocytopenia.

CONCLUSIONS

Children with cytopenias commonly have benign conditions than malignant conditions. Cytopenias due to primary haematological malignancies are more common than secondaries.

KEYWORDS

Bicytopenia, Cytopenia, Children, Aetiology, Paediatric Pancytopenia

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BACKGROUND

Peripheral cytopenia is defined as the reduction of any one of the three types of blood cells - RBCs, WBCs or platelets. Cytopenias are further classified into three types depending on number of cell lineages affected in peripheral blood. Reduction in any one of the blood cells can result in single cell cytopenias. Bicytopenias occur with reduction of any two types of cells and pancytopenia occurs when all the three lineages are reduced in peripheral blood. The causes of different types of cytopenias varies from mild viral fever to life threatening conditions like malignancies. Moreover, the causes of same type of cytopenias from same geographical background shows drastic changes between adult and paediatric population. Though pancytopenia and bicytopenia are reasonably well studied topics in paediatric population, we couldn't access a single study comparing all the three types of cytopenia in literature search. In our Centre the most common type of cytopenia a pathologist encountered was single cell cytopenia.

Peripheral cytopenia evaluation starts with routine blood counts. Though the type of blood cells affected in peripheral cytopenias can be understood with complete blood count, some of the cases require further evaluation with morphological studies like peripheral smear and bone marrow film examination. Though single cell cytopenias are more commonly seen in benian self - limiting conditions. they can be earliest haematological manifestations of lethal diseases like malignancies as well. The most important factors which result in peripheral cytopenias are hypo proliferative causes, peripheral destruction by immune / non immune mechanisms, neoplastic marrow infiltration causing suppression of haematopoiesis and ineffective hematopoiesis. 1 In general it is assumed that the severity of marrow pathology increases with the number of cell lineages affected and also the extent and grade to which they are reduced. Meticulous examination of morphology of blood cells in peripheral and bone marrow films and correlation with clinical and biochemical parameters is required for making a definitive diagnosis in peripheral cytopenias.² Correct diagnosis of the cause of cytopenia is an equally challenging task for clinician and pathologists alike.

The socio demographic factors like dietary habits, life style, genetic diseases, exposure to radiation and other carcinogenic substances result in the wide difference in the etiologic factors of different types of cytopenias across the world.³ Since cytopenias are the most common causes which prompts the clinician to undertake detailed haematological paediatric evaluation in cases, the study etiomorphological factors in paediatric cytopenia will throw some light in improving the management strategies of cytopenia cases in the future. The main objective of our study was to determine aetiologic and clinical profile of all the three types of cytopenias in children.

METHODS

The study was a cross sectional descriptive 5-year study done in the paediatric Haematology wing of Pathology

Department of a tertiary health care Centre in South India. The study period was from 2015 January to 2019 December after getting Institutional Ethical Committee clearance. All cases of peripheral cytopenias who underwent evaluation in haematology lab with peripheral blood and bone marrow examination were selected for this study. The cases were studied using clinical case records retrieved from the Medical records library, haematology lab registers with documented blood counts and details of morphological study. The filed Giemsa / Leishman stained slides were reviewed in certain cases. Those cases who had complete aetiologic diagnosis with documented clinical, biochemical and haematological diagnosis were included as study samples, while those with indefinite / inconclusive results were excluded. Peripheral blood film and bone marrow films were selected as hematologic diagnostic methods in most of the cases, though cases of aplastic marrow were selected only from those cases who underwent a subsequent bone marrow biopsy after aspiration studies. In our centre 3-part Differential Analyzer of Sysmex was used for blood counts.

The cut off values of blood cells was selected based on criteria's used by previous authors. Haemoglobin cut-off value for 0 - 2 months was 9.4 g / decilitre, 2 - 6 months 11.0 g / dl, 10.5 g / decilitre for > 6 month - 2 years and11.5 g / decilitre for > 2 years – 12 years. The cut of values taken for Leucocyte count was < 6000 / mm3 for 2 months -2 years, < 5500 / mm3 for > 2 - 4 years, < 5000 / mm3 for > 4 - 6 years and < 4500 / mm3 for > 6 - 12 years. For diagnosing thrombocytopenia Platelet count of < 150,000 / mm3 was considered in all children > 1 month - 12 years. Based on number of cell lineages affected, the total cases were classified into three categories - single cytopenia, bicytopenia and pancytopenia. The grading of anaemia was done into mild, moderate and severe categories based on Hb values (Mild anaemia - Hb of 10.0 – 10.9 g / dl; moderate anaemia – Hb of 7.0 – 9.9 g / dl, severe anaemia Hb less than 7.0 g / dl). Thrombocytopenia was also classified into mild (> 75,000 / mm3), moderate 20,000 - 75,000 / mm3 and severe < 20,000 / mm3.

Statistical Analysis

The complete data regarding clinical features, signs, blood count values, peripheral smear & bone marrow morphology, biochemical details and final diagnosis was entered in SPSS software (version 16.0) and was analysed with suitable statistical tools. All parameters were separately analysed for each type of cytopenias and studied.

RESULTS

Total study sample in this study was 365. In our study male children constituted 48.7 % (N = 178) and female children constituted 51.2 % (N = 187) with a slight female predominance (M: F = 1: 1.05). The predominant age of presentation of cytopenias was from one to five years of age (36.7 %, N = 134), followed by 132 cases (36.16 %) in 5 to 10 years age group. Infants constituted 16.16 % cases (N = 59), and children aged more than 10 years was 40 (10.95)

%) in number. Bicytopenia and pancytopenia were commonly observed between 1 - 5 years of age, while single cytopenias were more common in 5 - 10 year age group. The total number of patients with single cytopenia (isolated anaemia / leukopenia / thrombocytopenia) were 240 (65.7%), bicytopenia were 90 (24.6%) and pancytopenia were 35 (9.58%) in number. Single cytopenias were most commonly observed in males (50.4%) while females showed slight predominance in bicytopenia (55%) and pancytopenia cases (51.42%).

The chi square analysis of symptoms and signs in all cytopenia groups showed petechiae / purpura as most common presentation in single cytopenia (42.5 %, N = 102), followed by pallor. Fever was the most common presentation in bicytopenia (42.2 %, N = 38) and pancytopenia (74.3 %, n = 26) and type of cytopenias in our study. This observation is significant (P value < 0.05). The analysis and statistical correlation of three types of cytopenias with clinical symptoms is depicted in Table 1.

Clinical Symptoms & Signs	Single Cytopenia N = 240, 65.7 %		Bicytopenia N = 90, 24.6 %		Pancytopenia N = 35, 9.58 %		
Clinical S & Si	Present	Absent	Present	Absent	Present	Absent	P Value
Bleeding	16.2 % N = 39	83.8 % N = 201	17.8 % N = 16	82.2 % N = 74	17.1 % N = 6	82.9 % N = 29	0.944
Fever	19.2 % N = 46	80.8 % N = 194	42.2 % N = 38	57.8 % N = 52		25.7 % N = 9	< 0.05
Fatigability	2.9 % N = 7	97.1 % N = 233	3.3 % N = 3	96.7 % N = 87	8.6 % N = 3	91.4 % N = 32	0.239
Joint pain	2.9 % N = 7	97.1 % N = 233	5.6 % N = 5		17.1 % N = 6	82.9 % N = 29	< 0.05
Pallor	29.2 % N = 70	70.8 % N = 170		71.1 % N = 64	37.1 % N = 13	62.9 % N = 22	0.612
Jaundice	4.6 % N = 11	95.4 % N = 229	2.2 % N = 2	97.8 % N = 88	14.3 % N = 5	85.1 % N = 30	< 0.05
Hepatomegaly	3.3 % N = 8	96.7 % N = 232	3.3 % N = 3	N = 87		65.7 % N = 23	< 0.05
Splenomegaly	4.2 % N = 10	95.8 % N = 230	7.8 % N = 7	92.2 % N = 83	42.9 % N = 15	57.1 % N = 20	< 0.05
Petechiae / purpura	42.5 % N = 102	57.5 % N = 138	36.7 % N = 33			97 % N = 34	< 0.05
Lymphadenopathy	1.7 % N = 4	98.3 % N = 236	3.3 % N = 3	96.7 % N = 87	14.3 % N = 5	85.7 % N = 30	< 0.05
Table 1. Analysis and Statistical Correlation of the Three Types of Cytopenia's with Clinical Symptoms							

The distribution of cases according to aetiology in three groups of cytopenias is depicted in Table 2. In our study majority of patients had cytopenias due to benign conditions like ITP (43.5 %, N = 159), followed by Iron deficiency anaemia (11.2 %, n = 41), infection related changes, anaemia of chronic disorder (7.1 %, N = 26), Haemolytic anaemia (3.01 %, n = 11), hemophagocytic lymphohistiocytosis (HLH) (2.73 %, N = 10) etc. Malignancies constituted 25 cases (6.84 %), of which 84 % cases (N = 21) showed primary malignancy - Acute Lymphoblastic leukaemia and 16 % (N = 4) showed metastasis in bone marrow from primary tumours like Neuroblastoma, Wilm's tumour and Rhabdomyosarcoma.

Most common type of single cytopenia observed was thrombocytopenia followed by anaemia. Leukopenia was the least common isolated cytopenia observed. Among the single cytopenias ITP was the most common etiologic factor observed followed by Iron deficiency anaemia and anaemia

of chronic diseases and infections. Most common etiologic factor of bicytopenia in our study was ITP followed by ITP with iron deficiency anaemia and infections. Malignancy were seen in 11 cases of bicytopenia; 7 showing ALL and all the 4 cases of metastatic malignancies presented with bicytopenia. In pancytopenia group all was the most common aetiology observed followed by HLH and Aplastic anaemia. The statistical correlation between etiological factors and type of cytopenia showed a significant correlation in ANOVA test (P value < 0.05) and Bonferroni test (P value < 0.05).

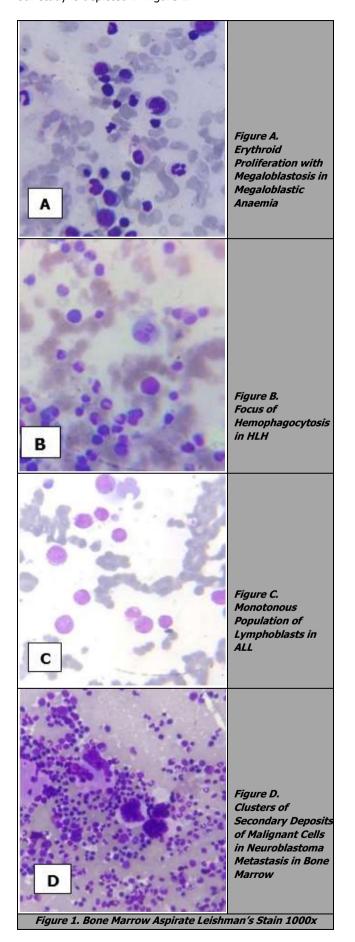
Aetiology	Single Cytopenia	Bicytopenia	Pancytopenia	Total			
ITP	131	28	0	159			
Iron deficiency anaemia	39	2	0	41			
ITP with iron deficiency anaemia	0	15	0	15			
ALL	0	7	14	21			
Infection related changes	13	12	1	26			
Anaemia of chronic disease	18	8	0	26			
HLH	1	2	7	10			
Haemolytic anaemia	10	1	0	11			
Metastasis	0	4	0	4			
Combined nutritional anaemia	4	1	1	6			
Normal marrow study	11	3	3	17			
Megaloblastic anaemia	2	1	2	5			
Chronic inflammatory conditions	2	5	0	7			
Anaemia due to blood loss	2	0	0	2			
Hypoplastic marrow/ aplastic marrow	1	1	7	2			
Myelodysplastic syndrome	0	1	0	1			
Parvovirus B19	2	0	0	2			
Splenic sequestration	1	0	0	1			
Thalassemia	2	0	0	2			
Total 240 90 35 365							
Table 2. Distribution of Cases According to Aetiology in the Three Groups of Cytopenias							

Anaemia was observed in 43.8 % (N = 116) cases of single cytopenia group and 93.4 % (N = 84) cases of bicytopenia group. Isolated Leukopenia was very rare in our study observed in single cytopenia group. Leukopenia was most commonly observed in pancytopenia group, 1.2 % cases (N = 3) cases of single cytopenia group and 31.1 % (N = 28) cases of bicytopenia group. Thrombocytopenia was seen in 58.3 % (N = 140) cases of single cytopenia group and 75.6 % (N = 68) cases of bicytopenia group.

In all the three groups, moderate was the most common grade of anaemia observed. Severe grade was observed in 33.3 % cases of isolated anaemia and bicytopenia cases while it was only 2.9 % in pancytopenia group (P value < 0.05). Among the 140 single cytopenia cases having thrombocytopenia; 72.1 % cases (N = 101) had moderate grade, 16.4 % cases (N = 23) had mild grade and 11.4 % cases (N = 16) had severe thrombocytopenia. In the bicytopenia group 75.0 % (N = 51) had moderate thrombocytopenia. Pancytopenia cases also had 71.4 % cases (N = 25) presenting with moderate grades of thrombocytopenia. The association of grades of thrombocytopenia with type of cytopenias showed no significance (P value = 0.972).

Isolated thrombocytopenia was the most common peripheral smear picture observed (N = 124, 33.9 %), followed by hypochromic microcytic picture (N = 56, 15.34 %) and combination of HMA with thrombocytopenia (N = $\frac{1}{2}$

36, 9.8 %). The bone marrow findings of different cases in our study is depicted in Figure 1.



DISCUSSION

Though most previous studies done on paediatric bicytopenias and pancytopenia cases reported male predominance, 4,5 our study showed slight female predominance (M: F = 1:1.05) on an evaluation of all three types of cytopenias. Our observation showed that most common age group of paediatric cytopenia in less than 5 years of age (37 %) was in concordance with many other similar studies conducted in different parts of the world. Higher incidence was reported by Sharif M et al. (61 %) and R. Warris et al. (50 %). 7,8

In the present study, since ITP constituted the major population of single lineage cytopenia; petechiae and purpura was the most common clinical presentation. In bicytopenia and pancytopenia groups, fever was the most common clinical feature observed. Memon et al. and Jan AZ et al. observed pallor and fever as the most common clinical presentation in paediatric pancytopenia. 9,10

Though comparison of various clinical morphologic and biochemical parameters between paediatric bicytopenia and pancytopenia were studied by many authors before; we couldn't find any previous study comparing all the three groups of cytopenias even after extensive literature search. Not only that the evaluation studies of aetiology of single cytopenias is also very rare in literature. In our study the majority of children presented with single cytopenias. Thrombocytopenia was the most commonly observed single cytopenia and the least common one was leukopenia. Immune thrombocytopenic purpura was the most common cause of isolated thrombocytopenia in our study. Most of the previous studies done in and outside India reported ITP as the most common cause of isolated paediatric thrombocytopenia. But discordant observations were made by Subramanian et al. in a study done in 644 paediatric cases in Chennai where infections were reported as the most common cause of paediatric thrombocytopenia. 11 Isolated anaemia was the second most commonly observed type of single lineage cytopenias with predominant ones having iron deficiency anaemia as the aetiologic factor. Other causes like haemolytic anaemia, infections, inflammations, B12 / folate / combined nutritional anaemia, bone marrow aplasia also caused isolated anaemia in our cases. Our observations on the aetiologic factors of anaemia was in concordance with Madoori and Venkitesh et al. and Janus J studies. 12,13,14 Leukopenia was rarely observed as an isolated cytopenia in our study. Among the three cases of isolated leukopenia, 2 cases had infection and one case had B12 deficiency as the aetiologic factor. A study on respiratory viral infectious aetiologies of transient cytopenia by Fettah et al. observed neutropenia as the most common type of leukopenia observed. 15 Similar finding was observed by Kauder et al. 16 In our study malignancy was not seen in any cases with single lineage cytopenia.

In the present study most common cause of bicytopenia were reactive conditions like ITP with and without anaemia, infections etc. But 7 cases showed acute lymphoblastic leukaemia and 4 cases showed metastatic malignancies. Our observations on bicytopenia was in concordance with Shano Naseem study who reported ITP as the most common cause

for bicytopenia in children.¹⁷ Shilpi Dosi observed most common non-malignant cause of paediatric bicytopenia as megaloblastic anaemia and combined nutritional anaemia and malignant cause of bicytopenia in their study were constituted by acute lymphoblastic leukaemia (ALL), Acute myeloid leukaemia (AML) and metastatic Neuroblastoma.¹⁸

Pancytopenia in children is an extensively studied topic by many researchers before in India. The observations made by different authors on causes of pancytopenia is summarized and compared with present study in Table 3. Though the total sample size studied is higher than comparison studies, the pancytopenia cases in present is lesser than others and this may be the probable reason for higher incidence of malignancy in our study.

Author	Year	Place	Fotal Sample Size	Pancytopenia Sample Size	Commonest Cause of Pancytopenia
Bhatnagar et al. ¹⁹	2005	India		109	Megaloblastic anaemia 28 %
Guptha et al. ²⁰	2008	India		105	Aplastic anaemia 43 %
Naseem et al.	2010	India		139	Aplastic anaemia 26.6 %
Shilpi Doshi et al. ¹⁶	2017	India		59	Megaloblastic anaemia 45.8 %
Present study	2020	India		35	ALL
Table 3. Comparison Studies on Causes of Pancytopenia					

In the present study, the most common age group of children affected by cytopenias was one to five years with slight female predominance. Single cytopenia was more common than bicytopenia and pancytopenia. Single cytopenias had slight male predominance and it was commonly observed in five to ten years of age. Single cytopenias presented with bleeding manifestations in majority of cases. Malignancies were observed in 25 cases (6.84%) with primary malignancies constituting 84% (N = 21) of cases.

CONCLUSIONS

Aetiology of different types of cytopenia is different in different parts of the world. This difference can be attributed to sociodemographic factors like dietary habits, life style, genetic diseases, radiation / carcinogenic substances exposure etc. The diagnosis of aetiology of cytopenias in children requires detailed clinicohaematological evaluation. Studies on aetiomorphological factors of paediatric cytopenias are very rare in global literature especially in India. Since nutritional deficiencies like Iron deficiency anaemia, megaloblastic anaemia etc. can cause different types of cytopenias, prevalence of these conditions is indeed a reflection of the nutritional status and effectiveness of national health care programs. More research in this field is necessary to understand the underlying profile of cytopenias and throw some light in improving the management strategies of these cases in the future.

The limitation of this study is that since the study was not a population-based, only severe cases of cytopenia who sought medical attention were included in this study.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

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